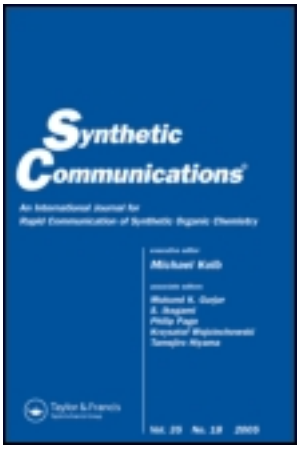

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Copper(I)-Catalyzed Cycloaddition of Methyl O-Propargylpodocarpate and Azides at Room Temperature

Dao M. Nguyen [a] & D. Howard Miles [a]
[a] Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, Florida, USA
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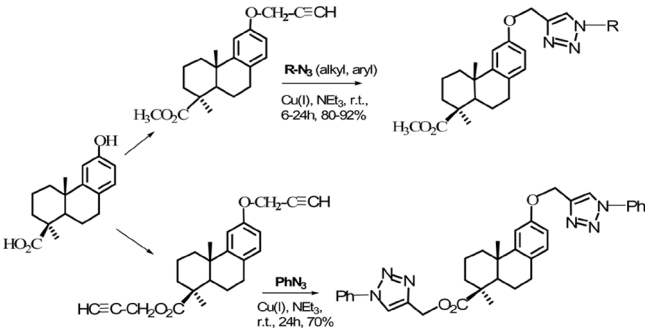
COPPER(I)-CATALYZED CYCLOADDITION OF METHYL O-PROPARGYLPODOCARPATE AND AZIDES AT ROOM TEMPERATURE

Dao M. Nguyen and D. Howard Miles
Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, Florida, USA

GRAPHICAL ABSTRACT



Abstract *Copper iodide was employed as an efficient catalyst for the synthesis of 1,2,3-triazole derivatives of podocarpic acid at room temperature through "click" chemistry cycloaddition reactions of methyl O-propargylpodocarpate and propargyl O-propargylpodocarpate with azides.*

Keywords Azides; copper(I) iodide; methyl O-propargylpodocarpate; podocarpic acid derivatives; 1,2,3-triazoles

INTRODUCTION

Triazoles are of great interest in organic synthesis because many compounds in this class have displayed a broad spectrum of biological activity.[1–3] The synthesis of 1,2,3-triazoles by thermal heating of a terminal alkyne and an azide has been known as the Huisgen 1,3-dipolar cycloaddition reaction since the 1960s.[4–6] However, this reaction is rather slow and yields a mixture of 1,2-disubstituted and 1.4-disubstituted 1,2,3-triazoles.

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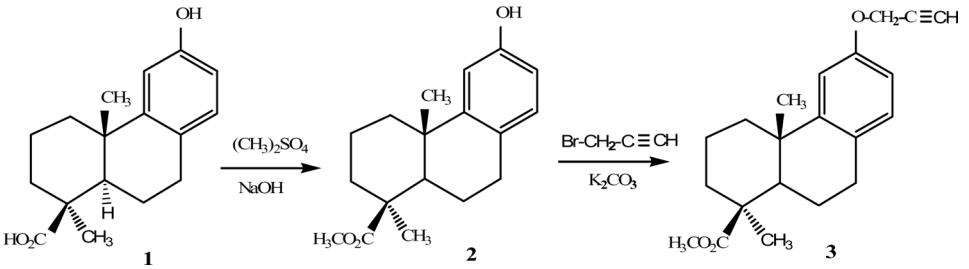
Address correspondence to D. Howard Miles, Natural Products Research Laboratory, Department of Chemistry, University of Central Florida, Orlando, FL 32816, USA. E-mail: dhmiles@pegasus.cc.ucf.edu

Sharpless and coworkers have demonstrated that copper(I) salt–catalyzed 1,3-dipolar cycloaddition reactions proceed efficiently in a polar medium such as a mixture of *tert*-butyl alcohol and water.[7] As a result, the term "click reaction" was utilized.[8,9] Click chemistry reactions are more practical and reliable because of thermodynamic driving forces of more than 20 Kcal mol^{-1}.[10] The click reaction between a terminal alkyne and an azide usually utilizes dimethylformamide (DMF) [or a mixture of dimethylsulfoxide (DMSO)/H_2O] at elevated temperatures (60–80°C) with a copper(I) catalyst that is generated in situ by employing copper(II) sulfate and sodium ascorbate in aqueous media.[11] Moreover, a sterically hindered base such as N,N-diisopropylethylamine or lutidine was required for optimal results.[9,12]

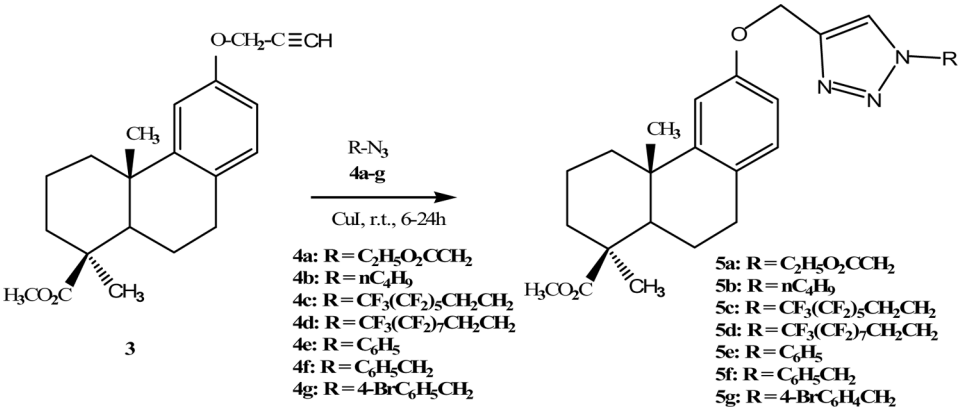
The naturally occurring terpenoids, podocarpic acid and its derivatives, have been known for their bioactive and antitumor properties.[13–15] This study reports upon the synthesis of 1,2,3-triazole derivatives of podocarpic acid utilizing a click chemistry approach that involved using copper(I) iodide in triethylamine as catalyst for the cycloaddition of terminal alkynes with azides in dioxane at room temperature. The reaction provides methodology for the preparation of triazoles in good yield and in a reasonable period of time (6–24 h), with a simple workup procedure. Selected 1,2,3-triazole derivatives of podocarpic acid are being evaluated relative to their potential as new drug leads for the treatment of cancer and other disease targets.

RESULTS AND DISCUSSION

Methyl podocarpate (**2**) was synthesized (Scheme 1) in 81% yield from podocarpic acid (**1**). This conversion involved selective monomethylation of podocarpic acid (**1**) by the utilization of a solution with 1 molar equivalent of dimethyl sulfate in sodium hydroxide solution. The resulting product was identical upon comparison of the mp, Infrared (IR), mass spectral (MS), and NMR data of **2** with an authentic sample of methyl podocarpate (**2**).[16] Methyl podocarpate (**2**) was treated with propargyl bromide and potassium carbonate in acetone to give methyl O-propargylpodocarpate (**3**) in 88% yield. The structure of **3** was confirmed by MS [high-resolution mass spectral (HRMS) analysis gave a molecular ion at 326.1886, which is consistent with a molecular formula of $C_{21}H_{26}O_3$] and NMR analysis (the ^{1}H NMR of **3** showed a 2H signal at 4.65 δ, which was not present



Scheme 1. Preparation of methyl O-propargylpodocarpate (**3**).



Scheme 2. Preparation of azides **5a–g**.

in **2**). In addition, there was a singlet 1H signal at 2.45 δ, which was consistent with the presence of the terminal alkyne in the propargyl functionality of **3**.

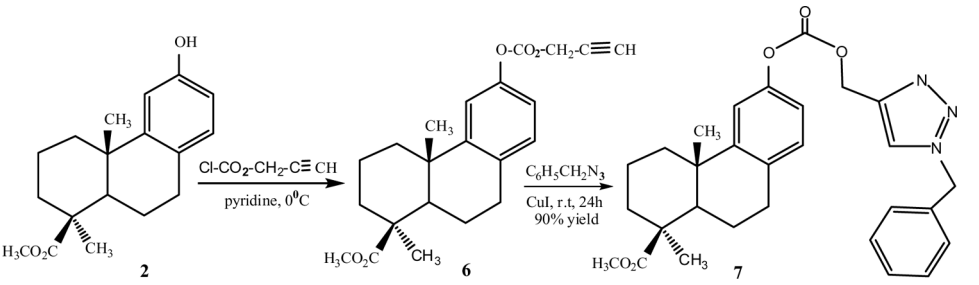
The seven novel 1,2,3-triazole derivatives of **3** (compounds **5a–g** in Scheme 2) were synthesized by the reaction of methyl O-propargylpodocarpate (**3**) with azides **4a–g** by using copper(I) iodide catalyst and triethylamine in dioxane at room temperature for a period of 6 to 24 h. The azides utilized were ethyl azidoacetate (**4a**), 1-azidobutane (**4b**), 1,1,1,2,2,3,3,4,4,5,5,6,6,-tridecafluoro-8-azidooctane (**4c**), 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-10-azidodecane (**4d**), azidobenzene (**4e**), azidomethylbenzene (**4f**), and 1-(azidomethyl)-4-bromobenzene (**4g**). Compounds **4b** and **4c** contained fluoroalkyl groups, which were selected to investigate the possibility of increased bioactivity due to fluorination.[17] Compounds **4a**, **4f**, and **4g** were synthesized in nearly quantitative yield via nucleophilic substitution of ethyl bromoacetate, benzyl chloride, and 1-(bromomethyl)-4-bromobenzene respectively with sodium azide in acetonitrile at 80°C with reaction times of from 4 to 20 h. Likewise, compounds **4b**, **4c**, and **4d** were synthesized by the reaction of 1-bromobutane, 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane, and 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-10-iododecane respectively with sodium azide in DMSO at 95 °C for 24 h. The NMR spectra of **4a**, **4b**, and **4f–g** were identical upon comparison with literature values for the respective compounds.[18–20] Compound **4e** was synthesized in 70% yield from phenyl hydrazine by a modified procedure reported by Lindsay and Allen.[21] The NMR spectrum of compound **4e** was identical upon comparison with the NMR data reported in the literature.[22] The HRMS analysis of **4c** gave a molecular ion of 489.0115, which corresponded to a molecular formula of $C_{10}H_4F_{11}N_3$. The IR of **4a–g** showed strong absorption bands in the region of 2100–2200 cm^{-1} that are consistent with the presence of azide functionality.

The reaction of **3** with azides **4a–g** utilized copper(I) iodide in triethylamine in dioxane to obtain derivatives **5a–g** in yields of 82, 84, 81, 80, 80, 92, and 90% respectively. The HRMS confirmed the molecular ions of **5a–g** as 455.2412, 425.2669, 715.1921, 815.1921, 445.2371, 459.2514, and 538.1689 respectively. These results were consistent with the formulas of $C_{25}H_{33}N_3O_5$, $C_{25}H_{35}N_3O_3$, $C_{29}H_{30}F_{13}N_3$, $C_{31}H_{30}F_{17}N_3$, $C_{27}H_{31}N_3O_3$, $C_{28}H_{33}N_3O_3$, and $C_{28}H_{32}BrN_3O_3$ respectively. The

^{1}H NMR spectra for **5a**–**g** indicated a downfield shift to 7.45–8.05 δ versus 2.5 δ in the starting **3**. This result indicated that the alkyne proton in **3** had disappeared and is consistent with the aromatic protons in the desired triazoles. A 2H signal was present at 4.3–4.4 δ in derivatives **5a**–**d**, **5f**, and **5g**, which could be assigned to the amino methylene group of the side chains. The presence of the desired alkyl and aryl functionalities in **5a**–**g** was indicated by additional signals in the aliphatic and aromatic regions respectively. Compound **5a** possessed an additional 2H signal at 4.15 δ, which could be assigned to the ethoxy group that was not present in **3**. Compound **5b** showed additional multiplets at 1.85, 1.35, and 1 δ, which integrated for a total of seven protons. This was consistent with the presence of the n-butyl group. The additional 2H multiplets at 2.85 δ in the ^{1}H NMR spectrum of **5c** and **5d** were consistent with the presence of a methylene group attached next to a nitrogen atom on the triazole rings. Signals were present in **5e** at 7.45, 7.55, and 7.75 δ, which accounted for the five aromatic protons of the phenyl group. Likewise, signals were present at 7.2 and 7.35 δ in **5f**, which integrated for 5H and could be assigned to the aromatic protons that are present in a benzyl moiety. Compounds **5f** and **5g** showed an additional 2H signal at 5.47 δ, which is consistent with the presence of benzylic protons in the assigned structures. Compound **5g** also showed two 2H signals at 7.18 and 7.55 δ that were not present in **3**. This was consistent with the presence of the four aromatic protons that are in the 4-bromophenyl group. The ^{13}C NMR spectra for **5a**–**g** showed signals at 124 and 146 ppm, respectively, which is consistent with the presence of the two carbons in the new 1,2,3-triazole moiety. In addition, the disappearance of alkyne carbons at 76–78 ppm is consistent with the assigned structures. Furthermore, additional signals (versus starting material compound **3**) for alkyl and aryl carbons were present in the ^{13}C NMR spectrum of all derivatives. Compound **5e** showed aromatic carbon signals at 136.7, 129.8, 129.6, 128.4, 120.9, and 120.6 ppm. Compound **5f** showed aromatic carbon signals at 134.4, 130.0, 128.5, 128.3, 128.2, and 122.0 ppm as well as signals for a benzylic carbon at 54.3 ppm. Compound **5g** showed aromatic carbon signals at 133.6, 132.4, 132.2, 129.6, 122.1, and 120.0 ppm as well as signals for a benzylic carbon signal at 53.5 ppm. Ester and ethoxy moieties were indicated in **5a** by the signals at 171 and 62.5 ppm. Compounds **5a**–**d** gave signals at 51.0, 49.0, 42.45, and 42.11 ppm, which could be assigned to amino carbons.

Scheme 3 shows the utilization of click chemistry for synthesis of 1,2,3-triazole derivatives of podocarpic acid (**7**) in 90% yield from **6**. Compound **6** synthesized in 95% yield from by reacting methyl podocarpate (**2**) with propargyl chloroformate in pyridine at 0 °C. The ^{1}H NMR of **6** showed a 2H singlet at 4.3 δ for the propargyl moiety and an additional 1H singlet proton at 2.2 δ, which was indicative of an alkyne functionality. In addition, compound **7** showed signals at 7.25 and 7.40 δ, which integrated for a total of five protons, which is consistent with the aromatic protons that are present in a benzyl group. There was an additional 2H signal at 5.50 δ, which could be assigned to the benzylic protons that were adjacent to the triazole ring. The HRMS analysis of **6** and **7** gave molecular ions at 370.1774 and 503.2312, respectively, which were consistent with the formulas of $C_{23}H_{26}O_5$ and $C_{29}H_{33}O_5N_3$.

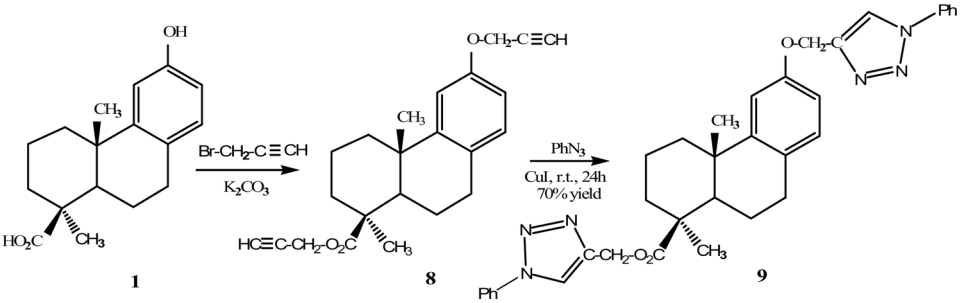
A 1,2,3-bis-triazole derivative of podocarpic acid (compound **9**) was synthesized in 70% yield from propargyl O-propargylpodocarpate (**8**), which had been



Scheme 3. Preparation of triazole **7**.

prepared by reacting podocarpic acid (**1**) with a two-fold excess of propargyl bromide in potassium carbonate in acetone (Scheme 4). The ^{1}H NMR analysis of **8** showed a 4H multiplet at 4.65 δ, which was consistent with the presence of two propargyl groups. Compound **8** showed two additional 1H signals at 2. 35 and 2.40 δ, which account for the two terminal alkynes moieties. Click chemistry was further explored in a reaction of a bis-alkyne functionality in **8** with phenyl azide catalyzed by copper(I) in dioxane at room temperature to obtain **9**. The ^{1}H NMR of **9** showed signals at 7.45, 7.55, and 7.75 δ, which integrated for a total of 10 protons and is consistent with the presence of the aromatic protons in the two benzyl groups. The benzylic protons that were adjacent to the triazoles rings were observed as two 2H signals at 5.25 and 5.35 δ respectively. Further evidence that **9** had been formed involved the disappearance of the two terminal alkyne protons that were present in the starting **8**. The HRMS analysis of **8** and **9** gave molecular ions at 350.1893 and 588.2843 that were consistent with the formulas of $C_{23}H_{26}O_3$ and $C_{35}H_{36}O_3N_6$, respectively.

In summary, 1,2,3-triazole derivatives of podocarpic acid (compounds **5a**–**g**, **7**, and **9**) were synthesized in good yield by the copper(I) iodide–catalyzed cycloaddition of methyl O-propargylpodocarpate and propargyl O-propargylpodocarpate with alkyl and aryl azides at room temperature. Thus, this work provides efficient methodology for the synthesis of novel 1,2,3-triazole derivatives of podocarpic acid. Furthermore, their potential as new drug leads is indicated by the fact that evaluation of the activity of compounds **5b**, **5e**, and **5f** against 60 human cancer



Scheme 4. Preparation of bis-triazole **9**.

cell lines by NIH/NCI Developmental Therapeutics Program (DTP) demonstrated that compound **5b** had significant activity (70%) relative to inhibiting the growth of melanoma SK-MEL-5 cells.

EXPERIMENTAL

Podocarpic acid (**1**) was recrystallized from methanol and dried under vacuum. IR spectra were recorded with a Perkin-Elmer spectrometer. NMR spectra were recorded with Mercury 300-MHz and Varian 500-MHz spectrometers in deuterated chloroform. Precaution was taken when azides were synthesized because they are potentially explosive. This was performed by heating at moderate temperatures and by working on a small scale.

Preparation of Methyl Podocarpate (2)

Podocarpic acid (**1**) (50 g, 0.18 mol) was dissolved in methanol (300 mL) in a 600 mL beaker. A solution of sodium hydroxide (7.3 g, 0.18 mol) in water (200 mL) was then added. The resulting solution was continually stirred until the podocarpic acid (**1**) was completely dissolved in the mixture. To this solution, dimethyl sulfate (19 mL, 0.18 mol) was added dropwise over a 30-min period at room temperature. For an additional 30 min, the solution was then allowed to solidify with stirring. At the end of this period, the solution was heated to boiling for 15 min and then allowed to cool to room temperature. A white precipitate formed and was removed (after cooling in an ice bath) by vacuum filtration to yield **2** (42 g, 0.15 mol) as a white solid (yield 80%). The resulting solid was recrystallized from methanol and dried under vacuum to obtain methyl podocarpate (**2**) as white needles with mp 206–208 °C. IR: 1720, 1600, 1540, 1490, 1460, 1200, 1190, 1150 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 6.95 (d, 1H), 6.80 (s, 1H), 6.65 (d, 1H), 3.58 (s, 3H), 2.80 (m, 2H), 2.25 (m, 3H), 1.95 (m, 2H), 1.40–1.60 (m, 4H), 1.28 (s, 3H), 1.05 (m, 1H), 1.00 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, Mercury 500 MHz): 178, 153.5, 149.6, 130.1, 127.6, 113, 112.1, 52.8, 51.3, 44, 39.4, 38.6, 37.6, 31.2, 28.6, 22.9, 21.1, 20 ppm.

Preparation of Methyl O-Propargylpodocarpate (3)

Compound **2** (4.6 g, 0.016 mol) was weighed and dissolved in acetone (60 mL) in a 200-mL flask. To this solution, potassium carbonate (6.6 g, 0.048 mol) and 18 crown 6 ether (50 mg) were added. Then a solution of 80% of propargyl bromide in toluene (3.1 g) was added, and the resulting solution was stirred using a magnetic stirring bar. The solution was then refluxed under a nitrogen atmosphere at 70 °C for 20 h. At the end of this period, the solution was allowed to cool to room temperature. The resulting solution was filtered and washed with ethyl acetate (60 mL), and the filtrate was evaporated in vacuo to obtain crude product **3**. The crude product was purified on a silica-gel column by using hexane and ethyl acetate (70:30) as eluents to obtain pure **3** (4.0 g, 0.012 mol) in 76% yield as a white powder with mp 89 °C. IR: 3267, 2987, 2852, 2172, 1713, 1605, 1581, 1502, 1459, 1380, 1304, 1241, 1191, 1072 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.00 (m, 1H), 6.90 (s, 1H), 6.75

(m, 1H), 4.66 (s, 2H), 3.67 (s, 3H), 2.65–2.85 (m, 2H), 2.50 (s 1H), 2.2–2.3 (m, 2H), 1.95–2.05 (m, 2H), 1.42–1.65 (m, 4H), 1.28 (s, 3H), 1.04–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): 177.90, 155.70, 149.38, 129.86, 128.65, 112.36, 112.13, 78.89, 75.31, 55.87, 52.75, 51.29, 44.00, 39.35, 38.67, 37.61, 31.26, 28.56, 22.89, 21.06, 19.98 ppm. HRMS calcd. for $C_{21}H_{26}O_3$ 326.4346; found 326.1886.

Synthesis of Ethyl Azidoacetate (4a)

Ethyl bromoacetate (5 g, 0.03 mol) was weighed and dissolved in acetonitrile (150 mL) in a 500-mL flask. To this solution, sodium azide (2.35 g, 0.036 mol) was added. The resulting mixture was stirred using a magnetic stirring bar and then refluxed under nitrogen at 80 °C for 4 h. At the end of this period, the solution was allowed to cool to room temperature and then filtered. The filtrate was evaporated under reduced pressure to obtain a crude product, which was further purified on a silica-gel column using hexane as the eluent to obtain ethyl azidoacetate (**4a**) (3.5 g, 0.027 mol) as a pure colorless liquid (90% yield). IR: 2986, 2106, 1744, 1426, 1373, 1288, 1195, 1024 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 4.26–4.30 (m, 2H), 3.87 (s, 2H), 1.30–1.36 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 168.30, 61.88, 50.37, 14.06 ppm.

Synthesis of Butyl Azide (4b)

1-Bromobutane (5.5 g, 0.04 mol) was weighed and dissolved in DMSO (50 mL) at room temperature in a 200 mL flask to which was added sodium azide (3.9 g, 0.06 mol). The solution was then refluxed under nitrogen at 95 °C for 24 h. At the end of this period, the solution was allowed to cool to room temperature. A white precipitate formed, and the resulting mixture was transferred into water (100 mL) in a separatory flask to which diethyl ether (50 mL) was added. The organic phase was then removed. The aqueous phase was then extracted three times with portions of ether (100 mL). The ether phases were then combined, washed with water, dried with sodium sulfate, and then evaporated in vacuo to yield butyl azide **9a** (3 g, 0.03 mol) in 80% yield as a colorless liquid. IR: 2090 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 3.18–3.21 (m, 2H), 1.49–1.55 (m, 2H), 1.30–1.37 (m, 2H), 0.86–0.89 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 39.97, 29.82, 18.87, 12.60 ppm.

Synthesis of 1,1,1,2,2,3,3,4,4,5,5,6,6,-Tridecafluoro-8-azidooctane (4c)

1,1,1,2,2,3,3,4,4,5,5,6,6,-Tridecafluoro-8-iodooctane (4.8 g, 0.010 mol) was weighed and dissolved in DMSO (25 mL), to which sodium azide (1.0 g, 0.015 mol) was added. The resulting mixture was heated to 95 °C for 24 h and then worked up as described in the procedure for **4b** to obtain **4c** (3.1 g, 0.007 mol) as a white solid (70% yield). IR: 2106, 1233, 1190, 1122, 1075 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 3.40 (m, 2H), 2.27–2.37 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 41.40, 29.06 ppm. HRMS calcd. for $C_{10}H_4F_{11}N_3$ 489.1345; found 489.0115.

Synthesis of 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-10-azidodecane (4d)

1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Heptadecafluoro-8-iodooctane (5.74 g, 0.010 mol) was weighed and dissolved in DMSO (25 mL) to give a solution to which sodium azide (1 g, 0.015 mol) was added. The resulting mixture was heated to 95 °C for 24 h and then worked up as described for **4b** to give **4d** (4.2 g, 0.009 mol) in 85% yield as a white solid. IR: 2107, 1200, 1146, 962 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 3.50–3.60 (m, 2H), 2.20–2.35 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 43.29, 30.79 ppm.

Synthesis of Phenyl Azide (4e)

Phenyl hydrazine (3.4 g, 0.031 mol) was weighed into a 30-mL beaker and then was added into a solution of hydrochloric acid (6 mL) and water (30 mL) at 0–5 °C in an ice bath. The resulting solution was stirred and maintained at this temperature. Diethyl ether (10 mL) was then added, which was followed by the dropwise addition of a solution of sodium nitrite (2.5 g, 0.042 mol) in water (5 mL). The resulting mixture was allowed to stand at this temperature for an additional 15 min, and then diethyl ether (10 mL) was added. It was poured into a 100-mL separatory flask and extracted with portions of diethyl ether (50 mL). The organic layers were combined, dried over sodium sulfate, and evaporated in vacuo to obtain a crude product. The crude product was purified on a silica-gel column using hexane as eluent to obtain a colorless liquid **4e** (2.2 g, 0.018 mol) in 60% yield. IR: 2125, 2094, 1594, 1492, 1294, 1281 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.36–7.39 (m, 2H), 7.05–7.18 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 140.0, 129.78, 124.89, 119.04 ppm.

Synthesis of Azidomethylbenzene (4f)

Benzyl chloride (3.8 g, 0.03 mol) was dissolved in acetonitrile (150 mL) to which 2.9 g of sodium azide (2.9 g, 0.045 mol) was added and then heated to 80 °C for 20 h. The crude product was purified on a silica-gel column using hexane as eluent to obtain azidomethylbenzene (**4f**) (3.0 g, 0.023 mol) as a colorless liquid (75% yield). IR: 2150 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35–7.43(m), 4.37(s) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 135.39, 128.93, 128.88, 128.40, 128.31, 128.26, 54.82 ppm.

Synthesis of 1-(Azidomethyl-4-bromobenzene) (4g)

4-Bromobenzylchloride (6.6 g, 0.030 mol) was utilized in a procedure that was identical to that used for the synthesis of **4f** to obtain **4g** (5.5 g, 0.026 mol) as a colorless liquid (85% yield). IR: 2932, 2095, 1592, 1488, 1456, 1406, 1341, 1283, 1195, 1070, 1012, 883 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.50–7.52 (m, 2H), 7.18–7.21 (m, 2H), 4.31 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 134.39, 132.10, 131.91, 129.92, 129.70, 122.35, 54.09 ppm.

General Procedure for the Preparation of 1,2,3-Triazole 5a–g

Copper(I) iodide (0.05 g, 0.003 mol) and triethylamine (2 mL) were added to a weighed amount (1.5 molar equivalent) of each azide dissolved in dioxane (10 mL) in

a 100-mL flask. This was followed by the addition of **3** (1.0 g, 0.003 mol). The resulting solution was stirred using a magnetic bar under a nitrogen atmosphere at room temperature for a period from 6 to 24 h. The resulting solution was filtered and washed with portions of ethyl acetate (60 mL). The filtrate was evaporated in vacuo to give a solid material, which was further purified by open column chromatography with 63- to 200-mesh silica gel. Hexane and ethylacetate (1:1) were used as the eluents to obtain the pure 1,2,3-triazole derivatives of podocarpic acid.

Data for Compounds 5a–g

Compound 5a. Ethyl azidoacetate (0.6 g) was utilized with the reaction time of 6 h to obtain **5a** (1.1 g, 0.0023 mol) as a white solid with mp 145 °C (82% yield). IR ($CHCl_3$): 2954, 2848, 1750, 1723, 1608, 1575, 1501, 1468, 1373, 1328, 1281, 1239, 1210, 1150, 1097, 1022, 972 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 7.80 (s, 1H), 7.00 (m, 1H), 6.92 (s, 1H), 6.78 (m, 1H), 5.16–5.20 (m, 2H), 4.35 (m, 2H), 4.25 (m, 2H), 3.66 (s, 3H), 2.65–2.85 (m, 2H), 2.18–2.30 (m, 3H), 1.90–2.02 (m, 2H), 1.50–1.62 (m, 2H), 1.25–1.42 (m, 7H), 1.05 (m, 1H), 1.02 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): 177.89, 171.15, 166.18, 156.36, 149.44, 145.0, 130.05, 128.31, 124.01, 111.96, 62.48, 60.15, 52.25, 51.11, 50.91, 43.98, 39.38, 38.67, 37.75, 31.22, 28.36, 22.77, 21.06, 19.97, 14.08 ppm. HRMS calcd. for $C_{25}H_{33}N_3O_5$ 455.5528; found 455.2412.

Compound 5b. Azidobutane (0.45 g) was utilized with the reaction time of 24 h to obtain an oily liquid **5b** (1.0 g, 0.0024 mol) in 84% yield. IR: 2956, 2872, 1721, 1608, 1574, 1501, 1465, 1379, 1327, 1282, 1245, 1211, 1190, 1149, 1098, 1033, 834 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.60 (s, 1H), 7.00 (m, 1H), 6.90 (s, 1H), 6.80 (m, 1H), 5.22 (s 1H), 4.40 (m, 2H), 3.66 (s, 3H), 2.65–2.85 (m, 2H), 2.20–2.35 (m, 3H), 1.90–2.00 (m, 4H), 1.50–1.65 (m,2H), 1.35–1.40 (m, 6H), 1.28 (s, 3H), 0.96–1.02 (m, 7H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): 177.85, 156.42, 149.43, 144.15, 130.01, 128.26, 122.23, 112.31, 112.05, 62.03, 52.23, 51.32, 48.95, 44.00, 39.57, 38.68, 37.63, 32.21, 31.24, 28.62, 22.86, 21.09, 21.00, 19.70, 13.49 ppm. HRMS calcd. for $C_{25}H_{35}N_3O_3$ 425.5698; found 425.2669.

Compound 5c. Compound **4c** (1.75 g) was utilized with the reaction time of 24 h to obtain 1.7 g of **5c** (1.7 g, 0.0024 mol) as a white solid with mp 60 °C (81% yield). IR: 2951, 1722, 1610, 1501, 1236, 1144 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 7.70 (s, 1H), 7.00 (m, 1H), 6.90 (s, 1H), 6.78 (m, 1H), 5.20 (s, 2H), 4.65 (m, 2H), 3.66 (s, 3H), 2.70–2.90 (m, 4H), 2.20–2.35 (m, 3H), 1.92–2.05 (m, 2H), 1.60 (m, 1H), 1.54 (m, 1H), 1.40 (m, 1H), 1.28 (s, 3H), 1.02–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.88, 156.22, 149.51, 145.10, 129.98, 128.44, 123.18, 112.18, 111.92, 62.06, 52.75, 51.30, 43.98, 42.45, 39.40, 38.68, 37.58, 31.81, 31.23, 28.56, 22.92, 21.04, 19.95 ppm. HRMS calcd. for $C_{29}H_{30}F_{13}N_3O_3$ 715.5535; found 715.1921.

Compound 5d. Compound **4d** (2.2 g) was utilized with the reaction time of 24 h to obtained 1.9 g of **5d** (1.9 g, 0.0023 mol) as a white solid with mp 70 °C (80% yield). IR: 2956, 1723, 1609, 1501, 1450, 1250, 1203, 1146, 1071 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 7.63 (s, 1H), 7.00 (m, 1H), 6.90 (s, 1H), 6.75 (m, 1H),

4.70 (m, 2H), 3.66 (s, 3H), 2.70–2.90 (m, 4H), 2.18–2.30 (m, 3H), 1.90–2.02 (m, 2H), 1.60 (m, 1H), 1.55 (m, 1H), 1.40 (m, 1H), 1.28 (s, 3H), 1.03–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.83, 156.31, 149.53, 145.10, 130.00, 128.44, 123.12, 112.25, 111.98, 62.04, 52.71, 51.30, 44.00, 42.11, 39.25, 38.68, 37.61, 31.85, 31.22, 28.60, 28.46, 22.97, 22.85, 20.43, 19.87 ppm. HRMS calcd. for $C_{31}H_{30}F_{17}N_3O_3$, 815.5670; found 815.1921.

Compound 5e. Azidobenzene (0.54 g) was utilized with a reaction time of 24 h to obtain 1 g of **5e** (1.0 g, 0.0022 mol) in 80% yield as a white solid with mp 118 °C IR: 2950, 2848, 1720, 1607, 1574, 1501, 1467, 1437, 1379, 1282, 1243, 1190, 1151, 1137, 1098, 989 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 8.02 (s, 1H), 7.75 (m, 2H), 7.65 (m, 2H), 7.50 (m, 1H), 7.00 (m, 1H), 6.95 (s, 1H), 6.80 (m, 1H), 5.28 (m, 2H), 3.67 (s, 3H), 2.85 (m, 1H), 2.75 (m, 1H), 2.20–2.30 (m, 3H), 1.90–2.05 (m, 2H), 1.60 (m, 1H), 1.55 (m, 1H), 1.40 (m, 1H), 1.28 (s, 3H), 1.04–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.89, 156.34, 149.52, 145.63, 136.70, 129.99, 129.79, 129.59, 128.86, 128.44, 120.88, 120.61, 112.23, 111.96, 62.09, 52.75, 51.28, 43.99, 39.41, 38.70, 37.60, 31.25, 28.57, 22.95, 21.06, 19.98 ppm. HRMS calcd. for $C_{27}H_{31}N_3O_3$ 445.5602; found 445.2371.

Compound 5f. Azidomethylbenzene (0.6 g) was utilized with a reaction time of 24 h to obtain an oily liquid **5f** (1.2 g, 0.0026 mol) in 92% yield. IR: 2954, 2852, 1722, 1610, 1576, 1500, 1458, 1439, 1382, 1284, 1193, 1123, 1072, 1035, 928 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 7.45 (s, 1H), 7.28–7.32 (m, 2H), 7.18–7.20 (m, 2H), 6.89 (m, 1H), 6.78 (s, 1H), 6.64 (m, 1H), 5.45 (s, 2H), 5.07 (s, 2H), 3.63 (s, 3H), 2.80 (m, 1H), 2.62–2.70 (m, 1H), 2.10–2.20 (m, 3H), 1.90–1.95 (m, 2H), 1.62 (s, 1H), 1.58 (m, 1H), 1.44 (m, 1H), 1.24 (m, 1H), 1.19 (s, 3H), 0.96–1.02 (m, 1H), 0.92 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.89, 156.36, 149.41, 145.10, 134.46, 130.00, 129.01, 128.88, 128.45, 128.30, 128.15, 122.13, 122.02, 112.26, 111.99, 62.19, 54.25, 52.35, 51.35, 43.98, 38.96, 38.66, 37.59, 31.24, 28.61, 22.94, 21.08, 19.99 ppm. HRMS calcd. for $C_{28}H_{33}N_3O_3$ 459.5870; found 459.2514.

Compound 5g. Compound **4g** (0.95 g) was utilized with the reaction time of 6 h to obtain 1.4 g of **5g** (1.4 g, 0.0026 mol) as a white solid with mp 45 °C (yield 90%). IR: 2950, 1720, 1605, 1500, 1470, 1450, 1280, 1210, 1180 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 7.55–7.60 (m, 3H), 7.18 (m, 2H), 6.95 (m, 1H), 6.85 (s, 1H), 6.75 (m, 1H), 5.47 (s, 2H), 5.16 (s, 2H), 3.66 (s, 3H), 2.65–2.75 (m, 2H), 2.05–2.15 (m, 3H), 1.95–2.00 (m, 2H), 1.75 (s, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.20–1.30 (s, 3H), 1.00–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.83, 156.34, 149.45, 145.76, 133.56, 132.41, 132.18, 129.82, 129.56, 128.34, 122.35, 122.10, 119.95, 112.07, 112.06, 62.18, 53.49, 52.35, 51.37, 44.00, 39.07, 38.67, 37.75, 31.23, 28.12, 22.36, 21.08, 20.01 ppm. HRMS calcd. for $C_{28}H_{32}BrN_3O_3$, 538.4841; found 538.1689.

Preparation of Compound 6

Methyl podocarpate (**2**) (2.88 g, 0.010 mol) was weighed and dissolved in pyridine (10 mL) and THF (10 mL) at 0 °C. To this solution, propargyl chloroformate (1.8 g, 0.015 mol) was added dropwise over a period of 15 min. The resulting solution

was stirred at this temperature for an additional 3 h and then poured into a cold solution of hydrochloric acid (9 mL) in water (50 mL). The resulting solution was transferred into a separatory flask and then extracted with diethyl ether (50 mL) three times. The organic phases were combined and washed with a solution of 5% sodium bicarbonate and then water. This solution was dried over sodium sulfate and evaporated in vacuo obtain a white solid. The crude product was further purified on a silica-gel column by using hexane and ethyl acetate (7:3) as eluents to obtain **6** (3.3 g, 0.009 mol), a white solid with a mp of 125–126 °C in 90% yield. IR: 3235, 2950, 2836, 1762, 1708, 1607, 1493, 1467, 1435, 1329, 1278, 1231, 1191, 1100 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 6.96–7.02 (m, 2H), 6.81–6.84 (m, 1H), 4.76 (s, 2H), 3.60 (s, 3H), 2.81–2.85 (m, 1H), 2.66–2.73 (m, 1H), 2.50 (s, 1H), 2.10–2.20 (m, 3H), 1.85–1.95 (m, 2H), 1.52–1.58 (m, 1H), 1.44–1.46 (m, 1H), 1.30–1.36 (m, 1H), 1.20 (s, 3H), 1.02–1.05 (m, 1H), 1.01 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 500 MHz): 177.76, 153.32, 149.56, 149.16, 133.41, 129.99, 118.0, 76.66, 76.09, 55.77, 52.42, 51.31, 43.96, 39.25, 38.64, 37.54, 31.45, 28.50, 22.95, 20.83, 19.86 ppm. HRMS calcd. for $C_{22}H_{26}O_5$ 370.4444; found 370.1774.

Preparation of Compound 7

Azidomethylbenzene (0.6 g, 0.0045 mol) was weighed and dissolved in dioxane (10 mL) in a 100-mL flask to which a solution of copper(I) iodide (0.05 g) and **6** (1.1 g, 0.003 mol) in triethylamine (2 mL) was added. The mixture was stirred (with a magnetic stirring bar) under a nitrogen atmosphere at room temperature for 24 h. The resulting solution was filtered and washed with portions of ethyl acetate (60 mL). The filtrate was evaporated in vacuo to give a solid material, which was further purified by open column chromatography with 63- to 200-mesh silica gel. Hexane and ethylacetate (1:1) were used as the eluents to obtain **7** (1.3 g, 0.0026 mol) in 90% yield as a white crystal with mp 90 °C. IR: 2952, 1758, 1721, 1500, 1454, 1227, 1145, 1047 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 7.80 (s, 1H), 7.60 (m, 3H), 7.50 (m, 2H), 7.00 (m, 2H), 6.80 (m, 1H), 5.77 (s, 2H), 5.32 (s, 2H), 3.62 (s, 3H), 2.85 (m, 1H), 2.75 (m, 1H), 2.25 (m, 1H), 2.10–2.19 (m, 2H), 1.92–2.00 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.40 (m, 1H), 1.25 (s, 3H), 1.02–1.08 (m, 1H), 1.00 (s, 3H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): 177.77, 153.88, 149.53, 149.10, 142.01, 134.27, 133.37, 129.97, 129.20, 128.93, 128.63, 128.20, 124.00, 118.05, 117.91, 61.41, 54.32, 52.40, 51.75, 43.95, 39.22, 38.62, 37.53, 31.45, 28.51, 22.95, 20.82, 19.86 ppm. HRMS calcd. for $C_{29}H_{33}N_3O_5$ 503.5968; found 503.2312.

Preparation of Propargyl O-Propargylpodocarpate (8)

Podocarpic acid (2.75 g, 0.01 mol) was weighed and dissolved in acetone (60 mL) in a 200-mL flask. To this solution, 12 g of potassium carbonate (12 g, 0.087 mol), 18 crown 6 ether (50 mg), and a solution of 80% propargyl bromide in toluene (4.5 g) were added. The resulting solution was then connected to a condenser under a nitrogen atmosphere and stirred on a hotplate at 70 °C for 20 h. At the end of this period, the solution was allowed to cool to room temperature. The resulting solution was filtered and washed with ethyl acetate (60 mL), and the filtrate was

evaporated in vacuo to obtain a crude product **8**. The product was purified on a silica-gel column using hexane and ethyl acetate (70:30) as eluents to obtain **8** (2.5 g, 0.007 mol) as a white powder with mp 99 °C in 70% yield. IR: 3300, 3275, 2955, 2205, 2167, 2034, 1994, 1970, 1719, 1606, 1571, 1282, 1231, 1179, 1136, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.00 (m, 1H), 6.93 (s, 1H), 6.85 (m, 1H), 4.65–4.70 (m, 4H), 2.65–2.95 (m, 2H), 2.50 (s, 1H), 2.45 (s, 1H), 2.20–2.30 (m, 3H), 2.00–2.10 (m, 2H), 1.55–1.65 (m, 2H), 1.40–1.42 (m, 1H), 1.35 (s, 3H), 1.05–1.10 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): 176.51, 155.72, 149.30, 129.87, 128.63, 112.36, 112.17, 78.50, 77.68, 75.34, 74.67, 55.87, 52.79, 51.56, 44.14, 39.29, 38.77, 37.58, 31.27, 28.46, 23.22, 21.02, 19.90 ppm. HRMS calcd. for $C_{23}H_{26}O_3$ 350.4566; found 350.1893.

Preparation of Compound 9

Copper(I) iodide (0.05 g), triethylamine (2 mL), and **8** (1.05 g, 0.003 mol) were added to azidobenzene (0.54 g, 0.0045 mol), which had been weighed and then dissolved in dioxane (10 mL) in a 100-mL flask. The mixture was stirred (with a magnetic stirring bar) under a nitrogen atmosphere at room temperature for 24 h. The resulting solution was filtered and washed with several portions of ethyl acetate (60 mL). The filtrate was evaporated in vacuo to give a solid material, which was further purified by using open column chromatography with 63- to 200-mesh silica gel. Hexane and ethyl acetate (1:1) were used as the eluents to obtain **9** (1.2 g, 0.002 mol) in 70% yield as a white solid with mp 85–87 °C. IR: 2931, 1717, 1607, 1506, 1465, 1246 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 8.05 (s, 2H), 7.70–7.74 (m, 4H), 7.52–7.54 (m, 6H), 6.95 (m, 1H), 6.85 (s, 1H), 6.80 (m, 1H), 5.25–5.32 (m, 4H), 2.85 (m, 1H), 2.75 (m, 1H), 2.30 (m, 1H), 2.15–2.20 (m, 2H), 2.00 (m, 2H), 1.75–1.85 (m, 2H), 1.38–1.40 (m, 1H), 1.29 (s, 3H), 1.15 (m, 1H), 0.92 (s, 3H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): 177.90, 156.15, 149.87, 145.10, 143.54, 137.25, 130.00, 129.82, 129.79, 129.00, 128.87, 128.21, 128.11, 122.23, 120.89, 120.61, 112.19, 112.01, 62.00, 57.05, 52.82, 44.13, 39.02, 38.75, 37.51, 31.00, 28.07, 23.03, 20.77, 19.98 ppm. HRMS calcd. for $C_{35}H_{36}O_3N_6$, 588.7066; found 588.2843.

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REFERENCES

1. Pirali, T.; Gatti, S.; Brisco, R. D.; Tacchi, S.; Zaninetti, R.; Brunelli, E.; Massarotti, A.; Sorba, G.; Canonico, P. L.; Moro, L.; Benazzani, A. A.; Tron, G. C.; Billington, R. A. Estrogenic analogues synthesiszed by click chemistry. *Chem. Med. Chem.* **2007**, *2*(4), 437–440.
2. Chen, X.-M.; Li, Z.-J., Ren, Z.-X.; Huang, Z.-T. Synthesis of glucosylated 1,2,3-triazole derivatives. *Carbohydrate Res.* **1999**, *315*(3–4), 262–267.

3. Lutz, J.-F.; Zarafshani, Z. Efficient construction of therapeutics, bioconjugates, biomaterials, and bioactive surfaces using azide-alkyne "click" chemistry. *Adv. Drug Delivery Rev.* **2008**, *60*(9), 958–970.
4. Huisgen, R. Cenetary lecture—1,3-Dipolar cycloadditions. *Proc. Chem. Soc.* **1961**, 357.
5. Huisgen, R. 1,3-Dipolar cycloadditions: Past and future. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598.
6. Huisgen, R. Kinetics and mechanism of 1,3-dipolar cycloadditions. *Anqew., Chem. Int. Ed. Eng.* **1963**, *2*, 633–645.
7. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.
8. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click chemistry: Diverse chemical function from a few good reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
9. Tornoe, C. W.; Christensen, C.; Mendal, M. Peptidotriazoles on solid phase: [1,2,3]-Triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.* **2002**, *67*, 3057–3064.
10. Jones, G. O.; Houk, K. N. Predictions of substituent effects in thermal azide 1,3-dipolar cycloadditions: Implications for dynamic combinatorial (reversible) and click (irreversible) chemistry. *J. Org. Chem.* **2008**, *73*, 1333–1342.
11. Oh, K.; Guan, Z. A convergent synthesis of new β-turn mimics by click chemistry. *Chem. Commun.* **2006**, 3069–3071.
12. Droumaguet, B. Le; Velonia, K. Click chemistry: A powerful tool to create polymer-based macromolecular chimeras. *Macromol. Rapid Commun.* **2008**, *29*, 1073–1089.
13. Parish, E. J.; Miles, D. H. Investigation of the antitumor activity of podocarpic acid derivatives. *J. Pharm. Sci.* **1984**, *73*(5), 694–696.
14. Staschke, K. A.; Hatch, S. D.; Tang, J. C.; Hornback, W. J.; Munroe, J. E.; Colacino, J. M.; Muesing, M. A. Inhibition of influenza virus hemagglutinin-mediated membrane fusion by a compound related to podocarpic acid. *Virology* **1998**, *248*, 264–274.
15. Liu, W.; Chen, S.; Dropinski, J.; Colwell, L.; Robins, M.; Szymonifka, M.; Hayes, N.; Sharma, N.; MacNaul, K.; Hernandez, M.; Burton, C.; Sparrow, C. P.; Menke, J. G.; Singh, S. B. Design, synthesis, and structure–activity relationship of podocarpic acid amides as liver X receptor agonists for potential treatment of atherosclerosis. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4574–4578.
16. Sherwood, I. R.; Short, W. F. Podocarpic acid. *J. Chem. Soc.* **1938**, 1006–1012.
17. Ojima, I. Use of fluorine in the medicinal chemistry and chemical biology of bioactive compounds: A case study on fluorinated Taxan anticancer agents. *Chem. Bio. Chem.* **2004**, *5*, 628–635.
18. Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. Benzyne click chemistry: Synthesis of benzotriazoles from benzynes and azides. *Org. Lett.* **2008**, *10*, 2409–2412.
19. Ciampi, S.; Bocking, T.; Kilian, K. A.; James, M.; Harper, J. B.; Gooding, J. J. Functionalization of acetylene-terminated monolayers on Si(100) surfaces: A click chemistry approach. *Langmuir* **2007**, *23*, 9320–9329.
20. Pal, B.; Jaisankar, P.; Giri, V. S. Versatile reagent for reduction of azides to amines. *Synth. Commun.* **2004**, *34*, 1317.
21. Lindsay, R. O.; Allen, C. F. H. Phenyl azide. *Org. Syn. Coll.* **1955**, *3*, 710–711.
22. Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. Copper-catalyzed synthesis of aryl azides and 1-aryl-1,2,3-triazoles from boronic acids. *Tetrahedron Lett.* **2007**, *48*, 3525–3529.