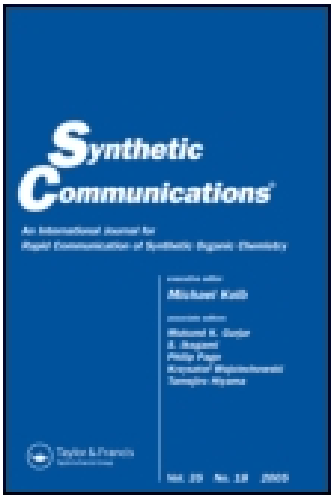

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Synthesis of C1-Substituted 7-Oxanorbornadienes

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SYNTHESIS OF C1-SUBSTITUTED 7-OXANORBORNADIENES

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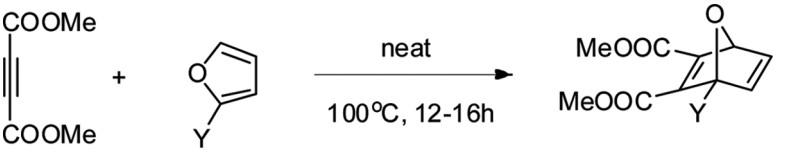
GRAPHICAL ABSTRACT



Abstract *7-Oxanorbornadienes are valuable synthetic intermediates as they can serve as general templates to create highly substituted ring systems. However, to date, only very few C1-substituted 7-oxanorbornadienes have been synthesized and can be found in the literature. In this article, synthesis of some C1-substituted 7-oxanorbornadienes was achieved by the Diels–Alder reaction between 2-substituted furans and dimethylacetylene dicarboxylate. Moderate to good yields (13–85%) of the Diels–Alder reactions were observed. These C1-substituted 7-oxanorbornadienes will find applications as valuable synthetic intermediates and are useful in the studies of transition-metal-catalyzed reactions.*

Keywords Bicyclic alkenes; Diels–Alder reaction; dimethylacetylene dicarboxylate; furan; 7-oxanorbornadienes

INTRODUCTION

7-Oxanorbornadiene **1** is a valuable synthetic intermediate as it can serve as a general template to create highly substituted ring systems.[1,2] For instance, asymmetric ring opening of these alkenes allows for the formation of several stereocenters in a single step.[2–5] We have recently investigated different modes of transition-metal-catalyzed reactions of oxanorbornadiene **1** and found that depending on the reaction conditions, several products (**2**–**7**) could be obtained (Scheme 1). For example, when 7-oxanorbornadiene **1** is treated with an alkyne in the presence of the ruthenium catalyst, $Cp^*Ru(COD)Cl$, a [2 + 2] cycloaddition is observed and cyclobutene cycloadduct **2** is formed.[6,7] When oxanorbornadiene **1** is treated with the secondary propargylic alcohol **8** in the presence of the neutral Ru catalyst, $Cp^*Ru(COD)Cl$, in MeOH or

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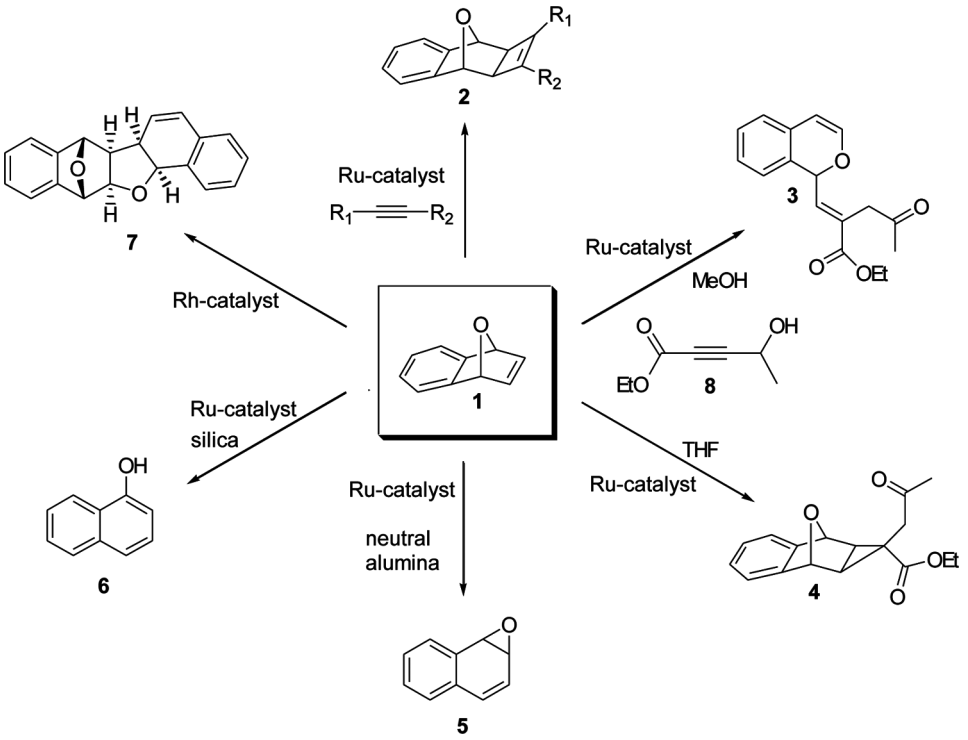
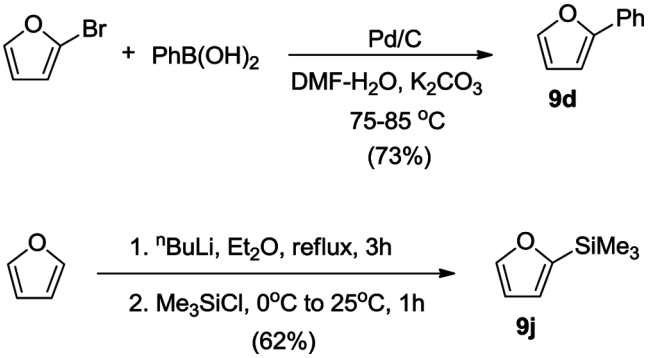


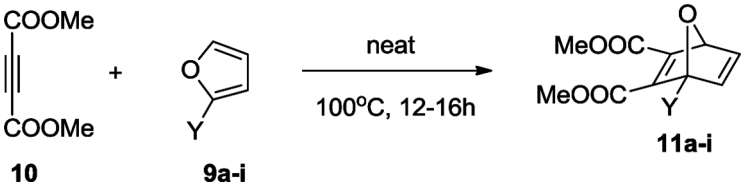
Scheme 1. Transition-metal–catalyzed reactions of oxabenzonorbornadiene **1**.

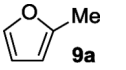
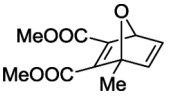
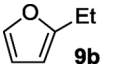
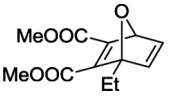
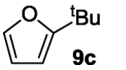
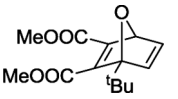
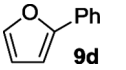
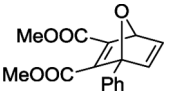
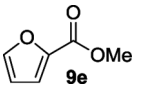
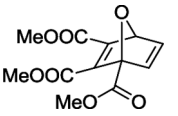
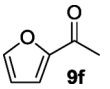
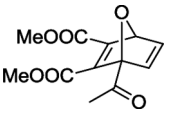
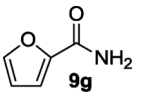
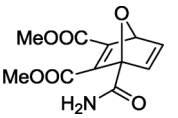
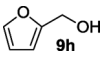
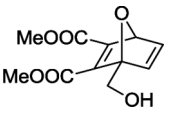
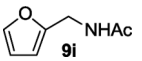
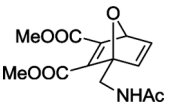
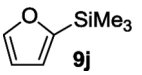
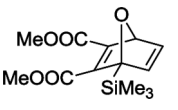
using a cationic Ru catalyst (e.g., $[CpRu(CH_3CN)_3]PF_6$), isochromene **3** is formed.[8,9] On the other hand, if the same reaction between oxanorbornadiene **1** and the secondary propargylic alcohol **8** is carried out with $Cp^*Ru(COD)Cl$ in tetrahydrofuran (THF), cyclopropane **4** is produced.[10] More recently, we have observed that in the absence of an alkyne, $Cp^*Ru(COD)Cl$ catalyzes the isomerization of oxanorbornadiene **1** to the corresponding naphthalene oxide **5** or naphthol **6**.[11,12] We have also



Scheme 2. Synthesis of 2-phenylfuran **9d** and 2-trimethylfuran **9 h**.

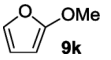
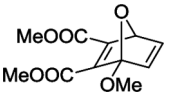
Table 1. Synthesis of C1-substituted 7-oxanorbornadienes



Entry	Furan	Product	Yield (%)[a]
1			85
2			85
3			34
4			42
5			37
6			50
7			13
8			75
9			51
10			35

(*Continued*)

Table 1. Continued

Entry	Furan	Product	Yield (%)[a]
11	 **9k**		0 (92)[b]

[a]Isolated yield after column chromatography.
[b]Compound **11k** was unstable and was aromatized to form compound **12** in 92% (see Scheme 3).

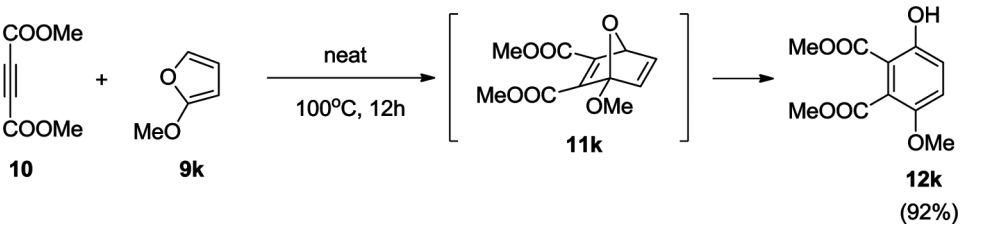
reported that asymmetric cationic rhodium(I)-catalyzed cyclodimerization of oxanorbornadiene **1** produces dimers **7** in excellent enantioselectivity (up to 99% *ee*).[13]

Because 7-oxanorbornadiene **1** is symmetrical, no regiochemical information could be gained from these studies. To explore the regioselectivity of these reactions, unsymmetrical 7-oxanorbornadienes needed to be synthesized. To our surprise, a search in the literature has shown that very few C1-substituted 7-oxanorbornadienes have been synthesized to date.[14] In this article, we report the synthesis of some C1-substituted 7-oxanorbornadienes **11** by the Diels–Alder reaction between 2-substituted furans **9** and dimethylacetylene dicarboxylate **10**.

RESULTS AND DISCUSSION

2-Substituted furans **9a–c, 9e–g**, and **9i** are commercially available. 2-Phenylfuran **9d** was prepared in 73% yield by recently reported Pd-catalyzed Suzuki coupling reaction between 2-bromofuran and phenyl boronic acid,[15] and furan-2-yltrimethylsilane **9j** was synthesized in 62% yield by deprotonation of furan followed by trapping with chlorotrimethylsilane[16] (Scheme 2). With the 2-substituted furans **9a–i** in hand, we studied the Diels–Alder reactions of these 2-substituted furans with dimethylacetylene dicarboxylate **10**, and the results are shown in Table 1.

C1-Substituted 7-oxanorbornadienes **11a** and **11b** with primary alkyl group (Y=Me and Et) were produced in excellent yields (85%, Table 1, entries 1 and 2). The yields of the Diels–Alder reactions were significantly lowed with a tertiary alkyl group (**11c**, Y $=^{t}$Bu, 34%) or with an aromatic group (**11d**, Y=Ph, 42% (entries 3–4). With carbonyl substituents (ester **11e**, Y=COOMe; ketone **11f**, Y=COMe; and amide **11 g**, Y=$CONH_2$), poor to moderate yields of the Diels–Alder reactions were observed (13–50% yields, entries 5–7). C1-Substituted 7-oxanorbornadienes **11 h** and **11i** with a primary alcohol and protected primary amine group (Y=CH_2OH and CH_2NHAc) were produced in good yields (75% and 51%, entries 8 and 9). Note that the Diels–Alder reaction with a nonprotected free primary amine group (CH_2NH_2) led to a complicated mixture of products and decomposition was observed. C1-Silyl substituted 7-oxanorbornadienes **11j** can also be produced in 35% yield (entry 10). However, C1-methoxy substituted 7-oxanorbornadiene **11k** was found to be unstable and was aromatized to phenol **12k** in 92% yield (Table 1, entry 11, and Scheme 3). We have attempted the Diels–Alder reactions of 2-substituted furans with Y=CN, NO_2, COOH, and Br, but in all these cases, complicated mixtures, of products were obtained, decomposition was observed, and no desired C1-substituted 7-oxanorbornadienes were isolated.



Scheme 3. Reaction of **9k** and **10**.

CONCLUSION

In conclusion, we have synthesized of some C1-substituted 7-oxanorbornadienes **11a–11j**, by the Diels–Alder reaction between 2-substituted furans **9a–9j** and dimethylacetylene dicarboxylate **10**. Moderate to good yields (13–85%) of the Diels–Alder reactions were observed. These C1-substituted 7-oxanorbornadienes will find applications as valuable synthetic intermediates and are useful in the studies of transition-metal-catalyzed reactions. Regioselectivity studies of different transition-metal-catalyzed reactions (such as those indicated in Scheme 1) of these C1-substituted 7-oxanorbornadienes **11a–11j** will be reported in the near future.

EXPERIMENTAL

All reactions are done in septum-sealed, flame-dried flasks under a nitrogen atmosphere. All commercial reagents were used as received from their respective suppliers. Reagent-grade furan and N-bromosuccinimide (NBS) purchased from Aldrich were used without additional purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references, and coupling constants are reported in hertz (Hz).

General Procedure for the Diels–Alder Reaction Between 2-Substituted Furans 9a–9j and Dimethylacetylene Dicarboxylate 10

The 2-substituted furan (1.1 eq.) was slowly charged into dimethylacetylene dicarboxylate (1.0 eq.) at room temperature. The resulting solution was heated to 90–100 °C in a screw-capped vial for 12–16 h. Reaction completion was monitored by thin-layer chromatography (TLC). The crude product was directly purified by column chromatography (EtOAc–hexanes mixtures) to give the product.

1-Methyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11a

$R_f = 0.40$ (EtOAc–hexanes, 1:4); IR (CH_2Cl_2): 2955, 1716, 1641, 1473, 1267, 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 5.58 (d, $J = 2.0$ Hz, 1H), 6.96 (d, J = 5.2 Hz, 1H), 7.16 (dd, J = 5.2, 1.6 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 100 MHz): 15.1 (CH_3), 52.2 (CH_3), 52.3 (CH_3), 83.3 (CH), 93.9 (qC), 144.6 (CH), 145.9 (CH), 151.2 (qC), 156.5 (qC), 162.8 (qC), 164.9 (qC). HRMS (CI) calcd. for $C_{11}H_{13}O_5$ (M + H): 225.0763; found: 225.0770.

1-Ethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11b

$R_f = 0.40$ (EtOAc–hexanes, 1:4); IR (CH_2Cl_2): 2955, 1726, 1639,1437, 1273, 1122 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.99 (t, $J = 7.4$ Hz, 3H), 2.07–2.22 (m, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 5.62 (d, $J = 1.9$ Hz, 1H), 6.95 (d, $J = 5.2$ Hz, 1H), 7.15 (dd, $J = 5.2$, 1.9 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 100 MHz): 9.0 (CH_3), 21.9 (CH_2), 52.2 (CH_3), 52.3 (CH_3), 83.2 (CH), 98.4 (qC), 144.7 (CH), 144.8 (CH), 151.4 (qC), 156.2 (qC), 162.7 (qC). 165.3 (qC). HRMS (CI) calcd. for $C_{12}H_{15}O_5$ (M +H): 239.0919; found: 239.0926.

1-*tert*-Butyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11c

$R_f = 0.26$ (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 2957, 1717, 1634, 1482, 1399, 1273, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.08 (s, 9H), 3.71 (s, 3H), 3.82 (s, 3H), 5.62 (d, $J = 1.6$ Hz, 1H), 7.10 (d, $J = 5.3$ Hz, 1H), 7.16 (dd, $J = 5.3$, 1.6 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): 26.3 ($3 \times CH_3$), 32.8 (qC), 52.1 (CH_3), 52.5 (CH_3), 82.3 (CH), 105.7 (qC), 142.8(CH), 145.2 (CH), 149.6 (qC), 159.3 (qC), 162.3 (qC), 167.8 (qC). HRMS (CI) calcd. for $C_{14}H_{19}O_5$ (M + H): 267.1232; found: 267.1233.

1-Phenyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11d

$R_f = 0.31$ (EtOAc–hexanes, 1:4); IR (CH_2Cl_2): 2955, 1717, 1700, 1635, 1436, 1362, 1286, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.62 (s, 3H), 3.77 (s, 3H), 5.82 (d, $J = 1.9$ Hz, 1H), 7.31 (dd, $J = 5.2$, 1.9 Hz, 1H), 7.44–7.33 (m, 4H), 7.50 (m, 2H); ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): 51.9 (CH_3), 52.1 (CH_3), 83.4 (CH), 97.8 (qC), 126.6 (CH), 128.4 (CH), 128.7 (CH), 133.6 (qC), 143.9 (CH), 144.8 (CH), 149.0 (qC), 158.5 (qC), 162.2 (qC), 164.8 (qC).

1,2,3-Trimethoxycarbonyl-7-oxanorbornadiene, 11e

$R_f = 0.48$ (EtOAc–hexanes, 1:1); IR (CH_2Cl_2): 3008, 2957, 2851, 1741, 1644, 1438, 1269, 1204, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.72 (d, $J = 2.1$ Hz, 1H), 7.25–7.29 (m, 2H); ^{13}C (APT) NMR ($CDCl_3$, 100 MHz): 52.5 (CH_3), 52.6 (CH_3), 53.1 (CH_3), 84.6 (CH), 94.0 (qC), 142.2 (CH), 144.3 (CH), 150.8 (qC), 153.6 (qC), 162.3 (qC), 162.9 (qC), 166.0 (qC). HRMS (CI) calcd. for $C_{12}H_{13}O_7$ (M + H): 269.0661; found: 269.0666.

1-Methylcarbonyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11f

$R_f = 0.26$ (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 2957, 1738, 1723, 1717, 1645, 1436, 1268, 1116 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 5.72(d, $J = 1.8$ Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 7.24 (dd, $J = 5.2$, 1.8 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 100 MHz): 26.6 (CH_3), 52.4 (CH_3), 52.6 (CH_3), 84.0 (CH), 99.2 (qC), 141.9 (CH), 144.3 (CH), 149.7 (qC), 154.6 (qC), 162.3 (qC),163.3 (qC), 201.7 (qC). HRMS (CI) calcd. for $C_{12}H_{13}O_6$ (M + H): 253.0712; found: 253.0719.

1-Aminocarbonyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11g

$R_f = 0.46$ (EtOAc–hexanes, 1:1); IR (CH_2Cl_2): 3177, 2955, 1717, 1669, 1433, 1297, 1254, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H), 3.83 (s, 3H), 5.73 (d, $J = 1.9$ Hz, 1H), 5.98 (brs, 1H), 6.28 (brs, 1H), 7.23 (dd, $J = 5.2$, 1.9 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H), ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): 52.4 (CH_3), 52.7 (CH_3), 83.5 (CH), 94.8 (qC), 142.8 (CH), 143.9 (CH), 147.5 (qC), 155.8 (qC), 162.1 (qC), 163.8 (qC), 167.4 (qC). HRMS (CI) calcd. for $C_{11}H_{12}NO_6$ (M + H): 254.0665; found: 254.0660.

1-Hydroxymethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11h

$R_f = 0.16$ (EtOAc–hexanes, 1:1); IR (CH_2Cl_2): 3493, 2955, 1716, 1637, 1438, 1302, 1271 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.78 (s, 3H), 3.82 (s, 3H), 4.25 (ABq, 2H), 5.65 (d, $J = 1.8$ Hz, 1H), 7.03 (d, $J = 5.3$ Hz, 1H), 7.22 (dd, $J = 5.3$, 1.8 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 100 MHz): 52.3 (CH_3), 52.5 (CH_3), 59.9 (CH_2), 83.9 (CH), 98.3 (qC), 142.5 (CH), 144.9 (CH), 152.6 (qC), 153.6 (qC), 162.9 (qC), 164.6 (qC). HRMS (CI) calcd. for $C_{11}H_{13}O_6$ (M + H): 241.0712; found: 241.0719.

1-Acetylaminomethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11i

$R_f = 0.24$ (EtOAc pure); IR (CH_2Cl_2): 3390, 2954, 1716, 1674, 1530, 1436, 1267, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.92 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 3.85–4.14 (m, 2H), 5.59 (d, $J = 1.7$ Hz, 1H), 5.96 (brs, 1H), 6.95 (d, $J = 5.3$ Hz, 1H), 7.17 (dd, $J = 5.2$, 1.6 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): 23.0 (CH_3), 37.8 (CH_2), 52.4 (CH_3), 52.6 (CH_3), 83.7 (CH), 96.9 (qC), 142.9 (CH), 145.3 (CH), 152.8 (qC), 153.6 (qC), 162.6 (qC), 163.9 (qC), 170.1 (qC).

1-Trimethylsilyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 11j

$R_f = 0.4$ (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 2954, 1717, 1436, 1251, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.16 (s, 9H), 3.73 (s, 3H), 3.70 (s, 3H), 5.68 (d, $J = 1.5$ Hz, 1H), 7.14 (d, $J = 5.2$ Hz, 1H), 7.19 (dd, J = 5.2, 1.5 Hz, 1H); ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): −3.3 ($3 \times CH_3$), 52.0 ($2 \times CH_3$), 85.3 (CH), 91.5 (qC), 143.3 (CH), 146.1 (CH), 150.4 (qC), 159.3 (qC), 163.0 (qC), 165.7 (qC). HRMS (CI) calcd. for $C_{13}H_{19}SiO_5$ (M + H): 283.1002; found: 283.1008.

2,3-Dimethoxycarbonyl-4-methoxyphenol, 12k

$R_f = 0.48$ (EtOAc–hexanes, 1:1); IR (CH_2Cl_2); 3145, 3025, 1738, 1677, 1475, 1456, 1227, 1119 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.75 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.97 (d, $J = 9.2$ Hz, 1H), 7.11 (d, $J = 9.2$ Hz, 1H), 10.44 (s, 1H); ^{13}C (APT) NMR ($CDCl_3$, 75 MHz): 52.5 (CH_3), 52.9 (CH_3), 57.2 (CH_3) 109.4 (qC), 119.4 (CH), 120.5 (CH), 124.1(qC), 148.8 (qC), 155.6 (qC), 167.4 (qC), 168.9 (qC); HRMS (CI) calcd. for $C_{11}H_{13}O_6$ (M + H): 241.0712; found: 241.0719.

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