Supporting Information for

Acid-Free Aza Diels-Alder Reaction of Danishefsky's Diene with Imines

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General Considerations

¹H NMR spectra were recorded in CDCl₃ on a Bruker AM300 at 25°C and chemical shifts were expressed in ppm with TMS as an internal standard (δ = 0 ppm). EI Mass spectra were obtained on a HP5989A spectrometer. HRMS was determined on a Kratos Concept instrument. Commercial reagents were used as received without further purification unless otherwise noted.

General Procedure for the aza-Diels-Alder Reaction of Danishefsky's Diene with Imines

To a solution of imine **2** (0.125 mmol) in 1 mL of methanol was added Danishefsky's diene **1** (50 μ L, 0.25 mmol). After the mixture was stirred for 2 hrs at room temperature, it was quenched with 0.5 mL of 1.0 M HCl. The reaction mixture was extracted with diethyl ether and concentrated. The crude material was purified by flash chromatography to give the cycloadduct.

Control Experiments for the aza-Diels-Alder Reaction of

Danishefsky's Diene with *N*-benzylideneaniline **2a**

In freshly distilled methanol: To a solution of *N*-benzylideneaniline **2a** (45 mg, 0.25 mmol) in 1 mL of methanol (freshly distilled over CaH₂) was added Danishefsky's diene **1** (100 μ L, 0.50 mmol). After the mixture was stirred for 2 hrs at room temperature, it was quenched with 0.5 mL of 1.0 M HCl. The reaction mixture was extracted with diethyl ether and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a**, 63 mg (100% yield). ¹H NMR (CDCl₃ / TMS) δ 7.71 (d, 1H, J = 10.3 Hz), 7.39-7.24 (m, 7H), 7.21-6.98 (m, 3H), 5.37-5.21 (m, 2H), 3.30 (dd, 1H, J = 7.4 Hz, 16.5 Hz), 2.79 (dd, 1H, J = 4.3 Hz, 13.5 Hz)

In the presence of 2,6-di-*tert*-butyl-4-methylpyridine: To a solution of *N*-benzylideneaniline **2a** (45 mg, 0.25 mmol) in 1 mL of methanol was added 2,6-di-*tert*-butyl-4-methylpyridine (5.0 mg, 0.025 mmol) and Danishefsky's diene **1** (100 μ L, 0.50 mmol). After the mixture was stirred for 2 hrs at room temperature, it was quenched with 0.5 mL of 1.0 M HCl. The reaction mixture was extracted with diethyl ether and concentrated. The crude material was purified by flash chromatography to give the cycloadduct **3a**, 63 mg (100% yield). ¹H NMR (CDCl₃ / TMS) δ 7.71 (d, 1H, J = 10.3 Hz), 7.39-7.24 (m, 7H), 7.21-6.98 (m, 3H), 5.37-5.21 (m, 2H), 3.30 (dd, 1H, J = 7.4 Hz, 16.5 Hz), 2.79 (dd, 1H, J = 4.3 Hz, 13.5 Hz)

General Procedure for Three-component One-pot of aza-Diels-Alder Reaction

The aldehyde **4** (0.25 mmol), amine **5** (0.25 mmol) and Danishefsky's diene **1** (100 μ L, 0.50 mmol) were added to 2 mL of methanol sequentially. After the solution was stirred for 2 hrs at room temperature, it was quenched with 0.5 mL of 1.0 M HCl. The reaction mixture was extracted with diethyl ether and concentrated. The crude

material was purified by flash chromatography to give the cycloadduct.

Spectral Data for Products¹

IR (KBr): 2926, 1652, 1593, 1571, 1496, 1362, 1308, 1278, 1203, 965, 788, 769, 696 cm^{-1} . EIMS m/z (relative intensity): 251 (M^+ , 44.89), 250 (100.00), 221 (23.69), 172 (65.98), 145 (62.05), 117 (65.98), 104 (31.97). ^1H NMR (CDCl_3 / TMS) δ 7.71 (d, 1H, $J = 10.3$ Hz), 7.39-7.24 (m, 7H), 7.21-6.98 (m, 3H), 5.37-5.21 (m, 2H), 3.30 (dd, 1H, $J = 7.4$ Hz, 16.5 Hz), 2.79 (dd, 1H, $J = 4.3$ Hz, 13.5 Hz).

IR (KBr): 3059, 1656, 1641, 1593, 1569, 1509, 1328, 1245, 1031, 823, 758, 693. EIMS m/z (relative intensity): 281 (M^+ , 7.96), 280 (30.51), 172 (100.00), 145 (23.54), 134 (54.06), 117 (33.62). ^1H NMR (CDCl_3 / TMS) δ 7.65 (d, 1H, $J = 8.1$ Hz), 7.33-7.26 (m, 2H), 7.20-7.01 (m, 3H), 7.03 (d, 1H, $J = 7.8$ Hz), 6.84 (d, 1H, $J = 8.4$ Hz), 5.29-5.23 (m, 2H), 3.78 (s, 3H), 3.27 (dd, 1H, $J = 7.2$ Hz, 16.5 Hz), 2.76 (dd, 1H, $J = 3.3$ Hz, 16.5 Hz).

IR (KBr): 3063, 1883, 1651, 1601, 1572, 1494, 1323, 1207, 1096, 824, 746, 699 cm^{-1} . EIMS m/z (relative intensity): 286 (M^+ , 11.64), 283 (100.00), 206 (55.05), 179 (96.03), 151 (57.73), 138 (53.48). ^1H NMR (CDCl_3 / TMS) δ 7.62 (d, 1H, $J = 7.5$ Hz),

7.37-7.23 (m, 7H), 6.98-6.93 (m, 2H), 5.31 (d, 1H, $J = 7.8$ Hz), 5.27-5.23 (m, 1H), 3.30 (dd, 1H, $J = 6.9$ Hz, 16.5 Hz), 2.84-2.76 (m, 1H).

IR (KBr): 3062, 1645, 1591, 1576, 1512, 1450, 1330, 1283, 1249, 1183, 1039, 829, 700, 541 cm^{-1} . EIMS m/z (relative intensity): 281 (M^+ , 21.19), 280 (87.12), 202 (55.19), 175 (100.00), 160 (62.53), 132(25.37). ^1H NMR (CDCl_3 /TMS) δ 7.56 (d, 1H, $J = 7.5$ Hz), 7.34-7.26 (m, 5H), 6.96 (d, 1H, $J = 8.7$ Hz), 6.81 (d, 1H, $J = 8.4$ Hz), 5.25-5.18 (m, 2H), 3.76 (s, 1H), 3.27 (dd, 1H, $J = 6.9$ Hz, 16.2 Hz), 2.77 (dd, 1H, $J = 3.9$ Hz, 16.2 Hz).

IR (KBr): 1738, 1651, 1649, 1573, 1515, 1492, 1350, 1210, 1102, 847, 759, 697 cm^{-1} . EIMS m/z (relative intensity): 296 (M^+ , 2.12), 294 (98.14), 266 (38.71), 219 (3.99), 1172 (28.85), 145 (100.00), 117 (90.37). ^1H NMR (CDCl_3 /TMS) δ 8.20 (d, 2H, $J = 9.0$ Hz), 7.72 (d, 2H, $J = 8.1$ Hz), 7.48 (d, 2H, $J = 8.4$ Hz), 7.35-7.27 (m, 2H), 7.15 (t, 1H, $J = 7.5$ Hz), 6.98 (d, 2H, $J = 8.1$ Hz), 5.41-5.38 (m, 1H), 5.33 (d, 1H, $J = 7.2$ Hz), 3.37 (dd, 1H, $J = 7.2$ Hz, 16.5 Hz), 2.78 (dd, 1H, $J = 1.8$ Hz, 16.2 Hz).

IR (KBr): 3065, 1650, 1638, 1582, 1571, 1361, 1293, 1213, 1203, 823, 757, 698 cm^{-1} . EIMS m/z (relative intensity): 286 (M^+ , 17.82), 284 (52.45), 255 (18.60), 219 (16.03), 172 (83.76), 145 (18.19), 117 (100.00). ^1H NMR (CDCl_3 /TMS) δ 7.67 (d, 1H, $J = 7.8$

Hz), 7.35-7.11 (m, 7H), 7.03-6.99 (m, 2H), 5.32-5.25 (m, 2H), 3.31 (dd, 1H, $J = 7.2$ Hz, 16.5 Hz), 2.75 (dd, 1H, $J = 3.3$ Hz, 15.3 Hz).

IR (KBr): 3448, 3056, 1647, 1576, 1496, 1343, 1213, 1001, 794, 757, 695 cm^{-1} . EIMS m/z (relative intensity): 250 (M^+ , 17.98), 221 (5.49), 172 (22.83), 146 (42.36), 130 (35.40), 117 (34.63), 104 (38.29), 77 (100.00). ^1H NMR (CDCl_3 / TMS) δ 8.65-8.63 (m, 1H), 7.73 (d, 1H, $J = 8.6$ Hz), 7.63 (t, 1H, $J = 9.0$ Hz), 5.37 (d, 1H, $J = 6.6$ Hz), 5.31 (d, 1H, $J = 7.5$ Hz), 3.27 (dd, 1H, $J = 7.5$ Hz, 16.8 Hz), 3.17-3.10 (m, 1H).

IR (KBr): 2916, 1647, 1571, 1494, 1342, 1224, 1216, 1179, 1015, 961, 791, 742, 694 cm^{-1} . EIMS m/z (relative intensity): 239 (M^+ , 46.53), 210 (6.97), 172 (7.11), 145 (51.65), 117 (84.38), 117 (97.00), 77 (100.00). ^1H NMR (CDCl_3 / TMS) δ 7.45-7.38 (m, 3H), 7.28-7.19 (m, 4H), 6.34-6.28 (m, 2H), 5.30-5.27 (m, 2H), 3.18 (dd, 1H, $J = 6.3$ Hz, 16.5 Hz), 2.93-2.84 (m, 1H).

IR (KBr): 3062, 1648, 1575, 1495, 1339, 1278, 1238, 1198, 755, 697 cm^{-1} . EIMS m/z (relative intensity): 279 (M^+ , 26.71), 278 (44.00), 219 (28.84), 172 (100.00), 145 (57.34), 104 (32.57). ^1H NMR (CDCl_3 / TMS) δ 7.43-6.98 (m, 11H), 5.23 (dd, 1H, $J = 0.9$ Hz, 7.5 Hz), 4.21-4.16 (m, 1H), 2.99 (dd, 1H, $J = 6.6$ Hz, 16.8 Hz), 2.77-2.66 (m, 1H), 2.60-2.50 (m, 1H), 2.35-2.30 (m, 1H), 2.06-1.98 (m, 2H).

IR (KBr): 1643, 1589, 1579, 1495, 1417, 1330, 1277, 1229, 1222, 1176, 964, 769, 758, 749, 695 cm^{-1} . EIMS m/z (relative intensity): 277 (M^+ , 100.00), 248 (76.22), 172 (29.42), 156(18.60), 145 (15.43), 117 (26.58). ^1H NMR (CDCl_3 / TMS) δ 7.50 (d, 1H, $J = 7.5$ Hz), 7.41-7.14 (m, 10H), 6.54 (d, 1H, $J = 15.9$ Hz), 6.39 (dd, 1H, $J = 5.8$ Hz, 16.2 Hz), 5.29 (d, 1H, $J = 10.2$ Hz), 4.87-7.85 (m, 1H), 3.17 (dd, 1H, $J = 9.6$ Hz, 16.2 Hz), 2.61 (d, 1H, $J = 16.5$ Hz).

IR (KBr): 3067, 2964, 1647, 1578, 1496, 1324, 1267, 1227, 1093, 759, 697 cm^{-1} . EIMS m/z (relative intensity): 217 (M^+ , 1.91), 216 (17.65), 172 (100.00), 144 (10.20), 117 (6.27), 104 (16.51). ^1H NMR (CDCl_3 / TMS) δ 7.46-7.38 (m, 3H), 7.22-7.17 (m, 3H), 5.17 (dd, 1H, $J = 0.9$ Hz, 7.8 Hz), 4.12-4.07 (m, 1H), 2.92 (dd, 1H, $J = 7.2$ Hz, 16.5 Hz), 2.63 (dd, 1H, $J = 4.2$ Hz, 16.8 Hz), 2.26 (m, 1H), 0.97 (d, 3H, $J = 6.9$ Hz), 0.91 (d, 3H, $J = 7.1$ Hz).

7a

IR (KBr): 3049, 2985, 2936, 2839, 1717, 1643, 1629, 1577, 1513, 1335, 1248, 1213, 1186, 1073, 965, 858, 833, 759, 546 cm^{-1} . EIMS m/z (relative intensity): 303 (M^+ , 23.26), 246 (3.40), 202 (100.00), 186 (6.93), 159 (9.61), 134 (6.76), 77 (6.18). ^1H NMR (CDCl_3 / TMS) δ 7.30 (d, 1H, $J = 8.1$ Hz), 7.15 (d, 2H, $J = 10.2$ Hz), 6.93 (d,

2H, $J = 10.2$ Hz), 5.16 (d, 1H, $J = 8.4$ Hz), 4.35 (dd, 1H, $J = 6.0$ Hz, 12.3 Hz), 4.19-4.12 (m, 1H), 3.88-3.81 (m, 4H), 3.45-3.40 (m, 1H), 2.96 (dd, 1H, $J = 9.6$ Hz, 16.5 Hz), 2.84-2.79 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H). HRMS (m/z) (EI) calc. for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1458.

References

1. (a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831-7834. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195-1202. (c) Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Lett.* **2001**, *42*, 7405-7408. (d) Ali, T.; Chauhan, K.K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621-5624.

7a+7b

Archive directory: /export/home/ding-k1/vnmr/sys/data
 Sample directory: yy-12-9_20jun2002

Pulse Sequence: COSY

Solvent: CDCl3

Ambient temperature

File: COSY

Mercury-300DB "MERCURYx300"

Relax. delay: 1.000 sec

Acq. time: 0.142 sec

Width: 3597.1 Hz

2D Width: 3597.1 Hz

45 repetitions

126 scans

ORSERV: H1 300.0279745 MHz

Sq. time bet: 0.071 sec

F1 DATA PROCESSING

Sq. time bet: 0.0906 sec

F2 size: 1024 x 1024

Total time: 12 min, 14 sec

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yy-10-89

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WY-10-81

yy-10-88