SUPPORTING INFORMATION

for

"Aminolysis of Epoxides in a Microreactor System: A Continuous Flow Approach Towards the Synthesis of Indacaterol and Metoprolol"

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Quantitative analysis procedures, characterization data, and ¹H NMR spectra for major aminolysis products.

pp S1-S50



Aminolysis of phenyl glycidyl ether with 2-aminoindan. Purified by preparative TLC (9:1 dichloromethane/methanol). 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 3 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using a gradient of 40% methanol in water to 75% methanol in water over 25 min and holding at 75% methanol in water for 5 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 15-20 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 254 nm. Retention times for phenyl glycidyl ether ~ 10.3 min, SI-1 ~ 5.0 min, SI-2 ~ 15.7 and 15.8 min, and naphthalene ~ 25.1 min.

PhO H
PhO H
NMR (400 MHz, CDCl₃) δ 7.32-7.26 (m, 2H), 7.23-7.16 (m, 4H), 6.98 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 4.10-4.05 (m, 1H), 3.99-3.98 (m, si-1
2H), 3.69-3.63 (m, 1H), 3.22-3.17 (dd, J = 6.0, 15.6 Hz, 2H), 2.97-2.94 (dd, J = 3.6, 12.0 Hz, 1H), 2.85-2.78 (m, 3H), 2.75 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 158.6, 141.6, 141.5, 129.5, 126.5, 124.8, 124.7, 121.0, 114.5, 70.4, 68.5, 59.7, 50.3, 40.1, 40.0; HRMS ESI *m/z* calcd for [M+H]⁺ 284.1645, obsd 284.1651.





Aminolysis of phenyl glycidyl ether with *tert*-butylamine. Purified by preparative TLC (9:1 dichloromethane/methanol). 5 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using a gradient of 40% methanol in water to 75% methanol in water over 25 min and holding at 75% methanol in water for 2 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 20 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 254 nm. Retention times for phenyl glycidyl ether ~ 10.3 min, SI-3 ~ 2.1 min, SI-4 ~ 8.8 min, and naphthalene ~ 25.2 min.



PhO $(M \to 0^{-1})^{-1}$ **3,3'-(***tert***-butylazanediyl)bis(1-phenoxypropan-2-ol) (SI-4**). ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.23 (m, 10H), 4.76-4.67 (m, 2H), 3.92 (br s, **si-4** 1H), 2.89-2.85 (dd, J = 3.6, 14.4 Hz, 1H), 2.81-2.56 (m, 3H), 1.12 (s, 9H); ¹³C NMR (CDCl₃) δ 142.9, 142.8, 128.4, 127.6, 127.5, 125.9, 125.8, 74.8, 72.7, 61.8, 59.9, 56.1, 55.7, 27.4, 27.3; HRMS ESI m/z calcd for $[M+H]^+$ 314.2115, obsd 314.2114.



Aminolysis of styrene oxide with *tert*-butylamine. Purified by chromatography on silica gel (9:1 dichloromethane/methanol). 5 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with dichloromethane. 1 μ L injections were made on the GC at a temperature of 75 °C and held for 5 min. The temperature was raised to 300 °C over 20 min. Yields were calculated based on normalization of response factors with 10 mol% dodecane as an internal standard in the epoxide reagent stream. Retention times for styrene oxide ~ 3.9 min, SI-5 ~ 10.3 min, SI-6 ~ 9.3 min, SI-7 ~ 14.2 min, and dodecane ~ 6.7 min.

CH Ph HN SI-5 δ 7.36-7.29 (m, 4H), 7.26-7.22 (m, 1H), 4.62-4.59 (dd, J = 3.6, 8.8 Hz, 1H), 2.83-2.79 (dd, J = 3.6, 11.6 Hz, 1H), 2.61-2.55 (dd, J = 8.8, 11.6 Hz, 1H), 1.05 (s, 3H).

2-(*tert***-butylamino)-2-phenylethanol (SI-6).** (Lit.)¹ ¹H NMR (400 MHz, CDCl₃) δ Ph OH 7.32-7.20 (m, 5H), 3.87-3.84 (dd, J = 4.8, 9.2 Hz, 1H), 3.54-3.50 (dd, J = 4.8, 10.4 **SI-6** Hz, 1H), 3.29 (t, J = 9.2 Hz, 1H), 2.87 (br s, 2H), 1.02 (s, 9H).

2,2'-azanediylbis(1-phenylethanol) (SI-7). ¹H NMR (400 MHz, CDCl₃) δ **7.25 (t**, *J* = 8.0 Hz, 4H), 6.93 (t, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 4H), 4.06- **SI-7 3.98 (m, 2H), 3.94-3.93 (m, 4H), 3.67 (br s, 1H), 2.99-2.95 (dd,** *J* **= 4.0, 14.4 Hz, 1H), 2.85-2.81 (dd,** *J* **= 3.2, 14.0 Hz, 1H), 2.69-2.60 (m, 2H), 1.12 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) \delta 158.7, 158.6, 129.5, 121.0 (2), 114.5 (2), 70.2, 70.1, 68.8, 56.1, 55.7, 55.6, 54.0, 27.1; HRMS** ESI *m/z* calcd for [M+H]⁺ 374.2326, obsd 374.2334.



Aminolysis of phenyl glycidyl ether with aniline. Purified by preparative TLC (4 x 3:1 hexanes/ethyl acetate). 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1.5 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using 80% methanol in water for 9 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with

10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for phenyl glycidyl ether ~ 2.1 min, **SI-8** ~ 2.8 min, **SI-9** ~ 5.2 and 7.2 min, and naphthalene ~ 4.6 min.

1-phenoxy-3-(phenylamino)propan-2-ol (SI-8). (Lit.) 2 ¹H NMR (400MHz, CDCl₃) δ 7.32 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.00 (t, J =SI-87.2 Hz, 1H), 6.94 (d, J = 7.6 Hz, 2H), 6.77 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 8.8Hz, 2H), 4.28-4.24 (m, 1H), 4.10-4.02 (m, 2H), 3.46-3.42 (dd, J = 4.4, 13.2 Hz, 1H), 3.30-3.28(dd, J = 6.8, 12.8 Hz, 1H).

3,3'-(phenylazanediyl)bis(1-phenoxypropan-2-ol) (SI-9). (Lit.)^{3 1}H NMR (400 MHz, CDCl₃) δ 7.30-7.17 (m, 6H), 6.98-6.84 (m, 7H), 6.76-6.72 (m, 2H), 4.43-4.38 (m, 1H), 4.35-4.29 (m, 1H), 4.24 (br s, 1H), 4.03-3.95 (m, 5H), 3.67-3.62 (dd, *J* = 4.0, 14.8 Hz, 1H), 3.58-3.52 (dd, *J* = 7.6, 14.8 Hz, 1H), 3.41 (br s, 1H), 3.31-3.25 (dd, *J* = 8.4, 15.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 158.4, 148.6, 147.6, 129.6, 129.4, 129.3, 121.3, 117.8, 117.2, 114.6, 114.5, 113.7, 112.4, 69.6, 69.5, 68.6, 68.1, 57.7, 55.3; HRMS ESI *m/z* calcd for [M+H]⁺ 394.2013, obsd 394.2020.



Aminolysis of 1,4-dihydronaphthalene 13 with indoline 12. Purified by preparative TLC

(95:5 dichloromethane/methanol). 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1.5 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using 75% methanol in water for 11 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for **13** ~ 2.5 min, **SI-10** ~ 8.7 min, and naphthalene ~ 6.5 min.

3-(indolin-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (SI-10). ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.14 (m, 4H), 7.12-7.08 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 4.19-4.13 (m, 1H), 3.89-3.81 (m, 1H), 3.57-3.52 (m, **si-10** 1H), 3.48-3.33 (m, 2H), 3.24 (s, 1H), 3.10-3.06 (m, 2H), 3.02-2.90 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 151.0, 134.5, 133.9, 130.4, 129.2, 129.1, 127.5, 126.3, 126.2, 124.8, 118.5, 107.7, 67.6, 58.1, 46.6, 37.8, 28.5, 26.9; HRMS ESI *m/z* calcd for [M+H]⁺ 266.1539, obsd 266.1545.



Aminolysis of 1-phenylcyclohexene oxide 15 with propylamine. Purified by chromatography on silica gel (9:1 hexanes/ethyl acetate). 10 μ L samples were taken from microwave batch

reactions or microreactor reactions and were diluted to 1 mL with methanol. 4 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using a gradient of 50% methanol in water to 75% methanol in water over 10 min and holding at 75% methanol in water for 7 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for **15** ~ 14.2 min, **SI-11** ~ 2.2 min, and naphthalene ~ 13.8 min.



Aminolysis of styrene oxide with aniline. Purified by preparative TLC (3 x 4:1 hexanes/ethyl acetate). **16** and **17** could not be cleanly separated from the bis-alkylated side products **18** thus concentrations for calibration curves were determined by quantitative ¹H NMR. 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1.5 μ L injections were made onto an Eclipse XDB-C18 reverse phase column

using a gradient of 75% methanol in water to 80% methanol in water over 5 min and holding at 80% methanol in water for 10 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for styrene oxide ~ 2.58 min, $17 \sim 3.2 \text{ min}$, $16 \sim 2.9 \text{ min}$, 18 and isomers ~ 5.2, 5.4, 7.9, 8.3 min, and naphthalene ~ 5.9 min.

1-phenyl-2-(phenylamino)ethanol (17). (Lit.)⁴ ¹H NMR (400 MHz, CDCl₃) δ **7.45-7.31 (m, 5H)**, 7.21 (t, *J* = 7.2 Hz, 2H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 2H), 4.91-4.88 (dd, J = 3.6, 8.4 Hz, 1H), 3.43-3.39 (dd, *J* = 3.6, 13.2 Hz, 1H), 3.31-3.25 (dd, *J* = 4.8, 13.2 Hz, 1H) (2.75 br s, 1H).

Ph. NH Ph. OH T.39-7.29 (m, 5H), 7.12 (t, J = 10.4 Hz, 2H), 6.71 (t, J = 6.4 Hz, 1H), 6.59 (d, J = 8.4Hz, 2H), 4.52-4.49 (dd, J = 4.0, 7.2 Hz, 1H), 4.50 (br s, 1H), 3.95-3.91 (dd, J = 4.4, 11.2 Hz, 1H), 3.76-3.72 (dd, J = 7.2, 11.2 Hz, 1H) 1.95 (br s, 1H).



Aminolysis for formation of metoprolol. Purified by chromatography on silica gel (9:1 dichloromethane/methanol). 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1.5 μ L injections were made

onto an Zorbax Eclipse Plus C18 reverse phase column using a gradient of 40% methanol in water to 75% methanol in water over 18 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for $20 \sim 9.6$ min, $19 \sim 2.3$ min, $21 \sim 7.6$ and 7.8 min, and naphthalene ~ 16.5 min.



metoprolol (19)

Metoprolol (19). (Lit.)⁵ ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 11.6 Hz, 2H), 4.05-3.99 (m, 1H), 3.96-3.89 (m, 2H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.33 (s, 3H), 2.87-2.78 (m, 5H), 2.71-2.66 (dd, *J* = 8.0, 12.0 Hz, 1H), 1.07 (d, *J* = 6.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.2, 131.3,

129.7, 114.4, 73.8, 70.6, 68.4, 58.6, 49.4, 48.9, 35.3, 23.0.



3,3'-(isopropylazanediyl)bis(1-(4-(2-methoxyethyl)phenoxy)propan-2ol) (21). ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, *J* = 8.4 Hz, 4H), 6.85-6.82 (dd, *J* = 2.4, 8.4 Hz, 4H), 4.03-4.02 (m, 2H), 3.95-3.93 (m, 4H), 3.55

(t, J = 7.2 Hz, 4H), 3.34 (s, 6H), 3.03-2.99 (m, 1H), 2.82 (t, J = 7.2 Hz, 4H), 2.78-2.71 (m, 2H), 2.67-2.57 (m, 2H), 1.09-1.00 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 157.2, 157.1, 131.3, 129.8, 114.5 (2), 73.8, 70.3, 70.2, 68.3, 67.7, 58.6, 53.9, 53.4, 52.3, 52.0, 35.3, 19.8, 18.2, 16.6; HRMS ESI m/z calcd for [M+H]⁺ 476.3007, obsd 476.3017.



Aminolysis of styrene oxide with 2-aminoindan 8. Purified by preparative TLC (9:1 dichloromethan/methanol). 10 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 1 mL with methanol. 1.5 μ L injections were made onto an Eclipse XDB-C18 reverse phase column using a gradient of 30% methanol in water to 75% methanol in water over 25 min and holding at 75% methanol in water for 3 min with a flow rate of 1 mL/min. Yields were calculated based on normalization of response factors with 10 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for styrene oxide ~ 13.9 min, **22** ~ 6.9 min, **23** ~ 8.7 min, **24** ~ 16.5 min, and naphthalene ~ 27.0 min.

2-(2,3-dihydro-1*H***-inden-2-ylamino)-1-phenylethanol (22)**. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.35 (m, 2H), 7.26-7.23 (m, 3H), 7.12-7.09 (m, 4H), 5.44 (d, *J* = 7.6 Hz, 1H), 4.03-3.96 (m, 1H), 3.46-3.27 (m, 4H), 3.25-3.17 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 140.1, 138.9, 128.6, 128.2, 127.3, 125.9, 124.6, 69.2, 58.9, 53.7, 36.1, 36.0; HRMS ESI *m/z* calcd for [M+H]⁺ 254.1539, obsd 254.1546.

2-(2,3-dihydro-1*H*-inden-2-ylamino)-2-phenylethanol (23). ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.29 (m, 5H), 7.18-7.11 (m, 4H), 3.96-3.93 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.74-3.70 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.62-3.54 (m, 2H), 3.14-3.01 (m, 2H), 3.07 (br s, 2H), 2.88-2.82 (dd, *J* = 6.8, 15.6 Hz, 1H), 2.76-2.70 (dd, *J* = 6.8, 15.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 141.4, 141.3, 140.2, 128.7, 127.8, 127.3, 126.5, 124.7,
124.5, 66.5, 63.1, 57.0, 40.5, 39.4; HRMS ESI *m/z* calcd for [M+H]⁺ 254.1539, obsd 254.1546.

2,2'-(2,3-dihydro-1*H***-inden-2-ylazanediyl)bis(1-phenylethanol) (24)**. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.26 (m, 10H), 7.19-7.13 (m, 4H), 4.82-4.79 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.74-4.70 (dd, *J* = 4.0, 8.8 Hz, 1H), 3.93-3.84 (m, 2H), 3.14-2.98 (m, 2H), 2.91-2.73 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 142.6, 142.4, 141.5, 141.4, 141.3, 128.5, 127.7, 127.6, 126.5, 126.0 (2), 124.7, 124.6, 124.5, 72.6, 71.2, 63.6, 63.4, 61.4, 60.5, 37.0, 35.6, 34.1; HRMS ESI *m/z* calcd for [M+H]⁺ 374.2115, obsd 374.2128.



Indacaterol Precursor: Aminolysis of 2 with 3. Purified by preparative TLC (9:1 dichloromethan/methanol). 5 μ L samples were taken from microwave batch reactions or microreactor reactions and were diluted to 0.8 mL with methanol. 0.6 μ L injections were made onto an Zorbax Eclipse Plus C18 reverse phase column using a gradient of 60% methanol in water to 75% methanol in water over 15 min and holding at 75% methanol in water for 3 min with a flow rate of 1.2 mL/min. Yields were calculated based on normalization of response

factors with 10-20 mol% naphthalene as an internal standard in the epoxide reagent stream and detection at 210 nm. Retention times for $2 \sim 5.58 \text{ min}$, $4 \sim 5.7 \text{ min}$, $5 \sim 6.5 \text{ min}$, $6 \sim 16.1 \text{ min}$, and naphthalene ~ 10.3 min.

(R)-8-(benzyloxy)-5-(2-(5,6-diethyl-2,3-dihydro-1H-inden-2-ylamino)- $1-hydroxyethyl)quinolin-2(1H)-one (4). ^{1}H NMR (400 MHz, CDCl_3) \delta$ 8.05 (d, J = 10.0 Hz, 1H), 7.39-7.34 (m, 5H), 7.23 (d, J = 8.4 Hz, 1H), 6.97 (s, 2H), 6.96 (d, J = 10.0 Hz, 1H), 6.58 (d, J = 9.6 Hz, 1H), 5.12 (s, 3H)

2H), 5.09-5.08 (m, 1H), 3.64-3.57 (m, 1H), 3.12-3.05 (m, 1H), 2.97-2.93 (dd, *J* = 3.2, 12.0 Hz, 1H), 2.80-2.68 (m, 3H), 2.61-2.55 (q, *J* = 7.2 Hz, 4H), 1.17 (t, *J* = 7.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 161.4, 143.9, 140.1, 138.9, 138.8, 136.6, 135.5, 131.5, 129.0, 128.8, 128.6, 127.9, 124.6, 122.1, 119.8, 117.3, 111.0, 70.9, 69.1, 59.6, 54.9, 39.8, 39.6, 25.5, 15.6; HRMS ESI *m/z* calcd for [M+H]⁺ 483.2642, obsd 483.2628.



8-(benzyloxy)-5-(1-(5,6-diethyl-2,3-dihydro-1*H*-inden-2-ylamino)-2hydroxyethyl)quinolin-2(1*H*)-one (5). ¹H NMR (400 MHz, CDCl₃) δ 9.21 (br s, 1H), 8.24 (d, *J* = 10.0 Hz, 1H), 7.40-7.35 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 11.2 Hz, 2H), 6.67 (d, *J* = 10.0 Hz, 1H), 5.14 (s, 2H), 4.41-4.38 (m, 1H), 3.73-3.69 (dd, *J* = 4.8,

10.8 Hz, 1H), 3.57-3.52 (m, 1H), 3.52-3.44 (m, 1H), 3.02-2.91 (m, 2H), 2.77-2.71 (dd, J = 6.8, 15.2 Hz, 1H), 2.64-2.58 (dd, J = 6.4, 15.2 Hz, 1H), 2.58-2.52 (q, J = 8.4 Hz, 4H), 1.14 (t, J = 7.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 161.3, 143.8, 140.0, 138.9, 138.8, 136.2, 135.4, 129.8,

129.2, 128.9, 128.7, 127.9, 124.6, 124.3, 122.5, 120.6, 118.4, 111.1, 71.0, 66.5, 58.5, 57.5, 40.4, 39.6, 25.4, 15.5; HRMS ESI *m*/*z* calcd for [M+H]⁺ 483.2642, obsd 483.2632.



5,5'-(2,2'-(5,6-diethyl-2,3-dihydro-1*H***-inden-2-ylazanediyl)bis(1-hydroxyethane-2,1-diyl))bis(8-(benzyloxy)quinolin-2(1***H***)-one) (6)**. ¹H NMR (400 MHz, CDCl₃) δ 9.21 (br s, 1H), 7.95 (d, *J* = 10.0 Hz, 2H), 7.37-7.30 (m, 10H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.98-6.95 (m, 4H), 6.58 (d, *J* = 9.6 Hz, 2H), 5.22-5.19 (m, 2H), 5.11 (s, 4H), 3.97-3.93

(m, 1H), 3.11-2.94 (m, 3H), 2.87-2.76 (m, 5H), 2.59-2.54 (m, 4H), 1.18-1.12 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 161.3, 143.9, 140.5, 140.4, 138.7, 138.5, 136.3, 135.4, 131.0, 129.1, 128.8, 128.7, 127.8, 124.5, 124.3, 122.4, 119.9, 117.3, 111.1, 71.0, 68.5, 63.5, 59.9, 36.8, 33.9, 25.5, 25.4, 15.6, 15.5; HRMS ESI *m/z* calcd for [M+H]⁺ 776.3694, obsd 776.3696.

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¹³C NMR spectrum of **21**



¹³C NMR spectrum of **22**

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