

Synthesis of 2,3-Disubstituted and 2,3,6-Trisubstituted 1*H*-Indol-5-ols from 3-Alkenylphenols

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Fused heteroaromatic systems, such as indoles and tetrahydrocarbazoles, bearing functional groups such as methoxy or hydroxyl at specific positions, represent particularly attractive synthetic targets.^{1,2}

The Fischer indole process, the Borsche process, and the Japp-Klingemann reaction are useful means of obtaining 5-methoxy-1*H*-indole derivatives.^{3,4} However, these methods do not provide 1*H*-indol-5-ols or 6-substituted 1*H*-indol-5-ols directly or selectively.

Using the Nenitzescu process, a 1*H*-indol-5-ol ring can be conveniently generated from a quinone and a β -(alkoxycarbonyl) enamine. Substitution at the 3-position of the 1*H*-indol-5-ols thus formed is restricted to an electron-attractive group such as the acyl or alkoxycarbonyl group.⁵

In a previous paper, a novel process was proposed to obtain 1-(arylamino)-3-alkyl (or aryl)-substituted 1*H*-indol-5-ols and tetrahydro-1*H*-carbazol-6-ols.¹ The arylamino group was removed reductively by Raney nickel to produce 1*H*-indol-5-ols with 3- or 2,3-substituents in good yield. This process is based on a diazo coupling reaction of 3-alkenylphenol with an arenediazonium salt. However, the scope and limitations of the method have yet to be determined. Such study is warranted because this process has some advantages over other available procedures for the synthesis of 1*H*-indol-5-ols, in terms of yields and ease.⁶

In this paper, we deal with the applicability of the method to alkenylphenols having (1) cycloalkenyl substituents other than 6-membered ones and (2) the *E* configuration only or a mixture of *E* and *Z* configurations. Further, we report a substituent effect on the cycloaddition

reaction by an alkoxy or an alkyl group at position 6 of the 3-alkenyl phenol.

Results and Discussion

The starting 3-(1-cycloalken-1-yl)phenols **1** were those having a 5- to 12-membered cyclic group (**1a-1e**) and 3-(3,4-dihydronaphthalen-2-yl)phenol (**1f**). The (*E*)- and (*Z*)-3-(1-substituted- α,β -unsaturated)phenol substrates studied included **2a-2e**.

In its simplest form, the present 1*H*-indol-5-ol synthesis is essentially a one-pot reaction in which an arenediazonium salt (**3**) is added to a 3-alkenylphenol to yield a 4-(aryloxy)-3-alkenylphenol as an intermediate. Upon treatment with dilute acid at room temperature, this intermediate rearranges to a 1-(arylamino)-1*H*-indol-5-ol spontaneously (Scheme I). Our results are shown in Table I.

As indicated, 1*H*-indol-5-ols **6** and **7** were readily prepared from **2** and **1**, respectively, under very mild reaction conditions, in good to excellent yield.

The effects of substituents on indole ring formation were systematically investigated. However, in general (1) an aryl group adjacent to an alkenyl group, (2) *E* vs *Z* configuration, (3) ring size, and (4) 6-substitution did not alter the outcome of the reaction. These results confirm the versatility of this new intramolecular cycloaddition reaction.

The diazo-type compound **4** was not isolated, but the formation of a compound of this type was indicated by ¹H NMR and direct inlet MS spectra of the reaction mixture of 3-(1-cyclohexen-1-yl)phenol with a benzene-*d*₅-diazonium salt under alkaline conditions.¹ These results suggest the presence of the probable indole precursor **5**, and in particular **5b**, as shown in Scheme I, which would not likely be affected by the configuration of the alkenyl group in producing indoles.

Conclusion

The reaction of a phenol that has an α,β -unsaturated substituent at the 3-position bearing one β -hydrogen atom with an arenediazonium salt provides a useful route to various kinds of 1*H*-indoles having a free hydroxyl group at the 5-position. The unusually mild conditions under which this synthesis of 1*H*-indoles proceeds should permit the construction of this ring system even in the presence of substituent groups sensitive to elevated temperature, strong acids, strong bases, or oxidation.

We plan to apply this method to the synthesis of several 1*H*-indol-5-ol derivatives, for which the Fischer process proved inadequate.

Research is in progress to further define the scope and limitations of this new intramolecular cycloaddition reaction.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. General synthetic and purification procedures are the same as those reported. The cyclic-type alkenylphenols were obtained by a procedure used for 3-(1-cyclohexen-1-yl)phenol, and the linear-type alkenylphenols were obtained as a procedure used for the preparation of 3-(1-phenylethenyl)phenol as disclosed in a previous paper.¹ Melting points and boiling points are uncorrected. ¹H NMR spectra were recorded on a Varian Gemini-

(1) Satomura, M. *J. Org. Chem.* 1993, 58, 3757. Satomura, M. U.S. Patent 4914213, 1990.

(2) Compounds **1a**, **1c**, **7a**, and **7c** are disclosed in our patent. Satomura, M. Japan, Tokkai Hei 4-235965, 1992. Compounds **1e**, **1f**, **7e**, and **7f** are disclosed in our patent. Satomura, M. Japan, Tokkai Hei 4-282364, 1992.

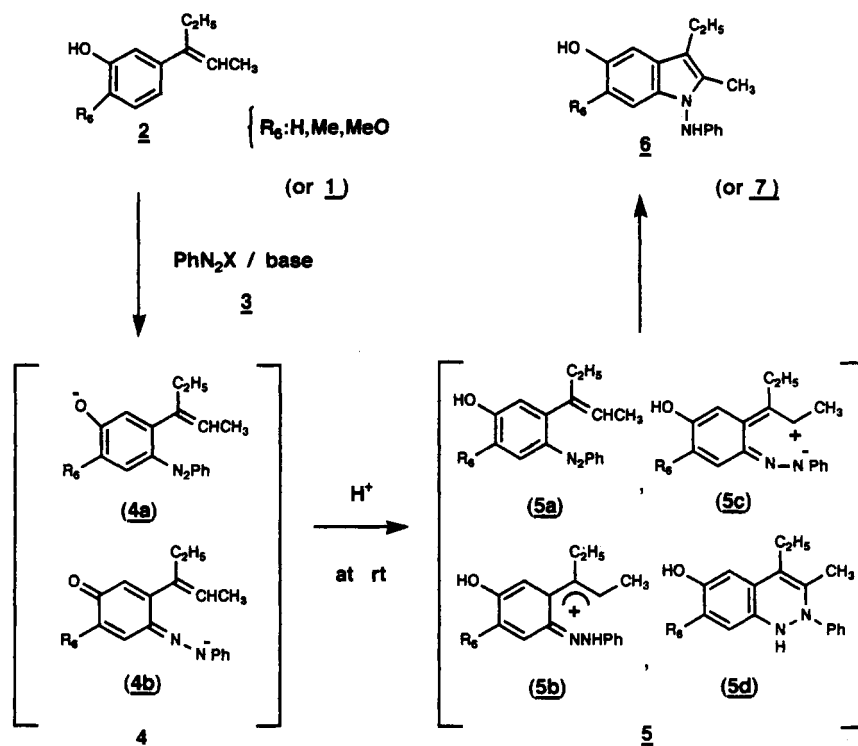
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Scheme I. Reaction Scheme of 1*H*-Indol-5-ol Synthesis and Probable Indole PrecursorsTable I. Preparation of 1*H*-Indol-5-ols and 3-Alkenylphenols

| structure | linear type | | | 1 <i>H</i> -indol-5-ol | | | 3-alkenylphenol | | |
|-----------|----------------|----------------------------------|----------------------------------|------------------------|-----------|-------------|-----------------|-----------|--------------|
| | R ₆ | R ₇ | R ₈ | no. | yield (%) | mp (°C) | no. | yield (%) | bp (°C/mmHg) |
| 6a-e | H | Me | Et | 6a | 88 | 134.2–135.4 | 2a | 46 | 143.5–145/14 |
| | H | Me | Ph | 6b | 86 | 139.8–140.7 | 2b | 68 | |
| 2a-e | H | C ₂ H ₄ Ph | C ₃ H ₆ Ph | 6c | 84 | 123.2–124 | 2c | 93 | |
| | Me | Me | Et | 6d | 82 | 130.2–131.8 | 2d | 50 | |
| | MeO | Me | Et | 6e | 82 | 135.2–136.8 | 2e | 72 | |
| structure | cyclic type | | | 1 <i>H</i> -indol-5-ol | | | 3-alkenylphenol | | |
| | n | m | x | no. | yield (%) | mp (°C) | no. | yield (%) | bp (°C/mmHg) |
| 7a-f | 5 | 0 | 0 | 7a | 54 | 152–154 | 1a | 55 | 124–127/2 |
| | 6 | 0 | 0 | 7b | 71 | 161–162 | 1b | 52 | 135–138/1 |
| | 10 | 0 | 0 | 7c | 61 | 166.5–167 | 1c | 51 | 187–190/1 |
| 1a-f | 1 | 0 | 1 | 7d | 51 | 178–180 | 1d | 37 | |
| | 2 | 0 | 1 | 7e | 32 | 103–105 | 1e | 56 | 165–172/2 |
| | 0 | 2 | 1 | 7f | 56 | 193–194.5 | 1f | 73 | |

3000 300-MHz spectrometer. The ¹H NMR spectra were determined, unless otherwise indicated, as solutions in acetone-*d*₆. The internal standard was TMS. UV spectra were recorded on a Shimadzu MPS-2000 UV/vis spectrophotometer as solutions in EtOH. HRMS spectra were recorded on a Hitachi M-80B double-focusing gas chromatograph mass spectrometer. HPLC spectra were recorded on a Shimadzu LC-6A, liquid chromatograph with an ODSH column.

Linear-Type 1*H*-Indol-5-ols. 3-Ethyl-2-methyl-1-(phenylamino)-1*H*-indol-5-ol (6a): eluent, hexane–EtOAc (8:2), recrystallized from benzene; ¹H NMR (300 MHz, acetone-*d*₆) δ ppm 8.16 (s, 1H), 7.60 (s, 1H), 7.15 (t, 2H, *J* = 8.5 Hz), 6.97 (d, 1H, *J* = 8.4 Hz), 6.96 (d, 1H, *J* = 2.3 Hz), 6.79 (t, 1H, *J* = 8.4 Hz), 6.63 (dd, 1H, *J* = 2.3, 8.4 Hz), 6.45 (d, 2H, *J* = 8.5 Hz), 2.68 (dd, 2H), 2.16 (s, 3H), 1.22 (t, 3H); UV [λ_{max} , nm (ϵ)] 228 (30 800), 282 (11 300); HRMS calcd for C₁₇H₁₈N₂O 266.1418, found 266.1435.

Anal. Calcd for C₁₇H₁₈N₂O: C, 76.67; H, 6.91; N, 10.51. Found: C, 76.77; H, 6.88; N, 10.38.

2-Methyl-3-phenyl-1-(phenylamino)-1*H*-indol-5-ol (6b): eluent, hexane–EtOAc (8:2), recrystallized from benzene–hexane; ¹H NMR δ ppm 8.33 (s, 1H), 7.67 (s, 1H), 7.54 (dd, 2H, *J* = 1.3, 8.2 Hz), 7.47 (t, 2H, *J* = 8.2 Hz), 7.29 (t, 1H, *J* = 7.2 Hz), 7.18 (t, 2H, *J* = 8.6 Hz), 7.10 (d, 1H, *J* = 2.3 Hz), 6.82 (t, 1H, *J* = 7.3 Hz), 6.70 (dd, 1H, *J* = 2.3, 8.6 Hz), 6.56 (dd, 2H, *J* = 1.1, 8.6 Hz), 2.39 (s, 3H); UV 227 (31 400), 280 (17 600). Anal. Calcd for C₂₁H₁₈N₂O: C, 80.23; H, 5.77; N, 8.90. Found: C, 80.40; H, 5.87; N, 8.88.

1-(Phenylamino)-2-(2-phenylethyl)-3-(3-phenylpropyl)-1*H*-indol-5-ol (6c): eluent, benzene, crystallized on treatment with hexane; ¹H NMR δ ppm 8.11 (s, 1H), 7.60 (s, 1H), 7.31–7.13 (m, 10H), 7.08 (dd, 2H, *J* = 1.6, 8.2 Hz), 6.96 (s, 1H), 6.94 (dd, 1H, *J* = 2.2, 8.3 Hz), 6.79 (t, 1H, *J* = 8.2 Hz), 6.64 (d, 1H, *J* =

8.5 Hz), 6.50 (d, 2H, $J = 7.9$ Hz), 2.86 (bs, 4H), 2.73–2.63 (m, 4H), 2.08–2.06 (m, 2H); UV 227 (35 500), 283 (12 700). Anal. Calcd for $C_{31}H_{30}N_2O$: 83.37; H, 6.77; N, 6.27. Found: C, 83.29; H, 6.90; N, 6.24.

2,6-Dimethyl-3-ethyl-1-(phenylamino)-1H-indol-5-ol (6d): eluent, $CHCl_3$ -MeCN (19:1), crystallized on standing; 1H NMR δ ppm 8.16 (s, 1H), 7.51 (s, 1H), 7.15 (dd, 2H, $J = 8.5$, 7.4 Hz), 6.94 (s, 1H), 6.88 (s, 1H), 6.78 (t, 1H, $J = 7.4$ Hz), 6.43 (dd, 2H, $J = 8.5$, 1 Hz), 2.67 (dd, 2H), 2.22 (s, 3H), 2.20 (s, 3H), 1.19 (t, 3H); UV 227 (28 400), 283 (10 500); HRMS calcd 280.1574, found 280.1493. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 10.0. Found: C, 77.04; H, 7.32; N, 9.92.

3-Ethyl-6-methoxy-2-methyl-1-(phenylamino)-1H-indol-5-ol (6e): eluent $CHCl_3$ -MeCN (19:1), recrystallized from benzene; 1H NMR δ ppm 8.17 (s, 1H), 7.14 (dd, 2H, $J = 8.6$, 7.4 Hz), 6.95 (s, 1H), 6.81 (s, 1H), 6.78 (t, 1H, $J = 7.4$ Hz), 6.42 (dd, 2H, $J = 8.6$, 1.0 Hz), 3.75 (s, 3H), 2.67 (dd, 2H), 2.17 (s, 3H), 1.19 (t, 3H); UV 229 (29 000), 283 (8760), 301 (8360); HRMS calcd 296.1524, found 296.1530. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.03; H, 6.95; N, 9.39.

Cyclic-Type 1H-Indol-5-ols. 5,6,7,8,9,10-Hexahydro-5-(phenylamino)cyclohept[b]indol-2-ol (7a): eluent, $CHCl_3$ -MeCN (19:1), recrystallized from hexane-EtOAc; 1H NMR (300 MHz, acetone- d_6) δ ppm 8.18 (s, 1H), 7.56 (s, 1H), 7.13 (t, 2H, $J = 7.4$ Hz), 6.96 (d, 1H, $J = 8.5$ Hz), 6.89 (d, 1H, $J = 2.3$ Hz), 6.77 (t, 1H, $J = 7.4$ Hz), 6.59 (dd, 1H, $J = 2.3$, 8.5 Hz), 6.42 (dd, 2H, $J = 1.1$, 7.4 Hz), 2.78 (bs, 4H), 1.87 (m, 2H), 1.76 (m, 2H), 1.67 (m, 2H); UV 229 (29 500), 284 (11 100); HRMS calcd for $C_{19}H_{20}N_2O$: 292.1573, found 292.1555. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.00; H, 6.99; N, 9.69.

6,7,8,9,10,11-Hexahydro-5-(phenylamino)-5H-cyclooct[b]indol-2-ol (7b): eluent, $CHCl_3$ -MeCN (19:1), recrystallized from hexane-benzene; 1H NMR δ ppm 8.15 (s, 1H), 7.54 (s, 1H), 7.12 (t, 2H, $J = 8.5$ Hz), 6.93–6.91 (m, 2H), 6.76 (t, 1H, $J = 8.5$ Hz), 6.59 (dd, 1H, $J = 2.3$, 8.5 Hz), 6.45 (dd, 2H, $J = 1.1$, 8.5 Hz), 2.82 (bs, 4H), 1.70 (bs, 2H), 1.59 (bs, 2H), 1.45 (bs, 4H); UV 229 (29 300), 284 (11 100); HRMS calcd for $C_{20}H_{22}N_2O$ 306.1731, found 306.1763. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.14; H, 7.49; N, 8.91.

6,7,8,9,10,11,12,13,14,15-Decahydro-5-(phenylamino)-5H-cyclododec[b]indol-2-ol (7c): eluent, hexane-EtOAc (8:2), recrystallized from hexane; 1H NMR δ ppm 8.14 (s, 1H), 7.55 (s, 1H), 7.13 (t, 2H, $J = 8.4$ Hz), 6.98 (d, 1H, $J = 2.2$ Hz), 6.85 (d, 1H, $J = 8.5$ Hz), 6.77 (t, 1H, $J = 8.4$ Hz), 6.59 (dd, 1H, $J = 2.2$, 8.5 Hz), 6.44 (dd, 2H, $J = 1$, 8.4 Hz), 2.73 (t, 2H), 2.67 (bs, 2H), 1.80 (bs, 4H), 1.55 (bs, 4H), 1.40 (m, 8H); UV 228 (31 000), 283 (11 200); HRMS calcd for $C_{24}H_{30}N_2O$ 362.2357, found 362.2374. Anal. Calcd for $C_{24}H_{30}N_2O$: C, 79.52; H, 8.34; N, 7.73. Found: C, 79.45; H, 8.42; N, 7.63.

5-(Phenylamino)-5,6-dihydroindeno[2,1-b]indol-2-ol (7d): eluent, hexane-EtOAc (8:2), crystallized upon treatment with EtOAc; 1H NMR δ ppm 8.50 (s, 1H), 7.90 (s, 1H), 7.62 (d, 1H, $J = 7.4$ Hz), 7.42 (d, 1H, $J = 7.4$ Hz), 7.35–7.3 (m, 2H), 7.24–7.18 (m, 3H), 7.07 (t, 1H, $J = 7.4$ Hz), 6.87 (t, 1H, $J = 7.4$ Hz), 6.78 (d, 1H, $J = 8.7$ Hz), 6.62 (d, 2H, $J = 1.1$, 7.4 Hz), 3.68 (s, 2H); UV 235 (27 200), 280 (24 200). Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.96. Found: C, 80.71; H, 5.30; N, 8.81.

5,6-Dihydro-7-(phenylamino)-7H-benzo[c]carbazol-10-ol (7e): eluent, $CHCl_3$ -MeCN (19:1), recrystallized from hexane with small portions of acetone; 1H NMR δ ppm 8.40 (s, 1H), 7.82 (s, 1H), 7.78 (d, 1H, $J = 7.6$ Hz), 7.51 (d, 1H, $J = 1.6$ Hz), 7.29 (t, 1H, $J = 7.6$ Hz), 7.25–7.12 (m, 4H), 7.05 (t, 1H, $J = 7.6$ Hz), 6.84 (t, 1H, $J = 7.5$ Hz), 6.74 (dd, 1H, $J = 2.2$, 8.6 Hz), 6.57 (dd, 2H, $J = 1.1$, 7.5 Hz), 2.98 (t, 2H, $J = 7.4$ Hz), 2.85 (m, 2H); UV 229 (28 400), 282 (21 000); HRMS calcd for $C_{22}H_{18}N_2O$ 326.1418, found 326.1384. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.91; H, 5.60; N, 8.53.

6,11-Dihydro-11-(phenylamino)-5H-benzo[a]carbazol-8-ol (7f): eluent, benzene-hexane (1:1), recrystallized from hexane with small portions of acetone; 1H NMR δ ppm 8.51 (s, 1H), 8.04–8.01 (m, 1H), 7.81 (s, 1H), 7.28–7.25 (m, 1H), 7.16 (t, 2H, $J = 7.3$ Hz), 7.14–7.09 (m, 2H), 7.00 (d, 1H, $J = 8.6$ Hz), 6.98 (d, 1H, $J = 2.3$ Hz), 6.80 (t, 1H, $J = 7.3$ Hz), 6.69 (dd, 1H, $J = 2.3$, 8.6 Hz), 6.59 (d, 2H, $J = 7.3$ Hz), 3.03 (t, 2H, $J = 7.2$ Hz), 2.91 (t, 2H, $J = 7.2$ Hz); UV 236 (27 000), 332 (23 600); HRMS calcd for $C_{22}H_{18}N_2O$ 326.1418, found 326.1414. Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 81.02; H, 5.67; N, 8.57.

3-Alkenylphenols. 3-(1-Cyclohepten-1-yl)phenol (1a): 1H NMR δ ppm 8.13 (s, 1H), 7.09 (t, 1H, $J = 8.3$ Hz), 6.80–6.77 (m, 2H), 6.70–6.66 (m, 1H), 6.06 (t, 1H, $J = 6.8$ Hz); HRMS calcd for $C_{13}H_{16}O$ 188.1197, found 188.1217.

3-(1-Cycloocten-1-yl)phenol (1b): 1H NMR δ ppm 8.13 (s, 1H), 7.10 (t, 1H, $J = 8.0$ Hz), 6.90–6.87 (m, 2H), 6.71–6.68 (m, 1H), 5.98 (t, 1H, $J = 8.3$ Hz); HRMS calcd for $C_{14}H_{18}O$ 202.1356, found 202.1362.

3-(1-Cyclododecen-1-yl)phenol (1c): HRMS calcd for $C_{15}H_{20}O$ 258.1977, found 258.1949.

3-(1H-Inden-3-yl)phenol (1d): liq HRMS calcd for $C_{15}H_{12}O$ 208.0885, found 208.0872.

3-(3,4-Dihydronaphthalen-1-yl)phenol (1e): HRMS calcd for $C_{16}H_{14}O$ 222.1041, found 222.1078. Anal. Calcd for $C_{16}H_{14}O$: C, 77.11; H, 7.67. Found: C, 76.71; H, 7.71.

3-(3,4-Dihydronaphthalen-2-yl)phenol (1f): liq HRMS calcd for $C_{16}H_{14}O$ 222.1041, found 222.1055.

3-(1-Ethyl-1-propenyl)phenol (2a): HRMS calcd for $C_{11}H_{14}O$ 162.1044, found 162.1071; *E/Z* ratio at 240 nm, HPLC detection 1.1.

3-(1-Phenyl-1-propenyl)phenol (2b): liq HRMS calcd for $C_{21}H_{18}O$ 286.1407, found 286.1401; *E/Z* ratio, unseparable.

3-[4-Phenyl-1-(3-phenylpropyl)-1-butenyl]phenol (2c): liq HRMS calcd for $C_{25}H_{26}O$ 342.2033, found 342.1969; *E/Z* ratio 3.7.

Methyl 3-hydroxy-4-methylbenzoate: mp 116.9–118.3 °C (lit.⁸ mp 116–117 °C).

α,α -Diethyl-3-hydroxy-4-methylbenzenemethanol: mp 84–84.7 °C (recrystallized from hexane); HRMS calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1311.

3-(1-Ethyl-1-propenyl)-6-methylphenol (2d): liq HRMS calcd for $C_{12}H_{16}O$ 176.1199, found 176.1135, *E/Z* ratio 2.2.

Methyl 3-hydroxy-4-methoxybenzoate: mp 63.8–64.3 °C (lit.⁹ mp 66–67 °C).

α,α -Diethyl-3-hydroxy-4-methoxybenzenemethanol: mp 82.9–84.7 °C (recrystallized from EtOAc-hexane); HRMS calcd for $C_{12}H_{18}O_3$ 210.1254, found 210.1268.

3-(1-Ethyl-1-propenyl)-6-methoxyphenol (2e): liq HRMS calcd for $C_{12}H_{16}O_2$ 192.1149, found 192.1222; *E/Z* ratio 1.6.

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Registry numbers provided by author: 1-bromo-3-methoxybenzene, 2398-37-0; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7; 2,3-dihydro-1H-inden-1-one, 83-33-0; 3,4-dihydro-1(2H)-naphthalenone, 529-34-0; 3,4-dihydro-2(1H)-naphthalenone, 530-93-8; methyl 3-hydroxybenzoate, 19438-10-9; methyl 3-hydroxy-5-methylbenzoate, 3556-86-3; methyl 3-hydroxy-5-methoxybenzoate, 6110-74-9; 3-bromopropylbenzene, 2114-36-5; (3-hydroxyphenyl)phenylmethanone, 13020-57-0.

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