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A Formal Synthesis of Iridoid 9-Deoxygelsemide†

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A formal total synthesis of iridoid 9-deoxygelsemide has been accomplished. Our approach features the use of (*S*)-carvone as starting material, Favorskii rearrangement to construct the functionalized cyclopentane core, Chugeav elimination to introduce the endocyclic double bond, and the ring-opening reaction of epoxide to build the second five-membered ring.

Keywords iridoid, 9-deoxygelsemide, Favorskii rearrangement, Chugeav elimination

Introduction

The iridoid 9-deoxygelsemide (**1**) was firstly isolated from the plant *Gelsemium elegans* Benth. in 1994.[1] It was one of the ancient folkloric medicines stored in the Shosoin imperial repository in Japan. 9-Deoxygelsemide has been a challenging target for chemical synthesis since its isolation. It has five continuous stereocenters on the cyclopentane ring and a *cis*-α-1,2-dioxygenated moiety at C-6 and C-7, which is unique in iridoid structures, occurring only in three other related iridoids **2**—**4** (Figure 1).[2,3] To date, only the Vidari's group has completed the total synthesis of this molecule as well as determination of its absolute configuration.[4] Herein, we report a formal enantioselective total synthesis of 9-deoxygelsemide.

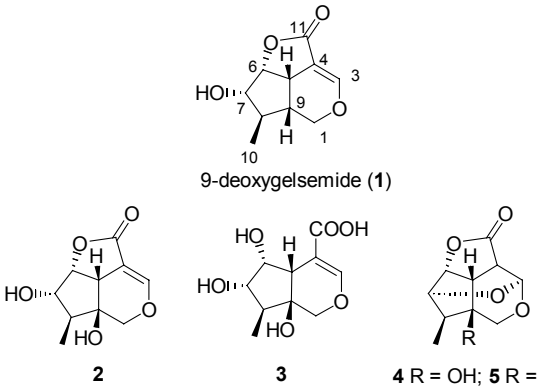
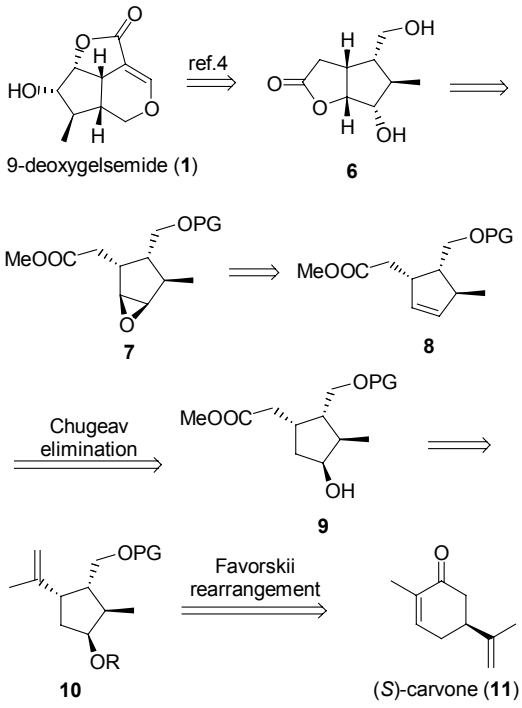


Figure 1 Structures of 9-deoxygelsemide (**1**) and plant iridoids (**2**—**5**) of the same family.

Results and Discussion

As illustrated retrosynthetically in Scheme 1, our synthetic plan is based on three key synthetic transformations including Favoskii rearrangement, Chugaev elimination and ring-opening of epoxide **7**. We envisioned that epoxide **7**, which might be generated from alkene **8**, could be converted into the target compound **6** through a ring-opening reaction with carboxylic group. Ultilizing Chugaev elimination reaction, the alkene **8** could be obtained from alcohol **9**, which is in turn available from alkene **10** by an oxidation and deprotection sequence. Alkene **10** would be synthesized from

Scheme 1 Retrosynthetic analysis of 9-deoxygelsemide (**1**)



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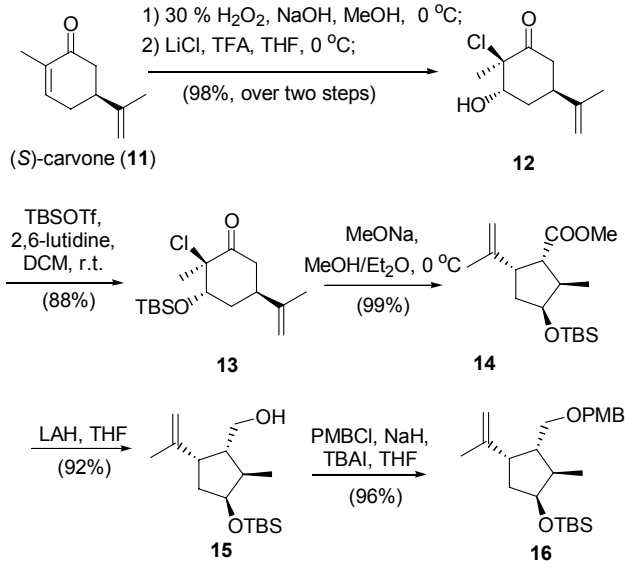
commercially-available (*S*)-carvone by several transformations including Favorskii rearrangement.

The synthesis commenced with commercially-available (*S*)-carvone, essentially following the same synthetic route originally described by Lee and coworkers from (*R*)-carvone.[5] A sequence of epoxidation,[6] chlorination[7] and protection of the OH functionality afforded the cyclohexanone **13** (Scheme 2). We chose *tert*-butyldimethylsilyl as the protecting group, and the subsequent Favorskii ring-contraction proceeded successfully to deliver functionalized cyclopentane unit **14** in excellent diastereoselectivity (*dr*＞19∶1). Reduction of **14** with $LiAlH_4$ and protection of the hydroxyl group as its *p*-methoxybenzyl ether produced compound **16**, which includes the requisite stereocenters at C5, C8 and C9.

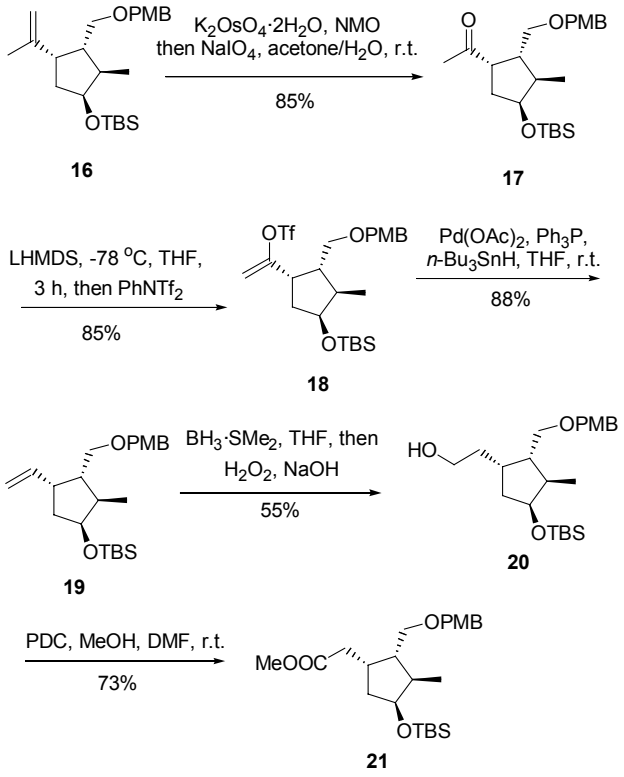
Scheme 2 Construction of the cyclopentane core



With **16** in hand, we next turned to the conversion of the 2-propenyl group. Firstly, the alkene **16** was dihydroxylated with K_2OsO_4/NMO in acetone/H_2O, and then treated with an excess of $NaIO_4$, which delivered ketone **17** in 85% yield (Scheme 3). Ketone **17** was deprotonated with LHMDS (1.2 equiv.) in THF at −78 ℃ for 3 h, and then trapped by $PhNTf_2$ (1.2 equiv.) to produce trifluoromethanesulfonate **18**. To our delight, the hydrogenolysis of **18** could be carried out under mild conditions with $Pd(OAc)_2$ (0.05 equiv.), Ph_3P (1.3 equiv.), and *n*-Bu_3SnH (1.3 equiv.) in THF at room temperature. Next, hydroboration of compound **19** with BH_3•SMe_2, followed by oxidation with H_2O_2/NaOH, gave product **20** in moderate yield as a single regioisomer. Sequentially, subjection of alcohol **20** to the Cr-mediated oxidation conditions [PDC (5.0 equiv.), MeOH (10 equiv.), DMF, r.t.] yielded ester **21**.

Now we were in a position to introduce the double bond between C6 and C7. The deprotection of compound **21** would be our first task. Treating **21** with

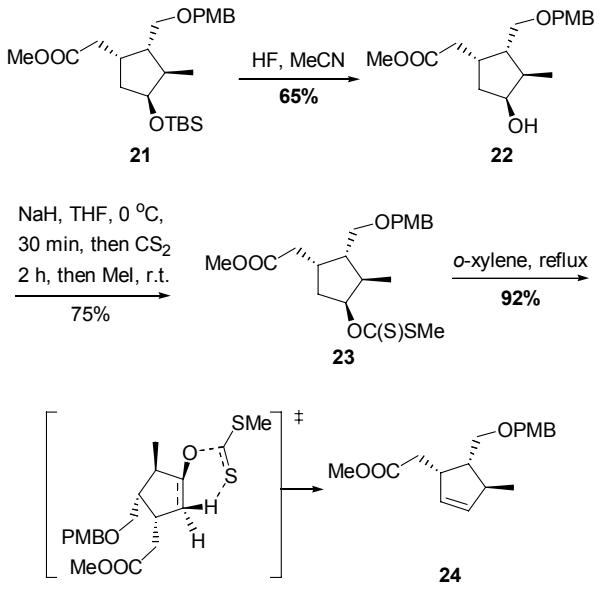
Scheme 3 Synthesis of the intermediate **21**



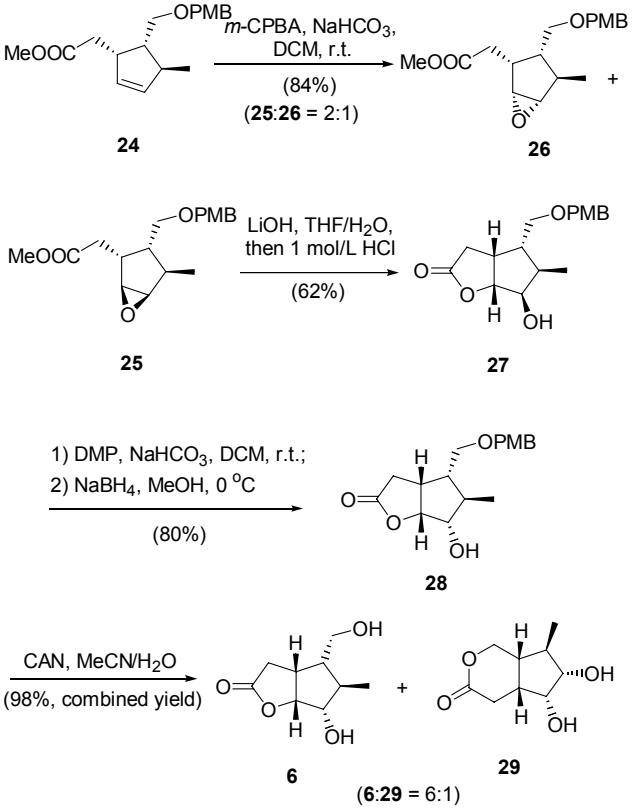
TBAF in THF gave product **22** in only 20% yield along with mostly the recovered starting material. Considering the steric hindrance of the substrate, we tried an acidic conditions (HF/MeCN).[8] To our delight, the reaction could proceed smoothly to provide the desired secondary alcohol **22** in 65% yield (Scheme 4). Next step would be the regioselective elimination of the hydroxyl group of **22**. A variety of conditions were attempted, such as $POCl_3$/py,[9] Martin sulfurane[10] and Burgess dehydrant,[11] but all of them gave a mixtures of regioisomers, which could not be separated by column chromatography. Finally, we solved the problem by using the condition of Chugaev elimination,[12] deprotonation of secondary alcohol **22** with NaH, and the following addition of CS_2 and MeI gave xanthate **23**, which was dissolved in *o*-xylene and heated to reflux overnight to give compound **24** as a single product in 69% yield over two steps. Notably, the regiospecific formation of alkene **24** was consistent with the established mechanism of the Chugeav reaction. The reaction proceeded through a six-membered ring transition state involving a *cis*-*β*-hydrogen atom of alcohol moiety and the thione sulfur atom of the xanthate.[13] The *β*-hydrogen atom and the xanthate group must be coplanar in the cyclic transition state. So the *trans*-*β*-hydrogen atom at C8 could not be involved in the reaction, only the *cis*-*β*-hydrogen atom of alcohol moiety at C6 was eliminated in Chugaev reaction.

So far, compared with the target molecule **1**, only one stereocenter at C7 was different. Considering the steric hindrance of the substrate, two steps involving

Scheme 4 Introduction of the endocyclic double bond by Chugeav elimination



Scheme 5 Stereoselective synthesis of the key intermediate **6**



oxidation and reduction were employed for the inversion of the configuration of C7. Firstly compound **27** was subjected to DMP/$NaHCO_3$ in DCM. After completion of the reaction, the crude product was then treated with $NaBH_4$ in a mixed solvent of THF and MeOH, and the desired compound **28** was obtained in 80% yield after column chromatography over two steps. The cleavage of PMB protecting group produced **6** and **29**,[14] with a ratio of 6∶1. Their ^1H and ^{13}C NMR spectral are in agreement with those reported by Vidari.[4] Since compound **6** has been converted into 9-deoxygelsemide in five steps, our synthetic route thus constitutes a formal total synthesis of (−)-9-deoxygelsemide.

Conclusions

In summary, starting from the known compound (*S*)-carvone, we have achieved the synthesis of the advanced intermediate **6** in 17 steps with an overall yield of 3.9%, which constitutes a formal total synthesis of (−)-9-deoxygelsemide.

Experimental

Unless otherwise indicated, all reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. Anhydrous THF was distilled from sodium and benzophenone. Anhydrous DCM was distilled from CaH_2. Column chromatograph was performed on silica gel (300−400 mesh). All ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Bruker-AMX 400 spectrometer in $CDCl_3$ or CD_3OD, with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Shimadazu IR-440 spectrophotometer and reported as wavenumber (cm^{-1}). Optical rotations were measured on JASCO P-1030 polarimeter operating at the sodium D line with a 100 mm path cell, and reported as follows: $[\alpha]_D^T$ (concentration/(g/100 mL), solvent).

2-((1*S*,2*S*,3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-((4-methoxybenzloxy)methyl)-3-methylcyclopentyl)-ethanol (20) A solution of BH_3•SMe_2 (17.0 mL of a 2.0 mol/L solution in THF, 34.0 mmol) was added dropwise at r.t. to a solution of **19** (8.87 g, 22.7 mmol) in anhydrous THF (80 mL). The mixture was stirred at r.t. for 10 h, then NaOH solution (20 mL, 3.0 mol/L in water) and H_2O_2 (20 mL, 30% in water) was added carefully, followed by stirring for 3 h. The reaction mixture was diluted with water (50 mL), and extracted with EA (50 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA =4∶1, *V*/*V*) to give the product **20** (4.88 g, 55%) as a colorless oil. $[\alpha]_D^{20}$ 44.5 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.25 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.42 (dd, *J*=11.6, 16.0 Hz, 2H), 4.02 (t, *J*=4.0 Hz, 1H), 3.80 (s, 3H), 3.70−3.64 (m, 1H), 3.60−3.54 (m, 1H), 3.43−3.37 (m, 2H), 2.41−2.33 (m, 1H), 2.07−1.99 (m, 1H), 1.90−1.81 (m, 1H), 1.76−1.73 (m, 1H), 1.66−1.60 (m, 1H), 1.43−1.37 (m, 1H), 0.94 (d, *J*=6.8 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 130.7, 129.4, 113.9, 75.3, 72.9, 70.7, 62.9, 55.4, 46.1, 42.3, 34.8, 33.9, 26.0, 18.3, 14.3, −4.5, −4.8; IR (film) *v*: 3412, 2955, 2850,

1713, 1514, 1036, 774 cm^{-1}; MS (ESI) *m/z*: 431.2 [M+Na]$^+$; HRMS calcd for $C_{23}H_{40}NaO_4Si$ 431.2588, found 431.2591.

Methyl 2-((1*R*,2*S*,3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-2-((4-methoxybenzyloxy)methyl)-3-methylcyclopentyl)acetate (21) PDC (8.12 g, 21.6 mmol) and anhydrous MeOH (1.2 mL, 30.8 mmol) was added to a solution of alcohol **20** (1.26 g, 3.08 mmol) in DMF (100 mL) at r.t. The mixture was stirred vigorously for 10 h, and then quenched with water (100 mL). The mixture was extracted with EA (50 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA=20∶1, *V*/*V*) to give the product **21** (987 mg, 73%) as a colorless oil. $[\alpha]_D^{20}$ 40.3 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.30 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 4.38 (dd, *J*=11.6, 21.2 Hz, 2H), 4.02 (t, *J*=3.2 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.39 (dd, *J*=4.4, 9.6 Hz, 1H), 3.33 (t, *J*=8.8 Hz, 1H), 2.83−2.77 (m, 1H), 2.62 (dd, *J*=6.0, 15.2 Hz, 1H), 2.18 (dd, *J*=9.6, 15.2 Hz, 1H), 2.09−2.02 (m, 1H), 1.80 (dd, *J*=7.2, 13.2 Hz, 1H), 1.72−1.68 (m, 1H), 1.45−1.39 (m, 1H), 0.93 (d, *J*=6.8 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 174.4, 159.3, 130.8, 129.3, 113.9, 75.4, 72.9, 70.2, 55.4, 51.4, 45.3, 42.1, 41.9, 36.0, 34.6, 26.0, 18.3, 14.1, −4.5, −4.8; IR (film) *v*: 2950, 2856, 1736, 1249, 1036 cm^{-1}; MS (ESI) *m/z*: 561.2 [M+Na]$^+$; HRMS calcd for $C_{24}H_{37}F_3NaO_6SSi$ 561.1924, found 561.1950.

Methyl 2-((1*R*,2*S*,3*R*,4*S*)-4-hydroxy-2-((4-methoxybenzyloxy)methyl)-3-methylcyclopentyl)acetate (22) HF (2 mL, 40% in water) was added to a solution of ester **21** (1.52 g, 3.49 mmol) in MeCN (20 mL). The mixture was stirred at r.t. for 10 h and diluted with water (20 mL). The mixture was extracted with EA (20 mL×3). The combined organic layer was washed with saturated $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA=3∶1, *V*/*V*) to give the product **22** (735 mg, 65%) as a colorless oil. $[\alpha]_D^{20}$ 34.1 (*c* 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.24 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 4.39 (dd, *J*=11.6, 22.4 Hz, 2H), 4.10 (s, 1H), 3.80 (s, 3H), 3.62 (s, 3H), 3.43−3.34 (m, 2H), 2.86−2.80 (m, 1H), 2.62 (dd, *J*=9.2, 15.6 Hz, 1H), 2.22 (dd, *J*=9.2, 15.6 Hz, 1H), 2.09−2.03 (m, 1H), 1.91 (dd, *J*=1.2, 7.2 Hz, 1H), 1.88−1.79 (m, 1H), 1.58−1.52 (m, 1H), 1.29 (br, 1H), 1.01 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 174.0, 159.2, 130.6, 129.2, 113.8, 75.0, 72.7, 69.8, 55.3, 51.4, 45.2, 41.4, 41.2, 35.8, 34.6, 13.2; IR (film) *v*: 3503, 2953, 2871, 1734, 1508, 1248, 821 cm^{-1}; MS (ESI) *m/z*: 345.1 [M+Na]$^+$; HRMS calcd for $C_{18}H_{26}NaO_5$ 345.1673, found 345.1675.

2-((1*R*,2*S*,3*R*,4*S*)-2-((4-Methoxybenzyloxy)methyl)-3-mthyl-4-(methylthiocarbonothioyloxy)cyclopentyl)acetate (23) NaH (60 mg, 40% in mineral oil, 1.5 mmol) was added in portions to a solution of **22** (63 mg, 0.20 mmol) in anhydrous THF (5.0 mL) at 0 ℃. 30 min later, CS_2 (0.10 mL, 1.65 mmol) was added to the reaction mixture, followed by stirring for another 2 h, and then MeI (0.10 mL, 1.61 mmol) was added to the mixture, followed by stirring for 10 h. The reaction was quenched with saturated NH_4Cl solution and diluted with water. The mixture was extracted with EA (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA=20∶1, *V*/*V*) to give the product **23** (60 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ 37.3 (*c* 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.24 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 5.94−5.92 (m, 1H), 4.40 (dd, *J*=11.6, 21.6 Hz, 2H), 3.81 (s, 3H), 3.62 (s, 3H), 3.46−3.36 (m, 2H), 2.83−2.77 (m, 1H), 2.61 (dd, *J*=6.8, 16.0 Hz, 1H), 2.54 (s, 3H), 2.26 (dd, *J*=9.2, 16.0 Hz, 1H), 2.18−2.12 (m, 3H), 1.77−1.70 (m, 1H), 1.01 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 215.6, 173.8, 159.4, 130.5, 129.3, 113.9, 88.0, 73.0, 69.4, 55.4, 51.6, 46.7, 40.6, 38.6, 35.7, 34.9, 18.9, 13.8; IR (film) *v*: 2960, 2856, 1735, 1248, 1053, 821 cm^{-1}; MS (ESI) *m/z*: 435.2 [M+Na]$^+$; HRMS calcd for $C_{20}H_{28}NaO_5S_2$ 435.1270, found 435.1271.

Methyl 2-((1*S*,4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-4-methylcyclopent-2-enyl)acetate (24) A solution of **23** (72 mg, 0.18 mmol) in *o*-xylene (5 mL) was heated to reflux overnight. The solvent was evaporated under vacuum. The crude product was purified by flash column chromatography (PE/EA=25∶1, *V*/*V*) to give the product **24** (49 mg, 92%) as a colorless oil. $[\alpha]_D^{20}$ 153.6 (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.25 (d, *J*=8.4 Hz, 2H), 6.87 (d, *J*=8.4 Hz, 2H), 5.69−5.66 (m, 1H), 5.61−5.59 (m, 1H), 4.46−4.38 (m, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 3.50−3.41 (m, 2H), 3.25−3.20 (m, 1H), 2.55 (dd, *J*=5.6, 15.2 Hz, 2H), 2.47−2.43 (m, 1H), 2.17−2.09 (m, 2H), 1.05 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.8, 159.3, 136.8, 132.9 130.7, 129.4, 113.9, 72.9, 69.7, 55.4, 51.5, 48.8, 43.1, 41.7, 35.0, 19.8; IR (film) *v*: 2952, 2867, 1734, 1508, 1248, 1088, 821 cm^{-1}; MS (ESI) *m/z*: 327.2 [M + Na]$^+$; HRMS (MALDI) calcd for $C_{18}H_{24}O_4Na$ 327.1567, found 327.1570.

Epoxides 25 and 26 *m*-CPBA (587 mg, 77%, 2.62 mmol) and $NaHCO_3$ (331 mg, 3.94 mmol) were added to a solution of **24** (400 mg, 1.31 mmol) in DCM (15 mL). The mixture was stirred at r.t. for 5 h and quenched with saturated Na_2SO_3 solution. The mixture was extracted with DCM (10 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA=3∶1, *V*/*V*) to give the product **25** and **26** (351 mg, 84% combined yield) as a colorless oil.

**(3a*R*,4*R*,5*R*,6*R*,6a*R*)-6-Hydroxy-4-((4-methoxybenzyloxy)methyl)-5-methylhexahydro-2*H*-cyclopenta-

[*b*]furan-2-one (27) LiOH•H_2O (23 mg, 0.55 mmol) was added to a solution of the mixture of **25** and **26** (118 mg, 0.37 mmol) in THF/H_2O (2.0 mL/2.0 mL). The mixture was stirred at r.t. for 10 h, followed by addition of HCl solution (2.0 mL, 1 mol/L in water), and stirred for another 3 h. The mixture was diluted with water and extracted with EA (5 mL×3). The combined organic layer was washed brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA＝1∶1, *V*/*V*) to give the product **27** (70 mg, 62%) as a colorless oil. $[\alpha]_D^{20}$ 26.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J*＝8.8 Hz, 2H), 6.88 (d, *J*＝8.8 Hz, 2H), 4.71 (d, *J*＝11.6 Hz, 1H), 4.42 (dd, *J*＝11.6, 26.8 Hz, 2H), 4.12 (d, *J*＝3.6 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, *J*＝3.6, 9.6 Hz, 1H), 3.33 (t, *J*＝9.2 Hz, 1H), 3.21－3.13 (m, 1H), 2.63－2.50 (m, 2H), 2.32－2.24 (m, 1H), 1.91－1.86 (m, 1H), 1.73 (br, 1H), 1.01 (d, *J*＝6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.8, 159.5, 130.2, 129.5, 114.1, 88.6, 77.9, 73.2, 68.6, 55.5, 44.4, 38.8, 37.5, 29.7, 11.6; IR (film) *v*: 3448, 2932, 2874, 1773, 1611, 1247, 1027, 816 cm^{-1}; MS(ESI) *m/z*: 329.2 $[M+Na]^+$; HRMS calcd for $C_{17}H_{22}NaO_5$ 329.1359, found 329.1365.

(3a*R*,4*R*,5*R*,6*S*,6a*R*)-6-Hydroxy-4-((4-methoxybenzyloxy)methyl)-5-methylhexahydro-2*H*-cyclopenta[*b*]furan-2-one (28) DMP (245 mg, 0.58 mmol) and $NaHCO_3$ (60 mg, 0.69 mmol) were added to a solution of **27** (70 mg, 0.23 mmol) in DCM (5.0 mL). The mixture was stirred at r.t. for 5 h and quenched with saturated Na_2SO_3 solution. The mixture was diluted with water and extracted with DCM (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was dissolved in MeOH (2.5 mL) and THF (2.5 mL). $NaBH_4$ (13 mg, 0.35 mmol) was added to the solution, followed by stirring at 0 ℃ for 30 min. The mixture was diluted with water and extracted with EA (5 mL×3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After concentration under vacuum, the crude product was purified by flash column chromatography (PE/EA＝1∶1, *V*/*V*) to give the product **28** (56 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ 1.33 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (d, *J*＝8.4 Hz, 2H), 6.89 (d, *J*＝8.4 Hz, 2H), 4.83 (t, *J*＝6.0 Hz, 1H), 4.41 (dd, *J*＝11.2, 24.0 Hz, 2H), 3.81 (s, 3H), 3.56－3.53 (m, 2H), 3.33 (t, *J*＝9.6 Hz, 1H), 3.03－2.96 (m, 1H), 2.61 (d, *J*＝6.8 Hz, 2H), 1,99 (br, 1H), 1.88－1.80 (m, 1H), 1,63－1.53 (m, 1H), 1.06 (d, *J*＝6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 159.6, 130.0, 129.6, 114.0, 83.9, 80.0, 73.2, 68.1, 55.5, 44.0, 39.2, 36.8, 30.0, 15.5; MS(ESI) *m/z*: 329.1 $[M+Na]^+$.

Compound 6 and 29 CAN (560 mg, 1.02 mmol) was added to the solution of **28** (125 mg, 0.41 mmol) in MeCN (4.0 mL) and H_2O (1.0 mL). The mixture was stirred at r.t. overnight. After concentration under vacuum, the crude product was purified by flash column chromatography (DCM/MeOH＝10∶1, *V*/*V*) to give the mixture **6** and **29** (75 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD) δ: 4.84－4.82 (m, 1H), 4.28 (dd, *J*＝4.0, 11.2 Hz, 1H)*, 4.11 (dd, *J*＝4.8, 11.2 Hz)*, 3.92 (dd, *J*＝4.4, 4.8 Hz, 1H)*, 3.75 (dd, *J*＝4.0, 11.2 Hz, 1H), 3.56－3.49 (m, 2H), 3.32－3.31 (m, 1H), 3.06－2.99 (m, 1H), 2.75－2.74 (m, 1H)*, 2.58－2.55 (m, 1H)*, 2.46 (dd, *J*＝8.0, 15.2 Hz, 1H)*, 2.71－2.69 (m, 2H), 1.90－1.89 (m, 2H)*, 1.78－1.70 (m, 1H), 1.64－1.54 (m, 1H), 1.11 (d, *J*＝6.0 Hz, 3H)*, 1.06 (d, *J*＝6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 180.5, 177.8*, 86.2, 81.1*, 80.4, 75.0*, 69.8*, 61.2, 46.8, 42.3*, 39.9*, 39.1, 38.1, 36.7*, 30.7, 29.5*, 16.5*, 15.7; MS(ESI) *m/z*: 209.1 $[M+Na]^+$; HRMS calcd for $C_9H_{14}NaO_4$ 209.0784, found 209.0789.

*signals of the minor product **29**.

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