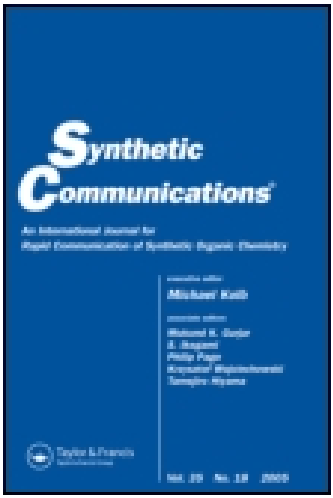

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A Novel Synthesis of 1-Isochromanols via Hetero Diels-Alder Reaction of Carbonyl Compounds with 1-Trimethylsilyloxy-benzocyclobutene as a Precursor of α-Oxy-o-Quinodimethane Under Mild Condition

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A NOVEL SYNTHESIS OF 1-ISOCHROMANOLS *VIA* HETERO DIELS-ALDER REACTION OF CARBONYL COMPOUNDS WITH 1-TRIMETHYLSILYLOXY-BENZOCYCLOBUTENE AS A PRECURSOR OF α-OXY-*o*-QUINODIMETHANE UNDER MILD CONDITION

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Abstract: Reaction of 1-trimethylsilyloxybenzocyclobutene(1) with carbonyl compounds catalyzed by tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) at room temperature gave 1-isochromanol derivatives as corresponding hetero Diels-Alder adducts in good yields.

Although a few syntheses of 1-isochromaol have been reported,[1,2] almost of these methods are photocyclization of *o*-tolualdehyde and have some limitation. Recently, we have found the convenient synthesis of 1-isochromaol by using isomerization of benzocyclobutene. Benzocyclobutene as one of precursors of

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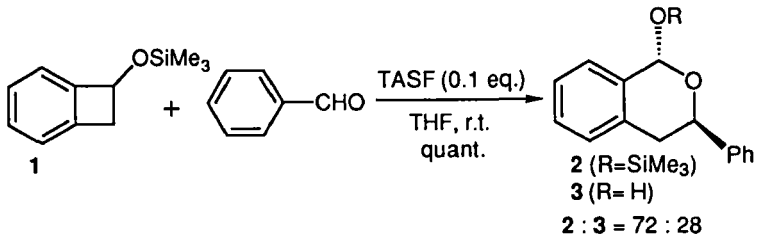
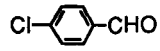
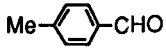
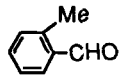
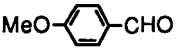


Scheme 1

o-quinodimethane is utilized to produce benzo-substituted cyclic compounds.[3] Generally, the thermal isomerization of benzocyclobutene to *o*-quinodimethane needs severe condition.[4] The isomerization temperature of the benzocyclobutenes is known to depend on their structures and electron donating substituent at the benzylic position lowers its temperature.[5,6] We have found that reactions using 1-trimethylsilyloxybenzocyclobutene (**1**) as a precursor of corresponding α-oxy-*o*-quinodimethane proceed with carbonyl compounds to afford 1-isochromanol derivatives as the corresponding hetero Diels-Alder products under very mild conditions. To a mixture of benzaldehyde(2 eq.) and a catalytic amount of tris(dimethylamino)sulfur (trimethylsilyl) difluoride (TASF) (0.1 eq.) in THF , **1**[7,8] was added at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. Conventional work up yielded 1-trimethylsilyloxy- and 1-hydroxy-3-phenyl isochroman (**2** and **3**, ratio 72 : 28), typical hetero Diels-Alder products, in a quantitative yield (Scheme 1). Use of 1.0 eq. of benzaldehyde caused a slight decrease yield (91%).

The structures of **2** and **3** were confirmed by the IR, ^{1}H-NMR, and ^{13}C-NMR spectra. Simple treatment of **2** with hydrochloric acid (1 M) in THF resulted in

Table 1. Reaction of **1** with Substituted Benzaldehydes[a)]

Time (h)	Benzaldehydes (2 eq.)	Yield[b)] (%)	Product Ratio R=TMS : R=H
0.5		98	63 : 37
0.5		83	58 : 42
0.5		85	61 : 39
24		82	64 : 36

a) r. t., THF (0.2 mol/l), TASF;10 mol%.
b) Total yield of the two products, Isolated by HPLC.

a complete conversion to **3**. The stereo chemistry of **3** was determined to be *trans* by the ^{1}H-NMR.[1] Similarly, benzyltrimethylammonium fluoride (10 mol%) also catalyzed this reaction to give a mixture of **2** and **3** under the same condition. However, CsF was not effective at all, probably because of its insolubility in the reaction solvent. Similar isochroman derivatives were obtained from a few substituted benzaldehydes under the same condition (10 mol% TASF) in high yields (Table 1).

The total yield decreased as electron-donating character of the substituents increased. The stereo chemistry of the hetero Diels-Alder adduct generated by the reaction of **1** with *o*-tolualdehyde was confirmed to be *trans* by X ray crystal structural analysis. *p*-Hydroxybenzaldehyde did not give any products, possibly because the hydroxy group would deactivate the catalyst. In the case of *p*-nitrobenzaldehyde, a complex mixture was obtained, which would be formed by the nitro group-participating reaction. The aromatic aldehydes (benzaldehydes) as hetero dienophiles were extended to alkyl and unsaturated aldehyde and

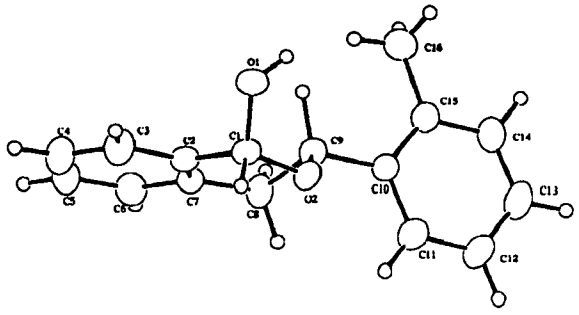
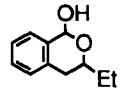
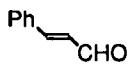
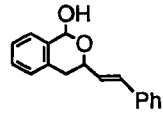
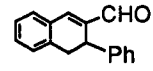
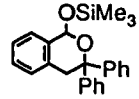
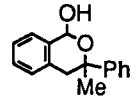
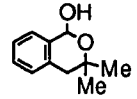
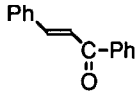
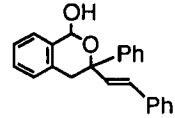
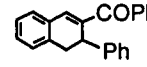
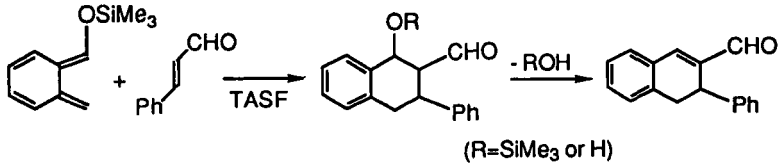


Figure 1 ORTEP drawing of 3-(2-methylphenyl)-1-isochromanol

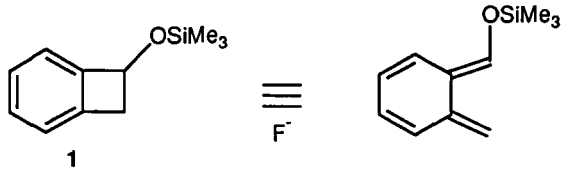
Table 2. Reaction of **1** with Various Carbonyl Compounds[a)]

Time(h)	Dienophiles[b)]	D-A adducts (Yield[c)])		
24	CH_3CH_2CHO		30%	
24			40%	 35%
0.5	PhCOPh		72%	
0.5	$PhCOCH_3$		40%	
0.5	CH_3COCH_3		27%	
0.5			22%	 60%

a) r. t., THF (0.2 mol/l), TASF;10 mol%. b) 2 eq.
c) Isolated by HPLC separation.



Scheme 2



Scheme 3

aromatic, alkyl, and unsaturated ketones. Table 2 summarizes the results of reactions with **1** under the same conditions(10 mol% TASF).

Corresponding 1-isochromanol derivatives were obtained in moderate yields and the by-product was mainly *o*-tolualdehyde which would be generated by the reaction of α-oxy-*o*-quinodimethane with α-proton of carbonyl compounds. In the reaction of benzophenone which having no α-hydrogen, the corresponding hetero Diels-Alder adduct was obtained in a good yield(72%). When α, β-unsaturated aldehyde and ketone were employed as dienophiles, 2-formyl- and 2-benzoyl-3-phenyl-3,4-dihydro naphthalene were also isolated in 35% and 60% yields, respectively. Formation of these products would be simply explained by usual Diels-Alder reaction of the C-C double bond followed by a successive elimination of ROH (Scheme 2).

Thus, novel synthesis of 1-isochromanol derivatives was achieved by using hetero Diels-Alder reaction of 1-trimethylsilyloxy-*o*-quinodimethane, which can be readily generated from **1** in the presence of TASF as a catalyst under very mild condition (Scheme 3).

EXPERIMENTAL

Melting point was measured on a Yanagimoto MP and is uncorrected. GC analyses were carried out using a Shimadzu GC8APF gas chromatography. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on JNM EX-90, and JNM GX-400 spectrometers. HPLC separations were carried out using a JNI LC-908 (eluent; THF, columns; JAIGEL-1H and 2H).

THF was distilled, under nitrogen, immediately prior to use from sodium benzophenone ketyl. 1-Trimethylsilyloxybenzocyclobutene(**1**) was synthesized according to the literature.[7,8] All other chemicals were purchased and purified by the conventional methods. All reactions were run under a dry nitrogen.

Typical Procedure: To a solution of 0.119 g (1.13 mmol) of benzaldehyde and 15.5 mg (0.0563 mmol) of TASF in 2 mL of dry THF was added 0.108 g (0.563 mmol) of 1-trimethylsilyloxybenzocyclobutene(**1**). The reaction mixture was stirred at room temperature for 0.5 h under nitrogen and then 10 mL of *n*-hexane and 30 mL of water were added into the mixture. The *n*-hexane layer was separated and the aqueous layer was extracted with several 5-10 mL portions of *n*-hexane. The total *n*-hexane solution was washed with 10 mL of water, dried

over $MgSO_4$, and evaporated to obtain 0.121 mg (0.405 mmol, 72%) of 1-trimethylsilyloxy-3-phenyl isochroman (**2**) and 0.036 mg (0.158 mmol, 28%) of 3-phenyl-1-isochromanol (**3**) by HPLC separation.

2; IR (neat): 1088 ($OSiMe_3$), 1022 ($-CH_2-O-CH_2-$) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.5 (m, 9H, Ph), 6.4 (s, 1H, CH), 5.5 (dd, *J*=6.84 Hz and 7.92 Hz, 1H, CH) 3.2 (d, *J*=1.71 Hz, 1H, CH_2), 3.1 (s, 1H, CH_2), 0.4 (s, 9H, $SiMe_3$). ^{13}C-NMR (90 MHz, $CDCl_3$): δ 142.00, 136.06, 133.69, 128.33, 128.29, 128.00, 127.83, 127.36, 127.01, 126.47, 126.00, 125.49, 92.66, 68.84, 36.15, 0.0. Anal. Calcd for $C_{18}H_{22}O_2Si$: C, 72.44; H, 7.43. Found: C, 73.26; H, 7.32.

3; Mp 106 °C (lit.[1] 105-106 °C). IR (KBr): 3300-3070 (OH), 1020 ($-CH_2-O-CH_2-$) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 9H, Ph), 6.2 (s, 1H, CH), 5.3 (dd, *J*=9.72 Hz and 5.2 Hz, 1H, CH), 3.2 (br, s, 1H, OH), 3.0 (d, *J*=5.2 Hz, 1H, CH_2), 2.9 (s, 1H, CH_2).

Spectral data

1-Trimethylsilyloxy-3-(4-chlorophenyl)isochroman; Yield 62 %. IR (neat): 1088 ($OSiMe_3$), 1022 ($-CH_2-O-CH_2-$) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.0 (m, 8H, Ph), 5.9 (s, 1H, CH), 5.0 (t, *J*=7.5 Hz , 1H, CH), 2.7 (d, *J*=7.5 Hz, 2H, CH_2), 0.3 (s, 9H, $SiMe_3$).

3-(4-Chlorophenyl)-1-isochromanol; Yield 36 %. IR (KBr): 3300-3060 (OH), 1019 ($-CH_2-O-CH_2-$) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 8H, Ph), 6.3 (s, 1H, CH), 5.2 (m, 1H, CH), 3.8 (br, s, 1H, OH), 2.9 (m, 2H, CH_2).

1-Trimethylsilyloxy-3-(4-methylphenyl)isochroman; Yield 48 %. IR (neat): 1089 ($OSiMe_3$), 1023 ($-CH_2-O-CH_2-$) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.5 (m, 8H, Ph), 6.4 (s, 1H, CH), 5.4 (dd, *J*=8.6 Hz and 5.9 Hz, 1H, CH), 3.2 (d,

J=2.9 Hz, 1H, CH_2) 3.1 (s, 1H, CH_2) 2.6 (s, 3H, CH_3), 0.5 (m, 9H, $SiMe_3$).

3-(4-Methylphenyl)-1-isochromanol; Yield 35 %. IR (KBr): 3310-3070 (OH), 1020 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.4 (m, 8H, Ph), 6.2 (s, 1H, CH), 5.3 (dd, J=10.0 Hz and 4.7 Hz, 1H, CH), 3.9 (br, s, 1H, OH), 3.0 (d, J=10.0 Hz, 1H, CH_2) 2.9 (d, J=4.5 Hz, 1H, CH_2), 2.5 (s, 3H, CH_3).

1-Trimethylsilyloxy-3-(2-methylphenyl)isochroman; Yield 52 %. IR(neat): 1089 ($OSiMe_3$), 1023 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.5 (m, 1H, Ph), 7.2 (m, 7H, Ph), 6.2 (s, 1H, CH), 5.4 (dd, J=8.6 Hz and 6.1 Hz, 1H, CH), 2.9 (d, J=2.4 Hz, 1H, CH_2), 2.9 (s, 1H, CH_2) 2.4 (s, 3H, CH_3), 0.2 (m, 9H, $SiMe_3$).

3-(2-Methylphenyl)-1-isochromanol; Yield 33 %. Mp 106 °C (lit.[1] 105-106 °C). IR(KBr): 3310-3070 (OH), 1021(-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.6 (m, 1H, Ph), 7.2 (m, 7H, Ph), 6.1 (s, 1H, CH), 5.4 (dd, J=10.2 Hz and 4.4 Hz, 1H, CH), 3.5 (br, s, 1H, OH), 3.0 (d, J=8.6 Hz, 1H, CH_2), 2.9 (d, J=4.4 Hz, 1H, CH_2), 2.4 (s, 3H, CH_3).

1-Trimethylsilyloxy-3-(4-methoxyphenyl)isochroman; Yield 52 %. IR(neat): 1240 (OMe), 1088 ($OSiMe_3$), 1025 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.2 (m, 8H, Ph,), 6.1 (s, 1H, CH), 5.2 (dd, J=9.3 Hz and 5.8 Hz, 1H, CH), 3.8 (s, 3H, OMe), 3.0 (d, J=9.3 Hz, 1H, CH_2), 2.9 (s, 1H, CH_2), 0.2 (m, 9H, $SiMe_3$).

3-(4-Methoxyphenyl)-1-isochromanol; Yield 30 %. IR (KBr): 3300-3060 (OH), 1245 (OMe), 1022 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.2 (m, 8H, Ph), 6.1 (s, 1H, CH), 5.1 (dd, J=10.0 Hz and 4.4 Hz, 1H, CH), 3.9 (br, s, 1H, OH), 3.8 (s, 3H, OMe), 3.0 (d, J=9.0 Hz, 1H, CH_2), 2.9 (s, 1H, CH_2).

3-Ethyl-1-isochromanol; Yield 30 %. IR (KBr): 3300-3080 (OH), 1021 (-CH_2-

O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.2 (m, 4H, Ph,), 6.2 (s, 1H, CH), 4.2 (m, 1H, CH), 2.7 (m, 3H, CH_2, OH), 1.8 (m, 5H, C_2H_5).

3-Phenethyl-1-isochromanol; Yield 40 %. IR (KBr): 3300-3070 (OH), 1630 (C=C), 1022 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 9H, Ph), 6.7 (dd, *J*= 16.1 Hz and 0.9 Hz, 1H, CH=CH), 6.3 (dd, *J*=16.1 Hz and 5.8 Hz, 1H, CH=CH), 6.1 (s, 1H, CH), 5.8 (m, 1H, CH), 3.7 (br, s, 1H, OH), 2.8 (d, *J*=5.8 Hz, 1H, CH_2), 2.7 (s, 1H, CH_2).

2-Formyl-3-phenyl-3,4-dihydro-naphthalene; Yield 35 %. IR(neat): 1676 (CHO), 1628 (C=C) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 9.6 (s, 1H, CHO), 7.3 (m, 10H, Ph, C=CH), 4.2 (dd, *J*=8.0 Hz and 1.9 Hz, 1H, CH), 3.3 (ddd, *J*=17.0 Hz, 8.0 Hz, and 0.5 Hz, 1H, CH_2), 3.0 (dd, *J*=17.0 Hz and 1.9 Hz, 1H, CH_2).

1-Trimethylsilyloxy-3,3-diphenyl isochroman; Yield 72 %. IR (neat): 1089 ($OSiMe_3$), 1022 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 14H, Ph), 5.6 (s, 1H, CH), 5.1 (dd, *J*=23.9 Hz and 18.0 Hz, 2H, CH_2), 0.3 (s, 9H, $SiMe_3$).

3-Methyl-3-phenyl-1-isochromanol; Yield 40 %. IR (neat): 3300-3070 (OH), 1023 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.4 (m, 9H, Ph), 6.3 (s, 1H, CH), 5.6 (dd, *J*=8.9 Hz and 5.7 Hz, 1H, CH), 3.1 (br, s, 1H, OH), 3.0 (d, *J*=5.9Hz, 1H, CH_2), 2.9 (d, *J*=5.9Hz, 1H, CH_2), 2.4 (s, 3H, CH_3).

3,3-Dimethyl-1-isochromanol; Yield 27 %. IR (KBr): 3300-3090 (OH), 1023 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.2 (m, 4H, Ph), 6.1 (s, 1H, CH), 5.4 (dd, *J*=10.2 Hz and 4.4 Hz, 1H, CH), 3.7 (br, s, 1H, OH), 3.0 (d, *J*=10.2 Hz, 1H, CH_2), 2.9 (d, *J*=4.4 Hz, 1H, CH_2), 2.4 (m, 6H, CH_3).

3-Phenyl-3-phenethyl-1-isochromanol; Yield 22 %. IR (KBr): 3300-3070 (OH), 1629 (C=C), 1024 (-CH_2-O-CH_2-) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.2 (m, 16H, Ph, HC=CH), 5.6 (s, 1H, CH), 3.0 (m, 3H, CH_2, OH).

2-Benzoyl-3-phenyl-3,4-dihydro-naphthalene; Yield 60 %. IR (neat): 1680 (CO), 1630 (C=C) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 15H, Ph, C=CH), 4.5 (dd, *J*=8.0 Hz and 3.3 Hz, 1H, CH), 3.5 (dd, *J*=16.3 Hz and 8.0 Hz, 1H, CH_2), 3.1 (dd, *J*=16.3 Hz and 3.3 Hz, 1H, CH_2).

X-ray crystal structural analysis of 3-(2-methylphenyl)-1-isochromanol; $C_{16}H_{16}O_2$: 240.30, monoclinic, space group C2/c, a=26.424(6), b=5.083(4), c=23.055(3) Å, β=122.61(1)°, V=2608(2) $Å^3$, Dc=1.224gcm^{-1}, and Z=8. Data were collected at 23 °C, and the structure was solved by direct methods and refined to R=0.065, Rw=0.060 for 1548 reflections with I>3.00σ(I).

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