Organic Process Research & Development **2009**, *13*, 1111–1121

An Efficient Synthesis of a Cyclic Ether Key Intermediate for 9-Membered Masked Enediyne Using an Automated Synthesizer

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Abstract:

Naturally occurring antibiotics containing 9-membered enediynes have received considerable attention for many years due to their potent DNA-cleaving activity. We previously reported the design and synthesis of a synthetic, masked 9-membered enediyne that possesses DNA-cleaving activity. Despite the importance of the 9-membered enediynes, application of these molecules is limited by their difficult synthesis. Herein, we report an improved process for the generation of a synthetic, masked 9-membered enediyne that uses an automated synthesizer for the production of a key synthetic intermediate.

Introduction

Automation of synthetic operations, such as mixing of compounds, temperature control of reaction mixtures, quenching of reactions, filtration, liquid−liquid extraction, and washing and drying, effectively improves both the reproducibility and reliability of the syntheses because automated synthesizers minimize the variability of the experimental manipulations.[1] Recently, automated synthesizers have been used for two to four steps of the solution-phase synthesis of condensed-azoles, tripeptides, quinazolinones, and spirooxazolinoisoxazolines.[2−6] We previously reported a formal total synthesis of taxol using an automated synthesizer that was developed in our laboratory. Use of the ChemKonzert[7] enabled production of a key synthetic intermediate in a 36-step, solution-phase synthesis.[8] However, automation of general solution-phase syntheses is limited by the wide variety of the experimental operations required compared with those used for solid-phase synthesis. In particular, automation of liquid−liquid extractions is not simple.[9] Moreover, it is sometimes necessary to modify reaction conditions and/or experimental operations to utilize an automated synthesizer.[3,6,8] Therefore, in general, application of an automated process to solution-phase synthesis is challenging. Nevertheless, it is important to apply various solution-phase reactions to an automated synthesizer.

Naturally occurring antibiotics, such as kedarcidin chromophore (**1**)[10,11] and C-1027 chromophore (**2**),[12,13] that contain a 9-membered enediyne skeleton have potent antitumor activity (Figure 1). In addition to their uses in pharmaceuticals,[14−16] the 9-membered enediynes are powerful tools for chemical biology because they cleave DNA strands via formation of a highly active biradical.[17,18] We previously demonstrated that the masked 9-membered enediyne **3**[19−21] exhibits DNA-cleaving activity. In addition, its derivatives, **4**,[22] **5**, and **6**[23,24] that contain sugars and/or a naphthoate moiety, possess base-selective DNA-cleaving activity (Figure 1).

Despite the importance of the 9-membered enediynes, the applications of these molecules are limited by the difficulty of their syntheses. Synthesis of the 9-membered enediynes, which are structurally complex and unstable, typically requires additional synthetic steps and careful manipulation. Thus, only a few laboratories can synthesize, modify, and utilize these

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10.1021/op9002455 CCC: $40.75
Published on Web 11/02/2009

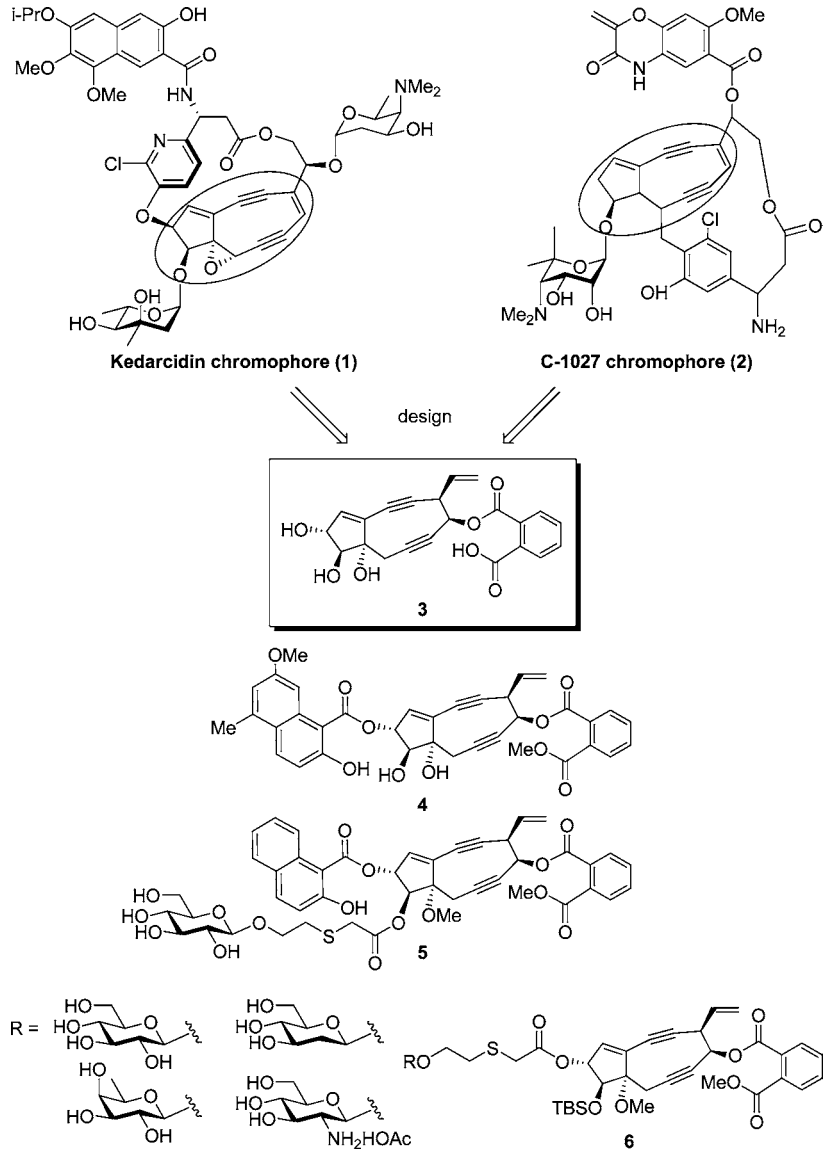

Figure 1. **Chemical structures of kedarcidin chromophore (1), C-1027 chromophore (2), the masked 9-membered enediyne 3, and their analogues 4−6.**

"molecular scissors" to cleave DNA.[10,11,13,25−29] Herein, we report the details of the synthesis of the 12-membered cyclic ether **7**, which is a chemically stable, key synthetic intermediate of **3**−**6**. To improve the reproducibility and efficiency of the synthesis, we used an automated synthesizer that was originally developed in our lab—the ChemKonzert (Figure 2)—in a 16-step process with some modifications of the reaction conditions.

Results and Discussion

The synthetic route for the masked 9-membered enediyne **3** is illustrated in Scheme 1. The transannular [2,3]-Wittig rearrangement[30] of the 12-membered cyclic ether **7** is the most crucial step in the construction of the highly strained 9-membered diyne, in which the newly formed secondary alcohol can be used to introduce a phthalic acid. A β-elimination of the phthalate "triggers" biradical formation. The cyclic ether **7** can be prepared via the Sonogashira coupling reaction between **8** and **9**, followed by intramolecular etherification. Selection of an appropriate protecting group for the allylic alcohol **9** is important. The protecting group must be stable under palladium-catalyzed reaction conditions. In addition, after the coupling reaction, it must be removed without affecting

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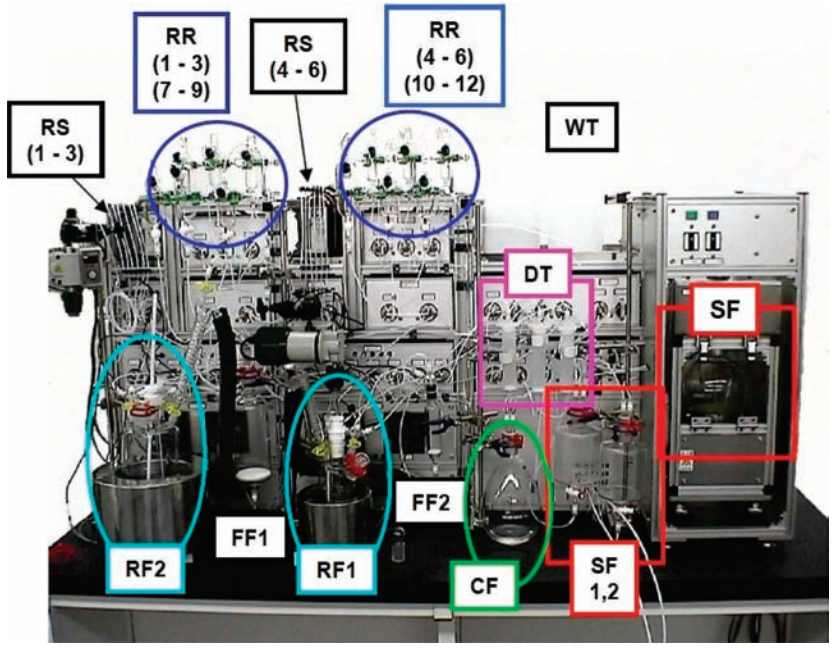
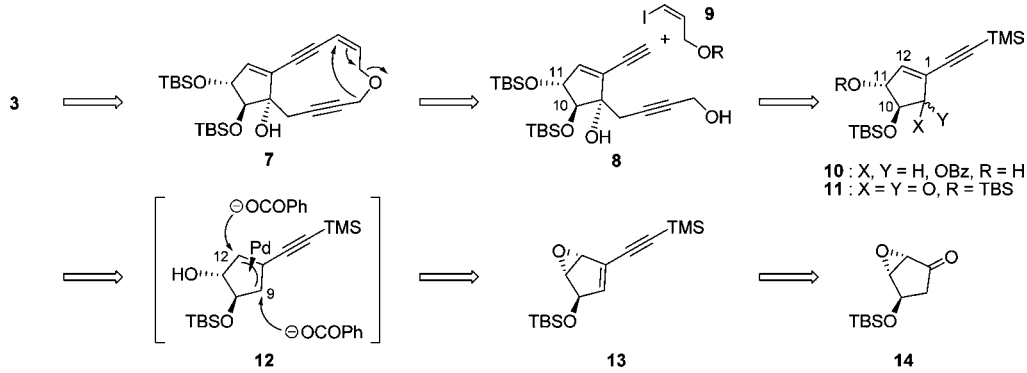


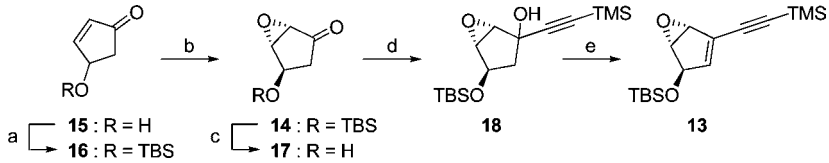
Figure 2. **Full picture of ChemKonzert, which consists of two reaction vessels (RF1, RF2), a centrifugal separator (SF, 700 mL), two receivers (SF1, SF2) (500 mL), two glass filters (FF1, FF2) (500 and 100 mL), twelve substrate and reagent reservoirs (RR1-RR12) (100−200 mL), six solvent and wash-solution bottles (RS1-RS6) (500 mL), three drying pads (DT1-DT3), a round flask (CF), two solvent tanks (WT1, WT2), and a computer controller. The glassware is interconnected with Teflon tubes, and solutions are transferred under reduced pressure by using a diaphragm pump. Separation of organic and aqueous layers is performed by measuring the electroconductivities of the two different phases with a sensor, and the liquid flow is regulated by solenoid valves controlled with an originally developed Windows software (KonzertMeister). The users input the procedures into the computer and add substrates and reagents to the reservoirs and fill the solvents. The synthesizer carried out the reaction procedures as follows: the substrate and reagents in the reservoirs, RR, were added to the reaction vessel, RF, at a controlled reaction temperature under a nitrogen atmosphere. After the reaction was complete (checking by TLC and/or HPLC by hand), quenching reagent in RR or RS was added to the reaction vessel, RF, and the mixture was transferred to the centrifugal separator, SF, with removal of the precipitate through the glass-filter, FF. After the centrifugal separation, the two resulting phases were separated by measurement of their electroconductivities with a sensor and transferred to two receivers, SF1 and SF2. The aqueous solution in SF1 was taken back to the reaction vessel, RF. After addition of the extraction solvent from the solvent bottle, RS, the mixuture was stirred and then transferred to the centrifugal separator, SF. After two or three extractions, the combined organic solution in the receiver, SF2, was washed with aqueous solutions of sodium bicarbonate and sodium chloride from the wash-solution bottles, RS, in the reaction flask, RF. The organic layer was separated in the centrifugal separator, SF, and transferrred to the receiver, SF2. The organic layer in SF2 was then passed through a $MgSO_4$ or Na_2SO_4 plug, DT, for drying. The filtrate was stored in a round flask, CF, for purification after evaporation of the solvent (manual). Unless purification was necessary, the filtrate was directly transferred to another reaction vessel, RF, and concentrated under reduced pressure; the next reaction was carried out sequentially. Finally, the whole apparatus was washed with water and acetone from the solvent tanks, WT, and dried under reduced pressure.**

Scheme 1. **Synthetic strategy for the masked 9-membered enediyne 3**



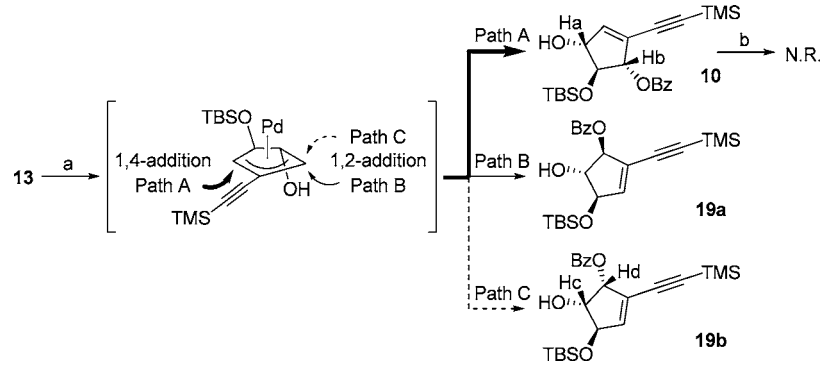
either the siloxy groups at the 10- and 11-positions or the unstable, conjugated dienyne moiety. The enediyne **8** was constructed by stereoselective 1,2-addition to ketone **11**. The second key reaction is the palladium-catalyzed addition of BzOH to the diene monoepoxide **13**.[31,32] This reaction induces *trans* stereochemistry between the hydroxy groups at the 10- and 11-positions and the $\Delta^{1,(12)}$ double-bond in **10**. Although the palladium-catalyzed reaction produces four possible regio- and stereoisomers by BzOH displacement from the α and β faces at the 9- and 12-positions via the π-allyl palladium complex **12**, all products could be converted into the enone **11** in three

Scheme 2. **Automated synthesis of the diene monoepoxide 13**[a]



[a] Reagents and conditions: (a) NEt_3, DMAP, CH_2Cl_2, 25 °C, 10 min, then TBSCl, CH_2Cl_2, 25 °C, 10 h, 73%; (b) Bu_4NHSO_4, NaClO aq, CH_2Cl_2, 0 °C, 6 h, 70%; (c) TBAF, THF, 0 °C, 5 min, 57%; (d) trimethylsilylacetylene, BuLi, THF, −78 to −40 °C, 1 h, then **14**, THF, −78 °C, 30 min, 71%; (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 1 h, 70%. DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride, Tf_2O = triflic anhydride.

Scheme 3. **Palladium-catalyzed addition of BzOH to diene monoepoxide 13 assisted by the automated synthesizer**[a]

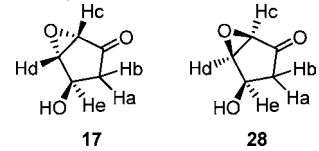


[a] Reagents and conditions: (a) 5 mol % $Pd(OAc)_2$, 20 mol % PPh_3, THF, 25 °C, 20 min, then BzOH, THF, 25 °C, 1 h, then **13**, THF, 0 to 25 °C, 10 h, 75%, **10**/**19a**/**19b** = 12:2:1; (b) 10 mol % $Pd(OAc)_2$, 40 mol % PPh_3, BzOH, THF, 25 °C, 1 h, then **10**, THF, 0 to 25 °C, 24 h.

steps. This methodology offers an enantioselective approach to **3**, starting from the optically active epoxide **14**, which is readily prepared from (*S*)-4-hydroxy-2-cyclopentenone.[33] Herein, we describe an efficient, automated synthesis of racemic **7**.

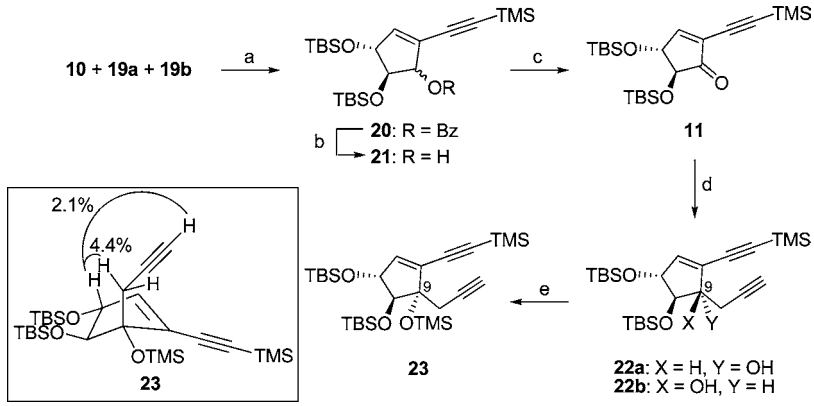
Epoxyalkene **13** was prepared with the use of the automated synthesizer (Scheme 2). Protection of 4-hydroxy-2-cyclopentenone (**15**) was carried out as follows. The computer controlling the automated synthesizer was programmed with a specific procedure. Substrate, reagents, solvents, and wash solutions were respectively added to the reaction vessel, RF1, reagent reservoir, RR1, solvent bottles, RS1, and wash-solution bottles, RS4−RS6. Then, the operation of the automated synthesizer was started. A solution of **15**, NEt_3, and DMAP in CH_2Cl_2 was stirred at 25 °C for 10 min under a nitrogen atmosphere in the reaction vessel, RF1. A solution of TBSCl in CH_2Cl_2, which was originally loaded into the reagent reservoir, RR1, was added to the reaction vessel, RF1. After stirring at 25 °C for 10 h, the reaction mixture was cooled to 0 °C. The reaction was then quenched by addition of 1 M HCl from the wash-solution bottle, RS4, and the reaction mixture was transferred to a centrifugal separator, SF. After centrifugation, the two resulting phases were separated by measurement of their electroconductivities with a sensor and transferred to two receivers, SF1 and SF2. The aqueous phase in SF1 was taken back to the reaction vessel, RF1. After addition of Et_2O from the solvent bottle, RS1, the mixture was stirred and then transferred to the centrifugal separator, SF. After performing the extraction twice, the combined organic mixture in the receiver, SF2, was washed with 10% aqueous $NaHCO_3$ and 10% aqueous NaCl from the wash-solution bottles, RS5 and RS6, in the reaction flask, RF. The organic layer was separated in the centrifugal separator, SF, and transferred to the receiver, SF2. The organic layer in SF2 was then passed through an anhydrous Na_2SO_4 plug and collected in a round flask, CF1. Finally, the entire apparatus was washed with water and acetone that had been added to the solvent tanks, WT1 and WT2, and was dried under reduced pressure. The collected solution was manually concentrated *in vacuo*. The obtained residue was purified manually using flash silica gel column chromatography to give silyl ether **16** in 73% yield. Subsequent stereoselective epoxidation of the enone **16** afforded **14** as a single diastereomer. The relative stereochemistry of the epoxide and the hydroxy group in **14** was determined to be the desired *trans* configuration on the basis of comparison of the NMR spectra of **17** with previously reported data.[34,35] Addition of lithium trimethylsilylacetylide to ketone **14** gave the alcohol **18** in 71% yield. Treatment of the resultant alcohol with Tf_2O and 2,6-lutidine at −78 °C, followed by warming to 0 °C, afforded the desired alkene **13** in 70% yield. For the 1,2-addition and subsequent β-elimination to afford enyne **13**, the reaction vessel, RF1, was dried by heating at 80 °C for 30 min under reduced pressure and then automatically cooled to 25 °C

(35) ^{1}H NMR spectra of alcohol **17** was compared to the reported ^{1}H NMR spectra of its diastereomer **28** in ref 32. Since the observed coupling constant between Ha and He of **17** was different from that of **28**, the relative stereochemistry of the epoxide and hydroxy group in **17** was determined to be the desired *trans* configuration. **17**: ^{1}H NMR ($CDCl_3$): δ = 2.04 (J = 18.5 Hz, Ha), 2.65 (J = 6.0, 18.5 Hz, Hb), 3.43 (J = 2.3 Hz, Hc), 3.92 (J = 2.3 Hz, Hd), 4.70 (J = 6.0 Hz, He). **28**: ^{1}H NMR ($CDCl_3$): δ = 2.28 (J = 6.6, 17.8 Hz, Ha), 2.52 (J = 8.2, 17.8 Hz, Hb), 3.49 (J = 2.5 Hz, Hc), 4.00 (J = 2.2, 2.5 Hz, Hd), 4.46 (J = 2.2, 6.6, 8.2 Hz, He).



17 **28**

Scheme 4. **Automated synthesis of diyne 23**[a]



[a] Reagents and conditions: (a) imidazole, DMF, 25 °C, 10 min, then TBSCl, DMF, 25 °C, 10 h, 90%; (b) MeLi, Et_2O, −78 to 0 °C, 1 h, 85%; (c) IBX, DMSO, 50 °C, 12 h, 55%; (d) $ZnCl_2$, Et_2O, −78°C, 1 h, then propargyl magnesium bromide, Et_2O, −78°C, 30 min, 84%, **22a**/**22b** = 6:1; (e) NEt_3, CH_2Cl_2, 0 °C, 10 min, then TMSOTf, 0 °C, 15 min, 80%. IBX = 2-iodoxybenzoic acid.

prior to addition of reagents and substrates to create an anhydrous reaction environment.

Palladium-catalyzed addition of BzOH to the diene monoepoxide **13** was carried out with the use of the automated synthesizer (Scheme 3). A solution of BzOH in THF, which had been added to the reagent reservoir, RR1, was added to a solution of $Pd(OAc)_2$ and PPh_3 in THF at 25 °C in the reaction vessel, RF1. After stirring for 1 h, a solution of the diene monoepoxide **13** in THF was added to the reaction mixture at 0 °C. The resulting mixture was stirred at 25 °C for 10 h. Automated workup and manual silica gel column purification afforded a 12:2:1 mixture of the 1,4-adduct **10** and the 1,2-adducts **19a** and **19b** in a combined yield of 75%. For the manual reaction, BzOH solids were added directly to the solution of $Pd(OAc)_2$ and PPh_3 in THF. However, the synthesizer could not transfer solids automatically. Thus, we used a solution of BzOH in THF. The relative stereochemistry of the benzoyl group in **10** was determined by observation of the NOE (4.4%) between Ha and Hb. In the 1,2-adducts, *cis* stereochemistry of the benzoyl and hydroxy groups in **19b** was confirmed by the large NOE (20%) between Hc and Hd. Because the isolated 1,4-adduct **10** remained intact under the reaction conditions used in the present study (30 mol % BzOH/10 mol % $Pd(OAc)_2$-PPh_3/THF/25 °C/16 h), this reaction is not under thermodynamic control. Bäckvall et al. reported that carboxylates are unique nucleophiles—addition of carboxylates to π-allyl palladium complexes can occur from either the same or the opposite sides of the palladium atom, depending on the reaction conditions.[36] It is conceivable that the 1,4-addition occurs exclusively from the side opposite the bulky siloxy group, while the 1,2-addition preferentially occurs from the side opposite the somewhat smaller hydroxyl group.

The diyne **23** was prepared utilizing the automated synthesizer (Scheme 4). The mixture of isomers **10**, **19a**, and **19b** was converted to two diastereomers of the silyl ether **20**. Without separation, **20** was treated with MeLi in Et_2O to afford the alcohol **21** in a combined yield of 85%. Treatment of **20** with K_2CO_3 in MeOH or with methyl Grignard reagent in Et_2O resulted in undesirable desilylation at the terminal alkyne or decomposition of the substrate. The previously reported reaction conditions for the oxidation of the allylic alcohol **21**—PCC in CH_2Cl_2[20]—were not suited for use with the synthesizer, as a large amount of chromium salts precipitated and obstructed the solution-transfer tubes. Therefore, other oxidation conditions were examined. IBX in DMSO was compatible with the synthesizer, as no precipitate formed. By contrast, DMSO oxidation, including both Swern and Parikh−Doering conditions, Dess−Martin oxidation, and TEMPO-NaClO oxidation gave unsatisfactory results. Subsequent 1,2-addition of propargyl magnesium bromide to the enone **11** was carried out using the automated synthesizer. Preparation of the Grignard reagent, which requires careful temperature control, was performed automatically. The reaction flasks, RF1 and RF2, were dried at 80 °C for 30 min under reduced pressure and were then cooled to 25 °C. A mixture of magnesium turnings, $HgCl_2$, and propargyl bromide (20 mol %) in Et_2O was stirred at 25 °C in the reaction vessel, RF2, under a nitrogen atmosphere. Then, a solution of 80 mol % of propargyl bromide in Et_2O was added to the mixture at −10 °C. The resulting mixture was stirred at 0 °C for 30 min to afford a solution of propargyl magnesium bromide. The Grignard reagent solution was added to a solution of **11** and $ZnCl_2$ in Et_2O at −78 °C in the reaction vessel, RF1. Automated workup and manual silica gel column purification afforded a separable 6:1 mixture of the α-alcohol **22a** and its β-isomer **22b** in a combined yield of 84%. Addition of $ZnCl_2$ is crucial to increase the α-selectivity of the reaction, as demonstrated by the reduced stereoselectivity in the absence of $ZnCl_2$, i.e., 9α-OH:9β-OH = 2:1. Protection of **22a** with TMSOTf gave the silyl ether **23** in 81% yield. NOE observation suggested that the stereochemistry of the trimethylsiloxy group of **23** was the desired α configuration (Scheme 4).

The 12-membered cyclic ether **7** was prepared by using the automated synthesizer (Scheme 5). Treatment of **23** with ethylmagnesium bromide in THF followed by addition of paraformaldehyde afforded the alcohol, which was converted to diol **8** by removal of the TMS group. Protection of the tertiary alcohol at the 9-position was essential for progression of the 1,2-addition reaction and, thus, the synthesis of the desired product. When methanol was used as the solvent during removal of the TMS group, automated extraction did not work because

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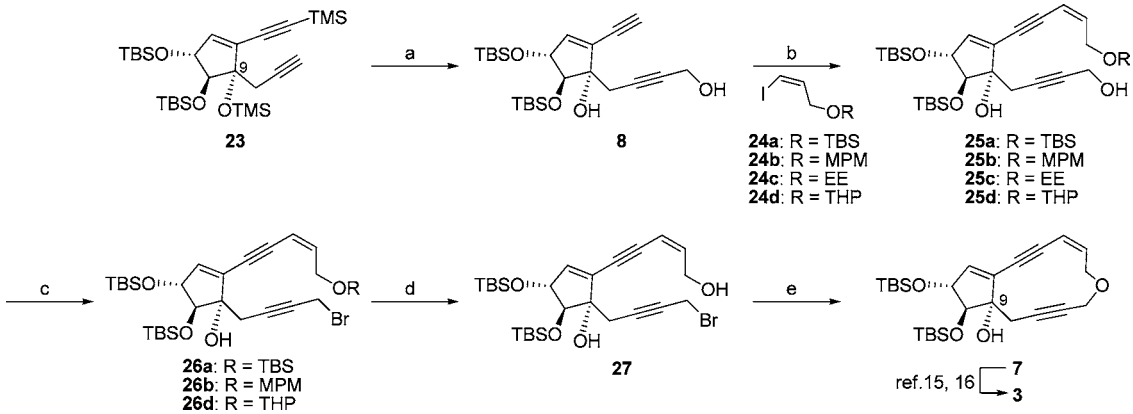
Scheme 5. **Automated synthesis of 12-membered cyclic ether 7**[a]



[a] Reagents and conditions: (a) (i) EtMgBr, THF, 50 °C, 1 h, then paraformaldehyde, 25 °C, 10 h, 75%, (ii) K_2CO_3, MeOH/THF = 1:3, 25 °C, 4 h, 90%; (b) **24b**, 5 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 10 mol % CuI, *t*-$BuNH_2$, toluene, 25 °C, 6 h, 65%; (c) CBr_4, PPh_3, 2,6-lutidine, MeCN, 0 to 25 °C, 30 min; (d) DDQ, CH_2Cl_2/H_2O = 30:1, 0 to 25 °C, 2 h, 2 steps 70% from **25b**; (e) NaH, THF, cat. H_2O, 25 °C, 1 h, 65%. DDQ = 2,3-dichloro-4,5-dicyanobenzoquinone.

the sensor could not detect a difference in electroconductivity between the aqueous and organic layers. Therefore, we used a solvent mixture, such as THF/MeOH, to overcome this problem. We previously reported a palladium-catalyzed coupling reaction between alkyne **8** and vinyl iodide **24a**, followed by bromination and selective deprotection of silyl ether to afford the cyclization precursor **27**. During selective deprotection, it is important to monitor the reaction continuously and to adjust the reaction time to prevent overdesilylation. However, the ChemKonzert begins workup operations after the programmed reaction time has elapsed. Therefore, this reaction cannot be performed using the automated synthesizer. We examined the palladium-catalyzed coupling reaction of the vinyl iodides **24b**−**d**, which have various protecting groups at the allylic hydroxyl group. Treatment of **8** with **24b** or **24d** in the presence of $Pd(OAc)_2$-PPh_3 and CuI-induced smooth coupling afforded the desired coupling products **25b** and **25d**, respectively. By contrast, treatment of **8** with **24c** under identical reaction conditions resulted in degradation of the vinyl iodides. After substitution of the propargyl hydroxyl group in **25d** with a bromide, selective removal of the THP group in **26d** was unsuccessful. On the other hand, the MPM group was chemoselectively deprotected by DDQ without affecting other functional groups to give the cyclization precursor **27** in 57% yield from **25b**. This deprotection condition is more suitable for use with the automated synthesizer than the previously described desilylation conditions, because the risk of overdesilylation during the deprotection step is much lower. A macro-etherification was successfully performed utilizing the automated synthesizer. A solution of **27** in THF was added to a suspension of NaH in THF with a catalytic amount of water in the reaction flask, RF1, under a nitrogen atmosphere. When workup of this reaction was performed manually, addition of a large amount of EtOAc enabled liquid−liquid extraction. However, the addition of EtOAc was not suitable for the synthesizer because the maximum solution volume of the centrifugal separation is 700 mL. Therefore, the reaction mixture was heated to 50 °C under reduced pressure to remove THF. Automated workup and manual silica gel column purification furnished the desired 12-membered cyclic ether **7** as a chemically stable solid, which can be stored at room temperature for long periods. For this cyclization, addition of a catalytic amount of water is crucial to obtain reproducible results. A catalytic amount of EtOH is also effective.[37] In addition, **7** can be converted to the masked 9-membered enediyne **3** in four steps, using the previously reported procedure.[19,20,38]

Conclusions

We developed an efficient synthetic route for **7**, which is a key synthetic intermediate of the 9-membered masked enediynes that possess DNA-cleaving activity. After tuning the reaction conditions, the automated synthesizer that was originally developed in our lab—the ChemKonzert—allowed for an efficient 16-step synthesis: two palladium-catalyzed reactions, three C−C bond formations, two oxidations, six protection and deprotection sequences, and three other transformation reactions on a scale ranging from 9.8 to 0.83 g. We also applied the automated synthesizer to a variety of other reactions. The synthesis of a new base-recognition, DNA-cleaving molecule from **7** is currently underway in our laboratory and will be reported in due course.

Experimental Section

General. NMR spectra were recorded in the indicated solvents. Chemical shifts are reported in units of parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm for ^1H, CH_2Cl_2: δ 5.32 ppm for ^1H, $CDCl_3$: δ 77.0 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br; broad), coupling constants (Hz), and integration. All reactions were monitored by thin-layer chromatography using E. Merck silica gel plates (60F-254) precoated plates (0.25 mm). TLC visualization was done with UV light and/or 5% ethanolic *p*-anisaldehyde or 10% ethanolic phosphomolybdic acid followed by heating. Flash column chromatography was performed on silica gel 60 N, purchased from Kanto Chemical Co. THF, Et_2O, and toluene

(37) The specific role of EtOH or water in the reaction remains unclear so far.

(38) We have reported the resolution of the racemic 9-membered masked enediyne via the separation of the diastereomeric MTPA ester in ref 19.

were dried by distillation from sodium/benzophenone ketyl. CH_2Cl_2 and Tf_2O were dried by distillation from P_2O_5. MeCN was dried by distillation from CaH_2. Acetone was dried by distillation from $CaSO_4$. 2,6-Lutidine was dried by distillation from BaO.

Synthesis. *4-tert-Butyldimethylsilyloxy-2-cyclopentenone (16).* A solution of 4-hydroxy-2-cyclopentenone (**15**) (9.81 g, 100 mmol, 1.0 equiv), NEt_3 (28.0 mL, 200 mmol, 2.0 equiv), and DMAP (300 mg, 2.50 mmol, 0.025 equiv) in dry CH_2Cl_2 (100 mL) was stirred at 25 °C for 10 min under a nitrogen atmosphere in RF1. The solution of TBSCl (19.6 g, 130 mmol, 1.3 equiv) in dry CH_2Cl_2 (30 mL, RR1) was added to the reaction vessel. After being stirred at the same temperature for 10 h, the reaction mixture was cooled to 0 °C and then quenched by addition of 1 M HCl (200 mL, RS4) and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (100 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (80 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (5% EtOAc in hexane) to give 4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**16**) (15.5 g, 73.1 mmol, 73%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 5.4, 2.4 Hz, 1H), 6.18 (dd, J = 5.4, 1.0 Hz, 1H), 4.98 (m, 1H), 2.70 (dd, J = 18.6, 5.9 Hz, 1H), 2.24 (dd, J = 18.6, 2.4 Hz, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 206.4, 163.9, 134.3, 70.8, 44.8, 25.6, 18.0, −3.6, −4.8; FT-IR (neat) 3433, 2956, 1724, 1572, 1355, 1254, 1109, 1072, 836, 670 cm^{-1}.

Epoxide 14. A solution of 4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**15**) (7.81 g, 36.8 mmol, 1.0 equiv) and Bu_4NHSO_4 (375 mg, 1.10 mmol, 0.030 equiv) in CH_2Cl_2 (50 mL) was placed in RF2 under a nitrogen atmosphere. After being cooled to 0 °C, aqueous NaClO solution (200 mL, RR2) was dropwisely added to RF2. After being stirred for 6 h at the same temperature, the reaction was quenched by addition of 50% aqueous $Na_2S_2O_3$ solution (180 mL, RS4) and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous $Na_2S_2O_3$ solution (100 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (5% EtOAc in hexane) to give epoxide **14** (5.88 g, 25.7 mmol, 70%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (d, J = 5.4 Hz, 1H), 3.79 (d, J = 2.0 Hz, 1H), 3.39 (d, J = 2.0 Hz, 1H), 2.59 (dd, J = 18.6, 5.8 Hz, 1H), 1.95 (d, J = 18.6, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 207.8, 67.6, 60.7, 54.1, 42.2, 25.6, 18.0, −4.8, −4.9; FT-IR (neat) 2931, 2859, 1758, 1472, 1259, 1084, 902, 780 cm^{-1}.

Alcohol 18. RF1 was dried at 80 °C for 30 min under reduced pressure and cooled to 25 °C. A solution of trimethylsilylacetylene (6.90 mL, 48.8 mmol, 1.1 equiv) in dry THF (100 mL) was placed in RF1 under a nitrogen atmosphere. After being cooled to −78 °C by attaching an acetone−dry ice bath manually to RF1, BuLi in hexane (1.60 M, 30.1 mL, 48.8 mmol, 1.1 equiv) was added to the solution manually at the same temperature. The resulting mixture was stirred at −40 °C for 1 h and cooled to −78 °C again. Then a dry THF (30 mL) solution of epoxyketone **14** (11.2 g, 44.3 mmol, 1.0 equiv, RR1) was dropwisely added to RF1 and stirred for 30 min at the same temperature. The reaction was quenched by 10% aqueous NH_4Cl solution (140 mL, RS4), diluted with EtOAc (100 mL, RS1), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (10% EtOAc in hexane) to give alcohol **18** (10.3 g, 31.4 mmol, 71%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, J = 5.4 Hz, 1H), 3.62 (d, J = 2.4 Hz, 1H), 3.43 (d, J = 2.4 Hz, 1H), 2.13 (d, J = 14.2 Hz, 1H), 1.86 (dd, J = 14.2, 5.4 Hz, 1H), 0.92 (s, 9H), 0.67 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 104.9, 91.0, 73.1, 71.4, 61.9, 59.6, 46.3, 25.8, 18.0, −0.13, −4.7, −4.8; FT-IR (neat) 3422, 2957, 2857, 2171, 1472, 1361, 1251, 1059, 837 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{16}H_{31}O_3Si_2$, 327.1812; found 327.1807.

Enyne 13. RF1 was dried at 80 °C for 30 min under reduced pressure and cooled to 25 °C. A solution of epoxyalcohol **18** (10.3 g, 31.4 mmol, 1.0 equiv) and 2,6-lutidine (20.2 mL, 173 mmol, 5.5 equiv) in dry CH_2Cl_2 (70 mL) was placed in RF1 under a nitrogen atmosphere. After being cooled to −78 °C by attaching an acetone−dry ice bath manually to RF1, a solution of Tf_2O (10.6 mL, 62.8 mmol, 2.0 equiv) in dry CH_2Cl_2 (30 mL, RR1) was dropwisely added to RF1 and stirred at 0 °C for 1 h. The reaction was quenched by addition of 10% aqueous NH_4Cl solution (200 mL, RS4), diluted with Et_2O (120 mL, RS1) and transferred to SF. After centrifugation, the two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 3 M HCl (60 mL, RS4), 10% aqueous NaCl solution (60 mL, RS6), 10% aqueous $NaHCO_3$ solution (60 mL, RS5), and 10% aqueous NaCl solution (60 mL, RS6). The resulting organic phase in SF2 was

dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (3% EtOAc in hexane) to give enyne **13** (6.81 g, 22.0 mmol, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J = 2.4, 1.9 Hz, 1H), 4.61 (dd, J = 1.5 Hz, 1H), 3.86 (ddd, J = 1.5 Hz, 1H), 3.79 (dd, J = 2.4 Hz, 1H), 0.91 (s, 9H), 0.21 (s, 9H), 0.13 (s, 3H,, 0.11 (s, 3H,); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 144.5, 129.4, 101.1, 98.8, 73.9, 62.2, 60.3, 25.7, 18.1, −0.3, −4.6, −4.7. FT-IR (neat) 2930, 2147, 1588, 1463, 1250, 844, 689 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{16}H_{29}O_2Si_2$, 309.1706; found 309.1705.

Benzoates 10, 19a and 19b. A solution of $Pd(OAc)_2$ (235 mg, 1.05 mmol, 0.050 equiv) and PPh_3 (1.10 g, 4.20 mmol, 0.20 equiv) in dry THF (50 mL) in RF1 was stirred for 20 min at 25 °C under a nitrogen atmosphere. A solution of BzOH (3.34 g, 27.2 mmol, 1.30 equiv) in dry THF (20 mL, RR1) was added to RF1 and stirred for 1 h at 25 °C. After being cooled to 0 °C, a solution of diene monoepoxide **13** (6.51 g, 21.0 mmol, 1.0 equiv) in dry THF (30 mL) was added to RF1. After being stirred for 10 h at 25 °C, the reaction was quenched by the addition of 10% aqueous $NaHCO_3$ solution (100 mL, RS4), diluted with Et_2O (60 mL, RS1), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (60 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of the solvent, the residue was purified by flash column chromatography on silica gel (10−20% Et_2O in hexane) to give benzoates (6.75 g, 15.7 mmol, 75%) (**10**:**19a**:**19b** = 12:2:1).

10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.14 (s, 1H), 5.82 (d, J = 5.4 Hz, 1H), 4.59 (m, 1H), 4.29 (dd, J = 4.9 Hz, 1H), 0.87 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H,), 0.00 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 165.7, 138.9, 133.0, 130.0, 129.6, 128.2, 124.9, 100.1, 97.9, 86.0, 82.2, 79.2, 25.6, 17.8, −0.7, −4.8, −4.9; FT-IR (neat) 3449, 2557, 2155, 1702, 1602, 1272, 1026, 861, 711 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{23}H_{35}O_4Si_2$, 431.2074; found 431.2094.

19a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 6.25 (d, J = 1.9, 1H), 5.87 (dd, J = 5.4, 1.0 Hz, 1H), 4.82 (dd, J = 1.9 Hz, 1H), 4.24 (dd, J = 5.4, 2.0 Hz, 1H), 0.90 (s, 9H), 0.15 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H,); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.9, 144.0, 133.2, 129.9, 129.7, 128.3, 123.7, 99.4, 98.9, 80.8, 78.7, 78.5, 25.7, 18.1, −0.2, −4.7, −4.9; FT-IR (solid) 3492, 2951, 2856, 2158, 1705, 1602, 1250, 1095, 762, 706 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{23}H_{35}O_4Si_2$, 431.2074; found 431.2055.

19b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 6.12 (s, 1H), 5.35 (d, J = 4.4 Hz, 1H), 4.73 (dd, J = 4.4 Hz, 1H), 4.17 (dd, J = 4.4 Hz, 1H), 0.92 (s, 9H), 0.19 (s, 6H), 0.13 (s, 9H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.8, 141.6, 133.5, 129.9, 129.4, 128.4, 125.5, 99.3, 98.2, 87.3, 85.8, 79.8, 25.7, 18.0, −0.3, −4.7, −5.0; FT-IR (solid) 3530, 3956, 2857, 2156, 1702, 1602, 1272, 1092, 844, 712 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{23}H_{35}O_4Si_2$, 431.2074; found 431.2089.

Silyl ether 20. A mixture of alcohols **10**, **19a**, and **19b** (6.74 g, 15.6 mmol, 1.0 equiv) and imidazole (19.2 g, 28.2 mmol, 1.8 equiv) in DMF (30 mL) was stirred at 25 °C for 10 min in RF1 under a nitrogen atmosphere. A solution of TBSCl (3.62 g, 23.5 mmol, 1.5 equiv) in DMF (15 mL, RR1) was added to RF1 at the same temperature. After being stirred for 10 h, the reaction mixture was cooled to 0 °C, then diluted with Et_2O (100 mL, RS1), quenched by addition of 1 M HCl (100 mL, RS4), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 1 M HCl (60 mL, RS4) twice, 10% aqueous $NaHCO_3$ solution (80 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (2% Et_2O in hexane) to give a mixture of disilylether **20** (7.63 g, 14.0 mmol, 90%).

Alcohol 21. RF1 was dried at 80 °C for 30 min under reduced pressure and cooled to 25 °C. The mixture of benzoates **20** (7.63 g, 14.3 mmol, 1.0 equiv) in dry Et_2O (80 mL) was placed in RF1 under a nitrogen atmosphere and cooled to −78 °C by attaching an acetone−dry ice bath manually to RF1. A solution of MeLi in Et_2O (1.09 M, 29.0 mL, 31.5 mmol, 2.2 equiv, RR1) was dropwisely added to RF1. The resulting solution was warm to 0 °C and stirred for 1 h. The reaction was quenched by addition of 10% aqueous NH_4Cl solution (80 mL, RS4), diluted with Et_2O (80 mL, RS1) and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (2% Et_2O in hexane) to give a mixture of alcohol **21** (5.34 g, 12.2 mmol, 85%).

Enone 11. The mixture of alcohol **21** (1.75 g, 4.00 mmol, 1.0 equiv) and IBX (3.40 g, 12.0 mmol, 3.0 equiv) in DMSO (20 mL) was heated to 50 °C in RF1 under a nitrogen atmosphere. After being stirred at the same temperature for 12 h, the reaction mixture was cooled to 25 °C. The solution was diluted with EtOAc (80 mL, RS1) and filtered by passing through FF1. A solution of 10% aqueous $NaHCO_3$ (100 mL RS5) was added to RF1, and the resulting mixture was

transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (60 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (60 mL, RS6) twice. The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (3% Et_2O in hexane) to give enone **11** (0.96 g, 2.2 mmol, 55%) as a colorless liquid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.27 (d, J = 2.0 Hz, 1H), 4.66 (dd, J = 2.0 Hz, 1H), 4.16 (d, J = 3.0 Hz, 1H), 0.92 (s, 9H), 0.91 (s, 9H), 0.21 (s, 9H), 0.19 (s, 3H), 0.13 (s, 3H), 0.15 (s, 3H), 0.13 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 198.9, 159.6, 127.7, 103.4, 94.1, 82.6, 76.4, 25.77, 25.66, 18.2, 17.9, −0.4, −4.3, −4.7, −4.8, −5.1; FT-IR (neat) 2957, 2858, 2160, 1744, 1598, 1251, 1094, 839, 780 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{22}H_{43}O_3Si_3$, 439.2503; found 439.2520.

Alcohols 22a and 22b. A 500 mL three necked flask was attached to ChemKonzert (RF2). The RF1 and RF2 were dried at 80 °C for 30 min under reduced pressure and cooled to 25 °C. The mixture of magnesium turnings (1.20 g, 44.0 mmol, 1.1 equiv), $HgCl_2$ (108 mg, 0.40 mmol, 0.010 equiv), and propargyl bromide (0.600 mL, 8.00 mmol, 0.20 equiv) in dry Et_2O (20 mL) was stirred at 25 °C under a nitrogen atmosphere in RF2. After being cooled to −10 °C, a solution of propargyl bromide (2.40 mL, 32.0 mmol, 0.8 equiv) in dry Et_2O (20 mL) was added dropwisely to RF2. The resulting mixture was stirred at 0 °C for 30 min to afford a solution of propargyl magnesium bromide (*c.a.* 1.0 M). A solution of enone **11** (5.42 g, 12.3 mmol, 1.0 equiv) and $ZnCl_2$ in Et_2O (1.0 M, 13.5 mL, 13.5 mmol, 1.1 equiv) in dry Et_2O (100 mL) was stirred at 25 °C for 1 h under a nitrogen atmosphere in RF1 and being cooled to −78 °C by attaching an acetone−dry ice bath manually to RF1. The solution of propargyl magnesium bromide in Et_2O (20 mL) described above was added to RF1 at −78 °C. After being stirred at the same temperature for 30 min, the reaction was quenched by addition of 1 M HCl solution (120 mL, RS4), diluted with Et_2O (80 mL, RS1), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (120 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (40 to 50% toluene in hexane) to give alcohols (4.95 g, 10.3 mmol, 84%) (**22a**:**22b** = 6:1).

22a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, J = 1.9 Hz, 1H), 4.46 (dd, J = 5,4, 1.5 Hz, 1H), 4.01 (d, J = 5.3 Hz, 1H), 2.67 (dd, J = 16.4, 2.9 Hz, 1H), 2.44 (dd, J = 17.1, 2.9 Hz, 1H), 1.98 (t, J = 2.9 Hz, 1H), 0.93 (s, 9H), 0.89 (s, 9H), 0.19 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.8, 129.9, 100.8, 98.2, 87.5, 81.6, 78.5, 71.4, 26.0, 25.9, 25.8, 18.1, −0.2, −4.3, −4.5; FT-IR (neat) 3561, 3313, 2957, 2147, 1611, 1472, 1250, 1140, 1007, 837, 778, 675 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{52}H_{47}O_3Si_3$, 479.2833; found 479.2828.

22b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, J = 1.9 Hz, 1H), 4.58 (dd, J = 3.4, 1.9 Hz, 1H), 4.14 (d, J = 3.4 Hz, 1H), 2.68 (dd, J = 17.1, 2.5 Hz, 1H), 2.54 (dd, J = 17.1, 2.5 Hz, 1H), 2.00 (t, J = 2.5 Hz, 1H), 0.93 (s, 9H), 0.89 (s, 9H), 0.20 (s, 9H), 0.18 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 139.9, 130.1, 100.3, 98.4, 81.0, 80.9, 80.7, 80.0, 70.8, 27.8, 25.9, 25.7, 0.3, 0.0, −4.0, −4.5; FT-IR (solid) 3459, 3283, 2930, 2858, 2149, 1595, 1472, 1385, 1250, 1083, 839, 777, 686 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{52}H_{47}O_3Si_3$, 479.2833; found 479.2841.

Silyl ether 23. A solution of alcohol **22a** (4.91 g, 10.3 mmol, 1.0 equiv) and NEt_3 (2.86 mL, 20.5 mmol, 2.0 equiv) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C and stirred for 10 min at the same temperature under a nitrogen atmosphere in RF1. A solution of TMSOTf (2.22 mL, 12.3 mmol, 1.2 equiv, RR1) was dropwisely added to RF1. After being stirred at the same temperature for 15 min, the reaction was quenched by addition of 10% aqueous NH_4Cl solution (100 mL, RS4), diluted with Et_2O (80 mL, RS1), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF, centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (2% Et_2O in hexane) to give silyl ether **23** (4.53 g, 8.24 mmol, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, J = 2.0 Hz, 1H), 4.49 (dd, J = 4.9, 2.0 Hz, 1H), 4.07 (d, J = 4.9 Hz, 1H), 2.54 (dd, J = 6.4, 2.6 Hz, 2H), 1.86 (dd, J = 2.6 Hz, 1H), 0.93 (s, 9H), 0.89 (s, 9H), 0.20 (s, 9H), 0.19 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 140.3, 129.4, 100.0, 99.6, 90.3, 87.1, 90.3, 87.1, 80.8, 79.6, 69.6, 26.9, 26.0, 25.9, 18.1, 18.0, 2.7, −0.1, −4.0, −4.1, −4.4; FT-IR (solid) 3268, 2953, 2148, 1601, 1472, 1249, 1071, 838, 667 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{28}H_{55}O_3Si_4$, 551.3228; found 551.3229.

Alcohol 28. A solution of ethylmagnesium bromide (1.0 M, 23.0 mL, 23.0 mmol, 2.5 equiv) in dry THF was manually added to a solution of alkyne **23** (5.08 g, 9.21 mmol, 1.0 equiv) in dry THF (15 mL) in RF1 at 25 °C, and the resulting mixture was heated to 50 °C. After being stirred at the same temperature for 1 h, the mixture was cooled to 25 °C. Then paraformaldehyde (828 mg, 27.6 mmol, 3.0 equiv) was added to RF1 manually. After being stirred at the same temperature for 10 h, the reaction was quenched by addition of 1 M HCl solution (100 mL, RS4), diluted with EtOAc (80 mL, RS1), and

transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (80 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (15% Et_2O in hexane) to give alcohol **28** (4.28 g, 7.36 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, J = 2.0 Hz, 1H), 4.47 (dd, J = 5.0, 2.0 Hz, 1H), 4.18 (dd, J = 2.2 Hz, 2H), 4.05 (d, J = 5.0 Hz, 1H), 2.55 (dd, J = 2.2 Hz, 2H), 0.93 (s, 9H), 0.92 (s, 9H), 0.21 (s, 9H), 0.20 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 140.3, 129.5, 100.2, 100, 90.1, 86.8, 83.1, 79.6, 79.4, 51.4, 27.1, 25.9, 25.8, 18.0, 17.9, 2.6, −0.2, −4.1, −4.2, −4.4, −4.5; FT-IR (solid) 3420, 2956, 2858, 2148, 1472, 1250, 1067, 837, 776 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{29}H_{57}O_4Si_4$, 581.3334; found 581.3323.

Alcohol 8. Potassium carbonate (585 mg, 3.70 mmol, 0.50 equiv) was added to a solution of silyl ether **28** (4.28 g, 7.40 mmol, 1.0 equiv) in methanol (5 mL) and THF (15 mL) in RF1 manually. After being stirred at 25 °C for 4 h, the reaction mixture was diluted with EtOAc (80 mL, RR1), quenched by addition of 1 M HCl solution (80 mL, RR4), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (60 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (80 mL, RS5) and 10% aqueous NaCl solution (60 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give alcohol **8** (2.90 g, 6.66 mmol, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, J = 1.5 Hz, 1H), 4.46 (d, J = 5.4 Hz, 1H), 4.22 (dd, J = 2.3 Hz, 2H), 4.01 (d, J = 5.4 Hz, 1H), 3.14 (s, 1H), 2.68 (dt, J = 17.1, 2.3 Hz, 1H), 2.47 (dt, J = 17.1, 2.3 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 140.1, 129.0, 87.7, 82.6, 81.8, 81.7, 81.4, 78.7, 77.6, 51.3, 26.0, 25.8, 25.7, 18.0, −4.4, −4.5, −4.6. FT-IR (solid) 3319, 3180, 2855, 1473, 1259, 1016, 834, 776, 603 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{23}H_{41}O_4Si_2$, 437.2543; found 437.2552.

Dienyne 25b. *t*-$BuNH_2$ (3.80 mL, 36.0 mmol, 3.0 equiv RR1) and a solution of $Pd(OAc)_2$ (134 mg, 0.600 mmol, 0.050 equiv), PPh_3 (629 mg, 2.40 mmol, 0.20 equiv), and CuI (228 mg, 1.20 mmol, 0.10 equiv) in toluene (30 mL, RR2) were added to a solution of alkyne **8** (5.24 g, 12.0 mmol, 1.0 equiv) and vinyl iodide **24b** (5.47 g, 18.0 mmol, 1.5 equiv) in toluene (150 mL) at 25 °C under a nitrogen atmosphere in RF1. After being stirred for 6 h at 25 °C, the reaction was quenched by addition of pH 8 aqueous NH_4Cl-NH_4OH buffer (100 mL, RR3) and diluted with EtOAc (80 mL, RS1) and transfer to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 1 M HCl solution (100 mL, RS4), 10% aqueous $NaHCO_3$ solution (100 mL, RS5) and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (20% EtOAc in hexane) to give dienyne **25b** (4.78 g, 7.81 mmol, 65%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.13 (dt, J = 10.8, 5.8 Hz, 1H), 5.96 (d, J = 2.0 Hz, 1H), 5.81 (d, J = 10.8, 1.0 Hz, 1H), 4.84 (s, 2H), 4.45 (dd, J = 5.4, 2.0 Hz, 1H), 4.33 (ddd, J = 14.0, 5.8, 1.0 Hz, 2H), 4.24 (ddd, J = 14.0, 5.8, 1.0 Hz, 2H), 4.16 (d, J = 5.9 Hz, 1H), 4.01 (d, J = 5.4 Hz, 1H), 3.80 (s, 3H), 2.69 (dt, J = 17.1, 2.3 Hz, 1H), 2.40 (dt, J = 16.6, 2.3 Hz, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 159.2, 139.8, 137.8, 132.1, 129.9, 129.8, 129.6, 113.83, 11378, 111.6, 90.3, 89.1, 87.6, 81.9, 81.6, 81.1, 78.7, 72.2, 67.3, 55.2, 50.9, 26.2, 25.8, 25.7, 21.3, −4.4, −4.6; FT-IR (solid) 3415, 2930, 2857, 1612, 1513, 1249, 1102, 1037, 837, 775, 574 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{34}H_{53}O_6Si_2$, 613.3381; found 613.3370.

Alcohol 27. RF1 was dried at 80 °C for 30 min under reduced pressure and cooled to 25 °C. A solution of MPM−ether **25b** (4.78 g, 7.80 mmol, 1.0 equiv), CBr_4 (4.38 g, 13.2 mmol, 1.5 equiv), and 2,6-lutidine (3.07 mL, 26.4 mmol, 3.0 equiv) in dry MeCN (20 mL) was cool to 0 °C. A solution of PPh_3 (2.25 g, 8.58 mmol, 1.1 equiv) in dry MeCN (10 mL) was dropwisely added to RF1 at 0 °C. The resulting solution was warmed to 25 °C and stirred for 30 min at the same temperature. The reaction was quenched by addition of 10% aqueous NaCl solution (80 mL, RS6), diluted with Et_2O, and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with Et_2O (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 3 M HCl solution (80 mL, RS4), 10% aqueous NaCl solution (80 mL, RS6), 10% aqueous $NaHCO_3$ solution (80 mL, RS5, and 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was used for the next reaction without further purification.

The solution of above residue in CH_2Cl_2 (30 mL) and H_2O (1.0 mL) was cooled to 0 °C. Then DDQ (3.54 g, 15.6 mmol) was added manually. The solution was warmed to 25 °C and

stirred for 2 h at the same temperature. The reaction was quenched by addition of 10% aqueous $NaHCO_3$ solution (80 mL, RS6), diluted with EtOAc and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (80 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (80 mL, RS6) twice. The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (10% Et_2O in hexane) to give alcohol **27** (3.03 g, 5.46 mmol, 70% for 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dt, J = 10.7, 6.3 Hz, 1H), 5.76 (d, J = 10.7 Hz, 1H), 6.00 (s, 1H), 4.53 (d, J = 4.9 Hz, 1H), 4.43 (d, J = 6.3 Hz, 2H), 4.00 (d, J = 4.9 Hz, 1H), 3.89 (t, J = 5.3 Hz, 2H), 2.67 (d, J = 17.1 Hz, 1H), 2.54 (d, J = 17.1 Hz, 1H), 0.94 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 142.2, 138.4, 129.0, 110.4, 90.1, 88.7, 88.2, 83.4, 82.8, 78.9, 77.5, 60.9, 26.0, 25.8, 17.9, 15.2, −4.3, −4.5, −4.6; FT-IR (solid) 3318, 3150, 2928, 2855, 1471, 1249, 835, 774 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{26}H_{44}O_4Si_2Br$, 555.1962; found 555.1965.

Cyclic ether 7. A suspension of NaH (55%, 1.18 g, 27.0 mmol, 10. eq.) in dry THF (700 mL) with a catalytic amount of water (0.10 mL) was placed in RF1. A solution of bromoalcohol **27** (1.50 g, 2.70 mmol, 1.0 equiv) in dry THF (110 mL) was added to RF1. After being stirred at 25 °C for 1 h, the reaction mixture was heated to 50 °C under reduced pressure for 5 min in order to remove THF. After being cooled to 0 °C, the reaction was quenched by addition of 10% NH_4Cl aqueous solution (100 mL, RS6), diluted with EtOAc (100 mL, RS1), and transferred to SF. After centrifugation, two phases were separated. The separated aqueous phase in SF1 was taken back to RF1 and extracted with EtOAc (100 mL, RS1). The mixture was transferred to SF and centrifuged, and the two phases were separated. After repeating this extraction process twice, the combined organic phase in SF2 was transferred to RF1. The organic phase was washed with 10% aqueous NaCl solution (80 mL, RS6). The resulting organic phase in SF2 was dried by passing through anhydrous Na_2SO_4 (DT1) and transferred to a round flask (CF1). After removal of solvent, the residue was purified by flash column chromatography on silica gel (5% Et_2O in hexane) to give cyclic ether **7** (833 mg, 1.75 mmol, 65% for 2 steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (ddd, J = 10.2, 9.3, 6.8 Hz, 1H), 5.96 (d, J = 10.2 Hz, 1H), 5.94 (d, J = 2.0 Hz, 1H), 4.49 (dd, J = 10.8, 9.3 Hz, 1H), 4.34 (d, J = 5.0 Hz, 1H), 4.26 (dd, J = 10.8, 10.2 Hz, 1H), 4.17 (d, J = 13.6 Hz, 2H), 4.06 (d, J = 5.0 Hz, 1H), 2.85 (dd, J = 17.1, 1.9 Hz, 1H), 2.25 (dd, J = 15.3, 1.0 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.4, 137.1, 130.1, 116.9, 90.5, 89.8, 87.4, 83.0, 80.5, 80.3, 78.5, 63.8, 56.5, 27.0, 25.9, 25.8, 18.0, 17.9, −4.3, −4.6; FT-IR (neat) 2950, 2854, 1469, 1360, 1250, 1143, 1117, 1072, 840, 778, 735 cm^{-1}; HRMS (ESI-TOF); $[M + H]^+$ calcd for $C_{26}H_{43}O_4Si_2$, 475.2700; found 475.2695.

Acknowledgment

We thank Dr. Tohru Sugawara, Mr. Kazuhiro Machida, Mr. Yoichiro Hirose (ChemGenesis Inc.), and Dr. Shigetoshi Sekiyama (SIC Co.) for their assistance with the development and maintenance of the ChemKonzert. We also thank Sumitomo Chemical Co., Ltd. for a generous supply of 4-hydroxy-2-cyclopentenone.

Supporting Information Available

Description of general experimental techniques, a detailed procedure for the synthesis of compound **24b**, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review September 17, 2009.

OP9002455