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Polymer-Assisted Solution-Phase Synthesis and Neurite-Outgrowth-Promoting Activity of 15-Deoxy-$\Delta^{12,14}$-PGJ_2 Derivatives

Hiroshi Tanaka,[b] Tsuyoshi Hasegawa,[b] Narumi Kita,[a] Hiroko Nakahara,[a] Takahiro Shibata,[a] Sho Oe,[b] Makoto Ojika,[a] Koji Uchida,*[a] and Takashi Takahashi*[b]

Abstract: An efficient solution-phase synthesis of *rac*-15-deoxy-$\Delta^{12,14}$-PGJ_2 (15dPGJ$_2$) derivatives that contain variable α and ω chains based on a polymer-assisted strategy and their neurite-outgrowth-promoting activity are described. The strategy for the synthesis of PGJ_2 derivatives involves the use of a vinyl iodide bearing cyclopentenone as a key intermediate, which undergoes Suzuki–Miyaura coupling and subsequent Lewis acid catalyzed aldol condensation for incorporation of the ω and α chains, respectively. For easy access to the PGJ_2 derivatives, a polymer-supported catalyst and scavengers were adapted for use in these four diverse steps, in which workup and purification can be performed by simple filtration of the solid-supported reagents. By using this methodology, we succeeded in the synthesis of 16 PGJ_2 derivatives with four alkyl boranes and four aldehydes. The neurite-outgrowth-promoting activity of the 16 synthetic compounds in PC12 cells revealed that the side-chains play a major role in modulating their biological activity. The carboxylic acid on the α chain improved the biological activity, although it was not absolutely required. Furthermore, a PGJ_2 derivative with a phenyl moiety on the ω chain was found to exhibit an activity comparable to that of natural 15dPGJ$_2$.

Keywords: aldol reaction · combinatorial chemistry · neurite outgrowth · polymer-assisted synthesis · prostaglandins

Introduction

Biologically active natural products and their derivatives are effective biochemical probes for the elucidation of new drug targets.[1] The combinatorial synthesis of small molecules based on the structures of these natural products is an effective and promising route to the development of new biochemical probes, which frequently requires novel and diverse synthetic strategies and methodologies instead of traditional approaches for the total synthesis of natural products.[2] We recently investigated the combinatorial syntheses of small molecule libraries based on the structures of natural products.[3] Solid-phase synthesis is a powerful tool for the rapid assembly of small molecules owing to the ease of manipulation and the adaptability to a split-and-pool methodology. However, optimization of reaction conditions in solid-phase synthesis frequently requires more time than in solution. Furthermore, solid-phase synthesis sometimes requires specific functional groups on the target compounds for loading onto polymer supports. On the other hand, polymer-assisted solution-phase synthesis that utilizes filterable solid-supported reagents, catalysts, and scavengers has recently emerged as an alternative method for the high-speed synthesis of small molecules.[4] It allows one to monitor reactions by conventional methods. Workup and purification involves only washing and filtration, which are relatively simple procedures.

The compounds Δ^{12}-PGJ_2 (**1**), 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15dPGJ$_2$; **2**), and Δ^{7}-PGA_1 (**3**) (Figure 1) are metabolites of cyclopentenone prostanoids PGA_2, PGA_1, and PGJ_2, respectively, and exhibit various biological activities, including

[a] N. Kita, H. Nakahara, Dr. T. Shibata, Prof. Dr. M. Ojika, Prof. Dr. K. Uchida
Department of Applied Molecular Bioscience
Graduate School of Bioagricultural Science
Nagoya University
Furocho, Chikusaku, Nagoya, Aichi, 464-8601 (Japan)
Fax: (+81) 52-789-5741
E-mail: uchidak@nuagr1.agr.nagoya-u.ac.jp

[b] Dr. H. Tanaka, Dr. T. Hasegawa, S. Oe, Prof. Dr. T. Takahashi
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2884
E-mail: ttak@apc.titech.ac.jp

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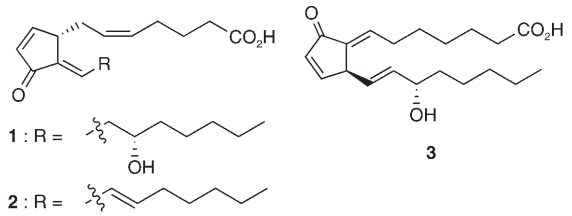


Figure 1. Structure of mammalian cross-conjugated prostanoids **1**, **2**, and **3**.

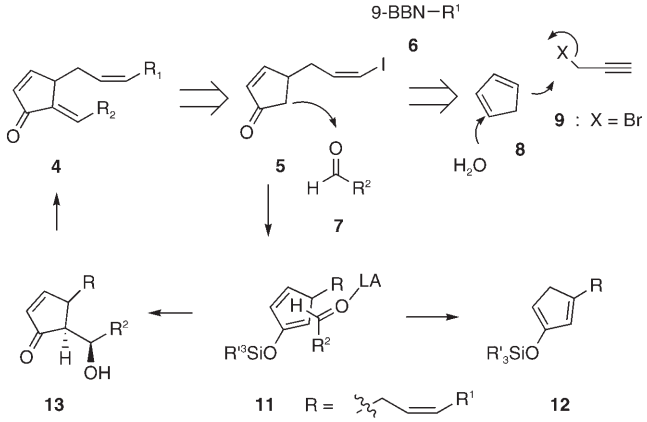
anti-inflammatory, antineoplastic, and antiviral activities.[5] In 1995, **2** was reported to be a high-affinity ligand for the nuclear receptor PPARγ and to modulate gene transcription by binding to this receptor by alkylation with the highly reactive cross-conjugated dienone system.[5a] Satoh, Watanabe, and co-workers recently reported that **2** promoted neurite outgrowth from PC12 cells.[6] In both cases, the cross-conjugated dienone moiety was found to be critical for biological activity, and **2** exhibited a stronger activity than **1**. These results suggest that the diene moiety on the ω chain is a significant factor and is related to the biological activities of such compounds. We envisaged that the variation of the α and ω chains of **2** would be an effective strategy for the development of new chemical probes to identify the target proteins related to the various biological activities promoted by **2**. However, most of the established methodologies for the synthesis of cross-conjugated prostanoids are based on traditional solution-phase synthesis.[7] Furthermore, established solid-phase syntheses of various prostaglandins require the presence of a hydroxy group on the cyclopentenone unit for loading of the substrate,[8] which is not available in **2**. Therefore, an effective method for the synthesis of the Δ^{12}-PGJ_2 derivatives continues to be sought after.[8] Herein we describe the efficient polymer-assisted solution-phase synthesis of *rac*-Δ^{12}-PGJ_2 derivatives with variable α and ω chains and their neurite-outgrowth-promoting activities.

Abstract in Japanese:

固相担持試薬は、後処理精製を簡便にすることにより。液相合成の効率を向上させる。本研究では、固相試薬を利用した交差ジエノン型プロスタノイド類縁体の合成と、その細胞突起伸長作用について述べる。合成鍵中間体として、ビニルヨウ素を有したシクロペンテノンを設計した。本中間体に対し、アルキルボラン試薬と固相担持パラジウム触媒を利用する鈴木―宮浦カップリング反応を行なうことにより、α鎖を導入した。続いて、シリルエノールエーテルを経由するアルデヒドとの酸性アルドール反応、続く、β一脱離反応により、ω鎖および、交差エノン構造を合成した。これらの反応では、反応の後処理に固相担持塩基を利用し、後処理操作の簡便化をはかった。その結果、鍵中間体から４工程の後処理を水を使うこと無く行ない、迅速な誘導体合成法の開発に成功した。本手法を用い４種類のアルキルボランと４種類のアルデヒドを用いるコンビナトリアル合成を行ない、１６種類の PGJ_2 類縁体の合成に成功した。さらに、本類縁体の細胞突起伸長作用を調べた結果、側鎖の形状が本生物活性に重要な役割を果たしていることを明らかにした。

Results and Discussion

The strategy for the polymer-assisted solution-phase synthesis of the Δ^{12}-PGJ_2 derivatives **4** is shown in Scheme 1. Cyclopentenone **5**, which contains a vinyl iodide, was designed as a key intermediate and can be subsequently coupled with

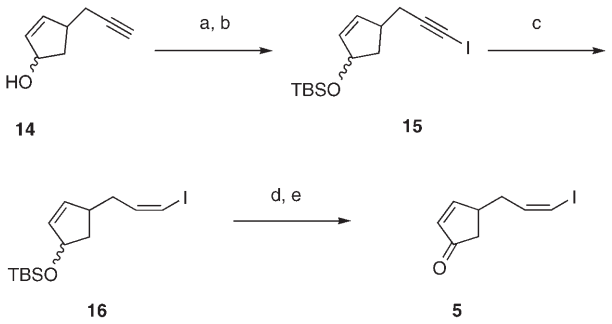


Scheme 1. Strategy for the synthesis of the 15dPGJ$_2$ derivatives **4**. 9-BBN = 9-borabicyclo[3.3.1]nonane, LA = Lewis acid.

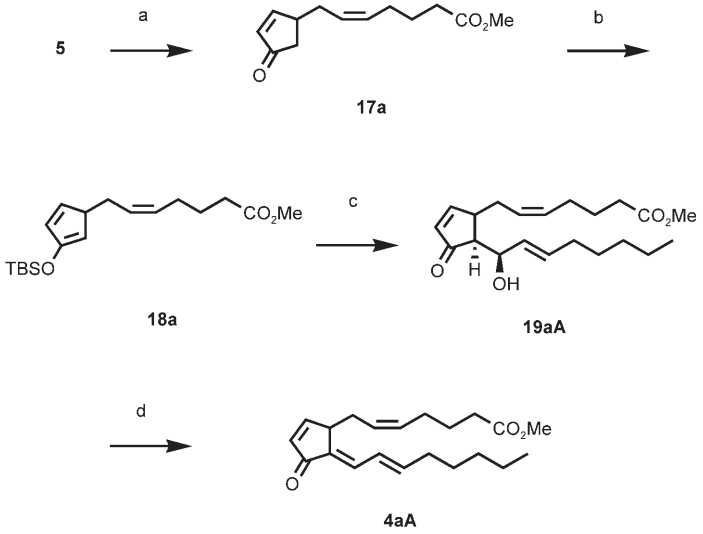
the α chain by Suzuki–Miyaura coupling with alkyl boranes **6** and the ω chain by Lewis acid catalyzed aldol condensation of **5** with aldehydes **7** via the silyl enol ether **11**. β Elimination of the resulting aldol products **13** provides the cross-conjugated dienones **4**. Lewis acid catalyzed aldol condensation via **11** enables the incorporation of base-labile functional groups into the α and ω chains and provides the *erythro*-aldol products **13** through an open transition state; these products smoothly undergo β elimination to afford the desired *E* olefins **4**. The diene intermediate **11** may undergo isomerization to the stable multisubstituted diene **12** through a 1,5 hydride shift.[9] Cyclopentenone **5** can be prepared by the electrophilic cycloaddition of propargyl halide **9** to cyclopentadiene (**8**). For easy access to the PGJ_2 derivatives **4**, polymer-supported reagents and scavengers could be adapted for the four diverse steps from the common intermediate **5**.

The synthesis of **5** is shown in Scheme 2. The diastereomeric mixture of *rac*-substiuted cyclopentene **14** was prepared from cyclopentadiene (**8**) and propargyl bromide (**9**) according to the established procedure.[10] Protection of the secondary alcohol **14** with TBSCl followed by iodination of the terminal acetylene with NIS and $AgNO_3$ afforded the alkynyl iodide **15** in 78% yield over two steps. The hydroboration of acetylene **15** with Cy_2BH followed by acidic hydrolysis provided the *cis*-vinyl iodide **16** in 68% yield.[11] Deprotection of the TBS ether followed by oxidation of the resulting alcohol provided enone **5** in 82% yield over two steps.

The synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 methyl ester (**4aA**) from **5** was examined next (Scheme 3). The vinyl iodide **5** was treated with pentyl 9-BBN **6a** (1.5 equiv) in the presence of [$PdCl_2$(dppf)] (5 mol%) and Ph_3As (20 mol%),



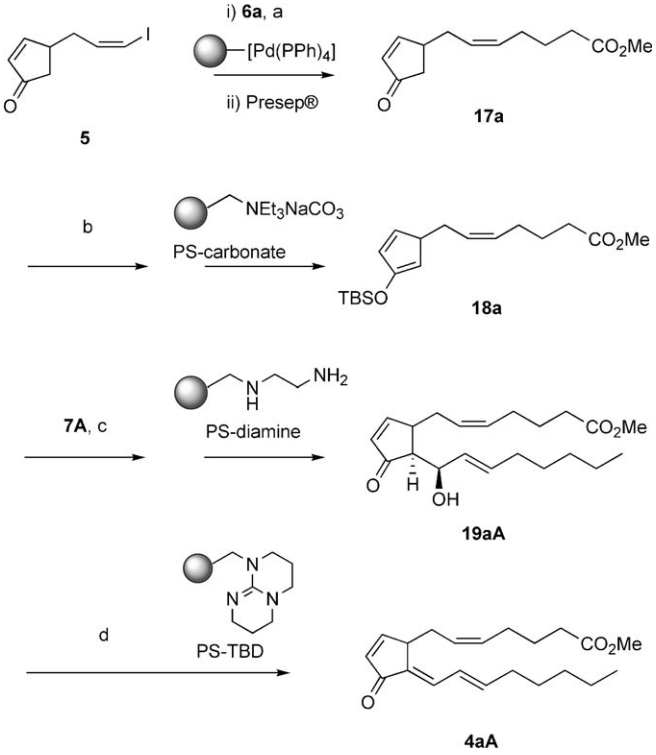
Scheme 2. Reagents and conditions: a) TBSCl, imidazole, CH_2Cl_2, 0 °C; b) NIS, $AgNO_3$, THF, room temperature, 78 %; c) Cy_2BH, Et_2O, room temperature, then, AcOH, room temperature, 68 %; d) CSA, MeOH, 0 °C; e) MnO_2, CH_2Cl_2, room temperature, 82 %. CSA = camphor-10-sulfonic acid, Cy = cyclohexyl, NIS = *N*-iodosuccinimide, TBS = *tert*-butyldimethylsilyl.



Scheme 3. Reagents and conditions: a) **6a**, $[Pd(PPh_3)_4]$, Ph_3As, H_2O, $CsCO_3$, DMF, room temperature, 84 %; b) TBSOTf, NEt_3; c) **7A**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 68 %; d) MsCl, DMAP, CH_2Cl_2, 78 %. DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl.

H_2O, and $CsCO_3$ (2.0 equiv) in DMF at 60 °C for 30 min to provide enone **17a** in 84 % yield. The use of $[Pd(PhP_3)_4]$ as a catalyst resulted in a comparable yield of **17a** (84 %). Lewis acid catalyzed aldol condensation via sily ether **18a** was examined. Treatment of **17a** with TBSOTf and NEt_3 at 0 °C for 20 min provided **18a**. Subsequent treatment of **18a** with aldehyde **7A** in the presence of $BF_3{\cdot}Et_2O$ (20 mol %) provided aldol product **19aA** in 68 % yield as a single diastereomer along with the recovered **17a** in 8 % yield. ^1H NMR spectroscopic analysis of **19aA** ($J_{C12,C13}$ = 3.4 Hz) indicated that the Lewis acid catalyzed aldol condensation of **17a** resulted in the *erythro*-aldol product **19aA**. The 1,5 hydride shift of **18a** did not occur during the reaction and workup. The corresponding trimethyl and triethyl silyl enol ethers did not function well in the aldol condensation and gave decreased product yields. Finally, treatment of **19aA** with MsCl in the presence of DMAP resulted in mesylation and β elimination to afford **4aA** in 78 % yield, along with the *Z* isomer in 7 % yield.

The polymer-assisted synthesis of **4aA** from **5** was examined next (Scheme 4). Vinyl iodide **5** was treated with **6a** (1.5 equiv) in the presence of polymer-supported (PS) palla-



Scheme 4. Reagents and conditions: a) H_2O (20 equiv), $CsCO_3$, DMF; b) TBSOTf, NEt_3; c) $BF_3{\cdot}OEt_2$, CH_2Cl_2; d) MsCl, CH_2Cl_2, 35 % from **5**.

dium catalyst[12] (5 mol %, 20 mol % based on **5**), H_2O (20 equiv), and $CsCO_3$ (2.0 equiv) in DMF at 60 °C for 30 min, followed by filtration of the reaction mixture to remove the catalyst, to provide **17a**. The filtrate was passed through a pad of silica gel (Presep) to remove small amounts of H_2O, the salts, and the remaining **6a**. The Lewis acid catalyzed aldol condensation via **18a** was examined. Treatment of the crude **17a** with TBSOTf and NEt_3 at 0 °C for 20 min provided **18a**. The reaction mixture was neutralized with PS carbonate.[13] Silyl ether **18a** then reacted with aldehyde **7A** in the presence of $BF_3{\cdot}Et_2O$ (20 mol %). $BF_3{\cdot}Et_2O$ and the remaining aldehyde were removed by treatment with PS diamines.[14] Finally, treatment of **19aA** with MsCl in the presence of PS 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[15] resulted in mesylation and β elimination to afford **4aA**. Solid-supported DMAP did not perform well in the β-elimination step. Purification of the crude product by silica-gel chromatography provided **4aA** in 35 % overall yield based on **5**. The average yield in each of the four diverse steps was 77 %.

The utility of the established methodology was demonstrated by the combinatorial synthesis of a small set of Δ^{12}-PGJ_2 derivatives **4** with four alkyl boranes **6a–d** and four aldehydes **7A–D** (Figure 2). In the synthesis of alcohols **4eA–D**, the TBS group was removed by additional exposure to

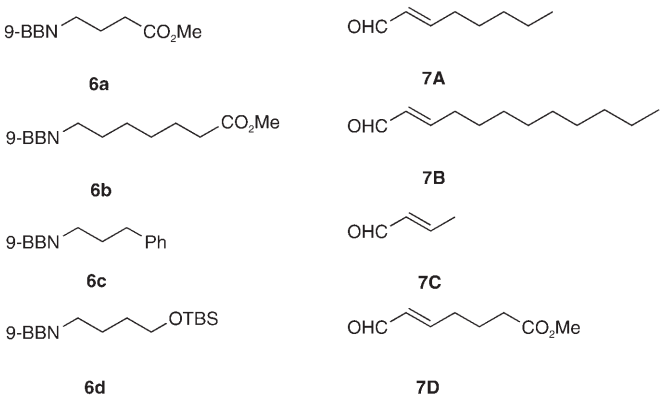


Figure 2. Building blocks for the synthesis of a small library.

mildly acidic conditions, followed by neutralization with PS carbonate.[13] Figure 3 shows all the structures of the derivatives **4**. The Δ^{12}-PGJ_2 derivatives **4aA–D**, **4bA–D**, and **4eA–D** were obtained in good total yields (Figure 3 and Table 1). However, the yields of the phenyl derivatives **4cA–D** were only moderate owing to the instability of the corresponding enol ether **18c**.

We next examined the neurite-outgrowth-promoting activity of **4** in PC12 cells. This was estimated by treatment of PC12 cells with **4** (1.0 μM) and nerve growth factor (NGF; 1.5 ng mL^{-1}) (Figure 4).[15] The results clearly suggest that

Table 1. Synthesis of the small combinatorial library **4**.

Entry	Alkylborane	Aldehyde	Product	Yield [%][a]
1	**6a**	**7A**	**4aA**	35
2	**6a**	**7B**	**4aB**	20
3	**6a**	**7C**	**4aC**	36
4	**6a**	**7D**	**4aD**	29
5	**6b**	**7A**	**4bA**	30
6	**6b**	**7B**	**4bB**	23
7	**6b**	**7C**	**4bC**	33
8	**6b**	**7D**	**4bD**	31
9	**6c**	**7A**	**4cA**	16
10	**6c**	**7B**	**4cB**	10
11	**6c**	**7C**	**4cC**	18
12	**6c**	**7D**	**4cD**	12
13	**6d**	**7A**	**4eA**	26
14	**6d**	**7B**	**4eB**	18
15	**6d**	**7C**	**4eC**	30
16	**6d**	**7D**	**4eD**	29

[a] Yields of **4** were based on **5**.

the carboxylic acid on the α chain is important for the enhancement of these effects, but that it is not absolutely necessary for biological activity. Furthermore, the neurite-outgrowth-promoting activity of **4cC**, which contains a phenyl group on the α chain, was found to be comparable to that of 15dPGJ$_2$. The effectiveness of the phenyl moiety on the side-chains for neurite-outgrowth-promoting activity was elucidated in the study of PGA_1 derivatives.[6b]

Conclusions

We have demonstrated herein the efficient combinatorial synthesis of the Δ^{12}-PGJ_2 derivatives with variable α and ω chains based on a polymer-assisted solution-phase synthetic

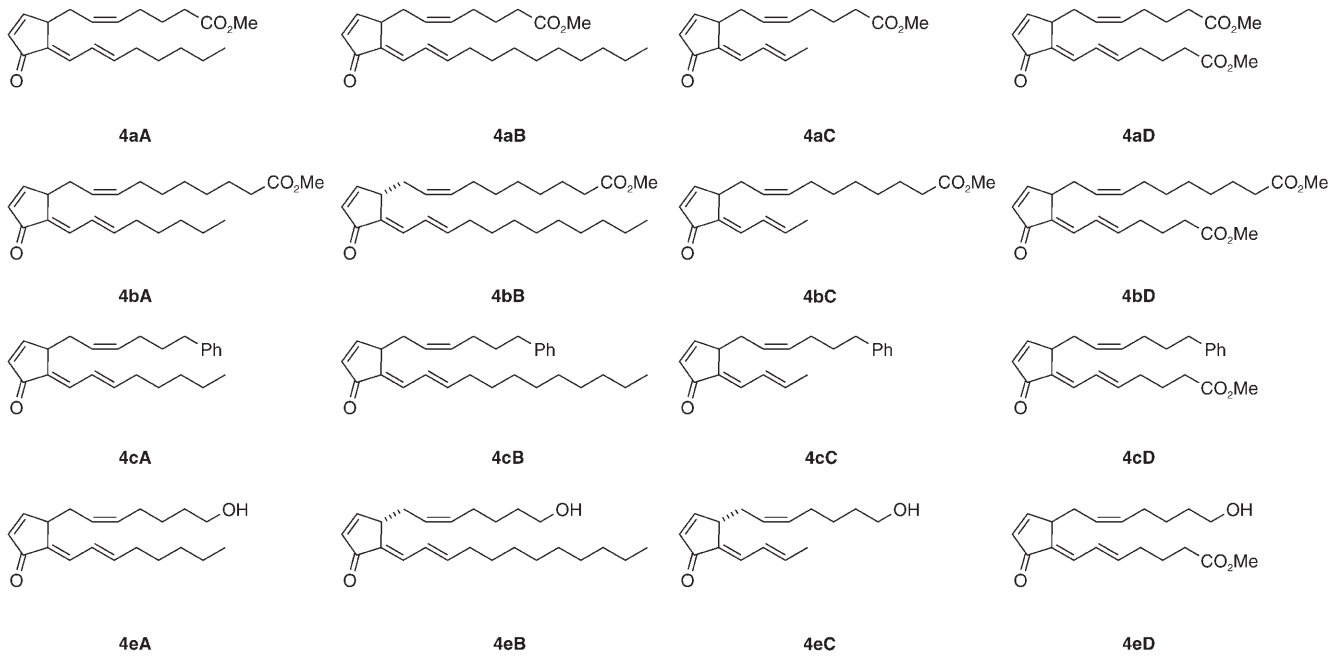


Figure 3. Structures of the small PGJ_2 combinatorial library **4**.

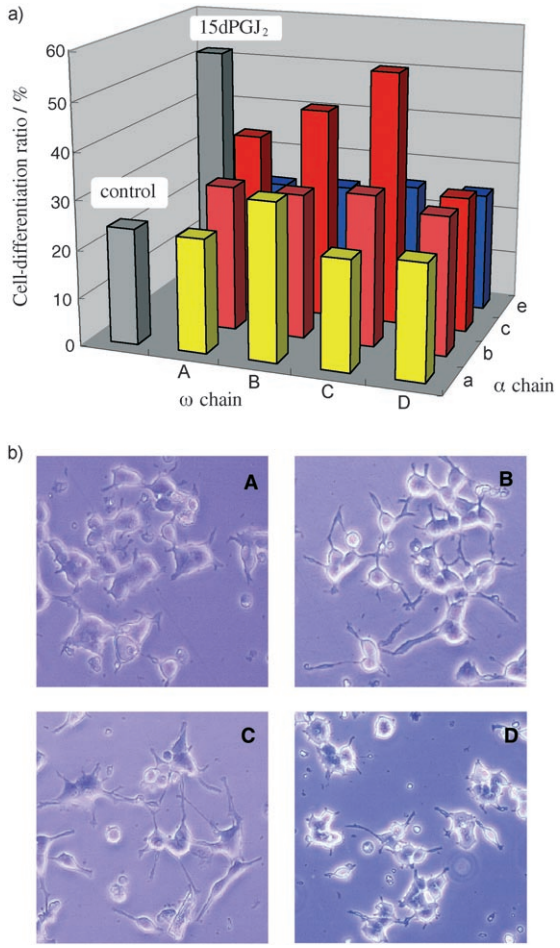


Figure 4. a) Neurite-outgrowth-promoting activity of the PGJ_2 derivatives **4** in PC12 cells. b) Representative images of PC12 cells treated with the prostaglandin (PG) samples. A = control, B = **2**, C = **4cC**, D = **4aA**.

strategy. Lewis acid catalyzed aldol condensation with silyl dienol ether was found to be effective for the introduction of the ω chain to the cyclopentenone core with an ester group. Furthermore, solid-supported reagents and scavengers can minimize the manipulations required in the diverse steps. By using the established method, we succeeded in the synthesis of a small combinatorial 15dPGJ$_2$ library. Biological assays that elucidated neurite-outgrowth-promoting activity in PC12 cells revealed that the side-chains influenced the outgrowth-promoting activity. The carboxylic acid on the α chain was found to be particularly important for enhancement of these effects, but it was not absolutely required for biological activity. Also, the neurite-outgrowth-promoting activity of **4cC**, which contains a phenyl group on the ω chain, was found to be comparable to that of **2**. A totally solid-assisted synthetic methodology would be effective in decreasing the requisite time for the synthesis of the library of compounds in comparison with traditional solution-phase synthesis, and would help in the rapid elucidation of the structure–activity relationships of the compounds. The synthesis and biological evaluation of larger libraries is currently in progress.

Experimental Section

General

NMR spectra were obtained on JEOL Model EX-270 and JEOL JNM-ECP 400 instruments with $CDCl_3$ as the solvent unless otherwise noted. ^{1}H NMR spectral data are reported as follows: chemical shifts relative to tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, integration. ^{13}C NMR signals are reported in ppm relative to $CDCl_3$ (77.0 ppm). IR spectra were recorded on a JASCO Model IR-700 spectrometer. FTIR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. Only significant diagnostic bands are reported, in cm^{-1}. GC was performed on a Shimazu Model GC-8A instrument equipped with a silicone DC-550 (3 mm × 3 m) column with He as carrier gas. Column chromatography was performed on silica gel (Merck). Analytical TLC was performed on Merk precoated TLC plates 60F 254 (silica gel), and visualization was made by black light and solutions of anisaldehyde/sulfuric acid/ethanol solution or phosphomolybdic acid/ethanol. HPLC was performed on a Nihon Seimitu Kagaku apparatus with a Senshu Pak Silica-3301-N column and a Japan Analytical Industry Model R1-3H refractive detector. Mass spectra were provided by a Mariner Biospectrometry Workstation from PE Science. Dry tetrahydrofuran, dry diethyl ether, dry toluene, and dry benzene were distilled from sodium wire containing a catalytic amount of benzophenone. Dry dichloromethane was distilled from P_2O_5. Dry methyl sulfoxide and dry pyridine were distilled from CaH_2. Dry methanol was distilled from Mg.

Syntheses

14: Propargyl bromide (1.8 mL, 23.7 mmol) and silver trifluoroacetate (5.26 g, 23.8 mmol) were added to a solution of cyclopentadiene (3.13 g, 47.4 mmol; from dicyclopentadiene heated at 160 °C) in dry pentane (30 mL) at 0 °C under argon. After being stirred at the same temperature for 2 h, the reaction mixture was filtered with celite. A solution of potassium hydroxide (1.72 g) in ethanol (7.6 mL) was added to the filtrate at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was poured into water (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/ethyl acetate = 70:30) to afford **14** (2.60 g, 21.3 mmol, 45 %) as yellow oil. R_f = 0.35 (hexane/ethyl acetate = 2:1); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.95–5.81 (m, 2H), 4.85 (m, 1H), 2.86 (m, 1H), 2.42 (m, 1H), 2.38 (dd, J = 1.8, 6.3 Hz, 2H), 2.23 (m, 1H), 2.01 ppm (d, J = 1.8 Hz, 1H).

15: Imidazole (1.65 g, 24.2 mmol) and *tert*-butyldimethylsilyl chloride (2.00 g, 13.3 mmol) were added to a stirred solution of **14** (1.48 g, 12.1 mmol) in dry dichloromethane (35 mL) at 0 °C under argon. After being stirred for 40 min at room temperature, the reaction mixture was partitioned between diethyl ether (50 mL) and saturated aqueous NH_4Cl (40 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was used for the next reaction without further purification. NIS (3.01 g, 13.3 mmol) and silver nitrate (206 mg, 1.21 mmol) were added to a stirred solution of the residue in dry tetrahydrofuran (40 mL) at 0 °C under argon. After being stirred for 9.5 h at room temperature, the reaction mixture was partitioned between diethyl ether (40 mL), saturated aqueous $Na_2S_2O_3$ (30 mL), and saturated aqueous $NaHCO_3$ (30 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/diethyl ether = 98:2) to afford **15** (3.41 g, 9.42 mmol, 78 % over two steps based on **14**) as pale-yellow oil. R_f = 0.65 (hexane/toluene = 6:1); IR (neat): $\tilde{\nu}_{max}$ = 3312, 2857, 1644, 1369, 1252 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.86 (m, 1H), 5.75 (m, 1H), 4.81 (m, 1H), 2.68 (m, 1H), 2.44 (d, J = 7.3 Hz, 2H), 2.38 (dd, J = 2.6, 7.3 Hz, 1H), 2.27 (dd, J = 2.6, 7.3 Hz, 1H), 0.89, 0.87 (s, 9H), 0.075, 0.073 ppm (s, 6H); HRMS (ESI-TOF): m/z calcd for $[C_{14}H_{23}IOSi]$ + Na: 385.0455; found: 385.0458.

16: Borane–methyl sulfide complex (0.99 mL, 9.38 mmol) was added to a stirred solution of cyclohexene (1.9 mL, 18.8 mmol) in dry diethyl ether (10 mL) at 0 °C under argon. The reaction mixture was then warmed to room temperature. After 1 h, a solution of **15** (1.36 g, 3.75 mmol) in dry diethyl ether (10 mL) at 0 °C was added to the mixture. After 1 h, glacial acetic acid (4 mL) was added dropwise at 0 °C over 20 min. After a further 30 min, the reaction mixture was partitioned between diethyl ether (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3×30 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/diethyl ether = 99:1) to afford **16** (929.1 mg, 2.55 mmol, 68 %) as a colorless oil. R_f = 0.68 (hexane/diethyl ether = 6:1); IR (neat): $\tilde{\nu}_{max}$ = 2930, 2857, 1634, 1256 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 6.27–6.13 (m, 2H), 5.86–5.69 (m, 2H), 4.83 (ddt, J = 1.7, 4.3, 5.9 Hz), 2.70–1.82 (m, 5H), 0.89, 0.87 (s, 9H), 0.075, 0.074 ppm (s, 6H); HRMS (ESI-TOF): m/z calcd for $[C_{14}H_{25}IOSi]+Na$: 387.0612; found: 387.0618.

5: (1*S*)-(+)-10-camphorsulfonic acid (40 mg, 0.172 mmol) was added to a stirred solution of **16** (929 mg, 2.55 mmol) in methanol (10 mL) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was neutralized with triethylamine (26 mL). The solvent was removed in vacuo. The residue was used for the next reaction without further purification. Manganese(IV) oxide (1.77 g, 20.4 mmol) was added to a stirred solution of the residue in dry dichloromethane (15 mL) at room temperature under argon. After being stirred for 14 h at the same temperature, the reaction mixture was filtered through celite. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (hexane/ethyl acetate = 70:30) to afford **5** (519 mg, 2.10 mmol, 82 % over two steps based on **16**) as yellow oil. R_f = 0.47 (hexane/ethyl acetate = 3:1); IR (neat): $\tilde{\nu}_{max}$ = 2921, 1713, 1588, 1290 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.63 (dd, J = 2.3, 5.6 Hz, 1H), 6.41 (dt, J = 1.3, 7.6 Hz, 1H), 6.22 (dd, J = 2.0, 5.6 Hz, 1H), 6.21 (dt, J = 7.3, 7.6 Hz, 1H), 3.14 (m, 1H), 2.55 (dd, J = 6.3, 18.8 Hz, 1H), 2.48–2.30 (m, 2H), 2.08 ppm (dd, J = 2.3, 18.8 Hz, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 209.1, 166.8, 137.2, 134.6, 85.6, 77.5, 40.2, 39.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_8H_9IO]+H$: 248.9771; found: 248.9779.

17a: A solution of 9-BBN dimer (39.2 mg, 0.321 mmol) in dry tetrahydrofuran (1.2 mL) was added dropwise to a stirred solution of methyl-3-butenoate (32.6 mL, 0.306 mmol) in dry tetrahydrofuran (0.20 mL) at 0 °C over 20 min under argon to provide **6a**. The reaction mixture was allowed to warm to room temperature and stirred for 5 h. When the above operation was completed, **5** (37.9 mg, 0.153 mmol) was added to a mixture of cesium carbonate (99.6 mg, 0.306 mmol), $[PdCl_2(dppf)]$ (12.5 mg, 0.0153 mmol), triphenylarsine (9.4 mg, 0.0306 mmol), and DMF (3.4 mL) in a separate flask. Water (55 mL) was then added with vigorous stirring, followed by addition of the above tetrahydrofuran solution of **6a**. After being stirred for 15 min, the contents of the flask were poured into ice-cold water (10 mL) and extracted with diethyl ether (3×30 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/ethyl acetate = 75:25) to afford **17a** (28.6 mg, 0.129 mmol, 84 %) as a colorless oil. R_f = 0.28 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2925, 1738, 1714 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ = 7.62 (dd, J = 2.3, 5.6 Hz, 1H), 6.18 (dd, J = 2.0, 5.6 Hz, 1H), 5.44–5.35 (m, 2H), 3.67 (s, 3H), 3.01 (m, 1H), 2.52 (dd, J = 6.6, 18.8 Hz, 1H), 2.32 (t, J = 7.6 Hz, 2H), 2.30–2.15 (m, 2H), 2.07 (dt, J = 7.3, 7.3 Hz, 2H), 2.00 (dd, J = 2.0, 18.8 Hz, 1H), 1.70 ppm (tt, J = 7.3, 7.6 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 209.7, 173.9, 167.8, 134.2, 131.4, 126.6, 51.5, 41.3, 40.5, 33.4, 31.9, 26.6, 24.7 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{13}H_{18}O_3]+Na$: 245.1148; found: 245.1156.

19aA: Triethylamine (70.5 mL, 0.506 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (58.1 mL, 0.253 mmol) were added to a stirred solution of **17a** (22.5 mg, 0.101 mmol) in dry dichloromethane (2.0 mL) at 0 °C under argon. After being stirred for 20 min at the same temperature, the reaction mixture was poured into an ice-cold mixture of diethyl ether (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with diethyl ether (3×10 mL), and the combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to give **18a**. The residue was used for the next reaction without further purification. Boron trifluoride diethyl etherate (2.6 mL, 20.2 mmol) was added dropwise to a stirred solution of the residue and **7A** (51.1 mg, 0.405 mmol) in dry dichloromethane (2.0 mL) at −78 °C under argon. After being stirred for 4 h at the same temperature, the reaction mixture was allowed to warm to −40 °C and stirred for a further 1 h. The reaction was poured into an ice-cold mixture of diethyl ether (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with diethyl ether (3×20 mL) The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/ethyl acetate = 75:25) to afford **19aA** (24.0 mg, 0.0688 mmol, 68 % over two steps based on **18a**) as colorless oil. R_f = 0.30 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 3431, 2925, 2855, 1739, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, J = 2.4, 5.8 Hz, 1H), 6.16 (dd, J = 1.9, 5.8 Hz, 1H), 5.74 (dt, J = 6.8, 15.0 Hz, 1H), 5.52–5.37 (m, 3H), 4.53 (m, 1H), 3.67 (s, 3H), 2.89 (ddt, J = 2.4, 4.8, 7.2 Hz, 1H), 2.31 (t, J = 7.2 Hz, 2H), 2.29 (dt, J = 6.8, 7.6 Hz, 2H), 2.22 (dd, J = 2.4, 3.4 Hz, 1H), 2.17–1.99 (m, 4H), 1.69 (tt, J = 7.2, 7.7 Hz, 2H), 1.40–1.21 (m, 6H), 0.88 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 168.4, 133.8, 133.4, 131.5, 129.2, 126.5, 72.1, 55.9, 51.5, 43.0, 33.4, 32.1, 31.3, 30.3, 29.7, 28.7, 26.6, 24.7, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{21}H_{32}O_4]+Na$: 371.2193; found: 371.2200.

4aA: 4-(Dimethylamino)pyridine (16.8 mg, 138 mmol) and methanesulfonyl chloride (5.4 mL, 68.5 mmol) were added to a stirred solution of **19aA** (6.0 mg, 17.2 mmol) in dry dichloromethane (1.0 mL) at 0 °C under argon. After being stirred for 2 h at room temperature, the reaction mixture was partitioned between diethyl ether (10 mL) and saturated aqueous NH_4Cl (10 mL) at 0 °C. The aqueous layer was extracted with diethyl ether (3×10 mL), and the combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo. The residue was subjected to flash chromatography (hexane/ethyl acetate = 80:20) to afford **4aA** (4.5 mg, 13.4 mmol, 78 %) as pale-yellow oil. R_f = 0.44 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2956, 2925, 2855, 1740, 1670, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (dd, J = 2.4, 5.8 Hz, 1H), 6.95 (d, J = 11.1 Hz, 1H), 6.36 (dd, J = 1.5, 5.8 Hz, 1H), 6.31 (dd, J = 11.1, 15.0 Hz, 1H), 6.25 (dt, J = 6.8, 15.0 Hz, 1H), 5.46 (dtt, J = 3.4, 7.2, 10.6 Hz, 1H), 5.37 (br dt, J = 6.8, 10.6 Hz, 1H), 3.66 (s, 3H), 3.58 (m, 1H), 2.60 (dt, J = 4.8, 14.5 Hz, 1H), 2.34 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 2.23 (dt, J = 7.2, 7.2 Hz, 2H), 2.03 (dt, J = 6.8, 7.7 Hz, 2H), 1.67 (tt, J = 7.3, 7.7 Hz, 2H), 1.32–1.26 (m, 6H), 0.89 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 176.8, 160.6, 148.1, 135.4, 135.0, 131.7, 131.3, 126.5, 125.5, 55.1, 43.4, 33.5, 32.6, 31.8, 30.7, 28.8, 26.5, 24.7, 22.4, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{21}H_{30}O_3]+Na$: 331.2268; found: 331.2268.

4aA by using polymer-supported reagents and scavengers: A solution of 9-BBN dimer (16.6 mg, 0.128 mmol) in dry tetrahydrofuran (0.40 mL) was added dropwise to a stirred solution of methyl-3-butenoate (13.8 mL, 0.130 mmol) in dry tetrahydrofuran (0.20 mL) over 20 min at 0 °C under argon to provide **6a**. The reaction mixture was allowed to warm to room temperature and stirred for a further 5 h. When the above operation was complete, **5** (8.1 mg, 32.5 mmol) was added to a mixture of cesium carbonate (42.4 mg, 0.130 mmol), PS $[Pd(PPh_3)_4]$ (21.7 mg, 0.30 mmol g^{-1} 6.50 mmol), and DMF (1.0 mL) in a separate flask. Water (20 mL) was then added with vigorous stirring, followed by addition of the above tetrahydrofuran solution of **6a**. The reaction mixture was heated to 60 °C and stirred for 4 h, then filtered through a silica-gel pad (Presep-C; hexane/diethyl ether = 5:1) to afford the alkylated enone as a yellow oil (6.9 mg, 31 mmol, 96 % crude). Triethylamine (21.7 mL, 156 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (17.9 mL, 78.0 mmol) were added to a stirred solution of enone (6.9 mg, 31 mmol) in dry dichloromethane (1.0 mL) at 0 °C under argon. After being stirred for 20 min at room temperature, one drop of water and PS biscarbonate (47.3 mg, 3.30 mmol g^{-1}, 0.156 mmol) was added to the reaction mixture at 0 °C, which was stirred at the same temperature for a further 1 h. The reaction mixture was filtered, and the resin was washed with diethyl ether (2×3.0 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **18a** as yellow oil. Boron

trifluoride diethyl etherate (1.1 mL, 6.24 μmol) was added dropwise to a stirred solution of **18a** and **7A** (15.8 mg, 0.125 mmol) in dry dichloromethane (1.0 mL) at −78 °C under argon. After being stirred for 4 h at the same temperature, the reaction mixture was allowed to warm to −40 °C and stirred for a further 1 h. PS diamine (156 mg, 3.0 mmol g^{-1}, 0.468 mmol) was then added to the reaction mixture at −78 °C, which was stirred at 0 °C for a further 2 h to remove excess **7a**. The reaction mixture was filtered, and the resin was washed with dichloromethane (2× 3.0 mL) and diethyl ether (2×3.0 mL). The filtrate was concentrated under reduced pressure to provide the aldol adduct as a yellow oil. PS TBD (184.7 mg, 1.9 mmol g^{-1}, 0.351 mmol) and methanesulfonyl chloride (12.6 mL, 0.164 mmol) were added to a stirred solution of aldol adduct in dry dichloromethane (1.0 mL) at 0 °C under argon. After being stirred for 4 h at room temperature, the reaction mixture was filtered, and the resin was washed with diethyl ether (2×3.0 mL). The filtrate was concentrated under reduced pressure to provide crude **4aA** as a yellow oil. The residue was subjected to flash chromatography (hexane/ethyl acetate = 80:20) to afford **4aA** (3.8 mg, 11 mmol, 35% over four steps based on **5**) as a pale-yellow oil.

4aB: R_f = 0.58 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2930, 2859, 1739, 1695, 1630, 1200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 2.4, 5.8 Hz, 1H), 6.94 (d, J = 11.0 Hz, 1H), 6.34 (dd, J = 1.9, 5.8 Hz, 1H), 6.34 (dd, J = 11.0, 15.0 Hz, 1H), 6.22 (dt, J = 6.8, 15.0 Hz, 1H), 5.47 (br dt, J = 7.2, 11.3 Hz, 1H), 5.32 (br dt, J = 8.1, 11.3 Hz, 1H), 3.66 (s, 3H), 3.57 (m, 1H), 2.58 (dt, J = 6.3, 13.8 Hz, 1H), 2.33 (m, 1H), 2.30 (t, J = 7.2 Hz, 2H), 1.95 (dt, J = 7.2, 7.2 Hz, 2H), 1.45 (tt, J = 7.2, 7.7 Hz, 2H), 1.33–1.17 (m, 14H), 0.89 ppm (t, J = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 174.5, 161.2, 146.5, 135.2×2, 132.4, 131.1, 125.3, 124.9, 51.2, 43.5, 34.0, 33.4, 31.5, 30.6, 29.7, 29.2, 29.0, 28.3, 27.5, 26.8, 25.2, 22.5, 21.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{25}H_{38}O_3]$+Na: 409.2835; found: 409.2837.

4aC: R_f = 0.47 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}$ = 2952, 1738, 1694, 1634, 1436 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (dd, J = 2.4, 5.8 Hz, 1H), 6.95 (d, J = 11.1 Hz, 1H), 6.35 (dd, J = 1.4, 5.8 Hz, 1H), 6.34 (dq, J = 6.8, 15.0 Hz, 1H), 6.24 (dd, J = 11.1, 15.0 Hz, 1H), 5.45 (br dt, J = 7.2, 11.1 Hz, 1H), 5.39 (br dt, J = 6.8, 11.1 Hz, 1H), 3.66 (s, 3H), 3.58 (m, 1H), 2.60 (ddd, J = 5.3, 5.3, 14.5 Hz, 1H), 2.30 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 2.03 (dt, J = 7.2, 7.2 Hz, 2H), 1.92 (d, J = 6.8 Hz, 3H), 1.67 ppm (tt, J = 7.2, 7.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 173.9, 160.6, 137.6, 135.3, 134.9, 131.4, 127.1, 125.9, 125.6, 51.5, 43.4, 33.4, 30.7, 26.7, 24.7, 19.1 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{17}H_{22}O_3]$+Na: 297.1461; found: 297.1462.

4aD: R_f = 0.43 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}$ = 2926, 1733, 1690, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, J = 1.4, 5.8 Hz, 1H), 6.87 (d, J = 11.6 Hz, 1H), 6.29 (dd, J = 1.9, 5.8 Hz, 1H), 6.28 (dd, J = 12.1, 15.0 Hz, 1H), 6.12 (dt, J = 6.8, 15.0 Hz, 1H), 5.40 (dtt, J = 3.9, 7.2, 11.3 Hz, 1H), 5.29 (br dt, J = 6.7, 11.3 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 3.52 (m, 1H), 2.53 (m, 1H), 2.28 (t, J = 7.2 Hz, 2H), 2.22 (t, J = 7.2 Hz, 2H), 2.25–2.13 (m, 2H), 1.96 (dt, J = 7.2, 7.2 Hz, 2H), 1.74 (tt, J = 7.2, 7.7 Hz, 2H), 1.60 ppm (tt, J = 7.2, 7.2 Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.3, 173.9, 173.7, 160.7, 144.7, 135.6, 135.3, 131.5, 131.1, 126.5, 125.9, 108.9, 51.6, 51.4, 43.4, 33.4, 32.7, 30.7, 26.7, 24.7, 23.9 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{21}H_{28}O_5]$+Na: 383.1838; found: 383.1829.

4bA: R_f = 0.55 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2929, 2857, 1739, 1695, 1634, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 2.4, 5.8 Hz, 1H), 6.95 (d, J = 11.1 Hz, 1H), 6.35 (dd, J = 1.9, 5.8 Hz, 1H), 6.33 (dd, J = 11.1, 15.0 Hz, 1H), 6.22 (dt, J = 6.8, 15.0 Hz, 1H), 5.48 (br dt, J = 7.2, 11.1 Hz, 1H), 5.33 (br dt, J = 8.2, 11.1 Hz, 1H), 3.66 (s, 3H), 3.57 (m, 1H), 2.60 (dt, J = 5.3, 14.0 Hz, 1H), 2.34 (m, 1H), 2.29 (t, J = 7.7 Hz, 2H), 1.96 (dt, J = 6.8, 7.2 Hz, 2H), 1.46 (tt, J = 7.2, 7.7 Hz, 2H), 1.32–1.19 (m, 12H), 0.90 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 174.2, 160.8, 146.7, 135.2, 135.2, 132.7, 131.6, 125.7, 124.9, 51.4, 43.6, 34.0, 33.4, 31.4, 30.8, 29.3, 29.7, 29.0, 28.4, 27.3, 24.9, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{24}H_{36}O_3]$+Na: 395.2119; found: 395.2117.

4bB: R_f = 0.53 (hexane/ethyl acetate = 3:2); IR (neat): $\tilde{\nu}_{max}$ = 2950, 1742, 1693, 1630, 1436 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 2.4, 5.8 Hz, 1H), 6.95 (d, J = 11.1 Hz, 1H), 6.35 (dd, J = 1.9, 5.8 Hz, 1H), 6.33 (dd, J = 11.1, 13.5 Hz, 1H), 6.30 (dt, J = 6.3, 13.5 Hz, 1H), 5.48 (br dt, J = 6.8, 10.6 Hz, 1H), 5.33 (br dt, J = 8.2, 10.6 Hz, 1H), 3.66 (s, 3H), 3.61 (m, 1H), 2.59 (m, 1H), 2.29 (t, J = 7.7 Hz, 1H), 2.26 (m, 1H), 2.22 (dt, J = 6.3, 7.7 Hz, 1H), 1.97 (dt, J = 6.8, 7.7 Hz, 1H), 1.63–1.57 (m, 6H), 1.40–1.23 (m, 16H), 0.88 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 174.2, 160.8, 146.7, 135.2, 132.7, 131.6, 127.2, 125.7, 124.9, 51.4, 43.6, 34.0, 33.5, 31.9, 30.8, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 29.0, 28.8, 27.3, 24.9, 22.7, 14.1 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{28}H_{44}O_3]$+Na: 451.3183; found: 451.3179.

4bC: R_f = 0.56 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}$ = 2952, 1740, 1695, 1630, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 2.4, 5.8 Hz, 1H), 6.94 (d, J = 11.1 Hz, 1H), 6.35 (dd, J = 1.9, 5.8 Hz, 1H), 6.34 (dd, J = 11.1, 15.0 Hz, 1H), 6.24 (dt, J = 6.9, 15.0 Hz, 1H), 5.48 (br dt, J = 7.3, 10.6 Hz, 1H), 5.33 (br dt, J = 6.8, 10.6 Hz, 1H), 3.66 (s, 3H), 3.56 (m, 1H), 2.60 (ddd, J = 5.3, 5.3, 14.5 Hz, 1H), 2.29 (t, J = 7.3 Hz, 2H), 2.25 (m, 1H), 1.97 (dt, J = 7.3 Hz, 2H), 1.91 (d, J = 6.9 Hz, 3H), 1.63–1.57 (m, 4H), 1.41–1.25 ppm (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 174.2, 160.8, 141.1, 135.2, 135.1, 132.7, 131.4, 127.2, 124.9, 51.4, 43.6, 34.0, 30.8, 29.3, 29.0, 28.9, 27.3, 24.9, 19.1 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{20}H_{28}O_3]$+Na: 339.1931; found: 339.1930.

4bD: R_f = 0.42 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}$ = 2930, 1739, 1695, 1634 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 2.4, 5.8 Hz, 1H), 6.93 (d, J = 11.6 Hz, 1H), 6.35 (dd, J = 1.4, 5.8 Hz, 1H), 6.35 (dd, J = 11.6, 14.5 Hz, 1H), 6.18 (dt, J = 7.2, 14.5 Hz, 1H), 5.47 (br dt, J = 7.2, 10.6 Hz, 1H), 5.32 (br dt, J = 8.7, 10.6 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.57 (m, 1H), 2.58 (dt, J = 5.3, 14.5 Hz, 1H), 2.35 (t, J = 7.7 Hz, 2H), 2.34 (m, 1H), 2.29 (t, J = 7.7 Hz, 2H), 2.29–2.25 (m, 2H), 1.95 (dt, J = 6.8, 7.2 Hz, 2H), 1.80 (tt, J = 7.2, 7.7 Hz, 2H), 1.45–1.25 ppm (m, 8H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.3, 174.2, 173.7, 160.9, 144.6, 135.7, 135.2, 132.8, 131.1, 126.6, 124.8, 51.6, 51.4, 43.5, 34.0, 33.3, 32.7, 30.8, 29.3, 29.0, 28.9, 27.3, 24.9, 23.9 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{24}H_{34}O_5]$+Na: 425.2300; found: 425.2299.

4cA: R_f = 0.53 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2953, 2930, 2860, 1685, 1637, 1580, 1455, 1205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, J = 2.4, 5.8 Hz, 1H), 7.29–7.25 (m, 2H), 7.19–7.14 (m, 3H), 6.94 (d, J = 11.1 Hz, 1H), 6.34 (dd, J = 1.9, 5.8 Hz, 1H), 6.32 (dd, J = 11.1, 15.0 Hz, 1H), 6.22 (dt, J = 6.8, 15.0 Hz, 1H), 5.51 (br dt, J = 7.2, 10.6 Hz, 1H), 5.36 (br dt, J = 6.3, 10.6 Hz, 1H), 3.56 (m, 1H), 2.59 (t, J = 7.7 Hz, 2H), 2.56 (m, 1H), 2.26 (ddd, J = 8.7, 8.7, 14.5 Hz, 1H), 2.21 (dt, J = 6.8, 7.2 Hz, 2H), 2.03 (dt, J = 6.8, 7.2 Hz, 2H), 1.66 (tt, J = 7.2, 7.7 Hz, 2H), 1.45 (tt, J = 7.2, 7.2 Hz, 2H), 1.32–1.22 (m, 4H), 0.89 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.3, 160.7, 146.7, 135.3, 135.1, 132.3, 131.6, 128.4, 128.3, 128.3, 125.8, 125.7, 125.3, 43.6, 35.5, 33.5, 31.4, 31.2, 30.9, 28.5, 26.9, 22.5, 14.0 ppm; HRMS (ESI-TOF): m/z calcd for $[C_{25}H_{32}O]$+Na: 371.2345; found: 371.2345.

4cB: R_f = 0.56 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2953, 2935, 2857, 1680, 1634, 1579, 1450, 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, J = 2.4, 5.8 Hz, 1H), 7.29–7.24 (m, 2H), 7.19–7.14 (m, 3H), 6.95 (d, J = 11.1 Hz, 1H), 6.35 (dd, J = 1.9, 5.8 Hz, 1H), 6.31 (dd, J = 11.1, 15.0 Hz, 1H), 6.22 (dt, J = 6.8, 11.1 Hz, 1H), 5.51 (br dt, J = 7.2, 11.1 Hz, 1H), 5.36 (br dt, J = 6.8, 11.1 Hz, 1H), 3.56 (m, 1H), 2.59 (t, J = 7.7 Hz, 2H), 2.57 (m, 1H), 2.27 (ddd, J = 8.7, 8.7, 14.5 Hz, 1H), 2.21 (dt, J = 6.8, 7.2 Hz, 2H), 2.02 (dt, J = 6.8, 7.2 Hz, 2H), 1.66 (tt, J = 7.2, 7.7 Hz, 2H), 1.43 (tt, J = 7.2, 7.2 Hz, 2H), 1.36–1.18 (m, 12H), 0.88 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 160.7, 146.8, 142.2, 135.2, 135.1, 132.3, 131.6, 128.3, 128.3, 125.8, 125.7, 125.3, 43.6, 35.5, 33.5, 31.9, 31.2, 30.8, 29.5, 29.4, 29.3, 29.2, 28.8, 26.9, 22.7, 14.1; HRMS (ESI-TOF): m/z calcd for $[C_{29}H_{40}O]$+Na: 427.2971; found: 427.2971.

4cC: R_f = 0.44 (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}$ = 2956, 2929, 2857, 1695, 1634, 1581, 1454, 1206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, J = 1.9, 5.8 Hz, 1H), 7.32–7.25 (m, 2H), 7.19–7.15 (m, 3H), 6.94 (d, J = 11.6 Hz, 1H), 6.34 (dd, J = 1.9, 5.8 Hz, 1H), 6.33 (ddd, J = 1.0, 11.6, 15.0 Hz, 1H), 6.23 (dq, J = 5.8, 15.0 Hz, 1H), 5.52 (br dt, J = 7.2, 10.6 Hz, 1H), 5.35 (br dt, J = 6.8, 10.6 Hz, 1H), 3.56 (m, 1H), 2.59 (t, J = 7.7 Hz, 2H), 2.57 (m, 1H), 2.27 (ddd, J = 8.2, 8.2, 14.5 Hz, 1H), 2.03 (dt, J = 7.2, 7.2 Hz, 2H), 1.90 (dd, J = 1.0, 5.8 Hz, 3H), 1.66 ppm (tt, J = 7.2, 7.7 Hz, 2H); 13C NMR (67.8 MHz, $CDCl_3$): δ = 197.4, 160.7, 142.2, 141.2, 135.3,

135.0, 132.3, 131.4, 128.4, 128.3, 127.2, 125.8, 125.3, 43.5, 35.5, 31.2, 30.8, 26.9, 19.2 ppm; HRMS (ESI-TOF): *m/z* calcd for $[C_{21}H_{24}O]+Na$: 315.1719; found: 315.1719.

4cD: $R_f=0.38$ (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}=3028$, 2928, 1739, 1634 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta=7.39$ (dd, $J=1.7$, 5.9 Hz, 1H), 7.18–7.07 (m, 5H), 6.86 (d, $J=11.2$ Hz, 1H), 6.27 (dd, $J=1.7$, 5.9 Hz, 1H), 6.27 (dd, $J=11.2$, 15.2 Hz, 1H), 6.10 (dt, $J=6.6$, 15.2 Hz, 1H), 5.46 (br dt, $J=6.9$, 11.2 Hz, 1H), 5.28 (br dt, $J=6.6$, 11.2 Hz, 1H), 3.60 (s, 3H), 3.49 (m, 1H), 2.40–2.20 (m, 4H), 2.35 (t, $J=7.6$ Hz, 2H), 2.27 (t, $J=7.3$ Hz, 2H), 1.96 (dt, $J=6.9$, 11.2 Hz, 1H), 1.77 (dt, $J=6.9$, 7.3 Hz, 1H), 1.77 (dt, $J=6.9$, 7.3 Hz, 2H), 1.59 ppm (dt, $J=5.3$, 7.6 Hz, 2H); HRMS (ESI-TOF): *m/z* calcd for $[C_{25}H_{30}O_3]+Na$: 401.2089; found: 401.2089.

4eA by using polymer-supported reagents and scavengers: A solution of 9-BBN dimer (59.0 mg, 0.484 mmol) in dry tetrahydrofuran (1.4 mL) was added dropwise to a stirred solution of *O-tert*-butyldimethylsilyl-3-beten-1-ol (98.7 mL, 0.403 mmol) in dry tetrahydrofuran (0.40 mL) over 20 min at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred for a further 5 h. When the above operation was complete, **5** (50.0 mg, 0.202 mmol) was added to a mixture of cesium carbonate (131.3 mg, 0.403 mmol), PS $[Pd(PPh_3)_4]$ (134.5 mg, 0.30 mmol g^{-1} 40.4 mmol), and DMF (4.4 mL) in a separate flask. Water (87 mL) was then added with vigorous stirring, followed by addition of the above solution of the borane. The reaction mixture was heated to 60 °C and stirred for 4 h, then filtered through a silica-gel pad (Presep-C; hexane/diethyl ether = 8:1) to afford the alkylated enone as a yellow oil (51.0 mg, 0.212 mmol, 105% crude). Triethylamine (22.6 mL, 0.162 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (18.6 mL, 0.0811 mmol) were added to a stirred solution of enone (10.0 mg, 32.4 mmol) in dry dichloromethane (1.0 mL) at 0 °C under argon. After being stirred for 20 min at room temperature, one drop of water and PS biscarbonate (50.4 mg, 3.30 mmol g^{-1}, 0.166 mmol) was added to the reaction mixture at 0 °C, which was stirred at the same temperature for a further 1 h. The reaction mixture was filtered, and the resin was washed with diethyl ether (2 × 3.0 mL). The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **18d** as a yellow oil. Boron trifluoride diethyl etherate (0.8 mL, 6.5 mmol) was added dropwise to a stirred solution of **18d** and **7A** (20.2 mg, 0.130 mmol) in dry dichloromethane (1 mL) at −78 °C under argon. After being stirred for 4 h at the same temperature, the reaction mixture was allowed to warm to −40 °C and stirred for a further 1 h. Then PS diamine (145 mg, 3.0 mmol g^{-1}, 0.424 mmol) was added to the reaction mixture at −78 °C and stirred at 0 °C for another 2 h to remove excess **7A**. The reaction mixture was filtered, and the resin was washed with dichloromethane (2 × 3.0 mL) and diethyl ether (2 × 3.0 mL). The filtrate was concentrated under reduced pressure to provide crude **19dA** as a yellow oil. PS TBD (95.8 mg, 1.9 mmol g^{-1}, 0.182 mmol) and methanesulfonyl chloride (7.0 mL, 91 mmol) were added to a stirred solution of **19dA** in dry dichloromethane (1.0 mL) at 0 °C under argon. After being stirred for 4 h at room temperature, the reaction mixture was filtered, and the resin was washed with diethyl ether (2 × 3.0 mL). The filtrate was concentrated under reduced pressure to provide crude **4dA** as a yellow oil. The compound was dissolved in tetrahydrofuran/glacial acetic acid/H_2O (1:2:1, 1.0 mL), and the solution was stirred at room temperature for 1 h. After the reaction mixture was cooled to room temperature, PS carbonate (50 mg) and tetrahydrofuran (1.0 mL) were added, the resulting mixture was filtered, and the resin was washed with diethyl ether (2 × 3.0 mL). The filtrate was concentrated under reduced pressure to provide a yellow oil. The residue was subjected to flash chromatography (hexane/ethyl acetate = 60:40) to afford **4eA** (2.7 mg, 8.4 mmol, 26% over five steps based on **5**) as a colorless oil. $R_f=0.14$ (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}=3416$, 2929, 2858, 1693, 1632, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.48$ (dd, $J=2.4$, 5.8 Hz, 1H), 6.95 (d, $J=11.6$ Hz, 1H), 6.35 (dd, $J=1.9$, 5.8 Hz, 1H), 6.33 (dd, $J=11.6$, 15.0 Hz, 1H), 6.23 (dt, $J=7.2$, 15.0 Hz, 1H), 5.49 (br dt, $J=7.2$, 11.1 Hz, 1H), 5.34 (br dt, $J=8.2$, 11.1 Hz, 1H), 3.63 (t, $J=6.3$ Hz, 2H), 3.56 (m, 1H), 2.60 (ddd, $J=5.8$, 5.8, 14.0 Hz, 1H), 2.29 (ddd, $J=8.7$, 8.7, 14.0 Hz, 1H), 2.22 (dt, $J=7.2$, 7.2 Hz, 2H), 2.02 (dt, $J=6.8$, 7.2 Hz, 2H), 1.59–1.40 (m, 10H), 0.90 ppm (t, $J=6.8$ Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta=197.4$, 160.1, 146.8, 135.3, 135.1, 132.5, 131.6, 125.7, 125.2, 62.8, 43.6, 33.5, 32.3, 31.4, 30.8, 28.5, 27.1, 25.7, 22.5, 14.0 ppm; HRMS (ESI-TOF): *m/z* calcd for $[C_{20}H_{30}O_2]+Na$: 325.2138; found: 325.2138.

4eB: $R_f=0.14$ (hexane/ethyl acetate = 2:1); IR (neat): $\tilde{\nu}_{max}=3418$, 2926, 2855, 1694, 1632, 1579, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.48$ (dd, $J=2.4$, 5.8 Hz, 1H), 6.95 (d, $J=11.1$ Hz, 1H), 6.35 (dd, $J=1.9$, 5.8 Hz, 1H), 6.33 (dd, $J=11.1$, 15.0 Hz, 1H), 6.23 (dt, $J=6.8$, 15.0 Hz, 1H), 5.47 (br dt, $J=7.2$, 11.1 Hz, 1H), 5.34 (br dt, $J=8.2$, 11.1 Hz, 1H), 3.63 (t, $J=6.8$ Hz, 2H), 3.57 (m, 1H), 2.60 (ddd, $J=8.2$, 8.2, 14.5 Hz, 1H), 2.30 (ddd, $J=8.2$, 8.2, 14.5 Hz, 1H), 2.22 (dt, $J=7.2$, 7.2 Hz, 2H), 2.01 (dt, $J=7.2$, 7.2 Hz, 2H), 1.55 (tt, $J=6.8$, 7.2 Hz, 2H), 1.53–1.26 (m, 16H), 0.88 ppm (t, $J=6.3$ Hz, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta=197.4$, 160.7, 146.8, 135.3, 135.1, 132.5, 131.6, 125.7, 125.2, 62.8, 43.6, 33.5, 32.3, 31.9, 30.8, 29.5, 29.5, 29.3, 28.8, 27.1, 25.7, 22.7, 14.1 ppm; HRMS (ESI-TOF): *m/z* calcd for $[C_{22}H_{38}O_2]+Na$: 381.2764; found: 381.2764.

4eC: $R_f=0.21$ (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}=3415$, 2930, 2860, 1693, 1635, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.48$ (dd, $J=2.4$, 5.8 Hz, 1H), 6.95 (d, $J=11.6$ Hz, 1H), 6.35 (dd, $J=1.4$, 5.8 Hz, 1H), 6.34 (dd, $J=11.6$, 15.0 Hz, 1H), 6.26 (dq, $J=6.3$, 15.0 Hz, 1H), 5.49 (br dt, $J=7.2$, 10.6 Hz, 1H), 5.34 (br dt, $J=6.8$, 10.6 Hz, 1H), 3.63 (t, $J=6.3$ Hz, 2H), 3.58 (m, 1H), 2.61 (ddd, $J=4.8$, 4.8, 14.5 Hz, 1H), 2.30 (ddd, $J=8.2$, 8.2, 14.5 Hz, 1H), 2.02 (dt, $J=6.8$, 7.2 Hz, 2H), 1.92 (dd, $J=1.0$, 6.8 Hz, 3H), 1.59–1.37 ppm (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta=197.4$, 160.7, 141.2, 135.3, 135.0, 132.5, 131.4, 127.2, 125.2, 62.8, 43.5, 32.3, 30.8, 27.1, 25.7, 19.2; HRMS (ESI-TOF): *m/z* calcd for $[C_{16}H_{22}O_2]+Na$: 269.1512; found: 269.1512.

4eD: $R_f=0.28$ (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}_{max}=3392$, 2926, 2855, 1733, 1694, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.49$ (dd, $J=2.4$, 5.8 Hz, 1H), 6.94 (d, $J=11.6$ Hz, 1H), 6.35 (dd, $J=1.4$, 5.8 Hz, 1H), 6.35 (dd, $J=11.6$, 14.5 Hz, 1H), 6.19 (dt, $J=7.2$, 14.5 Hz, 1H), 5.49 (br dt, $J=7.2$, 11.1 Hz, 1H), 5.34 (br dt, $J=8.2$, 11.1 Hz, 1H), 3.68 (s, 3H), 3.63 (t, $J=6.3$ Hz, 2H), 3.59 (m, 1H), 2.60 (m, 1H), 2.26 (m, 1H), 2.35 (t, $J=7.7$ Hz, 2H), 2.28 (dt, $J=7.2$, 7.7 Hz, 2H), 2.02 (dt, $J=5.8$, 7.2 Hz, 2H), 1.81 (tt, $J=7.7$, 7.7 Hz, 2H), 1.41 (tt, $J=4.3$, 6.3 Hz, 2H), 1.34 ppm (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$): $\delta=197.4$, 173.8, 160.8, 144.6, 135.7, 135.3, 132.5, 126.5, 62.7, 51.6, 43.5, 33.3, 32.6, 32.3, 30.8, 29.7, 27.1, 25.7, 23.9 ppm; HRMS (ESI-TOF): *m/z* calcd for $[C_{20}H_{28}O_4]+Na$: 355.1890; found: 355.1880.

Biological Evaluation

Cell culture: PC12 cells were grown in Dulbecco's modified Eagle's medium (DMEM) and supplemented with heat-inactivated fetal bovine serum (FBS; 10%), heat-inactivated horse serum (5%), penicillin (100 units mL^{-1}), streptomycin (100 mg mL^{-1}), and $NaHCO_3$ (0.2%) at 37 °C in an atmosphere of air (95%) and CO_2 (5%).

Neurite-outgrowth assay: PC12 cells (20000, 1.0 mL medium) were placed in each well of a 24-well plate and precultured. After 24 h, the medium was replaced by DMEM supplemented with FBS (0.5%) and containing NGF (1.5 ng mL^{-1}) and the indicated concentrations of PGs for 48 h. The morphological changes of the cells were monitored by a phase-contrast microscope. Cell differentiation was evaluated by counting cells with a length at least two times that of the diameter of the cell body. About 100 cells were counted from a randomly chosen field, and this was repeated three times.

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