A Facile and Practical Synthesis of Nicolaou's Key Intermediates, 2-Methyl- and 2,6-Dimethyltetrahydropyrans, toward the Total Synthesis of Ladder-Shaped Polyethers

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This paper is dedicated to the memory of Choji Ueno.

Abstract: A facile and robust method to prepare 2-methyl- and 2,6-dimethyltetrahydropyrans, most useful Nicolaou intermediates for the synthesis of ladder-shaped polyethers, is disclosed. The established highly practical recipe, adopting chemo- and stereoselective catalytic oxidations and one-pot reactions with few chromatographic purifications, would significantly facilitate the large-scale supply of pivotal monocyclic building blocks, which is a rate-determining process of gigantic tetrahydropyran-containing natural products synthesis.

Key words: total synthesis, ladder-shaped polyethers, *trans*/*syn*/*trans*-fused-ring system, one pot, selective oxidation

In recent decades, one of the hottest issues in the natural products chemistry field has been ladder-shaped polyethers (LSPs). LSPs, unique secondary metabolites of dinoflagellates,[1] are notorious marine toxins possessing gigantic structures (Figure 1). Of these, brevetoxins are known to cause red tide,[2] while ciguatoxins[3] and maitotoxin[4] exert extraordinarily potent neurotoxicity and are thought to be the causative toxins of 'ciguatera' seafood poisoning. Recently, brevisulcenal-F, a new toxic member with strong mouse lethality, was also isolated from a red-tide dinoflagellate.[5] Despite the potent toxicity of LSPs and societal needs for the detection and development of detoxification methods, there have been few mode-of-action studies.[6] The short supply of natural specimens, as well as the gigantic and complex structures, has hampered detailed investigations of biological function but, at the same time, has made LSPs attractive targets of total synthesis. Indeed, as a result of tight competition between rival groups, a considerable number of total syntheses of LSPs have been achieved to date,[6g,7] in which keen attention has been paid to the development of convergent strategies for the expeditious coupling of building blocks.

On the other hand, however, the basic methods for constructing tetrahydropyrans (THPs) with/without axial methyl group(s) at the 2,6-positions, the most commonly occurring structural units of LSPs, have remained unchanged for two decades. The Nicolaou group first reported the synthesis of THPs **1** and **2**[8b] from commercially available 2-deoxy-D-ribose (Scheme 1). Briefly, 2-deoxy-D-ribose was converted into alcohol **5** via Wittig olefination and protection of the 1,3-diol moiety. For the synthesis of compound **1**, the key intermediate, vinyl epoxide **11**, was prepared from **5** through silyl protection (**6**), reduction (**7**), Katsuki–Sharpless asymmetric epoxidation[9] (**8**), Parikh–Doering oxidation (**9**), Wittig reaction (**10**), and desilylation (**11**). Finally, the THP ring was regio- and stereoselectively constructed via the acid-mediated 6-*endo*-*tet*-mode cyclization of **11**, furnishing **1**. In order to synthesize compound **2**, Swern oxidation (alcohol **5** to ketone **12**) and the stereoselective installation of a methyl group (**13**) were additionally conducted before the sequential transformation via **14**, **15**, **16**, and **17**, to give **2**. Following this pioneering work, other THPs possessing some variation of the methyl groups at the 2,6-positions, such as **3** and **4**, were synthesized using the same strategy.[10]

As an alternative method of THP construction, around a decade later the Nakata group reported SmI_2-mediated radical cyclization of δ-acryloxy aldehyde **18** (Scheme 1).[11] This method can even be applied to the large-scale synthesis of **19**,[11,12] in only five steps from 2-deoxy-D-ribose, in excellent yield (70%).[13] Unfortunately, it was found that this radical cyclization method could not access THP rings equipped with an axial methyl group at the far-side anomeric position from the benzylidene acetal, such as compound **21**.[11c] Other than these, although many methodologies to construct 2,6-substituted THPs have also been developed,[14] few robust strategies have become widespread in the synthetic community for LSPs, probably due to scalability problems.

Consequently, to the best of our knowledge, the pioneering method of Nicolaou's group, adopting the 6-*endo*-*tet* cyclization of vinyl epoxides,[8] has been utilized in almost all the syntheses of LSPs, including brevetoxins,[15] ciguatoxins,[16] gambierol,[17] gymnocin-A,[18] brevenal,[19] brevisin,[20] gambieric acid A,[21] and probe molecules for elucidating the mode of action,[22] as well as in the worldwide-progressing synthetic studies of yessotoxins[23] and maitotoxin.[24]

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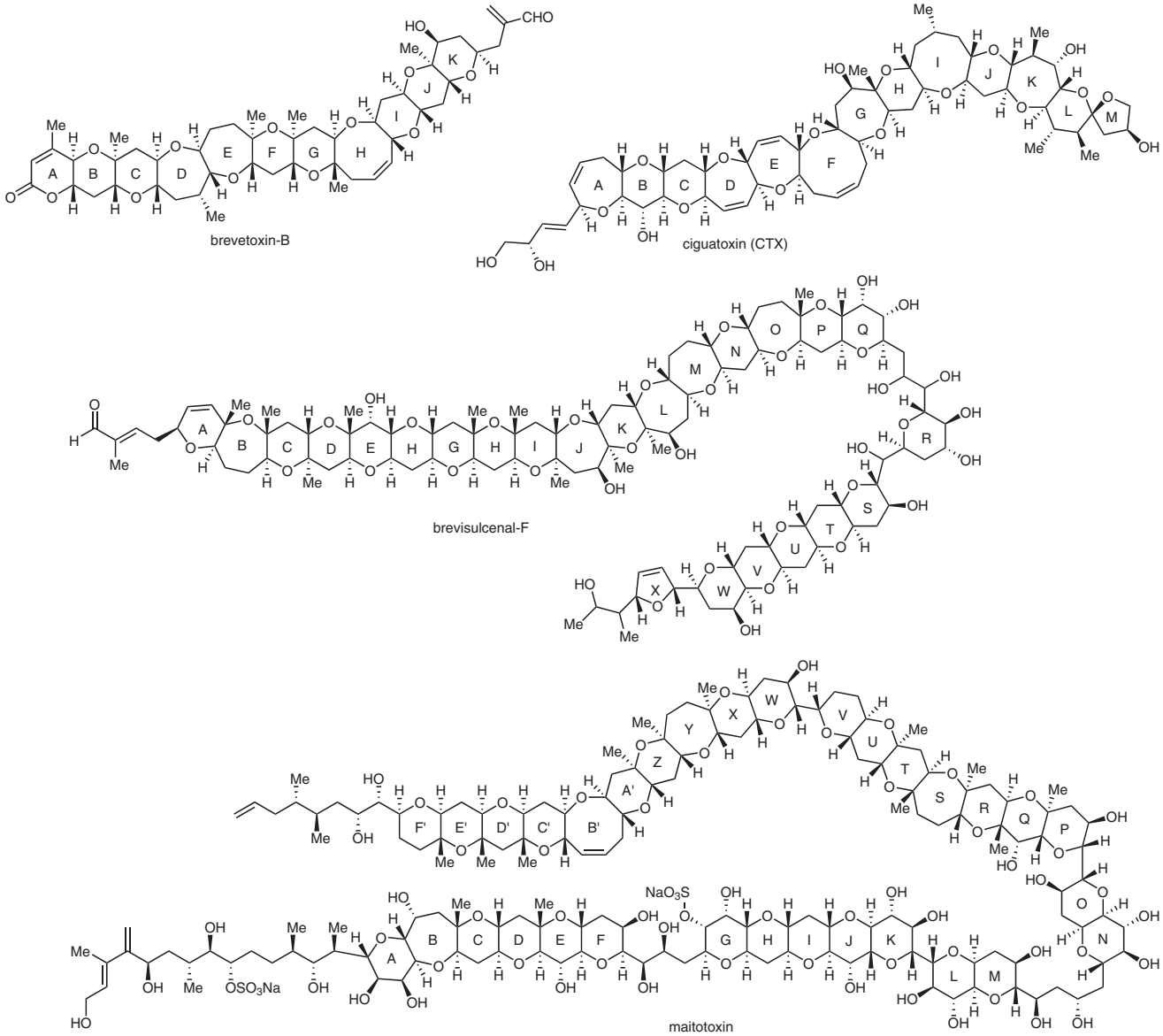


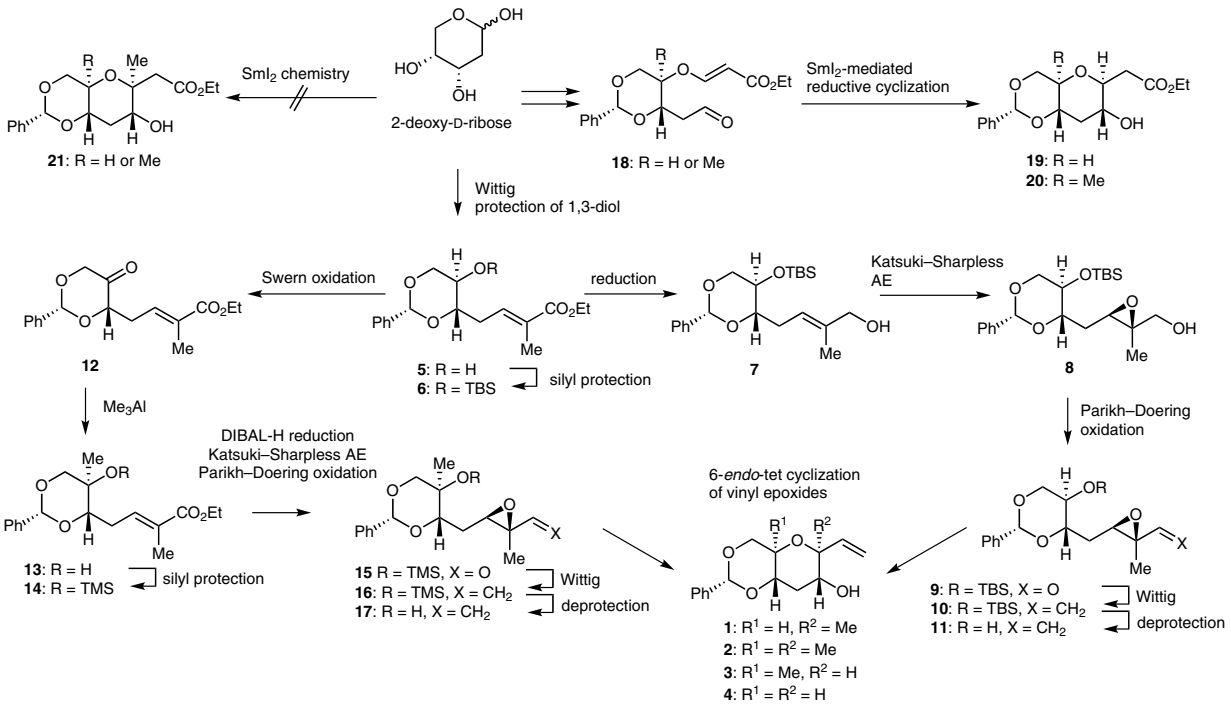
Figure 1 Structures of naturally occurring ladder-shaped polyethers

Although this clearly indicates that Nicolaou's method was, and still is, amazingly useful and sophisticated, in the course of our synthetic studies of yessotoxin and maitotoxin, we encountered some difficulties managing the large-scale preparation of THPs via this methodology.

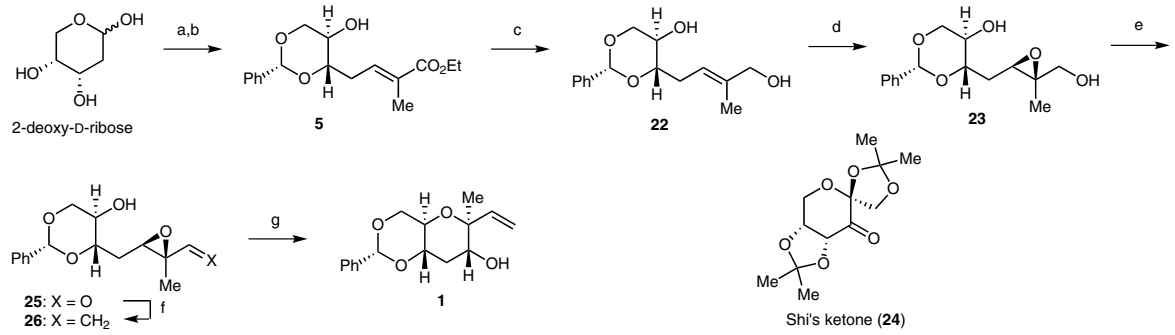
To solve the problems in the large-scale supply of building blocks, which is one of the most critical rate-determining processes in LSP synthesis through hundreds of steps, we believed reassessment of the conventional recipe taking into consideration the idea of blending modern synthetic methods, such as catalytic and time-integrated[25] process chemistries, was necessary. Herein, we report a facile and large-scale-friendly improved recipe for the most pivotal Nicolaou monocyclic intermediates to inform and aid synthetic chemists engaged in the preparation of LSPs and other THP-containing compounds.

To establish a facile and robust route for THP derivatives **1** and **2**, we envisaged that the following points of the traditional method needed to be improved: i) the laborious, long sequence (9 and 11 steps), which requires huge-scale chromatography in every step, ii) the air- and moisture-sensitive reactions using freshly purified reagents, iii) the offensive odor of dimethyl sulfide after DMSO-mediated oxidations, iv) the instability of ketone **12** and TMS ethers (e.g., **14**), which decreases the reproducibility, v) the emulsion formation after the Katsuki–Sharpless asymmetric epoxidation, and vi) the usage of expensive reagents. Focusing upon these points, we developed an improved recipe for THP **1** by making use of modern chemistries, as outlined in Scheme 2.

Wittig reaction of 2-deoxy-D-ribose with ethyl 2-(triphenylphosphoranylidene)propionate gave crude triol, which



Scheme 1 Conventional synthesis of tetrahydropyran intermediates **1** and **2** with/without angular methyl group(s) at the 2,6-positions. For **1**, total 9 steps, 8 chromatographic purifications; total yield: 55%. For **2**, total 11 steps, 8 chromatographic purifications; total yield: 43%.



Scheme 2 Improved recipe for tetrahydropyran **1**. *Reagents and conditions*: a) $Ph_3P{=}C(Me)CO_2Et$, THF, reflux; b) PhCHO, $CH(OMe)_3$, CSA, CH_2Cl_2, r.t., 86% (2 steps); c) DIBAL-H (3.3 equiv), CH_2Cl_2, –64 to –50 °C, 90%; d) Shi's ketone **24** (25 mol%), Oxone®, DMM, MeCN, KOH, K_2CO_3–AcOH buffer (pH 9.3), –10 °C; e) TEMPO (0.9 mol%), NaOCl, KBr (9 mol%), $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C; f) Ph_3PMeBr, *t*-BuOK, THF, 0 °C; g) silica gel 60N (neutral, spherical, particle size 40–50 μm), 120 °C, 44% (4 steps); total 7 steps, 3 chromatographic purifications; total yield: 34%.

was directly treated with benzaldehyde and trimethyl orthoformate (instead of expensive benzaldehyde dimethyl acetal) in the presence of 10-camphorsulfonic acid (CSA) to furnish alcohol **5** in 86% yield for the two steps. Although the traditional recipe prescribes the protection of **5** as the TBS ether **6**, we envisaged that the protection is not necessary if the asymmetric epoxidation of **22** and the selective oxidation of primary alcohol **23** could proceed. Thus, we first carried out DIBAL-H reduction of ester **5** without protecting the secondary hydroxy group to give diol **22** (90% yield). As a result of considerable experimentation, the desired conversion was achieved via the combination of two modern reactions: i) Shi asymmetric epoxidation (resulting in **23**)[26] catalyzed by ketone **24**,[27] and ii) the highly chemoselective, inexpensive, and odorless catalytic oxidation of primary alcohol into the corresponding aldehyde **25** using 0.9 mol% of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO).[23b,28] In this sequential manipulation, both the stereoselectivity and the functional group compatibility of the Shi epoxidation were excellent (dr >12:1, even in the presence of the two hydroxy groups), and the key to success for the TEMPO oxidation was the precise restriction of the amount of reoxidant (NaOCl) to avoid overoxidation of the resultant aldehyde into carboxylic acid. The subsequent sequential two steps were also able to be fulfilled without chromatography, i.e. the Wittig reaction [using inexpensive *t*-BuOK instead of sodium hexamethyldisilazide (NaH-

MDS) as a base], and solid-phase 6-*endo*-*tet* cyclization of vinyl epoxide **26** on silica gel 60N (instead of treatment with PPTS in the solution phase) at 120 °C for 4 hours, gave a crude material containing **1**, which had already been absorbed by the silica gel. Therefore, after the final step was finished, the solid reaction mixture was simply settled onto the top of a silica gel column and purified chromatographically to afford pure compound **1** (44% yield for 4 steps).

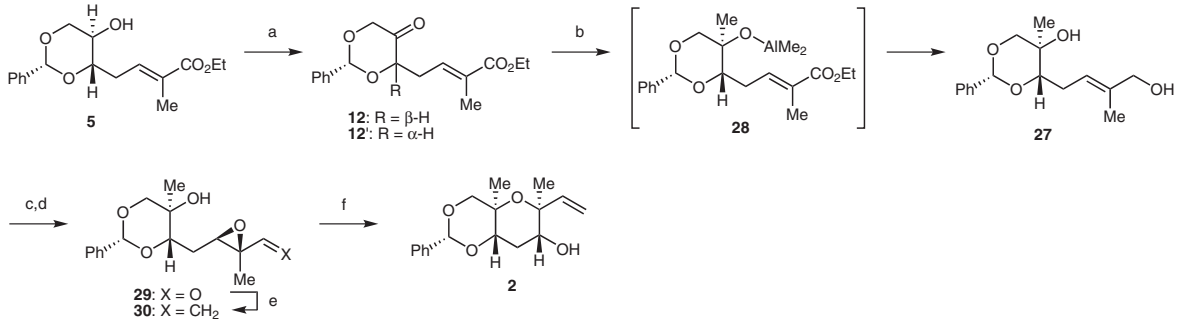
The total yield for the above sequence from 2-deoxy-D-ribose to THP **1** was 34%, and the average yield was 86% for each step. The number of steps (seven) and chromatographic purifications (three), as well as the cost (ca. >20% less[29]), have all been reduced relative to the conventional method with nine steps and eight chromatographic purifications. Finally, it should be emphasized that the developed recipe significantly facilitates the large-scale preparation of THP, with considerable operational simplicity and reproducibility.

After developing the effective and expeditious method to prepare **1**, we turned our attention to applying this methodology to the synthesis of THP derivative **2**, equipped with two angular methyl groups (Scheme 3). Commencing from a common intermediate **5**, the first task was the oxidation of secondary alcohol **5** into the corresponding ketone **12**. In this step, the ideal conditions to be pursued should result in the clean formation of ketone **12** without chromatographic purification, since ketone **12** was revealed to be labile under both mildly basic and acidic conditions; that is, treatment of **12** under the basic conditions resulted in the epimerization of **12** into **12′** and, furthermore, a critical loss of **12** was also observed upon sluggish purification using neutral silica gel.[30] As a result of examining various modern catalytic oxidations to overcome the above problems,[31] we finally found that only 0.05 mol% of 2-azaadamantane *N*-oxyl (AZADO)[32] in the presence of sodium hypochlorite as a reoxidant[33] worked satisfactorily to convert alcohol **5** into the corresponding ketone **12**, which was pure enough to be utilized in the next reaction without further purification.

The next task was the axial selective installation of a methyl group to the ketone moiety of **12**, and the subsequent 1,2-reduction of the α,β-unsaturated ester. Despite the conventional procedure, in which the hydroxy group generated after methylation is protected as the TMS ether **14**, we surmised that silylation had to be avoided, since the installed TMS group was found to cleave too easily during chromatographic purification. In addition, we noticed that if a silylating step could be skipped, there would be a second advantage. That is, 'time-integrated'[25] one-pot conversion of ketone **12** into diol **27** seemed to emerge since, in this methylation–reduction sequence, the same solvent (CH_2Cl_2) and the same workup procedure (treatment with MeOH followed by aqueous Rochelle salt) were to be utilized. Hence, a solution of the crude ketone **12** was first treated with Me_3Al at –20 °C; then, to the resulting mixture, DIBAL-H was added at –65 °C. As expected, the reaction proceeded smoothly and cleanly to give diol **27** in excellent yield (79% for 3 steps). Moreover, this 'time-integrated chemistry' resulted in a third benefit, namely, 'saving of the reagent.' In other words, this one-pot reaction required only 2.2 equivalents of DIBAL-H, in contrast to the reduction of hydroxy ester **5** (3.3 equiv; Scheme 2, step c), probably because the generated tertiary alcoholic moiety was in situ protected, temporarily but effectively, as the dimethylaluminum species **28**.

Finally, the end game of this synthesis was carried out via the same manipulations as for THP **1**: epoxidation and TEMPO/NaOCl oxidation of allylic alcohol **27** followed by Wittig olefination and silica-gel-assisted 6-*endo*-*tet* cyclization of vinyl epoxide **30** furnished THP **2** in successful yield (32% for 4 steps). Interestingly, in the case of **2**, the final 6-*endo* cyclization required treatment with silica gel 60 (Kanto Chemical Co., Inc.) at 60 °C, instead of silica gel 60N at 120 °C.[34]

Consequently, dozens of grams of THP **2** became accessible via only eight steps and three chromatographic purifications from the commercially available 2-deoxy-D-ribose in 22% total yield (cf. the original work of Nicolaou's group: the total yield was 43%, but in 11 steps



Scheme 3 Improved recipe for tetrahydropyran **2**. *Reagents and conditions*: a) AZADO (0.05 mol%), NaOCl, KBr (10 mol%), $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C; b) Me_3Al, CH_2Cl_2, –20 °C; then DIBAL-H, –65 °C, 79% (3 steps); c) Shi's ketone **24** (25 mol%), Oxone®, DMM, MeCN, KOH, K_2CO_3–AcOH buffer (pH 9.3), –10 °C; d) TEMPO (1 mol%), NaOCl, KBr, $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C; e) Ph_3PMeBr, *t*-BuOK, THF, 0 °C; f) silica gel 60 (spherical, particle size 40–50 μm), 50 to 60 °C, 32% (4 steps); total 8 steps, 3 chromatographic purifications; total yield: 22%.

requiring 8 chromatographic purifications). Additionally, the cost of the new recipe is comparable to the traditional procedure.[29]

In conclusion, we have disclosed a facile, odorless, and robust recipe to synthesize tetrahydropyran derivatives with axial methyl group(s) at the 2,6-positions. The developed practical recipe, adopting the chemoselective catalytic oxidations, the one-pot reaction, and only three chromatographic purifications, realized rapid access to THP **1** and **2** in only seven and eight steps, respectively. This revamped route, highlighting promptness and reproducibility, will accelerate the race for the total syntheses not only of LSPs, but also of other natural products.[35] At the same time, it indicates that the synergistic power of blending modern ideas, such as catalytic and time-integrated chemistries, should be recognized and used by synthetic chemists in the fight against structurally complex natural products, in the next generation.

Synthetic studies of ladder-shaped polyethers toward mechanistic elucidation of their biological activities, using large amounts of tetrahydropyran derivatives supplied by the improved recipe, are now in progress in our laboratory.

For all the moisture-sensitive reactions, the substrates were dried by azeotropic removal of water with toluene (ca. 100 mL, 2 ×). Anhyd CH_2Cl_2 and THF were purchased from Kanto Chemical Co., Inc. and used without further drying. All other chemicals were obtained from local venders and used as supplied. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25-mm thickness). For column chromatography, Kanto silica gel 60N (neutral, spherical, 100–210 μm) was utilized. Optical rotations were recorded on a JASCO P-1010 polarimeter. IR spectra were recorded on a JASCO FT-IR-4100 Fourier transform infrared spectrometer. NMR spectra were recorded on a JEOL JNM-ECA600 spectrometer. Chemical shifts are reported in ppm from TMS with reference to internal residual solvent [^{1}H NMR, $CHCl_3$ (7.26); ^{13}C NMR, $CDCl_3$ (77.0)]. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF II instrument under ESI-TOF conditions.

α,β-Unsaturated Ester 5

Under an argon atmosphere, to a soln of 2-deoxy-D-ribose (25.00 g, 0.1863 mol) in THF (150 mL) was added ethyl 2-(triphenylphosphoranylidene)propionate (81.71 g, 0.2255 mol). After being stirred under reflux for 2 h, the reaction mixture was cooled to r.t., the solvent was removed in vacuo, and the residue was dried by azeotropy with toluene.

Under an argon atmosphere at 0 °C, to a soln of the above crude material in CH_2Cl_2 (167 mL) were added benzaldehyde (23.0 mL, 0.225 mol), trimethyl orthoformate (24.7 mL, 0.225 mol), and (±)-10-camphorsulfonic acid (15.0 g, 0.0646 mol). After being stirred at r.t. for 22 h, the reaction mixture was quenched with Et_3N (13.5 mL, 0.0974 mol) at 0 °C and concentrated in vacuo. A mixed solvent (hexane–EtOAc–$CHCl_3$, 8:1:0.1, 50 mL) was added to the resultant oil to give a less viscous syrup, which was then absorbed onto dry silica gel (150 g). This silica gel, possessing crude material, was settled onto the top of a silica gel (750 g) column; the subsequent chromatographic purification (hexane–EtOAc, 8:1 to 5:1 to 3:1) gave α,β-unsaturated ester **5** [yield: 49.05 g (0.1601 mol, 86% for 2 steps)] as a colorless powder, whose spectroscopic data were fully identical to those in the literature.[8b]

Diol 22

Alcohol **5** (47.45 g, 0.1549 mol) was dried by azeotropy with toluene. At –64 °C under an argon atmosphere, to a soln of alcohol **5** in CH_2Cl_2 (150 mL) was added 1.0 M DIBAL-H in toluene (510 mL, 0.510 mol) over a period of 20 min. After being stirred at –64 to –50 °C for 75 min, the reaction mixture was quenched with MeOH. After vigorous gas evolution had ceased, sat. aq NH_4Cl was added and the mixture was then allowed to warm to 0 °C with care due to further evolution of gas. At 0 °C, to the mixture were added EtOAc and sat. aq sodium potassium tartrate (500 mL), and the reaction mixture was allowed to warm to r.t. The mixture was vigorously stirred at r.t. (overnight), until the layers became separable. The mixture was extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by silica gel (550 g) column chromatography (hexane–EtOAc, 3:1 to 1:1) to give diol **22**; yield: 36.86 g (0.139 mol, 90%); colorless, amorphous.

$[\alpha]_D^{21}$ –30.6 (*c* 0.35, $CHCl_3$); R_f = 0.20 (hexane–EtOAc, 1:1).

IR (film): 3333, 2937, 2921, 2858, 2831, 1455, 1398, 1366, 1314, 1294, 1217, 1182, 1129, 1074, 1022 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48–7.47 (m, 2 H), 7.40–7.38 (m, 3 H), 5.62 (dt, *J* = 6.9, 1.4 Hz, 1 H), 5.46 (s, 1 H), 4.21 (dd, *J* = 10.3, 4.1 Hz, 1 H), 3.98 (br s, 2 H), 3.64–3.59 (m, 2 H), 3.54 (dd, *J* = 10.3, 10.3 Hz, 1 H), 2.65 (br s, 1 H), 2.64–2.60 (m, 1 H), 2.48–2.43 (m, 1 H), 2.12 (br s, 1 H), 1.70 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.7, 137.1, 129.0, 128.9, 128.2, 126.1, 121.0, 100.9, 81.4, 71.1, 68.5, 65.4, 30.3, 14.0.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{20}O_4Na^+$: 287.1254; found: 287.1258.

Tetrahydropyran 1

Diol **22** (18.00 g, 68.10 mmol) and Shi's ketone **24** (4.40 g, 17.3 mmol) were placed in a 2-L, three-necked, round-bottomed flask equipped with two dropping funnels. DMM (330 mL), MeCN (165 mL), and pH 9.3 aq K_2CO_3–AcOH buffer [330 mL, prepared by mixing 0.1 M aq K_2CO_3 (500 mL) with AcOH (2.4 mL)] were added, and the reaction mixture was cooled to –10 °C. To the stirred solution were slowly added Oxone® soln [50.6 g, 0.0823 mol, in 0.4 M aq EDTA·2Na (187 mL)] and 1.47 M aq KOH (187 mL, 0.275 mol) from separate dropping funnels over a period of 3 h. After the reaction was quenched with sat. aq $Na_2S_2O_3$, the mixture was extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude epoxide **23**, which was used in the next reaction without further purification. Two times operation of the above process furnished 39.95 g of crude epoxide **23**.

To a mixture of crude alcohol **23** (39.95 g) and TEMPO (192 mg, 1.23 mmol) were added CH_2Cl_2 (450 mL) and 0.5 M aq KBr (24.5 mL, 12.3 mmol). At 0 °C, to this mixture was added a mixture of 1.96 M aq NaOCl (74.0 mL, 0.145 mol) and sat. aq $NaHCO_3$ (74.0 mL). After being stirred at 0 °C for 30 min, the reaction mixture was quenched with sat. aq $Na_2S_2O_3$ and extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude aldehyde **25** (34.94 g), which was used in the next reaction without further purification.

At 0 °C under an argon atmosphere, to a soln of methyltriphenylphosphonium bromide (110.0 g, 0.3079 mol, dried by warming in vacuo using a hair dryer) in THF (525 mL) was added *t*-BuOK (32.00 g, 0.2851 mol). After being stirred at 0 °C for 50 min, to the yellow suspension was added a soln of crude aldehyde **25** (34.94 g, dried by azeotropy with toluene) in THF (200 mL) over a period of 10 min, and the resulting reaction solution was stirred at 0 °C for 1 h. The reaction mixture was quenched with sat. aq NH_4Cl and dilut-

ed with EtOAc. The resulting mixture was extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude vinyl epoxide **26**, which was used in the next reaction without further purification.

To a soln of the crude vinyl epoxide **26** (all of previous) in EtOAc was added silica gel 60N (150 g, neutral, spherical, particle size 40–50 μm, Kanto Chemical Co., Inc.). The volatiles were removed in vacuo, and the residue was heated at 120 °C for 4 h. The residue was settled onto the top of a silica gel (650 g) column, and purified by chromatography (hexane–EtOAc, 7:1 to 5:1 to 4:1) to afford tetrahydropyran **1** (16.72 g, 60.5 mmol, 44% for 4 steps) as a colorless powder, whose spectroscopic data were fully identical to those in the literature.[8b]

Diol 27

To a soln of alcohol **5** (50.10 g, 0.1635 mol) in CH_2Cl_2 (370 mL) were added AZADO (13.7 mg, 90.0 μmol) and 0.50 M aq KBr (33.0 mL, 16.5 mmol). At 0 °C, to this mixture was added a mixture of 1.96 M aq NaOCl (115 mL, 0.225 mol) and sat. aq $NaHCO_3$ (420 mL). After being stirred at 0 °C for 2 h, the reaction mixture was quenched with sat. aq $Na_2S_2O_3$ and extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude ketone **12** (50.86 g), which was used in the next reaction without further purification.

Under an argon atmosphere at –20 °C, to a soln of the crude ketone **12** (50.86 g, dried by azeotropy with toluene) in CH_2Cl_2 (300 mL) was added 1.05 M Me_3Al in hexane (240 mL, 0.252 mol) over a period of 12 min. After being stirred at –20 °C for 1 h, the reaction mixture was cooled to –65 °C and 1.0 M DIBAL-H in toluene (370 mL, 0.370 mol) was added over a period of 16 min. After being stirred at –65 °C for 40 min, the reaction mixture was quenched with MeOH. After vigorous gas evolution had ceased, sat. aq NH_4Cl was added and the mixture was then allowed to warm to 0 °C with care due to further evolution of gas. At 0 °C, to the mixture were added EtOAc and sat. aq sodium potassium tartrate (500 mL), and the reaction mixture was allowed to warm to r.t. The mixture was divided into two flasks, and to both flasks was added additional sat. aq sodium potassium tartrate (500 mL each). Both reaction mixtures were vigorously stirred at r.t. (overnight), until the layers became separable. The mixture was extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by silica gel (400 g) column chromatography (hexane–EtOAc, 2:1 to 1:1) to give diol **27**; yield: 36.10 g (0.130 mol, 79% for 3 steps); colorless, amorphous.

$[\alpha]_D^{20}$ –68.4 (*c* 0.13, $CHCl_3$); R_f = 0.27 (hexane–EtOAc, 1:2).

IR (neat): 3373, 2975, 2925, 2858, 1454, 1396, 1310, 1213, 1095, 1074, 1025, 989, 960, 916, 888, 797, 748, 697, 666 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.49–7.47 (m, 2 H), 7.38–7.33 (m, 3 H), 5.57 (ddd, *J* = 6.8, 6.2, 1.4 Hz, 1 H), 5.47 (s, 1 H), 3.97 (s, 2 H), 3.86 (d, *J* = 10.3 Hz, 1 H), 3.63 (dd, *J* = 8.9, 4.1 Hz, 1 H), 3.61 (d, *J* = 10.3 Hz, 1 H), 2.51 (ddd, *J* = 15.1, 8.3, 4.1 Hz, 1 H), 2.25 (ddd, *J* = 15.1, 8.9, 7.6 Hz, 1 H), 1.69 (s, 3 H), 1.41 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.8, 136.4, 128.9, 128.2, 126.1, 121.9, 101.7, 84.0, 77.3, 68.4, 66.7, 27.5, 19.6, 13.9.

HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}O_4Na^+$: 301.1410; found: 301.1403.

Tetrahydropyran 2

Diol **27** (18.0 g, 64.7 mmol) and Shi's ketone **24** (4.00 g, 15.5 mmol) were placed in a 2-L, three-necked, round-bottomed flask equipped with two dropping funnels. DMM (330 mL), MeCN (165 mL), and pH 9.3 aq K_2CO_3–AcOH buffer (330 mL) were added, and the reaction mixture was cooled to –10 °C. To the stirred solution were slowly added Oxone® soln [46.00 g, 74.82 mmol, in 0.4 M aq EDTA·2Na (170 mL)] and 1.47 M aq KOH (170 mL, 0.250 mol) from separate dropping funnels over a period of 3 h. After the reaction was quenched with sat. aq $Na_2S_2O_3$, the mixture was extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to furnish crude epoxide, which was used in the next reaction without further purification. Two times operation of the above process furnished 46.80 g of crude epoxide.

To a mixture of the crude epoxide (46.80 g) and TEMPO (200 mg, 1.28 mmol) were added CH_2Cl_2 (450 mL) and 0.5 M aq KBr (26.0 mL, 13.0 mmol). At 0 °C, to this mixture was added a mixture of 1.86 M aq NaOCl (74.0 mL, 0.138 mol) and sat. aq $NaHCO_3$ (74.0 mL). After being stirred at 0 °C for 17 min, the reaction mixture was quenched with sat. aq $Na_2S_2O_3$ and extracted with EtOAc, and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude aldehyde **29**, which was used in the next reaction without further purification.

At 0 °C under an argon atmosphere, to a soln of methyltriphenylphosphonium bromide (100.0 g, 0.2799 mol, dried by warming in vacuo using a hair dryer) in THF (525 mL) was added *t*-BuOK (30.00 g, 0.267 mol). After being stirred at 0 °C for 40 min, to the yellow suspension was added a soln of crude aldehyde **29** (all of previous; dried by azeotropy with toluene) in THF (200 mL) over a period of 12 min, and the resulting reaction solution was stirred at 0 °C for 30 min. The reaction mixture was quenched with sat. aq NH_4Cl, and diluted with EtOAc. The resulting mixture was extracted with EtOAc and the extract was washed with sat. aq NaCl, dried over Na_2SO_4, and filtered. The filtrate was concentrated to give crude vinyl epoxide **30** (105.25 g), which was used in the next reaction without further purification.

To a soln of the crude vinyl epoxide **30** (all of previous) in EtOAc was added silica gel 60 (150 g, spherical, particle size 40–50 μm, Kanto Chemical Co., Inc.). The volatiles were removed from the smooth slurry in vacuo, and the residue was heated at 50 °C for 25 h, then at 60 °C for 18 h. The residue was settled onto the top of a silica gel (700 g) column, and purified by chromatography (hexane–EtOAc, 7:1 to 5:1 to 4:1) to afford tetrahydropyran **2** (12.00 g, 41.3 mmol, 32% for 4 steps) as a colorless powder, whose spectroscopic data were fully identical to those in the literature.[8b]

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(30) The yield of **12** in the traditional recipe (68–97%) highly depends on personal technique. For good yield, speed in carrying out the large-scale column chromatography (using more than 500 g of silica gel, within approximately 10 min) is required. Ketone **12** was found to epimerize slowly to **12′** even under the basic conditions (e.g., CH_2Cl_2, sat. aq $NaHCO_3$, 0 °C, 40 h; **12**/**12′** = 4:1).
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