Gold-Catalyzed Dimeric Cyclization of Isoeugenol and Related 1-Phenylpropenes in Ionic Liquid: Environmentally Friendly and Stereoselective Synthesis of 1,2,3-Trisubstituted 2,3-Dihydro-1*H*-indenes

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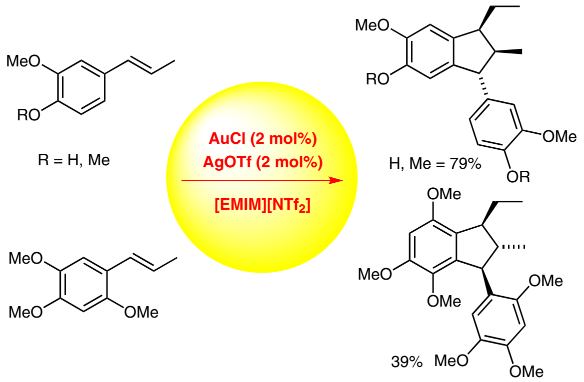

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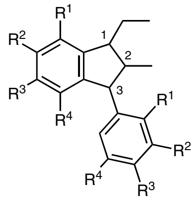
Abstract Gold-catalyzed dimerization of isoeugenol and related 1-phenylpropenes in ionic liquid enabled environmentally friendly, stereoselective synthesis of 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes. Dimerization of isoeugenol or isohomogenol afforded diisoeugenol or diisohomogenol, respectively, with α-configuration, whereas dimerization of α-asarone furnished diasarone with γ-configuration.

Key words gold-catalyzed dimerization, ionic liquid, addition, cyclization, 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes

Lignans and neolignans show tremendous structural diversity,[1] and dimers of phenylpropanoid units (C_6–C_3) form a huge family of secondary metabolites in nature. Among them, polyfunctionalized 2,3-dihydro-1*H*-indenes[2] such as diisoeugenol (**2**),[2a,3] diisohomogenol (**4**),[2b] diasarone (**6**),[4] and diisosafrole (**8**)[5] form an important group, within which four diastereomers are possible, namely α-(1,2-*cis*-2,3-*trans*), β-(1,2-*cis*-2,3-*cis*), γ-(1,2-*trans*-2,3-*trans*), and δ-(1,2-*trans*-2,3-*cis*) (Figure 1 and Figure 2). The α-diastereomers of diisoeugenol (**2**) and its derivatives exhibit various biological properties, including cytotoxic,[5] anti-inflammatory,[6] antioxidant,[7] spasmolytic, hypertensive, and thromboxane formation-inhibitory activities,[8] while the γ-diastereomer of diisoeugenol (**2**) protects perfumes from deterioration.[9] Because of the potential utility of these activities, and inadequate supplies of the compounds from natural sources, development of synthetic methods for 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes has attracted much interest.



diisoeugenol (**2**)
R^1 = H, R^2 = OMe, R^3 = OH, R^4 = H
diisohomogenol (**4**)
R^1 = H, R^2 = OMe, R^3 = OMe, R^4 = H
diasarone (**6**)
R^1 = OMe, R^2 = H, R^3 = OMe, R^4 = OMe
diisosafrole (**8**)
R^1 = H, R^2, R^3 = -OCH$_2$O-, R^4 = H

Figure 1 Structures of 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes

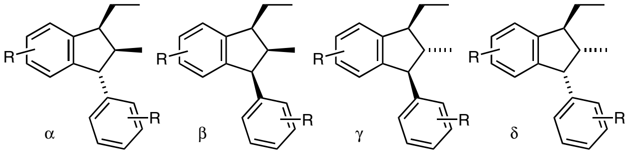
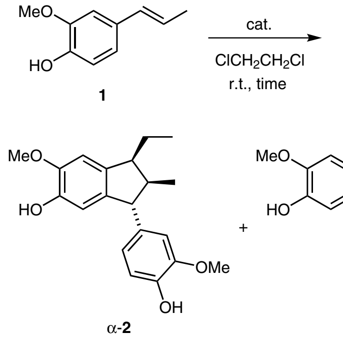


Figure 2 Four stereoisomers of 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes

Reported syntheses of 2,3-dihydro-1*H*-indene derivatives can be mainly divided into two groups: (i) dimerization of related 1-phenylpropenes[10–12] and (ii) intra-/intermolecular coupling reaction of 1-phenylpropan-1-ols and 1-phenylpropenes.[13,14] Most dimerizations of 1-phenylpropenes require the use of a toxic and volatile halogenated solvent (CH_2Cl_2 or $CHCl_3$) and a hazardous, corrosive reagent (H_2SO_4, HCl, or CF_3CO_2H). Recently, Kouznetsov's group developed the first green protocol for the large-scale preparation of γ-diisoeugenol (**2**) and related 2,3-dihydro-1*H*-indenes using PEG-400, a commercially available and easily degradable solvent, or silica-supported sulfuric acid (SiO_2-OSO_3H) as a reusable heterogeneous system.[10a] On the other hand, most coupling reactions of 1-phenylpropan-1-

ol derivatives and 1-phenylpropenes require a stoichiometric amount of reagents ($BF_3{\cdot}OEt_2$, $SnCl_4$, or $ZnCl_2$). The replacement of these potentially hazardous solvents and stoichiometric reagents with environmentally benign solvents and sustainable reagents is thus an important issue for green chemistry. Here, we report a gold-catalyzed, environmentally friendly, stereoselective synthesis of 2,3-dihydro-1*H*-indenes in ionic liquid.[15]

Table 1 Optimization of Reaction Conditions for the Gold-Catalyzed Dimerization of Isoeugenol (**1**) in Dichloroethane

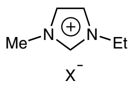


Entry	Cat. (mol%)	Time (h)	Yield (%)	Ratio α/γ
1	AuCl (2)	20	nd[a]	
2	AuCl (2)/AgOTf (2)	8	76	10:1
3	AuCl (1)/AgOTf (1)	20	80	10:1
4	AuCl (1)/AgNTf$_2$ (1)	20	61	8:1
5	AuCl (1)/AgBF$_4$ (1)	24	trace	
6	AuCl (1)/AgPF$_6$ (1)	24	trace	
7	AuBr$_3$ (2)	8	80	4:1
8	AuBr$_3$ (1)/AgOTf (3)	8	84	6:1
9	AuBr$_3$ (1)/AgNTf$_2$ (3)	3	80	6:1
10	AuBr$_3$ (1)/AgBF$_4$ (3)	24	trace	
11	AuBr$_3$ (1)/AgPF$_6$ (3)	24	trace	

[a] Not detected.

Initially, we investigated various catalyst systems for dimerization of isoeugenol (**1**) in dichloroethane, despite its environmental unsuitability (Table 1). Gold(I) catalyst, AuCl (2 mol%), failed to afford the desired diisoeugenol (**2**) (Table 1, entry 1), whereas cationic gold species generated from AuCl (2 mol%) and AgOTf (2 mol%) afforded α-diisoeugenol (α-**2**) in 76% yield with high stereoselectivity (entry 2). Next, the effect of the counter anion of silver was examined (entries 3–6). Combined use of AuCl (1 mol%) and AgOTf (1 mol%) furnished α-**2** in high yield with good selectivity (entry 3). Gold(III) catalyst, $AuBr_3$ (2 mol%), afforded diisoeugenol (**2**) in good yield, though with limited selectivity (entry 7). Various counter anions of silver catalysts with $AuBr_3$ (1 mol%) failed to provide a dramatic improvement in α-selectivity (entries 8–11). Taking into account both yield and stereoselectivity, combined use of AuCl (1 mol%) and AgOTf (1 mol%) appeared to be the best catalyst system for obtaining α-diisoeugenol (α-**2**).

We next examined the use of ionic liquids in the AuCl/AgOTf-catalyzed dimerization of isoeugenol (**1**) (Figure 3 and Table 2). The reaction in [EMIM][$(MeO)_2PO_2$] or [EMIM][$MeCO_2$] did not proceed at all (Table 2, entries 1 and 2). The reaction in [EMIM][HSO_4] or [EMIM][BF_4] selectively furnished α-diisoeugenol (**2**) in moderate yield, but the reaction time was long (Table 2, entries 3 and 4). In contrast, the reaction in [EMIM][NTf_2] smoothly proceeded to afford α-diisoeugenol (**2**) in better yield with good selectivity (entry 5). Further improvement was achieved by increasing the amounts of AuCl and AgOTf. Thus, the reaction of isoeugenol (**1**) in the presence of AuCl (2 mol%) and AgOTf (2 mol%) in [EMIM][NTf_2] gave diisoeugenol (**2**) in 79% yield with 9:1 α-selectivity (entry 6). In addition, the large-scale preparation of α-diisoeugenol (α-**2**) was also achieved from 1.0 g (6.1 mmol) of isoeugenol (**1**), affording the product α-**2** in 74% yield. Surprisingly, gold(I) catalyst itself, AuCl (2 mol%) in [EMIM][NTf_2] smoothly catalyzed dimerization of isoeugenol (**1**), furnishing α-diisoeugenol (**2**) in good yield (Table 2, entry 7), although AuCl (2 mol%) was completely inactive in dichloroethane (Table 1, entry 1). Lee's group reported various advantages of ionic liquids for catalytic reactions, including formation of more reactive catalysts or stabilization of reactive intermediates and transition states.[16] Although the reason for the high activity of AuCl in ionic liquid [EMIM][NTf_2] (Table 2, entry 7) remains unclear, two possibilities can be considered. The first is that an active gold species, $AuNTf_2$ might be generated by anion exchange between chloride ion of the gold catalyst and NTf_2 ion of the ionic liquid, [EMIM][NTf_2]. The second possibility would be the formation of reactive gold species bearing the NHC ligand,[17] which could be generated from the ethylmethylimidazolium cation of [EMIM][NTf_2].

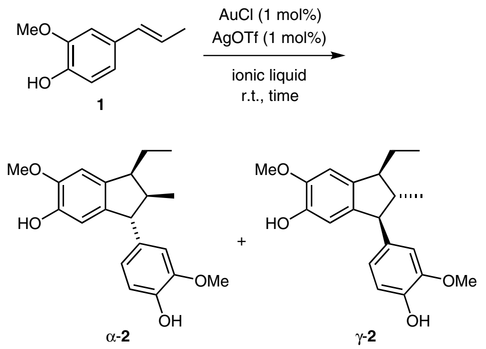


EMIM = ethylmethylimidazolium
$X^- = (MeO)_2PO_2^-$ [EMIM][$(MeO)_2PO_2$]
$X^- = MeCO_2^-$ [EMIM][$MeCO_2$]
$X^- = HSO_4^-$ [EMIM][HSO_4]
$X^- = BF_4^-$ [EMIM][BF_4]
$X^- = NTf_2^-$ [EMIM][NTf_2]

Figure 3 Ionic liquids as solvents

Next, the recycling of the gold-catalyst system in ionic liquid for dimerization of **1** was investigated (Table 3). After extraction of the product of the 1st run with diethyl ether (Table 3, entry 1), remaining AuCl (2 mol%) and AgOTf (2 mol%) in ionic liquid [EMIM][NTf_2] was directly used for the 2nd run; however, the yield of dimerization product **2** was low (entry 2). Since it was thought that the catalyst might have been deactivated by diethyl ether, increased amounts of catalysts were used. When 6 mol% of AuCl and 6 mol% of AgOTf were used in ionic liquid, the 2nd and the 3rd reac-

Table 2 Optimization of Dimerization in Ionic Liquids

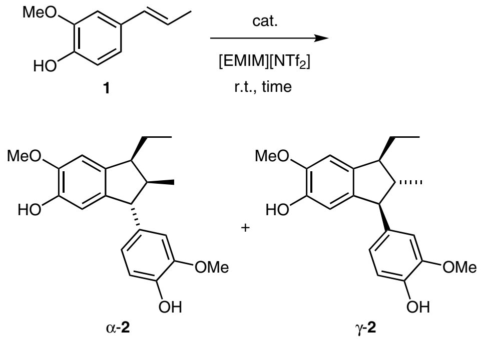


Entry	Ionic liquid	Time	Yield (%)	Ratio α/γ
1	[EMIM][$(MeO)_2PO_2$]	11 d	nr[a]	
2	[EMIM][$MeCO_2$]	11 d	nr	
3	[EMIM][HSO_4]	10 d	44	8:1
4	[EMIM][BF_4]	9 d	34	8:1
5	[EMIM][NTf_2]	4.5 h	60	9:1
6[b]	[EMIM][NTf_2]	4.5 h	79	9:1
7[c]	[EMIM][NTf_2]	4.5 h	73	4:1

[a] No reaction.
[b] With AuCl (2 mol%)/AgOTf (2 mol%).
[c] With AuCl (1 mol%).

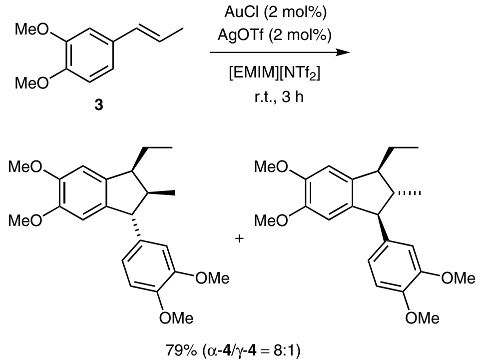
tions afforded the dimerization product **2** in 78 and 57% yield, respectively, although longer reaction periods were required (entries 3–5, runs 1–3).

Table 3 Recycling of Gold-Catalyzed Dimerization Reaction in Ionic Liquid

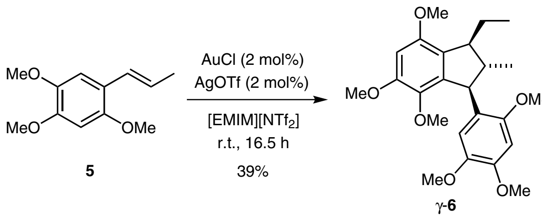


Entry	Run	Cat. (mol%)	Time (h)	Yield (%)	Ratio α/γ
1	1	AuCl (2)/AgOTf (2)	4.5	79	9:1
2	2		24	7	–
3	1	AuCl (6)/AgOTf (6)	2.5	82	9:1
4	2		6	78	9:1
5	3		9	57	8:1

Next, the gold-catalyzed dimerization of other related 1-phenylpropenes, isohomogenol (**3**) and α-asarone (**5**), in ionic liquid was examined (Schemes 1 and 2). Treatment of isohomogenol (**3**) with AuCl (2 mol%) and AgOTf (2 mol%) in [EMIM][NTf_2] afforded diisohomogenol (**4**) with α-configuration in good yield (Scheme 1). On the other hand, gold-catalyzed dimerization of α-asarone (**5**) surprisingly furnished γ-diasarone (**6**) in moderate yield (Scheme 2).



Scheme 1 Gold-catalyzed dimerization of isohomogenol (**3**)

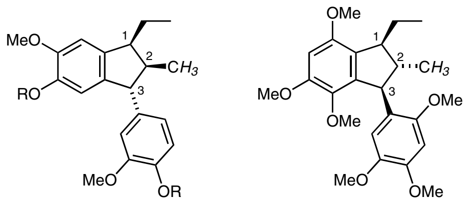


Scheme 2 Gold-catalyzed dimerization of α-asarone (**5**)

To confirm the stereochemistry of the synthesized 2,3-dihydro-1*H*-indenes, α-diisoeugenol (**2**), α-diisohomogenol (**4**), and γ-diasarone (**6**), their ^1H NMR spectra were compared with the reported data (Table 4).[11c,14b,e] The ^1H NMR spectra of the synthesized 2,3-dihydro-1*H*-indenes **2** and **4** were identical with those reported for α-**2** and α-**4** in both chemical shifts and coupling constants,[18] while the ^1H NMR spectrum of synthesized γ-diasarone (**6**) was consistent with the reported spectrum[18] of γ-**6**.

A plausible mechanistic model for gold-catalyzed dimerization of isoeugenol (**1**) in ionic liquid is shown in Scheme 3. Gold species could coordinate to the double bond[19] of isoeugenol (**1**), forming gold-quinone methide complex **A**. The gold center of complex **A** would coordinate to the double bond of another **1**, inducing addition reaction to complex **A** to afford intermediate **B** bearing an electron-rich aromatic ring and an electron-deficient ring. Cyclization takes place between the aromatic ring and benzylic position in complex **B** to furnish gold intermediate **C**, which undergoes aromatization and deauration to provide diisoeugenol (**2**) with α-configuration (1,2-*cis*-2,3-*trans*). The first carbon–carbon bond formation (addition step, **A** → **B**)

Table 4 Comparison of ^{1}H NMR Spectra of 2,3-Dihydro-1*H*-indenes **2**, **4**, and **6** in $CDCl_3$



α–Diisoeugenol: R = H
α–Diisohomogenol: R = Me

γ–Diasarone

Chemical shifts, δ

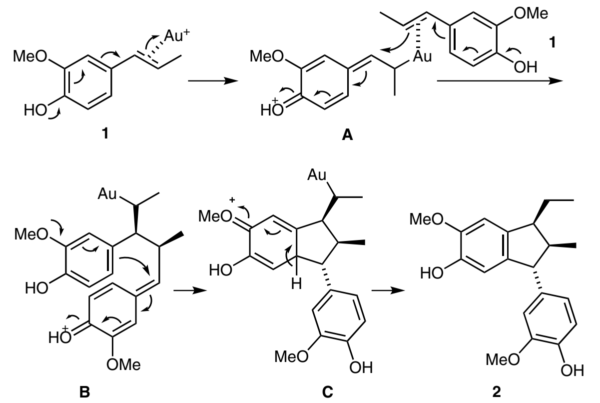
Dimer	H-1	H-2	H-3	CH_3
α-diisoeugenol (α-**2**)[a]	2.91	2.46	3.74	1.03
γ-diisoeugenol (γ-**2**)[b]	2.69	2.00	3.65	1.15
α-**2** (synthesized)	2.91	2.46	3.74	1.03
α-diisohomogenol (α-**4**)[a]	2.94	2.47	3.79	1.05
γ-diisohomogenol (γ-**4**)[c]	2.69	2.00	3.65	1.15
α-**4** (synthesized)	2.94	2.47	3.79	1.05
γ-diasarone (γ-**6**)[c]	2.67	2.07	4.27	1.17
γ-**6** (synthesized)	2.68	2.07	4.29	1.17

Coupling constants

Dimer	$J_{1,2}$ (Hz)	$J_{2,3}$ (Hz)
α-diisoeugenol (α-**2**)[a]	7.5	9.5
α-**2** (synthesized)	7.5	9.6
α-diisohomogenol (α-**4**)[a,c]	7.2	9.5
α-**4** (synthesized)	7.2	9.9
γ-diasarone (γ-**6**)[c]	4.2	4.3
γ-**6** (synthesized)	3.6	3.9

[a] See ref. 11c.
[b] See ref. 14b.
[c] See ref. 14e.

would be important to control the stereochemistry of α-diisoeugenol (**2**). In the addition step, π–π stacking between the electron-rich and electron-deficient rings in **A** would make the orthogonal approach favorable, leading to formation of 1,2-*cis*-diisoeugenol (**2**) (Figure 4). Cyclization proceeds again with π–π stacking in intermediate **B** to form a five-membered ring with α-configuration (1,2-*cis*-2,3-*trans*) (Figure 4). The dimerization of isohomogenol (**3**) would proceed in a similar manner, affording diisohomogenol (**4**) with α-configuration. In the case of dimerization of α-asarone (**5**), the orthogonal approach suffers from severe steric hindrance due to the additional methoxy group on the rings and hence addition reaction may proceed via an extended approach **A′** leading to **B′** with 1,2-*trans* stereochemistry (Figure 5). Intermediate **B′** cyclizes at the *ortho*-position of the aromatic group and propenyl group to provide **C′**, constructing the γ-configuration (1,2-*trans*-2,3-*trans*) of γ-diasarone (**6**) after aromatization and deauration.



Scheme 3 Plausible mechanism of gold-catalyzed dimerization

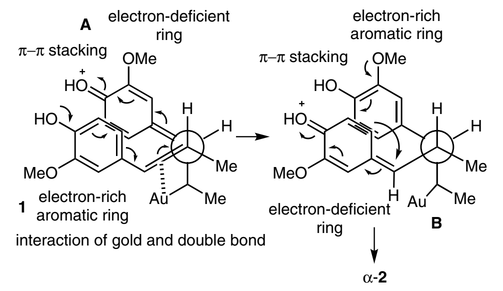


Figure 4 Mechanisms of addition and cyclization for construction of α-**2**

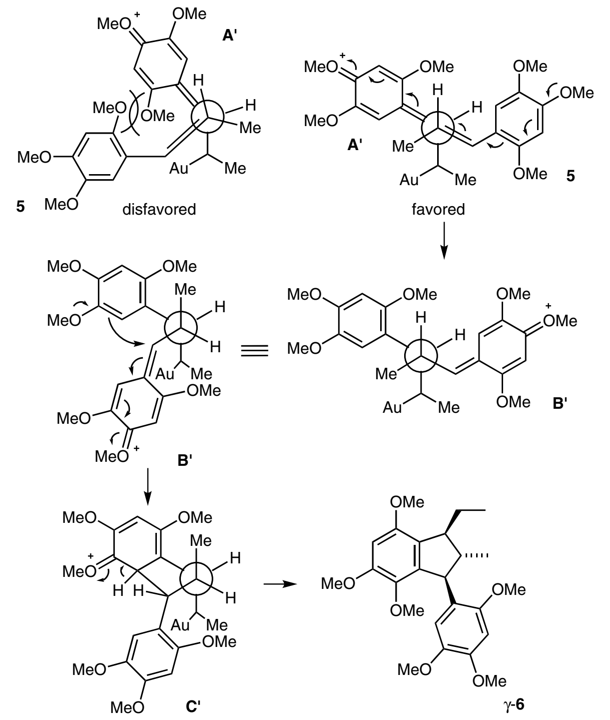


Figure 5 Reaction mechanism for construction of γ-**6**

In summary, we have developed a gold-catalyzed dimerization reaction of isoeugenol (**1**) and related 1-phenylpropenes **3** and **5** in ionic liquid and accomplished an environmentally friendly stereoselective synthesis of 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes. Dimerization of isoeugenol (**1**) and isohomogenol (**3**) gave the α-dimerized products, whereas α-asarone (**5**) afforded the γ-product. AuCl/AgOTf in [EMIM][NTf$_2$] solution could be recycled for further dimerization reaction of isoeugenol (**1**). We are now pursuing further applications of this environmentally benign and sustainable catalyst system.

^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-AL300 spectrometer at r.t. with TMS as an internal standard (CDCl$_3$ solution). Chemical shifts were recorded in ppm, and coupling constants (*J*) in Hz. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. Mass spectra were recorded on Jeol JMS-D300 and HX110 spectrometers. Merck silica gel 60 (1.09385) and Merck silica gel 60 F254 were used for column chromatography and TLC, respectively.

Gold(III)-Catalyzed Dimerization of 1-Phenylpropenes 1, 3, and 5 to 2,3-Dihydro-1*H*-indenes 2, 4, and 6 in Ionic Liquid; General Procedure

Gold catalyst (2 mol% of AuCl) and silver catalyst (2 mol% of AgOTf) were added at r.t. to a solution of 1-phenylpropene (**1**, **3**, or **5**) in [EMIM][NTf$_2$] and the mixture was stirred at the same temperature. After complete consumption of the 1-phenylpropenes (the reaction was monitored by TLC), the product was extracted with Et$_2$O and the solvent was removed in vacuo. The crude product was subjected to column chromatography on silica gel (hexane–EtOAc, 2:1) to give the corresponding 2,3-dihydro-1*H*-indenes **2**, **4**, and **6**, respectively.

α-Diisoeugenol (2)

Isoeugenol (**1**; 102 mg, 0.622 mmol), AuCl (3.5 mg, 0.015 mmol, 2 mol%), and AgOTf (3.6 mg, 0.014 mmol, 2 mol%) in [EMIM][NTf$_2$] (1 mL) furnished α-diisoeugenol (**2**) (80.0 mg, 79%, α/γ = 9:1) as a colorless solid; mp 179–180 °C.[11c]

IR (KBr): 3649, 3364, 2872, 1596, 1499, 1375, 1339, 1288, 1261, 1227, 1207, 1151, 1088, 1059, 1034, 866, 845, 818, 773, 760 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.38 (ddq, *J* = 13.5, 6.3, 4.5 Hz, 1 H), 1.70 (ddq, *J* = 13.2, 7.8, 5.4 Hz, 1 H), 2.46 (ddq, *J* = 9.6, 7.2, 6.9 Hz, 1 H), 2.91 (ddd, *J* = 8.7, 7.5, 5.4 Hz, 1 H), 3.74 (d, *J* = 9.6 Hz, 1 H), 3.82 (s, 3 H), 3.90 (s, 3 H), 5.46 (s, 1 H), 5.49 (s, 1 H), 6.47 (d, *J* = 0.6 Hz, 1 H), 6.61 (d, *J* = 1.8 Hz, 1 H), 6.65 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.77 (s, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.7, 14.2, 22.8, 49.0, 49.7, 56.4, 56.6, 57.2, 107.9, 111.1, 111.4, 114.4, 121.9, 136.2, 139.1, 139.6, 144.5, 145.0, 145.6, 146.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}O_4$: 328.1675; found: 328.1670.

α-Diisohomogenol (4)

Isohomigenol (**3**; 104 mg, 0.581 mmol), AuCl (2.6 mg, 0.011 mmol, 2 mol%), and AgOTf (3.3 mg, 0.013 mmol, 2 mol%) furnished α-diisohomogenol (**4**) (82.0 mg, 79%, α/γ = 8:1) as a colorless solid; mp 107–108 °C.[11c]

IR (KBr): 2957, 2831, 1606, 1514, 1464, 1418, 1261, 1217, 1155, 1140, 1096, 1028, 991, 854, 758 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 1.40 (ddq, *J* = 13.5, 6.3, 4.5 Hz, 1 H), 1.72 (ddq, *J* = 13.5, 7.8, 6.0 Hz, 1 H), 2.47 (ddq, *J* = 9.6, 7.5, 7.2 Hz, 1 H), 2.94 (ddd, *J* = 8.7, 7.2, 5.4 Hz, 1 H), 3.73 (s, 3 H), 3.79 (d, *J* = 9.9 Hz, 1 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 6.44 (s, 1 H), 6.65 (d, *J* = 2.1 Hz, 1 H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.81 (s, 1 H), 6.83 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.2, 13.7, 22.4, 48.5, 49.5, 55.8, 55.8, 55.9, 56.0, 56.9, 108.0, 108.1, 110.9, 111.3, 120.7, 136.6, 138.0, 139.4, 147.5, 147.6, 148.1, 148.8.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{28}O_4$: 356.1988; found: 356.1975.

γ-Diasarone (6)

α-Asarone (**5**; 100 mg, 0.481 mmol), AuCl (2.4 mg, 0.010 mmol, 2 mol%), and AgOTf (2.3 mg, 0.0090 mmol, 2 mol%) furnished γ-diasarone (**6**) (39.0 mg, 39%) as a colorless solid; mp 99–100 °C.[11d]

IR (KBr): 2955, 2836, 1603, 1508, 1464, 1437, 1396, 1337, 1319, 1232, 1205, 1178, 1119, 1082, 1036, 980, 885, 866, 841, 814, 781, 737 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.98 (t, J = 7.5 Hz, 3 H), 1.17 (d, J = 6.9 Hz, 3 H), 1.54–1.42 (m, 1 H), 1.84 (ddd, J = 10.5, 7.5, 2.7 Hz, 1 H), 2.07 (ddq, J = 9.6, 7.2, 2.7 Hz, 1 H), 2.68 (dt, J = 9.0, 3.6 Hz, 1 H), 3.38 (s, 3 H), 3.64 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.29 (d, J = 3.9 Hz, 1 H), 6.38 (s, 1 H), 6.43 (s, 1 H), 6.55 (s, 1 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.8, 22.0, 26.7, 47.7, 49.9, 52.4, 55.5, 56.1, 56.6, 56.7, 56.8, 59.9, 97.0, 97.9, 113.0, 127.0, 127.6, 139.2, 139.7, 142.7, 147.5, 151.2, 152.0, 152.2.

HRMS (FAB): m/z [M + H]$^+$ calcd for $C_{24}H_{32}O_6$: 416.2199; found: 416.2189.

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Supporting Information

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