Total Synthesis of Asparenydiol by Two Sonogashira Cross-Coupling Reactions Promoted by Supported Pd and Cu Catalysts

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Abstract Asparenydiol, which is an important natural compound with potential pharmacological activities, was synthesized through two Sonogashira cross-coupling reactions catalyzed by supported Pd and Cu catalysts and by a Mitsunobu etherification. The optimization of the Sonogashira couplings allowed the use of catalysts supported on different matrices with good results in terms of catalytic efficiency and yields.

Key words Asparenydiol, Sonogashira cross-coupling, Mitsunobu etherification, total synthesis, solid-supported palladium catalyst

Asparenydiol is an acetylenic compound that was isolated for the first time from *Asparagus officinalis* by Terada and co-workers in 1995,1 and afterwards found in *Asparagus cochinchinensis*2 and also in *Asparagus racemosus*.3 These plants have long been known for their use in ethnomedicine. Notably, *A. cochinchinensis* was reported to be used for treating fever, cough, kidney diseases, and benign breast tumors in China, and *A. racemosus* was used to treat gastric ulcers, diabetes and to improve immunity in India. Asparenydiol was found to exhibit moderate bioactivity on some tumoral cell lines (KB, Col-2, LNCaP, Lu-1 and HUVEC), with IC50 values between 4 and 20 μg/mL.4 Despite the potential pharmacological applications, the difficult and low-yielding process of extraction (2 mg of Asparenydiol from 5 kg of roots) limits an extensive screening of its properties. Moreover, to our knowledge, there are still no examples of synthetic pathways that are suitable for large-scale production of Asparenydiol.

After careful retrosynthetic analysis, we envisioned the possibility of formally applying three main disconnections, as shown in Scheme 1, which could allow the use of commercially available building blocks or easy to synthesize intermediates. Disconnection A could synthetically correspond to a formal etherification, while B and C disconnections suggest the possibility of building the Asparenydiol core around its triple bond, using a formal double ethynyl donor synthon. More specifically, in Scheme 2, the chosen building blocks are shown based on the disconnections proposed. For disconnection A, we planned an etherification between a phenol and an allylic alcohol through a Mitsunobu reaction, which allows neutral conditions and it is compatible with sensitive allylic substrates that are at risk of regioisomerization.5,6

Scheme 1 General retrosynthetic analysis for Asparenydiol
To avoid oligomer formation and homoetherification, the initial protection of one of the hydroxyl groups of hydroquinone and subsequent intermediates is necessary. Among the most common protecting groups for phenol protection, we chose to use \textit{tert}-butyldimethylsilyl ether, for its chemical stability and the orthogonality compared to trimethylsilyl ether, necessary for the synthesis of intermediate compound 3. We also considered the possibility of using a two-step Williamson etherification, in which the allylic alcohol is previously transformed into the corresponding chloride, bromide, mesylate or tosylate, followed by nucleophilic substitution of the phenol under basic conditions. Preliminary results, however, suggested that, in this case, the Mitsunobu reaction is more reliable. For disconnection B and C, we envisioned the use of the Sonogashira reaction,\(^7\) that, in its original version, promotes the alkylation of aryl or alkenyl halides, co-catalyzed by Pd and Cu(I), in the presence of a base.\(^8\)

Today, the Sonogashira reaction is commonly performed under homogeneous catalysis conditions,\(^9\) it does not require preformed organometallic acceptor species in stoichiometric amounts, as in the case of Negishi cross-coupling reactions,\(^10\) which is also used for the synthesis of natural compounds.\(^11\) For larger-scale and greener applications of the Sonogashira reaction, several methods have been developed, including copper-free reactions, solvent-less reactions, and, notably, Pd-based supported catalysts such as Pd/C.\(^12\) Depending on the order of disconnection between B and C, the structure of the intermediates could change (12 or 4), even though the building blocks to obtain 8 are essentially the same; 4-\textit{tert}-butyldimethylsilyl-1-iodobenzene (2), \((E)-3\text{-bromoacrylate (7)}\) and trimethylsilylacetylene (13). Nevertheless, there is only one example of the synthesis of 12, through a cross-coupling reaction in Pd/Cu homogeneous catalysis, reported by Garrais et al. in 2009,\(^13\) whereas we had extensive experience in the preparation of intermediate 4.\(^14\) In particular, disconnection B would correspond to a Sonogashira reaction between terminal alkyne 4 and an \((E)-1\text{-halo-3-hydroxy-1-propene to yield 8, with both nascent hydroxy groups protected. Even though there are several examples of the latter substrate being used successfully in homogeneous catalysis at room temperature,}\(^15–18\) there are none in heterogeneous catalysis, probably due to the instability at higher temperatures, or to the possibility to form oxidative addition complexes with palladium. Therefore, we opted to use methyl \((E)-3\text{-bromoacrylate (7)},\) which can be easily reduced afterwards with DIBALH at low temperature without regio-isomerization, as reported by several groups.\(^19,13\) For example, in 2000, Takeuchi et al. proposed a stereoselective synthesis of 2-alken-4-ynoates through Sonogashira reaction between arylalkynes and vinyl iodides,\(^20\) which looked promising for our purpose. We
also considered alternatives such as an oxidative alkylation catalyzed by palladium, as proposed by Nishimura et al., and a cross-coupling between \( (E)-3\)-iodoacrylate and phenylacetylene promoted only by Cu(I), proposed by Bates et al. However, for these two methods, the catalyst loadings and the temperatures were too high for our system. Interestingly, Ranu et al. studied the reaction between \( (E)\)-1,2-diiodostyrenes and acrylates catalyzed by palladium nanoparticles in homogeneous catalysis and, afterwards, they minimized the palladium contamination by using palladium supported on hydroxyapatite, and using a low catalyst loading (4.5 × 10^{-3} mol% of Pd). Unfortunately, this method is not suitable in our case, because reaction conditions require potassium carbonate and high temperature, which could potentially lead to deprotection of the phenol needed in the next step of etherification; furthermore, \( (E)\)-1,2-diiodostyrenes are not directly available.

The first step of the Asparenydiol synthesis was the protection of 4-iodo-phenol with TBDMSO, using a slightly modified version of the reported procedure, giving compound 2 in quantitative yield. For the first Sonogashira cross-coupling, we tested a range of commercially available supported palladium catalysts [Pd EnCat™40, FibreCat 1007, PdCl\(_2\)(PPh\(_3\))\(_2\)/PS, and PdCl\(_2\)(PPh\(_3\))\(_2\)/PS] and two polyvinylpyridine (PVPy)-supported catalysts recently developed by our research group (Cu/PVPy and Pd-Cu/PVPy). The ability of the PVPy resin to promote M–H-type alkylations, ensuring also very low metal leaching, was previously reported.

The reaction conditions were initially optimized using Pd EnCat™40 as a catalyst (Table 1), because this was already successfully tested for the synthesis of some natural compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PdEnCat™40 (Pd mol%)</th>
<th>CuI (Cu mol%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>1</td>
<td>-</td>
<td>95</td>
<td>3.5</td>
<td>96</td>
<td>28</td>
</tr>
<tr>
<td>2*</td>
<td>0.5</td>
<td>1</td>
<td>90</td>
<td>1</td>
<td>73</td>
<td>-</td>
</tr>
<tr>
<td>3*</td>
<td>3</td>
<td>84</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>4*</td>
<td>5</td>
<td>95</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>5*</td>
<td>0.5</td>
<td>1</td>
<td>70</td>
<td>2.5</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>6*</td>
<td>0.5</td>
<td>0.25</td>
<td>90</td>
<td>1</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td>7*</td>
<td>5</td>
<td>88</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>8*</td>
<td>9</td>
<td>&gt;99</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9*</td>
<td>0.5</td>
<td>0.25</td>
<td>90</td>
<td>1</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>10‡</td>
<td>8</td>
<td>&gt;99</td>
<td>51</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>11†</td>
<td>0.5</td>
<td>0.25</td>
<td>90</td>
<td>1</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>12‡</td>
<td>16</td>
<td>25</td>
<td>-</td>
<td></td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

* Reaction conditions: 2 (2.0 mmol), 13 (1.5 equiv), pyrrolidine (3.0 equiv), Pd EnCat™40, Cu, argon.
‡ Reaction conditions: 2 (2.0 mmol), 13 (1.5 equiv), pyrrolidine (2.0 equiv), DMF (3 mL), Pd EnCat™40, Cu, argon.
† Apparent conversion based on the disappearance of precursor 2, calculated by GC analysis as percentage ratio between the sum of the areas of the product and sub-products and whole addition of the areas.

The reaction was performed in the absence of copper (Table 1, entry 1), however, although the starting material disappeared after 3.5 h, many different side-products were formed, and a low yield of the desired product was obtained. The reaction was therefore tested under more classical Sonogashira conditions with a 2:1 ratio between palladium and copper, and with reduced catalyst loading (0.5 mol% of Pd; entries 2–4); also in this case, after 5 h, many collateral reactions took place. In an attempt to minimize the formation of by-products, the reaction was performed at 70 °C (entry 5), but a low conversion was obtained, showing that the supported catalysis lost efficiency below certain temperatures. A decrease of the amount of copper, instead, led to the formation of lower amounts of by-products, albeit with longer reaction time (9 h), and allowed the isolation of the product with 40% yield (entries 6–8). The reaction was also tested in the presence of two different solvents, DMF and toluene (entries 9–12), but irrespective of the polarity of the solvent, lower conversions were obtained. These results suggest that the collateral reactions are dependent on the amount of copper iodide that is soluble in pyrrolidine. Therefore, as the homogeneous catalysis of copper could be more efficient than the supported palladium catalysis, we tested a previously described supported copper species Cu/PVPy. As detected by X-ray absorption fine structure spectroscopy and high-resolution transmission electron microscopy, this catalyst contains Cu(I) nanoparticles (mean diameter of 3.3 nm) in form of copper oxide (CuO). Reaction rate and isolated yield (53%) significantly increased in this case (Table 2, entries 1 and 2), although it was still not satisfactory.

Consequently, other palladium supported catalysts were tested under the latter conditions, with the best results being obtained using PdCl\(_2\)(PPh\(_3\))\(_2\)/PS with a yield of 70% after 1.5 h (Table 2, entry 7). An improvement of the isolated yield (81%) was obtained by increasing the reaction time to 3.5 h, even when the amount of catalyst loading was reduced to 0.25 mol% of Pd, as shown in Table 2, entry 12. For a direct comparison of efficiency between the supported co-catalyst and its homogeneous version, the reaction using PdCl\(_2\)(PPh\(_3\))\(_2\) and Cu was tested (entry 13). As expected, the reaction ran with homogeneous catalysis led to better results in terms of yield (93%), temperature (20 °C), and reaction time. However, the opportunity to carry out cross-coupling reactions with supported catalysis can offer several advantages with respect to the development of sustainable...
cross-coupling, the reaction was previously tested on phenylacetylene (14), to establish optimal reaction conditions. However, regardless of the catalyst used, when pyrrolidine was added as a base, an exothermic reaction was observed, forming (E)-methyl 3-(pyrrolin-1-yl)acrylate, as the major product. Therefore, it was necessary to test several sterically hindered amines, as bases, using PdCl₂(PPh₃)₂/PS as a catalyst, under the same conditions described above. N-Methyl- and N-butyl-pyrrolidine did not bring any improvement, whereas DABCO (in 4:1 DMF/H₂O solution) and triethylamine lead mainly to the homodimerization of phenylacetylene. The best results were obtained using 2,2,6,6-tetramethylpiperidine as a base, as shown in Table 3. The use of Pd-Cu/PVPy was particularly effective, with a yield of 62% in only 3.5 h; therefore, these conditions were used to optimize the next step.

As shown in Table 4, Pd-Cu/PVPy was a good catalyst for the synthesis of 8, even with a loading of 0.5 mol% in Pd and 0.25 mol% in Cu (entries 1 and 2). These results were unfortunately not comparable with the excellent yield obtained with homogeneous catalysis (entry 5) and the choice of supported catalyst is a compromise with the need to develop greener methods.

It is worth noting that, in the first Sonogashira step, the use of the two separated supported catalysts, PdCl₂(PPh₃)₂/PS and Cu/PVPy (Table 2, entry 11), was highly effective, whereas for the synthesis of 8 it was not reactive enough (Table 4, entry 4). For the second Sonogashira step, it was necessary to use the supported co-catalyst Pd-Cu/PVPy (Table 4, entries 1 and 2). Rationalization of this different behavior is not obvious but can be ascribed to the different reactivity of the two systems, rather than to instability of reagents or product, because, in both cases, the corresponding halides could be recovered. Pd-Cu/PVPy is not a simple mixture of segregated Pd and Cu nanoparticles dispersed on PVPy. In this catalyst, an oxidized Cu(II) phase is

Methyl (E)-3-bromoacrylate (7), which was necessary for the next cross-coupling reaction, was prepared through a known two-step synthesis. For the second Sonogashira

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**Table 2** Screening of Pd Supported Catalysts under the Optimized Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>‘Pd’ (mol% Pd)</th>
<th>‘Cu’ (mol% Cu)</th>
<th>t (h)</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>PdEnCat™40 (0.5)</td>
<td>Cu/PVPy (0.25)</td>
<td>1</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>2*</td>
<td>Pd FibreCat® 1007 (0.5)</td>
<td>Cu/PVPy (0.25)</td>
<td>2</td>
<td>&gt;99</td>
<td>53</td>
</tr>
<tr>
<td>3*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.25)</td>
<td>1</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>4*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.25)</td>
<td>2</td>
<td>80</td>
<td>–</td>
</tr>
<tr>
<td>5*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.25)</td>
<td>4</td>
<td>95</td>
<td>–</td>
</tr>
<tr>
<td>6*</td>
<td>PdCl₂(PPh₃)₂/PS (0.5)</td>
<td>Cu/PVPy (0.25)</td>
<td>1</td>
<td>1.5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7*</td>
<td>Pd-Cu/PVPy (0.5–0.25)</td>
<td>Cu/PVPy (0.25)</td>
<td>1</td>
<td>51</td>
<td>70</td>
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<tr>
<td>8*</td>
<td>Pd-Cu/PVPy (0.5–0.25)</td>
<td>Cu/PVPy (0.25)</td>
<td>5</td>
<td>29</td>
<td>67</td>
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<tr>
<td>9*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.125)</td>
<td>1</td>
<td>62</td>
<td>40</td>
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<tr>
<td>10*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.125)</td>
<td>2</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td>11*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.125)</td>
<td>3.5</td>
<td>&gt;99</td>
<td>81</td>
</tr>
<tr>
<td>12*</td>
<td>PdCl₂(PPh₃)₂ (0.25)</td>
<td>Cu/PVPy (0.125)</td>
<td>2</td>
<td>93</td>
<td>93</td>
</tr>
</tbody>
</table>

* Reaction conditions: 2 (2.0 mmol), 13 (1.5 equiv), pyrrolidine (3 equiv), Pd, ‘Cu’, 90 °C, argon.
** Reaction conditions: 2 (2.0 mmol), 13 (1.5 equiv), pyrrolidine (3 equiv), PdCl₂(PPh₃)₂, Cu/PVPy, 90 °C, 20 °C, argon.
† Apparent conversion based on the disappearance of precursor 2, calculated by GC analysis as percentage ratio between the sum of the areas of the product and sub-products and whole addition of the areas.
‡ Isolated yield of 3 after flash chromatography.

**Table 3** Cross-Coupling Reaction Optimization with 14 and 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>‘Pd’ (mol% Pd)</th>
<th>‘Cu’ (mol% Cu)</th>
<th>t (h)</th>
<th>2,2,6,6-tetramethylpiperidine (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PPh₃)₂ (2)</td>
<td>CuI (4)</td>
<td>22</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(PPh₃)₂ (2)</td>
<td>CuI (4)</td>
<td>22</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Pd-Cu/PVPy (2–1)</td>
<td>CuI (4)</td>
<td>3.5</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>Pd-Cu/PVPy (0.5–0.25)</td>
<td>CuI (4)</td>
<td>3.5</td>
<td>6</td>
<td>40</td>
</tr>
</tbody>
</table>

* Reaction conditions: 14 (1.0 mmol), 7 (1.5 equiv), base, ‘Pd’, ‘Cu’, 85 °C, argon.
‡ Isolated yield of 20 after flash chromatography.

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Scheme 3 Selective deprotection of 3

Screening of Pd Supported Catalysts under the Optimized Conditions

For the selective deprotection of the trimethylsilyl acetylene moiety, a reported method using silver nitrate (10 mol%) was applied, as shown in Scheme 3, with a yield of 97%.

Methyl (E)-3-bromoacrylate (7), which was necessary for the next cross-coupling reaction, was prepared through a known two-step synthesis. For the second Sonogashira

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present, forming thin and incomplete shells around the Pd-rich cores. The specific interaction between Pd and Cu at the nanoparticle surface was demonstrated to be responsible of the observed marked increase in catalytic efficiency in Sonogashira-like reactions. Afterwards, the obtained ester was reduced to the corresponding allylic alcohol using DIBALH as reducing agent, at low temperature, with an isolated yield of 90% (Scheme 4). Although alkynes can undergo hydroalumination reactions,20,33,34 maintaining a low temperature, especially during the addition of DIBALH, enables selective reduction of the ester moiety. Moreover, when only three equivalents of DIBALH were used, the reaction was compatible with the presence of the TBDMS protecting group; application of an excess of the reducing agent led to partial deprotection of the phenol.

For the next step, the monosilylation of hydroquinone was achieved using a slightly modified reported method,35,36 with a yield of 10 of 74% (see the experimental section). Mitsunobu etherification between 9 and 10 was performed under classical conditions,37,38 using diethyl azodi-

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**Table 4** Cross-Coupling Reaction Optimization with 4 and 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>‘Pd’ (mol% Pd)</th>
<th>‘Cu’ (mol% Cu)</th>
<th>t (h)</th>
<th>2,2,6,6-tetramethylpiperidine (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Pd-Cu/PVPy (2–1)</td>
<td></td>
<td>3.5</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>2*</td>
<td>Pd-Cu/PVPy (0.5–0.25)</td>
<td></td>
<td>3.5</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>3*</td>
<td>PdCl2(PPh3)2/PS (2)</td>
<td></td>
<td>48</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>4†</td>
<td>PdCl2(PPh3)2/PS (0.5) Cu/PVPy (0.25)</td>
<td></td>
<td>7</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>5†</td>
<td>PdCl2(PPh3)2 (0.5) Cu (0.25)</td>
<td></td>
<td>4</td>
<td>Et3N (6 equiv)</td>
<td>92</td>
</tr>
</tbody>
</table>

* Reaction conditions: 4 (2.0 mmol), 7 (1.5 equiv), base, ‘Pd’, ‘Cu’, 85 °C, argon.
† Reaction temperature was increased to 95 °C after 2 h.
‡ Reaction temperature was increased to 100 °C after 3 h. After 7 h, the reaction reached only 10% of apparent conversion. The product was not isolated.
§ Isolated yield of 8 after flash chromatography.
carboxylate (DEAD) and PPh₃, as shown in Scheme 5. The reaction was monitored by TLC, and reached completion after 6 h. The crude material was purified by flash chromatography and the intermediate 11 was isolated with a yield of 84%. The final step involved treatment of 11 with tetra-n-butylammonium fluoride (TBAF), to deprotect the two hydroxyl moieties. Asparenydiol (15) was obtained and easily purified by flash chromatography and isolated in quantitative yield.

In conclusion, the total synthesis of Asparenydiol (15) was accomplished with an overall yield of 30%, starting from 4-iodophenol, through two Sonogashira cross-coupling reactions catalyzed by supported catalysts and a Mitsunobu etherification (Scheme 6). Therefore, this work will make possible an extensive screening of its pharmacological activities. Moreover, it was an interesting application of our supported Pd and Cu catalysts, which allowed, in this case, higher conversions and yield, with respect to most common commercially available supported catalysts.

When not otherwise specified, all reactions were performed under argon atmosphere; solvents and reagents were handled using hypodermic syringes conveniently stored in a desiccator. Commercial reagents were directly used without further purification. Dichloromethane and triethylamine were dried over calcium hydride and distilled, whereas hexane and toluene were dried respectively over LiAlH₄ and sodium and then distilled. When specified, solvents were purged by argon bubbling. Catalysts, PdCl₂(PPh₃)₂ (CAS: 13965-03-2), PdCl₂(PPh₃)₂/PS (Pd: 0.25 mol% Pd), FibreCat™ 1007 (Pd: 0.72 mmol/g), and Pd En Cat™ 40 (Pd: 0.42 mmol/g) were purchased from Merck–Sigma–Aldrich. 4-Iodophenol (CAS: 540-38-5), tert-butyldimethylsilylchloride (TBDMSCl; CAS: 18162-48-6), pyrrolidine (CAS: 123-75-1), AgNO₃ (CAS: 7761-88-8), pyridine (CAS: 110-86-1), propionic acid (CAS: 471-25-0), diethyl 1,2-hydrazinedicarboxylate (ca. 40% in toluene; CAS: 1972-28-7), tert-butyldimethylsilylchloride (TBDMSCl), or tetrabutylammonium fluoride (1 M in THF; CAS: 429-41-4) were purchased by Merck–Sigma–Aldrich and used without further purification. Reactions were followed by GC and GC/MS on small reaction samples. Purification of the crude reaction mixtures were performed by flash chromatography using Silica Gel 60 (40–63 μm, Merck–Sigma–Aldrich), or by fractional distillation. TLC silica gel plates were purchased from Merck (Merck 60 F254). Gas chromatography (GC) analyses were performed with a Dani GC 1000 with PTV injector, FID detector and two bonded FSOT columns (Alltech, 30 m 0.25 mm i.d., 0.25 mm): AT-5 (column 1) and AT-35 (column 2). Gas chromatography mass spectrometry (GC/MS) analyses were performed with an Agilent apparatus: mass selective detector 5973 Network, 6890 N Network GC system and HP-5MS bonded column (30 m 0.25 mm i.d., 0.25 mm). NMR spectra were recorded with Bruker 400 MHz, Bruker Avance II DRX 400, or Varian INOVA 600 MHz.

Scheme 6  Optimized total synthesis of Asparenydiol
tert-Butyldimethylsilyloxy-4-iodobenzene (2)

In a 250 ml two-necked, round-bottom flask, equipped with a reflux condenser, under an inert atmosphere, 4-iodophenol (1; 6.6 g, 30.0 mmol) was dissolved in anhydrous CH₂Cl₂ (40 mL). Freshly distilled triethylamine (5.00 mL, 36.0 mmol) and TBDMSCl (5.00 g, 33.0 mmol) were added to the solution, and the mixture was stirred at reflux temperature for 22 h. The reaction was quenched with HCl 2 M and the residue was poured on a saturated solution of NaHCO₃ (50 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was obtained as a yellowish oil with 57% yield (0.360 g).

1H NMR (CDCl₃, 400 MHz): δ = 7.5 (dd, J = 6.8, 2.1 Hz, 2 H), 6.6 (dd, J = 6.6, 2.1, 2 Hz), 0.9 (s, 9 H), 0.18 (s, 6 H).

M.S (EI): m/z (%) = 335 (8), 334 [M⁺] (44), 279 (27), 278 (34), 277 (100), 151 (80), 150 (49), 149 (60), 135 (34).

Methyl (E)-3-Bromoacylate (7)

In a 500 mL three-necked, round-bottom flask, equipped with a reflux condenser and mechanical stirrer, under an inert atmosphere, Pd and Cu catalysts were added in the amounts indicated in Table 2. Pyrrolidine (300 or 500 µL, 4.00 or 6.00 mmol), 2 (0.668 g, 2.00 mmol) and trimethylsilylacetene (13) (415 µL, 3.00 mmol) were added to the solution. The mixture was stirred at 90 °C for 3.5 h (Table 1, entry 12), then the reaction was quenched with a saturated solution of NH₄Cl. The mixture was extracted with Et₂O (3 × 50 mL) and the combined organic phases were dried over Na₂SO₄ filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pure hexane) and the product was isolated as a colorless oil with a yield of 97% (2.25 g) (purity > 99% by GC). Spectroscopic data were consistent with reported values.¹⁴

1H NMR (CDCl₃, 400 MHz): δ = 7.4 (d, J = 8.6 Hz, 2 H), 6.8 (d, J = 8.7 Hz, 2 H), 3.0 (s, 1 H), 1.0 (s, 9 H), 0.2 (s, 6 H).

13C NMR (CDCl₃, 100 MHz): δ = 156.3, 133.6, 127.1, 120.2, 114.8, 83.7, 75.9, 25.6, 18.2, –4.4.

M.S (EI): m/z (%) = 232 [M⁺] (19), 177 (6), 176 (24), 175 (100), 159 (3), 145 (5), 115 (4).

Methyl (E)-3-Bromoacrylate (7)

In a 500 mL three-necked, round-bottom flask, equipped with a reflux condenser and mechanical stirrer, under an inert atmosphere, were introduced propionic acid (25 g, 357 mmol) and HBr (48% solution, 150 mL). The resulting mixture was stirred at 100 °C for 2 h. The reaction flask was cooled to r.t. and, subsequently, cooled in an ice bath to induce crystallization of (E)-3-bromoacrylic acid. The precipitate was filtered, washed with cool water and dried. The product was obtained as a crystalline white solid with a yield of 74% (40.3 g) and identified as (E)-3-bromoacrylic acid. Spectroscopic data were consistent with reported values.³²

M.p. = 117–118 °C (lit.¹² 117.5–118.5 °C).

1H NMR (CDCl₃, 600 MHz): δ = 11.0 (s, 1 H), 7.7 (d, J = 14.3 Hz, 1 H), 6.5 (d, J = 143 Hz, 1 H).

M.S (EI): m/z (%) = 152 (98), 150 (100) [M⁺], 135 (57), 133 (58), 124 (14), 107 (35), 105 (36), 71 (76), 45 (28).

In a 500 mL three-necked, round-bottom flask, equipped with a reflux condenser and mechanical stirrer, under an inert atmosphere, (E)-3-bromoacrylic acid (19.2 g, 128 mmol) was dissolved in anhydrous MeOH (200 mL) and 15 drops of concentrated H₂SO₄ were added. The reaction mixture was stirred at reflux temperature for 24 h. The solvent was removed through distillation under reduced pressure and the residue was poured on a saturated solution of NaHCO₃ (50 mL). The mixture was extracted with Et₂O (3 × 50 mL) and the combined organic phases were dried over Na₂SO₄ filtered and concentrated under reduced pressure. Spectroscopic data were consistent with reported values.

B.p. = 72–75 °C, 70 mbar (lit.²⁰ 69 °C, 55 mbar).

1H NMR (CDCl₃, 600 MHz): δ = 7.6 (d, J = 12.0 Hz, 1 H), 6.5 (d, J = 12.0 Hz, 1 H), 3.7 (s, 3 H).

M.S (EI): m/z (%) = 166 (24), 164 (24), 135 (99), 133 (100), 107 (28), 105 (28), 85 (45), 54 (5), 53 (5).

Methyl 5-(E)-4-tert-Butyldimethylsilyloxy-phenyl-pent-2-en-1-ate (8)

In a 10 mL Schlenk flask, equipped with a two-neck connection, with a reflux condenser, under inert atmosphere, Pd and Cu catalysts were added in the amounts indicated in Table 4. 2,2,6,6-Tetramethylpiperidine (1 or 2 mL, 6.00 or 12.00 mmol), 4 (0.696 g, 3.00 mmol) and 7 (0.330 g, 2.00 mmol) were added to the solution. In the best condition found (Table 4, entry 2) the mixture was stirred at 85 °C for 3.5 h and the reaction was quenched with a saturated solution of NH₄Cl. The mixture was extracted with Et₂O (3 × 15 mL) and the combined organic phases were dried over Na₂SO₄ filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hex/EtOAc, 95:5). The product was obtained as a yellowish oil with 57% yield (0.360 g).
5-((E)-4-tert-Butyldimethylsilyloxy-phenyl-pent-2-en-4-yn-1-ol (9)

In a 250 mL two-necked, round-bottom flask, under an inert atmosphere, 8 (3.16 g, 10.0 mmol) was dissolved in anhydrous CH₂Cl₂ (65 mL). The solution was cooled to –60 °C and DIBALH (1 M in hexane, 30 mL) was slowly dropped into the solution. The mixture was stirred at 0 °C for 1.5 h and the temperature was allowed to warm up to –20 °C. The reaction was quenched, at low temperature, by slowly dropping in MeOH (20 mL), followed by HCl (1 M 20 mL) and a saturated solution of Rochelle salt (50 mL). The resulting mixture was stirred for 1.5 h and the timelapse was achieved to allow for saturated solution of NaCl (50 mL). The mixture was extracted with CH₂Cl₂ (3 × 30 mL) and the combined organic phases were washed with Rochelle salt (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Hex/EtOAc, 1:1) and the product 9 was isolated as a yellowish oil with a yield of 90% (2.59 g) (purity > 99% by GC). Spectroscopic data were consistent with reported data. 36

1H NMR (CDCl₃, 400 MHz): δ = 7.3 (d, J = 8.5 Hz, 2 H), 6.7 (m, 2 H), 6.3 (dt, J = 15.8, 5.3 Hz, 1 H), 5.9 (m, 1 H), 4.2 (m, 2 H), 0.9 (s, 9 H), 0.2 (s, 6 H). MS (EI): m/z (%) = 289 (11), 288 (50) [M]+, 233 (7), 232 (23), 231 (100), 229 (8), 128 (8), 75 (16), 73 (8). Anal. Calcd. for C₁₈H₂₄N₃Si: C 68.32, H 7.64. Found: C 68.27, H 7.61.

Asparenedyol (15)

A solution of 11 was transferred to a 25 mL two-necked, round-bottom flask and TBAF (1 M in THF, 11 mL, 2.5 equiv) was added. The mixture was stirred at r.t. for 2.5 h, then the reaction was quenched with a saturated solution of NH₄Cl (20 mL) and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic phases were concentrated under reduced pressure, dissolved in acetone, filtered, and then the residue was purified by flash chromatography on silica gel (CHCl₃/acetone, 1:1) and the product 15 was isolated as a white solid with a yield of 84% (0.448 g). Spectroscopic data were consistent with reported data. 19

1H NMR (CDCl₃, 400 MHz): δ = 7.3 (d, J = 8.5 Hz, 2 H), 6.7 (m, 2 H), 6.3 (dt, J = 15.9, 5.3 Hz, 1 H), 6.0 (d, J = 15.9, 1.6 Hz, 2 H), 1.0 (s, 18 H), 0.22 (s, 6 H), 0.19 (s, 6 H). MS (TOF MS ES+): [M + Na]+ calcd for C₂₉H₄₂O₃Si₂: 517.2565; found: 517.2553. Analytical HPLC purity 91%.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690852.

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