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A Concise Synthesis of Paucifloral F and Related Indanone Analogues via Palladium-Catalyzed α-Arylation

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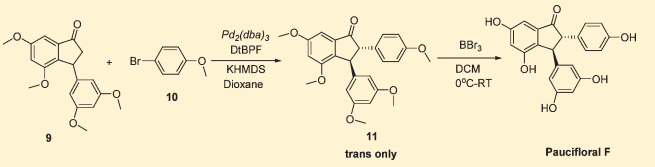
Supporting Information

ABSTRACT: A concise approach to synthesize paucifloral F was developed via a stereoselective palladium-catalyzed α-arylation reaction. The approach has also been applied in the synthesis of indanone analogues of Paucifloral F.



Indanone and indane are privileged structures[1] in drug discovery research, commonly seen in many pharmaceutical compounds exhibiting a variety of interesting biologic activities. For example, indanones and indanes are incorporated in some marketed drugs such as Donepezil and Indinavir. Donepezil (**1**) was discovered as a potent AchE (acetylcholinesterase) inhibitor applied in the treatment of mild to moderate Alzheimer's disease,[2] while Indinavir[3] was identified as an HIV protease inhibitor applied in the treatment of AIDS disease. On the other hand, indanone and indane structures are also commonly found in numerous bioactive natural products.[4] For example, indane compound *Caraphenol B* (**2**) was *isolated* from *Caragna sinica,* which was used in Chinese folk medicine for treating asthenia syndrome and vascular hypertension.[5] Interestingly, potent cytotoxic similar natural indanone products **3** and *Pterosin B* were isolated from marine cyanobacterium[6] and *pteris ensiformis* burm[7] independently (Figure 1). Our ongoing medicinal chemistry research project recently led us to pursue screening and synthesis of some multifunctionalized indanone compounds. In this context, we became interested in paucifloral F (**5**).

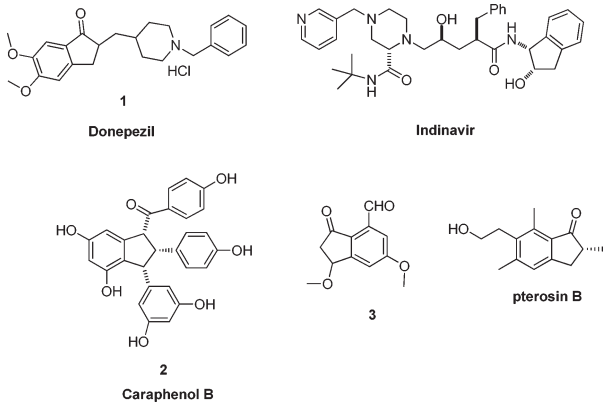


Figure 1

Paucifloral F is a polyphenolic natural product belonging to a larger family of compounds believed to arise from the dimerization of resveratrol[8] (Figure 2). Resveratrol (**4**) is the simplest and the most widely distributed polyphenolic products exhibiting a variety of biologic activities.[9] Some of those activities potentially provide health benefits such as antiaging/life extension[10] and cancer prevention.[11] Despite its promising array of bioactivities, the clinical potential of resveratrol has been barely proved.[12] This is in part due to the poor drug-like properties of resveratrol itself.[13] Therefore, there is increasing interest in its more complex oligomers including paucifloral F and other unnatural analogues. Inspired by the biosynthetic pathway, the Snyder group published their total synthesis of Paucifloral F along with other complicate resveratrol-based natural products via an elegant biomimetic strategy in 2009.[14] Sarpong et al. also reported a total synthesis of paucifloral F using a Larock annulation strategy.[15] However, when we approached the architecture of this natural product, we preferred keeping the indanone moiety as a core structure for the possible structural derivatization in the synthesis. Therefore we were interested in

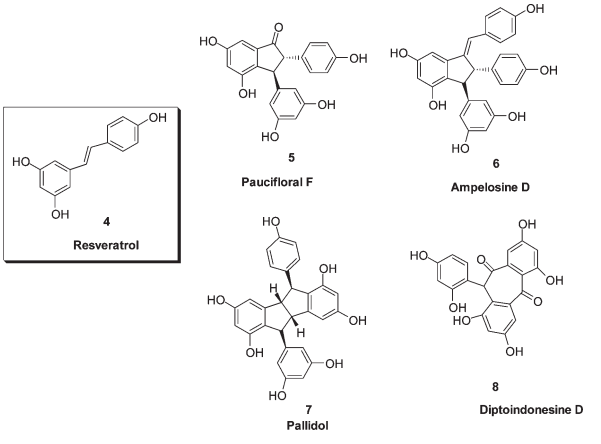


Figure 2

developing a novel and concise synthetic approach toward paucifloral F, which is more amenable for conducting analogue

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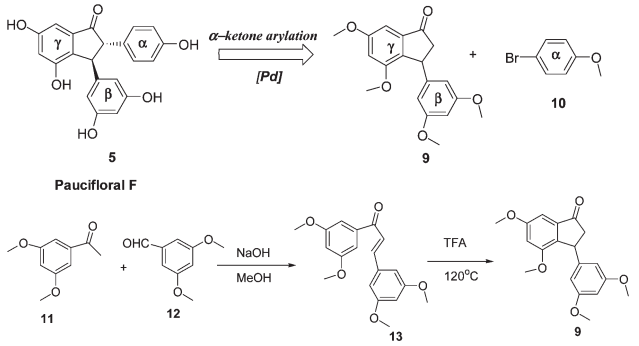
Scheme 1



Scheme 2

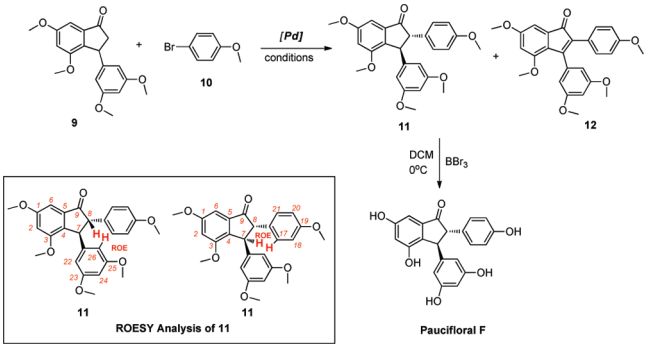


Table 1. Palladium-Catalyzed α Arylation of Indanone 9

entry	cat./ligand[c]	base/solvent	temp (°C)	yield[a] (%)	11/12[b]
1	A/Dppf	NaO^{t}Bu (3 equiv) /dioxane	100	0	
2	B/X-Phos	Cs_2CO_3 (5 equiv) toluene	110	0	
3	C/P(^{t}Bu)$_3$	NaHMDS (3 equiv) toluene	100	>5	
4	C/BINAP	NaO^{t}Bu (3 equiv) dioxane	70	80	1.5/1
5	C/DtBPF	NaO^{t}Bu (3 equiv) dioxane	100	78	1/2
6	C/DtBPF	KHMDS (3 equiv) dioxane	100	81	2/1
7	C/DtBPF	KHMDS (2.2 equiv) dioxane	75	77	5/1

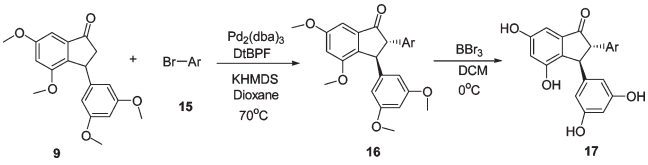
[a] Conversion yields were determined by HPLC. [b] Ratios between **11** and **12** were determined by HPLC. [c] Cat: Pd(dppf)Cl_2 (A); Pd(OAc)$_2$ (B); $Pd_2(dba)_3$ (C).

synthesis. Herein, we account our effort on the synthesis of paucifloral F and its analogue compounds via a stereoselective palladium-catalyzed carbonyl α-arylation strategy.

We envisioned that the construction of paucifloral F could be realized via α-arylation of the corresponding indanone compound (**9**) with 4-bromo anisole (**10**). Such a strategy allows for the convenient introduction of structural diversity at the α position of the indanone core. Thus the key intermediate **9** was assembled via a two-step synthesis. The chalcone intermediate **13** was prepared by an aldol reaction of corresponding 3,5-dimethoxyacetophenone (**11**) with 3,5-dimethoxybenzaldehyde (**12**).[16] The subsequent cyclization of **13** was carried out cleanly in TFA to give indanone **9** in good yield[17] (Scheme 1).

The palladium-catalyzed α-arylation of indanone **9** with 4-bromoanisole **10** was explored extensively under various conditions.[18] The screened coupling conditions and their results are summarized in Table 1. The results show that using catalyst $Pd_2(dba)_3$ with DtBPF as ligand was superior among others providing good yields[19] (entries 5, 6, and 7). However, in most cases, a dehydrogenated byproduct (**12**) was observed. We found that by reducing the amount of base employed and the temperature of the reaction, the production of **12** could be minimized.[20] (entry 7). On the other hand, we also found that under most reaction conditions employed, the arylation reactions proceed with excellent stereoselectivity. Only the trans isomer was observed and isolated from the reaction. The stereochemistry of the product (**11**) was confirmed via 2-D NMR.[21] In the ROESY experiment of **11**, there is an ROE signal between the proton at carbon number 8 and the proton at carbon 26. Another ROE signal between the protons at carbon number 7 and the proton at carbon 17 was also

Scheme 3



observed. (Scheme 2). The bulky 3,5-dimethoxyphenyl group at the β-position of the indanone ring may account for the stereochemical result in α-arylation. We believe excess base in the reaction system led to the second enolation of the indanone coupling product. Quenching the reaction at higher temperature yields predominately the low-energy favored trans product (**11**), as the result of thermodynamic control.[22] Subsequent treatment of compound **11** with BBr_3 in DCM led to global phenol demethylation to give synthetic paucifloral F in moderate yield (49%). The analytical data of our synthetic paucifloral F sample are identical with the corresponding data reported in the literature.[23]

Beyond the total synthesis of paucifloral F, we have also demonstrated the amenability of our route to the synthesis of analogues of paucifloral F. Starting from intermediate **9**, structural diversification at the α position of indanone scaffold can be conveniently realized through the similar arylation reactions. Under similar reaction conditions, some close analogue compounds of paucifloral F were synthesized in good yields (Scheme 3), the results of which are summarized in Table 2. We expect that the close analogues of paucifloral F (**16a**−**e**, **17a**−**e**)[24] are potentially valuable in the biological activity study toward resveratrol-based natural products.

In conclusion, a concise approach to synthesize paucifloral F was developed via a stereoselective palladium-catalyzed α-arylation strategy. Our total synthesis of paucifloral F is highly convergent and practical (four steps in good overall yield from simple commercial available materials). This approach has also been demonstrated to be amenable to synthesis of analogues to conduct structural diversification at the indanone core of the natural product. We expect that this approach can be applied to the synthesis of other indanone-based natural products in the future.

EXPERIMENTAL SECTION

Representative Procedure for Palladium-Catalyzed α-Arylation Reaction

***trans*-3-(3,5-Dimethoxyphenyl)-4,6-dimethoxy-2-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one (11).** To the flask containing DtBPF (0.025 mmol 0.05 equiv) and $Pd_2(dba)_3$ (0.05 mmol,

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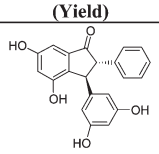
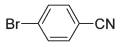
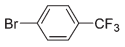
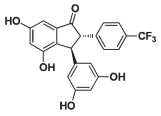
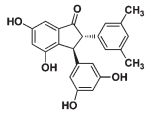
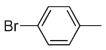
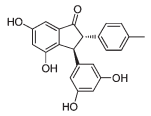
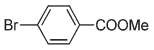
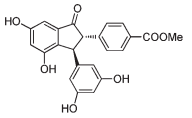
Table 2. The Synthesis of Analogues of Paucifloral F

Entry	15	16 (Yield)	17 (Yield)
1	 **15a**	**16a** (64%)	 (77%)
2	 **15b**	**16b** (33%)	NA[24]
3	 **15c**	**16c** (71%)	 (52%)
4	 **15d**	**16d** (60%)	 (58%)
5	 **15e**	**16e** (72%)	 (41%)
6	 **15f**	**16f** (55%)	 (62%)

0.1 equiv) in dioxane (1 mL) was added KHMDS (1.1 mmol, 2.2 equiv). The reaction was then purged with nitrogen and stirred at room temperature for 10 min. Indanone (**9**) (0.5 mmol, 1 equiv) was then added to the reaction followed by 1-bromo-4-methoxybenzene (**10**) (1.5 mmol, 3 equiv). The reaction temperature was raised to 80 °C and the mixture was stirred at the same temperature for 5 h. The reaction was quenched with ice-cold 1 N HCl solution (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine and dried over sodium sulfate. After concentration, the crude product was purified by flash chromatograph to give product as a colorless oil (148 mg, isolation yield: 69%). ^{1}H NMR (400 MHz, $CDCl_3$ 25 °C) δ 3.56 (d, J = 2.8 Hz, 1H), 3.59 (s, 3H), 3.61 (s, 6H), 3.68 (s, 3H), 3.78 (s, 3H), 4.35 (d, J = 2.8 Hz, 1H), 6.07 (d, J = 2.4 Hz, 2H), 6.23 (t, J = 2.4 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.75 (m, 2H), 6.81 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 55.9, 55.2, 55.2, 55.6, 55.8, 64.1, 96.4, 98.1, 105.1, 106.5, 114.3, 128.8, 131.5, 137.6, 138.7, 145.9, 157.8, 158.7, 160.8, 162.0, 205.9; LC-MS 100% (purity), m/e 435 (M + 1), 457 (M + Na); HRMS calcd for $C_{26}H_{27}O_6$ (M + 1) 435.1807, found 435.1811.

The Synthesis of *trans*-3-(3,5-Dihydroxyphenyl)-4,6-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1*H*-inden-1-one (5, Paucifloral F). To the DCM (2 mL) solution of **11** (0.2 mmol 87 mg) was added BBr_3 (10 equiv 1 M in DCM, 2 mL) at 0 °C. The reaction was allowed to warm to room temperature and then stirred overnight. The reaction was poured into the mixture of methanol (5 mL) and ice water (5 mL) and extracted with the mixed solvent of chloroform and isoproanol (3/1, 4 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over sodium sulfate. After concentration, the crude product was purified by flash chromatography. Synthetic paucifloral F (34 mg, 49%) was obtained. ^{1}H NMR (400 MHz, MeOD, 25 °C) δ 3.36 (d, J = 2.4 Hz, 1H), 4.18 (d, J = 2.4 Hz, 1H), 5.85 (d, J = 2.0 Hz, 2H), 5.99 (t, J = 2.4 Hz, 1H), 6.52 (d, J = 2.0 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, MeOD, 25 °C) δ 53.2, 66.3, 100.5, 101.7, 106.4, 110.9, 116.5, 129.9, 132.0, 136.1, 140.0, 147.5, 157.3, 157.6, 159.6, 160.8, 209.3; LC-MS 100% (purity), m/e 365 (M + 1); HRMS calcd for $C_{21}H_{17}O_6$ (M + 1) 365.1025, found 365.1025.

■ ASSOCIATED CONTENT

Supporting Information. Characterization of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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■ REFERENCES

(1) Duarte, C. D.; Barreiro, E. J.; Fraga, C. A. *Mini-Rev. Med. Chem.* **2007**, *7*, 1108.

(2) (a) Birks, J.; Harvey, R, J. *Cochrane Database Syst Rev (1)*: CD001190 2006. (b) Whitehead, A.; Perdomo, C.; Pratt, R. D.; Briks, J.; Wilcock, G. K.; Evans, J. G. *Int. J. Geriatr. Pyschiatry* **2004**, *19* (7), 624–33.

(3) Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotib, L.; Hooloway, M. K.; Lin, J.; Chen, I. W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci.* **1994**, *91*, 4096.

(4) For naturally occurring indanone compounds see: Fugmann, B.; Lang-Fugmann, S.; Steglich, W.; Adam, G. *Rompp Encyclopedia of Natural Products*; Thieme: New York, 2000.For more examples of pharmaceutical indanone compounds see: Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783 and reference cited therein.

(5) Luo, H. F; Zhang, L. P.; Hu, C. O. *Tetrahedron* **2001**, *57*, 4849.

(6) Nagle, D. G.; Zhou, Y. D.; Park, P. U.; Paul, V. J.; Rajbhandari, I.; Duncan, C. J. G.; Pasco, D. *J. Nat. Prod* **2000**, *63*, 1431.

(7) Van der Hoeven, J. C. M.; Lagerweij, W. J.; Posthumus, M. A.; van Veldhuizen, A.; Holterman, H. A. *J. Carcinogenesis* **1983**, *4*, 1587.

(8) For the isolation and characterization of Paucifloral F see: Ito, T.; Tanaka, T.; Linuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932.

(9) For recent reviews see: (a) Pervaiz, S.; Holme, A. L.; Aggarwal, B. B.; Anekonda, T. S.; Baur, J. A.; Gojkovic-Bukarica, L.; Della Ragione, F.; Kim, A. L.; Pirola, L.; Saiko, P. *Antioxid. Redox Signal.* **2009**, *11*, 2851. (b) Marques, F. Z.; Markus, M. A.; Morris, B. J. *Int. J. Biochem. Cell Biol.* **2009**, *41*, 2125.

(10) (a) Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L. L.; Scherer, B.; Sinclair, D. A. *Nature* **2003**, *425*, 191. (b) Wood, J. G.; Rogina, B.; Lavu1., S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. *Nature* **2004**, *430*, 686.

(11) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W.; Fong., H. H.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218.

(12) The clinic trial of resveratrol (SRT501) sponsored by GlaxoSmithKline was recently suspended. See: http://www.clinicaltrials.gov/ct2/results?term=SRT501.

(13) Oral bioavailability of resveratrol is low. It is rapidly metabolized in intestines and liver after oral dose, see: Walle, T.; Hsieh, F.; DeLegge, M. H.; Oatis, J. E.; Walle, U. K. *Drug Metab. Dispos.* **2004**, *32*, 1377.

(14) (a) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753. (b) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186.

(15) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450. The total synthesis of Paucifloral F is also reported by Li et al. using a palladium-catalyzed Heck cyclization strategy: Bo, C.; Lu, J. P.; Xie, X. G.; Shem, X. G.; Pan, X. F. *Youji Huaxue* **2006**, *26*, 1300.

(16) Lahtchev, K. L.; Batovska, D. I.; Parushev, St. P.; Ubiyvovk, V. M.; Sibirny, A. A. *Eur. J. Med. Chem.* **2008**, *43*, 2220.

(17) Saxena, H. O.; Faridi, U.; Srivastava, S.; Kumar, J. K.; Darokar, M. P.; Luqman, S.; Chanotiya, C. S.; Krishma, V; Negi, A. S.; Khanuja, S. P. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3914.

(18) For an excellent review on palladium-catalyzed α-arylation see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234 and reference cited therein.

(19) (a) Grasa, G. A.; Colacot, T. J. *Org. Process Res. Dev.* **2008**, *12*, 522. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

(20) Compound **12** can also be applied as a key intermediate for the synthesis of *Paucifloral F* by a different approach. See: Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450.

(21) For 2-D NMR of **11** see the Supporting Information

(22) (a) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379. (b) Zimmerman, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 1168.

(23) For analytical data of paucifloral F in literature see: (a) Ito, T.; Tanaka, T.; Linuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932. (b) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753. (c) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450.

(24) Unfortunately, the attempted synthesis of **17b** failed. Only a trace of **17b** was detected after the demethylation reaction, which was conducted at room temperature in the presence of BBr_3. We suspect that the nitrile group could not be well tolerated under such conditions.