Supporting Information

Efficient Synthesis of Tricyclic Benzobisoxazines by Silica Gel Catalysis

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1. Materials and Special Procedures.

All reactions catalyzed by silica were carried out in round bottom flask closed with PTFE cap and run under air atmosphere. Chemicals were obtained from commercial sources. The silica used as catalyst was purchased from EMD Chemicals (Geduran® Silica Gel 60 40–63µm, pH 6.5–7.5 for 10% suspension). Column chromatography was carried out with silica gel (Geduran® Silica Gel 60 40–63µm, pH 6.5–7.5 for 10% suspension), which was deactivated according to the following procedure. Deactivated silica gel was prepared by stirring silica gel with 2% triethylamine (99.5%) in pentane, followed by the transfer into a large column and drying with air flow overnight; subsequently, the silica was placed in a round bottom flask and the volatiles were removed on vacuum line, equipped with two liquid nitrogen traps. After 2 h under vacuum, the deactivated silica was stored in a tightly closed container and it was used for column chromatography within several days (label: MT490). In the indicated, rare separations, TLC-grade silica gel without deactivation, was used for column chromatography. Preparative TLC (PTLC) was carried out using silica plates (Analtech, tapered with a preadsorbent zone) with deactivated silica. PTLC plates with deactivated silica were prepared by treatment with 2% triethylamine (99.5%) in pentane, followed by drying under low vacuum (diaphragm pump, <10 Torr) for 3 h.

Previously unknown compounds were synthesized, purified, and then characterized by ¹H NMR, ¹³C NMR, and IR spectroscopies, as well as HR-MS.

For melting point determination, temperature calibration was carried out with 2-bromobenzoic acid (m.p. 148–150 °C).

Diol-diamine **1** was prepared in five-step synthesis from 4,6-dibromo-*meta*-xylene.^{S1,S2}

2. NMR Spectroscopy and Other Analyses.

NMR spectra were obtained at 500 or 400 MHz using benzene-*d*₆, and acetone-*d*₆ as solvents. The chemical shift references were as follows: for ¹H NMR spectra, benzene-*d*₅ at 7.160 ppm, acetone-*d*₅ at 2.050 ppm, and for ¹³C NMR spectra, acetone-*d*₆ at 29.9 ppm and benzene-*d*₆ at 128.4 ppm. Typical 1D FID was subjected to exponential multiplication with an exponent of 0.1 Hz (for ¹H) and 1.0–2.0 Hz (for ¹³C); for selected spectra, both exponential and Gaussian multiplications were used, with exponents indicated as LB and GB (in units of Hz) for each applicable spectrum.

IR spectra were obtained using an FT-IR instrument, equipped with an ATR sampling accessory. A few drops of the compound in CH₂Cl₂ were applied to the surface of a ZnSe ATR plate horizontal parallelogram (45°). After the solvent evaporated, the spectrum was acquired (128 scans, 2 cm⁻¹ resolution).

MS analyses were carried out at the Nebraska Center for Mass Spectrometry.

3. Synthesis of Diol-Diamine 3.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0586	148	12 h	Treatment with pentane	427	77
2	GS0660	420	12 h	Treatment with pentane	1340	85

Diol-Diamine 3. Diester-diamine (148.7 mg, 0.664 mmol, 1.0 equiv, MT0419) was dissolved in THF (3.6 mL) and dodecane magnesium bromide (9.3 mL, 9.29 mmol, 14 equiv) was added dropwise at 0 °C, under N₂ (label: GS0586). The reaction mixture was allowed to warm up to RT and kept stirring overnight. After cooling down to 0 °C, brine (20 mL) was added dropwise and the aqueous phase was extracted 3 times with ethyl acetate (30 mL). The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude was suspended in pentane and filtered over a sintered funnel to yield a white solid (427 mg, 77%). M.p. 96–98 °C (label: GS0660Fil). ¹H NMR (400 MHz, C₆D₆): δ = 6.660 (s, 1H), 5.526 (s, 1H), 4.369 (s, 4H), 2.13 – 1.88 (m, 8H), 1.58 – 1.15 (m, 72H), 0.933 (t, *J* = 6.4 Hz, 12H). ¹³C{¹H} NMR (100 MHz, C₆D₆): δ = 146.9, 117.3, 106.6, 79.6, 40.9, 32.7, 31.30, 30.77, 30.72, 30.66, 30.63, 30.57, 30.25, 25.1, 23.5, 14.7. HR FAB-MS (3-NBA matrix): *m/z* (ion type, %RA or *m/z* = 843–838, deviation for the formula): 842.8507 ([M+1+H]⁺, 7%, 1.9 ppm for ¹²C₅₅¹³C₁H₁₀₉N₂O₂), 841.8456 ([M+1]⁺, 19%, –1.3 ppm for ¹²C₅₅¹³C₁H₁₀₈N₂O₂), 840.8412 ([M]⁺, 28%, –0.1 ppm for ¹²C₅₆H₁₀₈N₂O₂), 839.8316 ([M–H]⁺, 6%, 1.9 ppm for ¹²C₅₆H₁₀₇N₂O₂), 838.8277 ([M–2H]⁺, 5%, –2.7 ppm for ¹²C₅₆H₁₀₆N₂O₂). IR (cm^{–1}): 3492 (N–H or O–H), 3380 (N–H or O–H), 3357 (N–H or O–H), 2919 (C–H), 2850 (C–H), 1627, 1509, 1467.

4. Procedures for Synthesis of Tricyclic Benzoxazines.

General Procedure A, Silica Gel Catalysis. Diol-diamine **1** or **3** was suspended in pentane (~0.1 M) and ketone (5 equiv, except when indicated otherwise) was added. Subsequently, silica was added in a 5:1 ratio w/w with respect to diol-diamine **1** or **3**, except when indicated otherwise. The reactions were performed at room temperature. The disappearance of the starting material and the appearance of monoannulated, and

then bisannelated products were followed by TLC and, in selected cases, by NMR spectroscopy. The reactions were stopped by addition of ethyl acetate and filtration of silica. Evaporation under reduced pressure gave the crude products, which were purified by deactivated silica PTLC, deactivated silica flash gel chromatography, or treatment with specified solvent.

Typical Procedure B, Acid Catalysis. In a round bottom flask with a Dean-Stark apparatus, under N₂ atmosphere, diol-diamine **1** (0.446 mmol) was suspended in pentane (17 mL) (label: GS0555). At 0 °C, the ketone (5.68 mmol) and acetic acid (0.402 mmol) as a solution in benzene (8 mL) were added. Nitrogen was flushed with a PTFE needle directly inside the reaction mixture at a rate of ~80 bubbles per minute. The flask was then dipped into a 85–90 °C preheated oil bath and kept stirring until the mixture became clear (about 2 h). The reaction mixture was cooled to RT, and then poured into 20 mL of a cold 5% NaHCO₃ aqueous solution. The phases were separated and the aqueous phase was saturated with NaCl to be extracted with 2 volumes of benzene, 2 volumes of ethyl acetate, and dried by sodium carbonate and potassium sulfate. Concentration under reduced pressure gave the crude products which were purified by deactivated PTLC or flash deactivated silica gel chromatography.

5. Condensation Reactions of Diol-Diamine 1 with Aldehydes and Ketones.

Diol-Diamine 1 with Acetaldehyde.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0624	5.0	1 h	Flash chromatography and treatment with pentane	25.0	59 ^a
2	GS0736	30.0	1 h 20			

a: yield of 72% after flash chromatography. The residue (5 mg), obtained after treatment with pentane, contained ~80 % of target material by ¹H NMR spectroscopy.

Diastereomeric excess			
ID	Crude	Purification method	Purified product
GS 06 24	1.0:1.0	Flash chromatography and treatment with pentane	After chrom.: ~1.4:1.0 Crop: 2.1:1.0 Residue: 1.0:1.9
GS 07 36	1.7:1.0		

The general procedure A was followed. M.p. 187–189 °C (label: GS0736fp). ¹H NMR (400 MHz, acetone-*d*₆, label: GS0736fpwashed): δ = 6.768, 6.764 (s, s, 0.7H, 0.3H), 5.875, 5.870 (s, s, 0.7H, 0.3H), 4.972 (br s, 2H), 4.82 – 4.73 (m, 2H), 1.460, 1.443 (s, s, 1.8H, 4.2H), 1.405, 1.388 (s, s, 4.2H, 1.8H), 1.266, 1.252 (s, s, 3H, 3H). ¹³C{¹H} NMR (100 MHz, acetone-*d*₆, label: gs0736fp13c): δ = aromatic region: expected 8 resonances for 2 diastereomers, found 8 resonances at 142.17, 142.12, 123.16, 123.04, 121.99, 121.95, 102.90, 102.75; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 75.21, 75.15, 75.02, 74.96; aliphatic region: expected 6 resonances for 2 diastereomers, found 2 resonances at 31.6, 21.9. HR FAB-

MS (3-NBA matrix): m/z (ion type, %RA or $m/z = 279-274$, deviation for the formula): 278.1942 ($[M+1+H]^+$, 4%, 2.9 ppm for $^{12}C_{15}^{13}C_1H_{25}N_2O_2$), 277.1902 ($[M+H]^+$, 29%, 5.2 ppm for $^{12}C_{16}H_{25}N_2O_2$), 276.1841 ($[M]^+$, 100%, -1.1 ppm for $^{12}C_{16}H_{24}N_2O_2$), 275.1761 ($[M-H]^+$, 15%, -0.7 ppm for $^{12}C_{16}H_{23}N_2O_2$), 274.1688 ($[M-2H]^+$, 2%, -2.6 ppm for $^{12}C_{16}H_{22}N_2O_2$). IR (cm^{-1} , label: gs0736fp): 3356 (N-H), 2972, 2929, 2864 (C-H), 1632, 1465, 1342, 1242, 1194, 1143, 1081.

Diol-Diamine **1** with Benzaldehyde.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0748	30.0	1	Flash chromatography and treatment with pentane	25	46 ^{a,c}
2	GS0794	15.0	1.5	Flash chromatography and treatment with pentane	8.8	33 ^{b,c}

a: yield of ~53% after flash chromatography. The residue (3.3 mg), obtained after treatment with pentane, contained ~90 % of target material by 1H NMR spectroscopy. b: yield of 84% after flash chromatography. The residue (12.6 mg), obtained after treatment with pentane, contained ~95 % of target material by 1H NMR spectroscopy. c: no diastereomeric excess was detected after treatment by pentane.

The general procedure A was followed. M.p. 136–138 °C (label: GS0794fp). 1H NMR (400 MHz, acetone- d_6 , label: GS0748fp2washed): δ = 7.62 – 7.53 (m, 4H), 7.44 – 7.31 (m, 6H), 6.946, 6.942 (s,s, 0.5H, 0.5H) 6.165, 6.159 (s, s, 0.5H, 0.5H), 5.70 – 5.62 (m, 2H), 5.229 (s, 2H), 1.627, 1.614 (s, s, 3H, 3H), 1.535, 1.522 (s, s, 3H, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, acetone- d_6 , label: gs0748fp213c): δ = aromatic region: expected 16 resonances for 2 diastereomers, found 14 resonances at 142.62, 142.54, 141.70, 141.69,

129.31, 128.98, 128.074, 128.067, 123.38, 123.28, 122.54, 122.49, 103.76, 103.56; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 80.44, 80.36, 76.36, 76.31; 60.6 (residual AcOEt); aliphatic region: expected 4 resonances for 2 diastereomers, found 2 resonances at 31.70, 31.68; 20.9 (residual AcOEt), 14.6 (residual AcOEt). HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or $m/z = 403\text{--}398$, deviation for the formula): 402.2246 ($[M+1+H]^+$, 10%, 4.0 ppm for $^{12}C_{25}^{13}C_1H_{29}N_2O_2$), 401.2210 ($[M+H]^+$, 46%, 4.8 ppm for $^{12}C_{26}H_{29}N_2O_2$), 400.2157 ($[M]^+$, 100%, -1.6 ppm for $^{12}C_{26}H_{28}N_2O_2$), 399.2079 ($[M-H]^+$, 12%, -1.6 ppm for $^{12}C_{26}H_{27}N_2O_2$), 398.1988 ($[M-2H]^+$, 2%, 1.6 ppm for $^{12}C_{26}H_{26}N_2O_2$). IR (cm^{-1}): 3338 (N-H), 3032 (C-H), 2973 (C-H), 2928 (C-H), 2865 (C-H), 1625, 1507, 1457, 1437, 1310, 1237, 1188, 699.

Diol-Diamine 1 with *p*-Nitrobenzaldehyde.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0673	5.0	1	Flash chromatography	11.4	99
2	GS0731	30.0	1	Flash chromatography	58.4	99

The general procedure A was followed. M.p. 196–198 °C (label: GS0731fp). 1H NMR (500 MHz, acetone- d_6 , label: gs0731fp-2): δ = 8.284 (d, J = 8.5 Hz, 4H), 7.877 (d, J = 8.5 Hz, 4H), 7.011, 7.007 (s, s, 0.5H, 0.5H), 6.200, 6.195 (s, s, 0.5H, 0.5H), 5.85 – 5.80 (m,

2H), 5.46 (s, 1.5H), 1.660, 1.646 (s, s, 3H, 3H), 1.573, 1.560 (s, s, 3H, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6 , label: gs0731fp13c): δ = aromatic region: expected 16 resonances for 2 diastereomers, found 13 resonances at 149.1, 148.4, 129.31, 129.30, 124.2, 142.21, 142.11, 123.50, 123.41, 123.00, 122.96, 104.32, 104.13; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 79.46, 79.39, 76.84, 76.80; aliphatic region: expected 4 resonances for 2 diastereomers, found 1 resonance at 31.6. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 493 – 488, deviation for the formula): 492.1964 ($[\text{M}+1+\text{H}]^+$, 12%, 0.0 ppm for $^{12}\text{C}_{25}^{13}\text{C}_1\text{H}_{27}\text{N}_4\text{O}_6$), 491.1903 ($[\text{M}+1]^+$, 45%, –3.5 ppm for $^{12}\text{C}_{25}^{13}\text{C}_1\text{H}_{26}\text{N}_4\text{O}_6$), 490.1854 ($[\text{M}]^+$, 100%, –0.4 ppm for $^{12}\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_6$), 489.1767 ($[\text{M}-\text{H}]^+$, 14%, 1.5 ppm for $^{12}\text{C}_{26}\text{H}_{25}\text{N}_4\text{O}_6$), 488.1682 ($[\text{M}-2\text{H}]^+$, 2%, 2.8 ppm for $^{12}\text{C}_{26}\text{H}_{24}\text{N}_4\text{O}_6$). IR (cm^{-1}): 3366 (N–H), 2975 (C–H), 2930 (C–H), 2861 (C–H), 1625, 1518 (N=O), 1346 (N=O), 1238, 1188, 850.

Diol-Diamine **1** with Cyclohexanone.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0621	5.0	4	PTLC	6.5	75
2	GS0792	20.0	4.5	PTLC	26.9	78

The general procedure A was followed. M.p. 121 °C (label: MT0369). ^1H NMR (500 MHz, acetone- d_6 , label: gs0621fp2): δ = 6.784 (s, 1H), 5.994 (s, 1H), 4.870 (s, 2H), 1.830 – 1.570 (m, 8H), 1.570 – 1.400 (m, 10H), 1.390 – 1.230 (m, 2H), 1.441 (s, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6 , label: MT-3-72-pure-3-13C): δ = 140.8, 121.75, 121.59, 103.0, 82.9, 73.8, 38.6, 32.8, 26.4, 23.4. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 387–382, deviation for the formula): 386.2860 ($[\text{M}+\text{H}+1]^+$, 7%, 7.4 ppm for $^{12}\text{C}_{23}^{13}\text{C}_1\text{H}_{37}\text{N}_2\text{O}_2$), 385.2810 ($[\text{M}+1]^+$, 38.5%, 0.1 ppm for $^{12}\text{C}_{23}^{13}\text{C}_1\text{H}_{36}\text{N}_2\text{O}_2$), 384.2765 ($[\text{M}]^+$, 100%, 3.1 ppm for $^{12}\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_2$), 383.2692 ($[\text{M}-\text{H}]^+$, 18%, 1.6 ppm for $^{12}\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_2$), 382.2611 ($[\text{M}-2\text{H}]^+$, 2.5%, 2.5 ppm for $^{12}\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_2$). IR (cm^{-1}): 3356 (N-H), 2972 (C-H), 2933 (C-H), 2856 (C-H), 1625, 1447.

Diol-Diamine 1 with Acetone.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0707	280.0	8	Flash chromatography	290	75
2	GS0809	500.0	9	Treatment with pentane/ether, 1:1	447	66 ^a

a: the residue (180 mg), obtained after treatment with pentane, contained ~60 % of target material by ^1H NMR spectroscopy.

The general procedure A was followed. M.p. 151–152 °C (label: GS0809Crop1, lit.^{S2,S3} 143–145 °C). ^1H NMR (400 MHz, acetone- d_6 , label: gs0790crop1): δ = 6.812 (s, 1H), 5.906 (d, J = 0.8 Hz, 1H), 4.915 (s, 1.5H), 1.435 (s, 12H), 1.335 (s, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6 , label: gs0790crop1-13C): δ = 141.3, 121.90, 121.55, 102.9,

82.4, 74.0, 32.6, 29.6. HR FAB-MS (3-NBA matrix, label: gs0790crop1): m/z (ion type, %RA or m/z = 307 – 303, deviation for the formula): 306.2249 ([M+1+H]⁺, 3%, 4.5 ppm for ¹²C₁₇¹³C₁H₂₉N₂O₂), 305.2199 ([M+1]⁺, 23%, –4.7 ppm for ¹²C₁₇¹³C₁H₂₈N₂O₂), 304.2148 ([M]⁺, 73%, 1.1 ppm for ¹²C₁₈H₂₈N₂O₂), 303.2077 ([M–H]⁺, 9%, –1.4 ppm for ¹²C₁₈H₂₇N₂O₂). IR (cm^{–1}): 3341 (N–H), 2988 (C–H), 2933 (C–H), 1627, 1486, 1360, 1175, 1138, 1020, 892.

Diol-Diamine 1 with 2-Butanone.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0753	25.0	2.5	PTLC	16	44

The general procedure A was followed. M.p. 76–80 °C (label: GS0753fp). ¹H NMR (400 MHz, acetone-*d*₆, label: gs0753fpbefore13c): δ = 6.793 (s, 1H), 5.940 (s, 1H), 4.833 (s, 2H), 1.615 (q, *J* = 7.2 Hz, 4H), 1.460 (s, 6H), 1.407 (s, 6H), 1.276 (s, 6H), 0.909 (t, *J* = 7.2 Hz, 6H). ¹³C{¹H} NMR (100 MHz, acetone-*d*₆, label: gs0753fp13c): δ = aromatic region: expected 8 resonances for 2 diastereomers, found 5 resonances at 141.4, 121.60, 121.36, 102.55 (LB = 0.10 Hz, GB = 0.0 Hz), 102.54 (LB = 0.10 Hz, GB = 0.0 Hz); aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 2 resonances at 84.4, 73.8; aliphatic region: expected 10 resonances for 2 diastereomers, found 8 resonances at 35.20, 35.19, 32.88, 32.87, 32.33, 32.32, 27.0, 8.7. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 335–330, deviation for the formula):

334.2553 ($[M+1+H]^+$, 6%, 6.8 ppm for $^{12}C_{19}^{13}C_1H_{33}N_2O_2$), 333.2513 ($[M+1]^+$, 39%, -4.6 ppm for $^{12}C_{19}^{13}C_1H_{32}N_2O_2$), 332.2467 ($[M]^+$, 100%, -1.0 ppm for $^{12}C_{20}H_{32}N_2O_2$), 331.2384 ($[M-H]^+$, 13%, 0.5 ppm for $^{12}C_{20}H_{31}N_2O_2$), 330.2299 ($[M-2H]^+$, 1%, 2.6 ppm for $^{12}C_{20}H_{30}N_2O_2$). (cm^{-1} , label: gs0753fp): 3354 (N-H), 2974 (C-H), 2930 (C-H), 1625, 1513, 1250.

Diol-Diamine 1 with Triethylglycol Methyl Ketone.

Run	ID	Scale (mg)	Time (h)	Purification ^a	Yield	
					mg	%
1	GS0608	68.0	4	Washing with water and flash chromatography	124	65
2	GS0837	70.0	4	Washing with water and flash chromatography	124	63
3	GS0555	100.0	2	Washing with water and flash chromatography and PTLC	63	22 ^b

a: washing with water helps to remove the excess of the ketone b: The run 3 was carried out according to the general procedure B.

The general procedure A was followed for runs 1 and 2; the general procedure B was followed for run 3. 1H NMR (400 MHz, acetone- d_6 , label: gs0608f1): δ = 6.816, 6.813 (s, s, 0.5H, 0.5H), 6.092, 6.076 (t, t, J = 1.4, 1.2 Hz, 0.5H, 0.5H, LB = 0.05 Hz, GB = 0 Hz), 4.988, 4.971 (s, s, 0.6H, 0.6H), 3.710 – 3.440 (m, 24H), 3.440 – 3.250 (m, 4H), 3.290 (s, 6H), 1.461, 1.456 (s, s, 3H, 3H), 1.437, 1.430 (s, s, 3H, 3H), 1.336 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, acetone- d_6 , LB = 3.0 Hz, GB = 0.0 Hz, label: gs0544f2bw13c): δ = aromatic region: expected 8 resonances for 2 diastereomers, found 7 resonances at

141.13, 141.06, 121.93, 121.86, 120.98, 102.85, 102.75; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 84.18, 84.10, 76.56, 76.44; aliphatic region: 76.56, 76.44, 74.43, 74.41, 72.76, 71.95, 71.87, 71.38, 71.28, 71.24, 71.17, 58.9, 32.7, 31.77, 31.69, 26.34, 26.29. HR FAB-MS (Glycerol matrix): m/z (ion type, %RA or m/z = 631–627, deviation for the formula): 630.4040 ($[M+1+H]^+$, 36%, 1.1 ppm for $^{12}C_{31}^{13}C_1H_{57}N_2O_{10}$), 629.4019 ($[M+H]^+$, 100%, –0.9 ppm for $^{12}C_{32}H_{57}N_2O_{10}$), 628.3958 ($[M]^+$, 9%, –3.7 ppm for $^{12}C_{32}H_{56}N_2O_{10}$), 627.3845 ($[M-H]^+$, 7%, 1.9 ppm for $^{12}C_{32}H_{55}N_2O_{10}$). IR (cm^{-1}): 3331 (N–H), 2976 (C–H), 2870 (C–H), 1625 (Ar C=C), 1107 (C–O).

Diol-Diamine 1 with Methyl Acetoacetate.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0780	20.0	6.5	PTLC	14	37
2	GS0805	120.0	12	Flash chromatography and treatment with pentane	68	30 ^a

a: the residue (25 mg), obtained after treatment with pentane, contained ~70 % of target material by 1H NMR spectroscopy.

Diastereomeric Excess			
ID	Crude	Purification method	Purified product
GS 07 80	~1.0:1.2	PTLC	~1.1:1.0
GS 08 05	1.1:1.0	Flash chromatography and treatment with pentane	After chrom.: ~1.5:1.0 Crop1: 1.0:1.8 Crop2: 4.5:1

The general procedure A was followed. M.p. 116–119 °C (label: GS0805fpcrop1). ^1H NMR (400 MHz, acetone- d_6 , label: gs0805fpcrop1): δ = 6.883 (s, 1H), 6.051 (s, 1H), 5.184 (s, 1.3H), 3.617, 3.612 (s, s, 2.2H, 3.8H, LB = 0.50 Hz, GB = 0 Hz), 2.695, 2.587 (AB, J = 14.6 Hz, 0.7H, 0.7H, LB = –0.80 Hz, GB = 0.40 Hz), 2.687, 2.590 (AB, J = 14.4 Hz, 1.3H, 1.3H, LB = –1.21 Hz, GB = 0.70 Hz), 1.469 (s, 6H), 1.426 (s, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6 , label: gs0805fpcrop1C13): δ = carbonyl region: expected 2 resonances for 2 diastereomers, found 2 resonances at 171.76 (LB = 0.50 Hz, GB = 0 Hz), 171.75 (LB = 0.50 Hz, GB = 0 Hz); aromatic region: expected 8 resonances for 2 diastereomers, found 7 resonances at 140.72 (LB = 0.30 Hz, GB = 0 Hz), 140.72 (LB = 0.30 Hz, GB = 0 Hz), 122.44, 122.42, 121.32, 103.47, 103.42; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 3 resonances at 83.22, 83.19, 74.6; methyl ester region: expected 2 resonances for 2 diastereomers, found 2 resonances at 51.71, 51.69; aliphatic region: expected 8 resonances for 2 diastereomers, found 6 resonances at 45.68, 45.64, 32.64, 32.61, 31.5, 27.9. HR FAB-MS (3-NBA matrix, label: gs0781fp): m/z (ion type, %RA or m/z = 423–419, deviation for the formula): 422.2352 ($[\text{M}+1+\text{H}]^+$, 10%, 4.7 ppm for $^{12}\text{C}_{21}^{13}\text{C}_1\text{H}_{33}\text{N}_2\text{O}_6$), 421.2321 ($[\text{M}+\text{H}]^+$, 48%, 4.1 ppm for $^{12}\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_6$), 420.2265 ($[\text{M}]^+$, 100%, –1.1 ppm for $^{12}\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_6$), 419.2197 ($[\text{M}-\text{H}]^+$, 5%, –3.6 ppm for $^{12}\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_6$). IR (cm^{-1}): 3368 (N–H), 2977 (C–H), 2935 (C–H), 1727 (C=O), 1625, 1436, 1261, 1210, 1130, 1012.

6. Condensation Reactions of Diol-Diamine 3 with Aldehydes and Ketones.

Diol-Diamine 3 with Acetaldehyde.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0737	30.0	1.3	Flash chromatography	27	84

The general procedure A was followed. M.p. 90–93 °C (label: GS0737fp). ^1H NMR (400 MHz, benzene- d_6 , label: gs0737fpbefore13c): δ = 6.728, 6.711 (s, s, 0.46H, 0.54H), 5.847, 5.832 (s, s, 0.54H, 0.46H), 4.82 – 4.72 (m, 2H), 3.33 (s, 2H), 2.27 – 2.05 (m, 4H), 2.10 – 1.55 (m, 12H), 1.55 – 1.05 (m, 72H), 0.99 – 0.87 (m, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, benzene- d_6 , label: gs0737fp13c): δ = aromatic region: expected 8 resonances for 2 diastereomers, found 8 resonances at 142.49, 142.36, 123.52, 123.42, 122.4, 122.0, 105.5, 104.8; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 79.54, 79.49, 75.16, 75.07; aliphatic region: 42.80, 42.75, 41.6, 41.2, 32.7, 31.41, 31.39, 31.2, 31.1, 30.9, 30.75, 30.70, 30.66, 30.63, 30.58, 30.54, 30.52, 30.23, 30.21, 24.59, 24.57, 24.3, 24.2, 23.5. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 895–890, deviation for the formula): 894.8851 ($[\text{M}+1+\text{H}]^+$, 25%, –1.7 ppm for $^{12}\text{C}_{59}^{13}\text{C}_1\text{H}_{113}\text{N}_2\text{O}_2$), 893.8778 ($[\text{M}+1]^+$, 67%, –2.4 ppm for $^{12}\text{C}_{59}^{13}\text{C}_1\text{H}_{112}\text{N}_2\text{O}_2$), 892.8737 ($[\text{M}]^+$, 100%, –1.5 ppm for $^{12}\text{C}_{60}\text{H}_{112}\text{N}_2\text{O}_2$), 891.8691 ($[\text{M}-\text{H}]^+$, 65%, –5.1 ppm for $^{12}\text{C}_{60}\text{H}_{111}\text{N}_2\text{O}_2$), 890.8608 ($[\text{M}-2\text{H}]^+$, 26%, –4.6 ppm for

$^{12}\text{C}_{60}\text{H}_{110}\text{N}_2\text{O}_2$) IR (cm^{-1}): 3349 (N–H), 2922 (C–H), 2852 (C–H), 1629, 1466, 1296, 1190, 1086.

Diol-Diamine 3 with Acetone.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0596	100.0	15	-	74	66
2	GS0720	80.0	30	-	67	76

The general procedure A was followed. M.p. 47–51 °C (label: GS0819crude). The crude products already had adequate purity for synthetic purposes. ^1H NMR (500 MHz, benzene- d_6 , label: gs0720crude): δ = 6.872 (s, 1H), 5.698 (s, 1H), 3.292 (s, 2H), 2.136 (dt, J = 13.0, 3.5 Hz, 4H), 1.944 (dt, J = 12.0, 3.5 Hz, 4H), 1.820 – 1.655 (m, 4H), 1.655 – 1.525 (m, 4H), 1.500 – 1.180 (m, 84H), 0.926 (t, J = 6.5 Hz, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, benzene- d_6 , label: gs059613c): δ = 141.3, 122.66, 121.61, 104.3, 82.1, 78.6, 43.0, 32.7, 31.19, 30.77, 30.70, 30.60, 30.54, 30.22, 30.04, 24.6, 23.5, 14.8. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 923–918, deviation for the formula): 922.9126 ($[\text{M}+1+\text{H}]^+$, 27%, 2.4 ppm for $^{12}\text{C}_{61}^{13}\text{C}_1\text{H}_{117}\text{N}_2\text{O}_2$), 921.9062 ($[\text{M}+1]^+$, 63%, 1.0 ppm for $^{12}\text{C}_{61}^{13}\text{C}_1\text{H}_{116}\text{N}_2\text{O}_2$), 920.9001 ($[\text{M}]^+$, 100%, 3.9 ppm for $^{12}\text{C}_{62}\text{H}_{116}\text{N}_2\text{O}_2$), 919.8945 ($[\text{M}-\text{H}]^+$, 88%, 1.4 ppm for $^{12}\text{C}_{62}\text{H}_{115}\text{N}_2\text{O}_2$), 918.8856 ($[\text{M}+1-3\text{H}]^+$, 31%, –2.2

ppm for $^{12}\text{C}_{61}^{13}\text{C}_1\text{H}_{113}\text{N}_2\text{O}_2$). IR (cm^{-1} , label: gs0720): 3352 (N–H), 2922 (C–H), 2852 (C–H), 1625, 1466, 1378, 1188.

Diol-Diamine 3 with Triethylglycol Methyl Ketone.

Run	ID	Scale (mg)	Time (h)	Purification ^a	Yield	
					mg	%
1	GS0592	10.0	2.5	Washing by water	~13	~85 ^b
2	GS0602	80.0	5	Washing by water, followed by flash chromatography on non-deactivated silica	90	76

a: washing with water helps to remove the excess of the ketone; b: the product in run 1 contained about 10% of residual ketone, as determined by ^1H NMR spectroscopy.

The general procedure A was followed. M.p. $\sim 29^\circ\text{C}$ (label: GS0602f1). ^1H NMR (400 MHz, C_6D_6 , label: gs0602-F2): δ = 6.885, 6.873 (s, s, 0.45H, 0.55H), 6.098, 6.089 (s, s, 0.55H, 0.45H), 4.800, 4.774 (s, s, 1.1H, 0.9H), 3.62 – 3.28 (m, 28H), 3.170, 3.163 (s, s, 2.7H, 3.3H), 2.28 – 1.96 (m, 8H), 1.84 – 1.55 (m, 15H), 1.55 – 1.22 (m, 72H), 0.99 – 0.88 (m, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , label: gs060213c): δ = aromatic region: expected 8 resonances for 2 diastereomers, found 6 resonances at 142.05, 142.01, 122.24, 119.94, 119.90, 103.26; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 4 resonances at 84.14, 84.08, 77.02, 76.83; triethylene glycol region: 79.4, 72.75, 71.78, 71.63, 71.43, 71.38, 71.34, 71.24, 71.16, 71.08, 59.1; aliphatic region: 43.1, 41.59, 41.51, 32.7, 31.36, 31.32, 31.18, 30.83, 30.78,

30.70, 30.66, 30.61, 30.55, 30.42, 30.38, 30.22, 27.00, 26.94, 25.2, 24.76, 24.74, 23.5, 14.7. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or $m/z = 1244$ – 1250 , deviation for the formula): 1244.0702 ($[M-2H+1]^+$, 47%, -0.3 ppm for $^{12}C_{75}^{13}C_1H_{142}N_2O_{10}$), 1245.0812 ($[M]^+$, 49%, 0.7 ppm for $^{12}C_{76}H_{144}N_2O_{10}$), 1246.0907 ($[M+H]^+$, 100%, -0.6 ppm for $^{12}C_{76}H_{145}N_2O_{10}$), 1247.0939 ($[M+H+1]^+$, 82%, -0.5 ppm for $^{12}C_{75}^{13}C_1H_{145}N_2O_{10}$), 1248.0973 ($[M+2H+1]^+$, 41%, 3.0 ppm for $^{12}C_{75}^{13}C_1H_{146}N_2O_{10}$), 1249.0981 ($[M+3H+1]^+$, 15%, 8.7 ppm for $^{12}C_{75}^{13}C_1H_{147}N_2O_{10}$). IR (cm^{-1}): 3339 (N–H), 2921 (C–H), 2852 (C–H), 1625, 1466, 1301, 1141, 1110.

Diol-Diamine 3 with Methyl Acetoacetate.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0667	10.0	8	PTLC	10.1	85
2	GS0732	80.0	7.5	Flash chromatography	65.7	66

The general procedure A was followed. M.p. ~ 36 °C (label: GS0732fp2). 1H NMR (400 MHz, C_6D_6 , label: gs0667fp): δ = 6.860, 6.851 (s, s, $\sim 0.5H$, $\sim 0.5H$), 5.784, 5.725 (s, s, $\sim 0.5H$, $\sim 0.5H$), 4.985, 4.973 (s, s, $\sim 1H$, $\sim 1H$), 3.228 (s, 6H), 2.873, 2.667 (AB, $J = 15.4$ Hz, 1H, 1H), 2.861, 2.667 (AB, $J = 15.4$ Hz, 1H, 1H), 2.19 – 1.88 (m, 8H), 1.72 – 1.50 (m, 14H), 1.50 – 1.20 (m, 72H), 0.99 – 0.88 (m, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6 , label: gs0732fp213c): δ = carbonyl region: expected 2 resonances for 2 diastereomers,

found 2 resonances at 172.13, 172.10; aromatic region: expected 8 resonances for 2 diastereomers, found 7 resonances at 141.45, 141.44, br 122.3, 120.59, 120.49, 103.95, 103.85; aliphatic quaternary carbon region: expected 4 resonances for 2 diastereomers, found 2 resonances at 83.08, 79.43; aliphatic region: 51.38, 51.36, 45.80, 45.75, 42.84, 42.82, 41.97, 41.90, 32.73, 31.21, 31.18, 31.13, 30.78, 30.76, 30.73, 30.68, 30.63, 30.60, 30.55, 30.54, 30.23, 28.07, 28.03, 24.90, 24.85, 24.78, 24.72, 23.50, 14.74. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 1038–1034, deviation for the formula): 1037.9162 ($[M+1]^+$, 59%, 1.8 ppm for $^{12}C_{65}^{13}C_1H_{120}N_2O_6$), 1036.9125 ($[M]^+$, 100%, 2.1 ppm for $^{12}C_{66}H_{120}N_2O_6$), 1035.9069 ($[M-H]^+$, 82%, -0.1 ppm for $^{12}C_{66}H_{119}N_2O_6$), 1034.8970 ($[M-2H]^+$, 22%, 1.9 ppm for $^{12}C_{66}H_{118}N_2O_6$). IR (cm^{-1}): 3370 (N-H), 2922 (C-H), 2852 (C-H), 1731 (C=O), 1625, 1466, 1437, 1207, 1114.

Diol-Diamine 3 with Dimethyl 1,3-Acetonedicarboxylate.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0668	10.0	30	PTLC	6.5	47
2	GS0788	10.0	58	PTLC	6.6	48
3	GS0735	150.0	40	Flash chromatography and PTLC	70.9	34 ^a

a: in run 3, yield was “sacrificed” to obtain a sample of pure product.

The general procedure A was followed. ^1H NMR (400 MHz, C_6D_6 , label: gs0752f2before13c): δ = 6.822 (s, 1H), 5.470 (s, 1H), 5.248 (s, 2H), 3.303 (s, 12H), 3.265, 2.818 (AB, J = 15.4 Hz, 4H, 4H), 2.18 – 2.10 (m, 4H), 2.10 – 1.88 (m, 4H), 1.68 – 1.49 (m, 8H), 1.50 – 1.20 (m, 72H), 0.98 – 0.88 (m, 12H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6): δ = 171.6, 140.6, 122.3, 120.4, 103.7, 83.8, 80.1, 51.5, 44.3, 41.7, 32.7, 30.76, 30.70, 30.63, 30.60, 30.55, 30.2, 24.8, 23.5, 14.7. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 1155–1150, deviation for the formula): 1154.9319 ($[\text{M}+1+\text{H}]^+$, 50%, 4.3 ppm for $^{12}\text{C}_{69}^{13}\text{C}_1\text{H}_{125}\text{N}_2\text{O}_{10}$), 1153.9298 ($[\text{M}+1]^+$, 100%, –0.7 ppm for $^{12}\text{C}_{69}^{13}\text{C}_1\text{H}_{124}\text{N}_2\text{O}_{10}$), 1152.9249 ($[\text{M}]^+$, 94%, 0.6 ppm for $^{12}\text{C}_{70}\text{H}_{124}\text{N}_2\text{O}_{10}$), 1151.9148 ($[\text{M}+1-2\text{H}]^+$, 42%, –1.3 ppm for $^{12}\text{C}_{69}^{13}\text{C}_1\text{H}_{122}\text{N}_2\text{O}_{10}$), 1150.9074 ($[\text{M}+1-3\text{H}]^+$, 15%, –1.6 ppm for $^{12}\text{C}_{69}^{13}\text{C}_1\text{H}_{121}\text{N}_2\text{O}_{10}$). IR (cm^{-1}): 3369 (N–H), 2923 (C–H), 2852 (C–H), 1735 (C=O), 1625, 1437, 1344, 1202, 1069.

7. Exchange Reactions of **2e** and **4b** with Methyl Acetoacetate.

Exchange of Acetone Moiety for Methyl Acetoacetate Moiety in Both 3,1-Oxazines Rings of **2e**.

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0746	8.0	9	PTLC	4.3	39 ^a
2	GS0781	30.0	7	Flash chromatography and treatment with pentane	18.1	44 ^b

a: in run 1, ratio of 50:1 w/w of silica to **2e** was used. The purified product showed an inadequate purity for analytical purposes. b: in run 2, the residue (5.4 mg), obtained after treatment with pentane, contained ~70% of target material by ¹H NMR spectroscopy.

Diastereomeric excess			
ID	Crude	Purification	Purified product
GS0746	~1:1	PTLC	~1:1
GS0781	1:1	Flash chromatography and treatment with pentane	After chromatography: ~1:1 Crop1: 1:6.5 Crop2: 1:0.7 residu: 1:0.4

Benzobisoxazine **2e** (30.0 mg, 0.0987 mmol, 1 equiv) was suspended in pentane (1.9 mL) and methyl acetoacetate (286.0 mg, 2.47 mmol, 25 equiv) was added (label: gs0781). Subsequently, silica (1.10 g, 35:1 w/w) was added. After vigorous stirring at RT for 7 h, the reaction was stopped by addition of ethyl acetate (2 mL) and filtration of silica through a sintered funnel. Evaporation under reduced pressure yielded crude

product (66 mg). The crude product was purified by flash chromatography on deactivated silica gel (benzene/ethyl acetate, 98:2) to give a yellow solid (25 mg). This solid was purified further by treatment with pentane to yield to 2 crops of a pure white solid (18 mg, 44%). ¹H NMR (400 MHz, acetone-*d*₆, label: gs0781fpwashed=crop1): δ = 6.883 (s, 1H), 6.050 (s, 1H), 5.181 (s, 1.6H), 3.617, 3.612 (s, s, 0.8H, 5.2H, LB = −0.30 Hz, GB = 0 Hz), 2.694, 2.591 (AB, *J* = 14.8 Hz, 0.2H, 0.2H, LB = −0.17 Hz, GB = 0.0 Hz), 2.687, 2.591 (AB, *J* = 14.6 Hz, 0.8H, 0.8H, −0.17 Hz, GB = 0.0 Hz), 1.469 (s, 6H), 1.430 (s, 6H), 1.426 (s, 6H).

Exchange of Acetone Moiety for Methyl Acetoacetate Moiety in One of The 3,1-Oxazines Rings of 2e.

Run	ID	Scale (mg)	Time (h)	Purification	Products	¹ H NMR Relative Integration (Crude)	Yield	
							mg	%
1	GS0777	20.0	2	PTLC	5 2h 2e	52 21 26	6.6 3.4 2.3	28 12 11
2	GS0783	60.0	2	Flash chromatography and PTLC	5 2h 2e	51 13 36	13.4 4.4 ~8	19 5 13

Benzobisoxazine **2e** (60.0 mg, 0.197 mmol, 1 equiv) was suspended in pentane (2.5 mL) and methyl acetoacetate (572.0 mg, 4.93 mmol, 25 equiv) was added (label: gs0783). Subsequently, silica (1.50 g, 25:1 w/w) was added. The progression of the

reaction was monitored by ^1H NMR spectroscopy. After vigorous stirring at RT for 2 h, the reaction was stopped by addition of ethyl acetate (2 mL) and filtration of silica through a sintered funnel. Evaporation under reduced pressure yielded crude product (81 mg). The residue was purified by flash chromatography on deactivated silica gel (benzene/ethyl acetate, 98:2) to give two fractions: fraction 1 was a mixture of **2h** and **5** (24 mg) and the fraction 2 was the unreacted starting material **2e** (8 mg). The mixture of **2h** and **5** was further purified by PTLC (deactivated silica, benzene/ethyl acetate, 93:7) to yield to the product **2h** (4.4 mg, 5%) and the target compound **5** (13.4 mg, 19%). ^1H NMR (400 MHz, acetone- d_6 , label: GS0803F2/gS0783): δ = 6.846 (s, 1H), 5.968 (s, 1H), 5.095 (s, 1H), 5.008 (s, 1H), 3.613 (s, 3H), 2.687, 2.583 (AB, J = 14.4 Hz, 1H, 1H), 1.480 (s, 3H), 1.442 (s, 6H), 1.418 (s, 6H), 1.344 (s, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- d_6 , label: gs0803f213C): δ = 171.8, 141.6, 140.4, 122.2, 121.7, 121.6, 103.1, 83.2, 82.4, 74.56, 74.02, 51.7, 45.6, 32.69, 32.58, 31.6, 29.6, 27.9. HR FAB-MS (3-NBA matrix): m/z (ion type, %RA or m/z = 365–360, deviation for the formula): 364.2300 ($[\text{M}+1+\text{H}]^+$, 9%, 4.9 ppm for $^{12}\text{C}_{19}^{13}\text{C}_1\text{H}_{31}\text{N}_2\text{O}_4$), 363.2261 ($[\text{M}+1]^+$, 45%, –6.0 ppm for $^{12}\text{C}_{19}^{13}\text{C}_1\text{H}_{30}\text{N}_2\text{O}_4$), 362.2200 ($[\text{M}]^+$, 100%, 1.6 ppm for $^{12}\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_4$), 361.2136 ($[\text{M}-\text{H}]^+$, 9%, –2.4 ppm for $^{12}\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_4$). IR (cm^{-1}): 3366 (N–H), 2976 (C–H), 2933 (C–H), 1727 (C=O), 1625, 1513, 1435, 1360, 1258, 1202, 1135, 1015.

Exchange of Acetone Moiety for Methyl Acetoacetate Moiety in Both 3,1-Oxazines Rings of **4b.**

Run	ID	Scale (mg)	Time (h)	Purification	Yield	
					mg	%
1	GS0722	10.0	72	PTLC	7.8	69
2	GS0743	5.0	48	PTLC	4.2	68 ^a

a: 25 equiv of ketone and the ratio of 17:1 w/w of silica to **4b** were used. Although, crude product did not show mono-exchanged product, purification by deactivated PTLC did not provide an analytically pure compound.

Benzobisoxazine **4b** (10.0 mg, 0.0109 mmol, 1 equiv) was suspended in pentane (0.2 mL) and methyl acetoacetate (12.6 mg, 0.109 mmol, 10 equiv) was added (label: GS0722). Subsequently, silica (50 mg, 5:1 w/w) was added. After vigorous stirring at RT for 3 d, the reaction was stopped by addition of ethyl acetate (2 mL) and filtration of silica through a sintered funnel. Evaporation under reduced pressure yielded crude product (10.9 mg). The crude product was purified by deactivated PTLC (pentane/diethyl ether, 8:2) to give the soapy product **4d** (7.8 mg, 69%), with 5–10% admixture of **6**, as determined by ¹H NMR spectra. ¹H-resonances for **4d** are only reported. ¹H NMR (400 MHz, C₆D₆, label: gs0722fp): δ = 6.860, 6.851 (s, s, ~0.5H, ~0.5H), 5.787, 5.728 (s, s, ~0.5H, ~0.5H), 4.983, 4.971 (s, s, ~1H, ~1H), 3.229 (s, 6H),

2.870, 2.665 (AB, $J = 15.4$ Hz, 1H, 1H), 2.858, 2.665 (AB, $J = 15.6$ Hz, 1H, 1H), 2.22 – 1.88 (m, 8H), 1.75 – 1.52 (m, 14H), 1.51 – 1.20 (m, 72H), 0.99 – 0.89 (m, 12H).

Exchange of Acetone Moiety for Methyl Acetoacetate Moiety in One of The 3,1-Oxazines Rings of **4b.**

Run	ID	Scale (mg)	Time (h)	Purification	Products	Ratio of products from ^1H NMR of crude	Yield	
							mg	%
1	GS0718	5.0	2	PTLC	6	40	1.9 ^a	35
					4d	17		
					4b	43	2.8	56
2	GS0823	40.0	2.6	PTLC	6	28	9.4	21
					4d	9		
					4b	64	16.3	40

a: in run 1, 5 equiv of ketone were used. **6** and **4d**, which had coincident R_F -values on deactivated PTLC, were isolated as 70:30 mixture, as determined by ^1H NMR spectroscopy.

Benzobisoxazine **4b** (40.0 mg, 0.0435 mmol, 1 equiv) was suspended in pentane (0.8 mL) and methyl acetoacetate (50.5 mg, 0.435 mmol, 10 equiv) was added (label: GS0823). Subsequently, silica (200 mg, 5:1 w/w) was added. The progression of the reaction was monitored by ^1H NMR spectroscopy. After vigorous stirring at RT for 2 h 45 min, the reaction was stopped by addition of ethyl acetate (1 mL) and filtration of silica through a sintered funnel. Evaporation under reduced pressure yielded crude product (45 mg). The crude product was purified by deactivated PTLC (pentane/diethyl ether, 8:2, developed twice) to give two fractions: fraction 1 (*cf.* ^1H and ^{13}C NMR spectra

in Figures S49 and S50) was mainly a 5:1 mixture of **6** and **4d** (9.4 mg, 21%) and the fraction 2 was the unreacted starting material **4b** (16.3 mg, 40%). ¹H NMR spectrum of fraction 1 indicated a 5:1 mixture of **6** and **4d**, as well as 3% of **4b** and 3 % of an unknown impurity. ¹H- and ¹³C-resonances are reported for **6** only. ¹H NMR (500 MHz, acetone-*d*₆, label: gs0823f1): δ = 6.855 (s, 1H), 5.740 (s, 1H), 5.141 (s, 1H), 3.242 (s, 3H), 2.915, 2.667 (AB, *J* = 15.5 Hz, 1H, 1H), 2.21–2.05 (m, 4H), 2.05–1.88 (m, 4H), 1.80–1.51 (m, 11H), 1.50 – 1.20 (m, 78H), 0.98 – 0.89 (m, 12H). ¹³C{¹H} NMR (100 MHz, acetone-*d*₆, label: gs0823f113C): δ = 171.4, 141.80, 141.11, 122.48, 121.19, 120.51, 103.9, 81.13, 82.10, 79.50, 78.59, 51.4, 45.4, 43.01, 42.93, 41.89, 32.7, 31.20, 31.13, 30.77, 30.72, 30.69, 30.60, 30.54, 30.22, 30.17, 30.03, 28.1, 24.90, 24.69, 24.57, 23.5, 14.7. HR FAB-MS (3-NBA matrix, label: gs0723f1): *m/z* (ion type, %RA or *m/z* = 976–982, deviation for the formula): 980.9197 ([*M*+1+*H*]⁺, 29%, 0.7 ppm for ¹²C₆₃¹³C₁H₁₁₉N₂O₄), 979.9164 ([*M*+*H*]⁺, 76%, 0.6 ppm for ¹²C₆₄H₁₁₉N₂O₄), 978.9082 ([*M*]⁺, 96%, 1.0 ppm for ¹²C₆₄H₁₁₈N₂O₄), 977.8994 ([*M*–*H*]⁺, 53%, 1.9 ppm for ¹²C₆₄H₁₁₇N₂O₄), 976.8935 ([*M*–2*H*]⁺, 21%, 0.0 ppm for ¹²C₆₄H₁₁₆N₂O₄). IR (cm^{–1}): 3370 (N–H), 2922 (C–H), 2852 (C–H), 1730 (C=O), 1625, 1466, 1206.

8. Acknowledgments.

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9. References for Supporting Information.

- S1. Field, J. E.; Hill, T. J.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 6071–6078.
- S2. Rajca, A.; Takahashi, M.; Pink, M.; Spagnol, G.; Rajca, S., to be submitted.
- S3. Rassat, A.; Sieveking, U. *Angew. Chem. Int. Ed.* **1972**, *11*, 303–304.

10. Figures S1 – S51: ^1H NMR, ^{13}C NMR, and IR Spectra.

GS 05-77-Pent2

Figure S1: 400 MHz 1H NMR spectrum of **3** in benzene- d_6

GS 05-77-Pent 2

Figure S2: 100 MHz ^{13}C NMR spectrum of **3** in benzene- d_6

GS 0720crude r1 Thu Jul 13 16:19:32 2006 (GMT-05:00)

Number of sample scans: 128
 Number of background scans: 128
 Resolution: 2.000
 Sample gain: 8.0
 Mirror velocity: 0.6329
 Aperture: 100.00

Figure S3: IR spectrum of **3**

GS 07-36-FP

Figure S4: 400 MHz ^1H NMR spectrum of **2a** in acetone- d_6

GS 07-36-FP

Figure S5: 100 MHz ¹³C NMR spectrum of **2a** in acetone-*d*₆

GS 0736FP r1

Thu Jul 13 17:19:45 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S6: IR spectrum of **2a**

GS 07-48-FP2

Figure S7: 400 MHz ^1H NMR spectrum of **2b** in acetone- d_6

GS 07-48-FP2

Figure S8: 100 MHz ¹³C NMR spectrum of **2b** in acetone-*d*₆

GS 07-48-FP2

Sat Jul 29 11:31:52 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S9: IR spectrum of **2b**

GS 07-31-FP

Figure S10: 500 MHz ^1H NMR spectrum of **2c** in acetone- d_6

GS 07-31-FP

Figure S11: 100 MHz ^{13}C NMR spectrum of **2c** in acetone- d_6

GS 0731FP r1

Thu Jul 13 16:47:38 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S12: IR spectrum of 2c

GS 06-21-FP

Figure S13: 500 MHz ¹H NMR spectrum of **2d** in acetone-*d*₆

MT-3-72-pure-3

Figure S14: 100 MHz ^{13}C NMR spectrum of **2d** in acetone- d_6

GS 07 92

Sat Nov 04 12:05:49 2006 (GMT-06:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S14: IR spectrum of **2d**

GS 07-90-Crop1

Figure S16: 400 MHz ^1H NMR spectrum of **2e** in acetone- d_6

GS 07-90-Crop1

Figure S17: 100 MHz ^{13}C NMR spectrum of **2e** in acetone- d_6

GS 08-09-Crop1

Tue Oct 24 15:36:39 2006 (GMT-05:00)

Number of sample scans: 128
 Number of background scans: 128
 Resolution: 2.000
 Sample gain: 8.0
 Mirror velocity: 0.6329
 Aperture: 100.00

Figure S18: IR spectrum of 2e

GS 07-53-FP

Figure S19: 400 MHz ¹H NMR spectrum of **2f** in acetone-*d*₆

GS 07-53-FP

Figure S20: 100 MHz ^{13}C NMR spectrum of **2f** in acetone- d_6

GS 07-53-FP

Sat Jul 29 11:53:37 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S21: IR spectrum of **2f**

GS 06-08-F1

Figure S22: 400 MHz ^1H NMR spectrum of **2g** in acetone- d_6

Chemical structure of **2g** is shown above the spectrum. The spectrum displays peaks corresponding to the structure, with the following chemical shifts (ppm) labeled above the peaks:

- 141.130, 141.058
- 121.929, 121.855, 120.981
- 102.847, 102.748
- 84.183, 84.098, 76.560, 76.441, 74.428, 74.409, 72.762, 71.946, 71.867, 71.380, 71.283, 71.236, 71.171
- 58.890, 32.687, 31.772, 31.688, 30.814, 30.498, 30.305, 30.113, 29.921, 29.729, 29.536, 29.344, 26.338, 26.293

An inset spectrum shows a zoomed-in view of the aromatic region, with peaks labeled at 122 ppm and 121 ppm.

S51

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S24: IR spectrum of **2g**

GS 08-05-FP-Crop1

Figure S25: 400 MHz ¹H NMR spectrum of **2h** in acetone-d₆

GS 08-05-FP

Figure S26: 100 MHz ¹³C NMR spectrum of **2h** in acetone-*d*₆

GS 08-05-FP Crop1

Tue Oct 24 15:15:51 2006 (GMT-05:00)

Number of sample scans: 128
 Number of background scans: 128
 Resolution: 2.000
 Sample gain: 8.0
 Mirror velocity: 0.6329
 Aperture: 100.00

Figure S27: IR spectrum of **2h**

GS 07-37-FP

Figure S28: 400 MHz 1H NMR spectrum of **4a** in $benzene-d_6$

GS 07-37-EP

Figure S29: 100 MHz ¹³C NMR spectrum of **4a** in benzene-*d*₆

GS 0737FP r1

Thu Jul 13 17:14:56 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S30: IR spectrum of 4a

GS 07-20-Crude

Figure S31: 500 MHz 1H NMR spectrum of **4b** in $benzene-d_6$

GS 05-96-Crude

Figure S32: 100 MHz ^{13}C NMR spectrum of **4b** in benzene- d_6

GS 0720crude r1

Thu Jul 13 16:19:32 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S33: IR spectrum of **4b**

Figure S34: 400 MHz 1H NMR spectrum of **4c** in $benzene-d_6$

GS 06-02-FP

Figure S35: 100 MHz ^{13}C NMR spectrum of **4c** in benzene- d_6

GS 06-02-F2 r2

Thu Jul 13 16:02:07 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S36: IR spectrum of 4c

GS 06-67-FP

Figure S37: 400 MHz 1H NMR spectrum of **4d** in benzene- d_6

GS 07-32-FP2

Figure S38: 100 MHz ^{13}C NMR spectrum of **4d** in benzene- d_6

GS 0667FP r1

Thu Jul 13 15:57:10 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S39: IR spectrum of **4d**

GS 07-52-F2

Figure S40: 400 MHz 1H NMR spectrum of **4e** in benzene- d_6

GS 07-52-F2

Figure S41: 100 MHz ^{13}C NMR spectrum of **4e** in benzene- d_6

GS 07-52-F2

Sat Jul 29 11:41:35 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S42: IR spectrum of 4e

GS 07-81-FP

Figure S43: 400 MHz ¹H NMR spectrum of **2h** in acetone-*d*₆, from complete exchange of **2e** acetone moiety for methyl acetoacetate moiety

GS 08-03-F2

Figure S44: 400 MHz ¹H NMR spectrum of **5** in acetone-*d*₆, from partial exchange of **2e** acetone moiety for methyl acetoacetate moiety

Chemical structure of compound **5** is shown in the top left. The ¹³C NMR spectrum (CDCl₃) is displayed below, with peaks labeled in ppm:

171.817, 141.595, 140.388, 122.172, 121.739, 121.635, 103.082, 83.199, 82.389, 74.563, 74.018, 51.684, 45.563, 32.693, 32.579, 31.557, 30.496, 30.304, 30.111, 29.919, 29.727, 29.629, 29.535, 29.342, 27.907.

S73

GS 08-03-F2

Tue Oct 24 14:56:05 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S46: IR spectrum of **5**

GS 07-22-FP

Figure S47: 400 MHz 1H NMR spectrum of **4d** in $benzene-d_6$, from complete exchange of **4b** acetone moiety for methyl acetoacetate moiety, run 1

GS 07-43-FP2

Figure S48: 400 MHz ¹H NMR spectrum of **4d** in benzene-*d*₆, from complete exchange of **4b** acetone moiety for methyl acetoacetate moiety, run 2

GS 08-23-F1

Figure S49: 500 MHz ¹H NMR spectrum of **6** in benzene-*d*₆ from partial exchange of **4b** acetone moiety for methyl acetoacetate moiety

GS 08-23-F1

Figure S50: 100 MHz ^{13}C NMR spectrum of **6** in benzene- d_6 , from partial exchange of **4b** acetone moiety for methyl acetoacetate moiety

GS 08-23-F1

Tue Oct 24 15:05:25 2006 (GMT-05:00)

Number of sample scans: 128
Number of background scans: 128
Resolution: 2.000
Sample gain: 8.0
Mirror velocity: 0.6329
Aperture: 100.00

Figure S51: IR spectrum of **6**