Supplementary Material (ESI) for Organic and Biomolecular Chemistry

A diastereoselective and concise synthesis of functionalised vinyl epoxides having a Morita-Baylis-Hillman backbone

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General informations

NMR spectra were recorded on a Bruker DPX 250 (^{1}H: 250 MHz, ^{13}C: 63 MHz) or on a Bruker DRX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instruments in $CDCl_3$ unless indicated otherwise. Data appear in the following order: chemical shift δ in ppm, multiplicity (s singulet, d doublet, t triplet, m multiplet), number of protons, coupling constant *J* in Hz. TMS is the internal standard for the $CDCl_3$ solutions.

IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer. Vibrations ν were reported in cm^{-1}.

Mass spectra were recorded on a Varian GC/MS/MS instrument equipped with CP 3800 (GC) and Saturn 2000 (MS/MS) modules.

Exact mass spectra were recorded on a Waters Q-TOF Micro apparatus (LC/MS) with a Xterra MS column.

Purification by flash[1] chromatography of compounds was achieved with Merck 60 silica gel (40-63 μm).

Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (1.1 mm, Merck) and the plates were visualised with UV light (254 nm), a potassium permanganate solution (1 g with 2 g of K_2CO_3 in 200 mL of water) or a phosphomolybdic acid solution (1 g in 100 mL of *i*-PrOH).

All reagents and solvents are commercially available and used without further purification unless otherwise noted.

Dry solvents were obtained from a PURESOLV™ apparatus developed by Innovative Technology Inc. (http://www.solventpurification.com). Toluene, CH_2Cl_2, MeCN, THF and ether were passed through activated alumina columns under nitrogen pressure. Toluene was also treated by mean of a copper column to remove traces of oxygen. The level of water was measured with a Coulometer (Karl Fisher method). The system provided solvent with 5-15 ppm of water.

[1] Still W. C., Kahn M., Mitra A., *J. Org. Chem.*, **1978**, *43*, 2923—2924.

I. Synthesis of the epoxidation precursors

N,*N*-Dimethyl-2-(hydroxymethyl)-acrylamide 7.

Paraformaldehyde (924 mg, 30 mmol), DABCO (693 mg, 6 mmol) and phenol (141 mg, 1.5 mmol) were put in a 10 mL flask equipped with a stirring bar. The vessel was fitted with a septum and gently flushed with argon. A *t*-BuOH/H_2O 3:7 solvent mixture (370 µL) and *N*,*N*-dimethylacrylamide (618 µL, 6 mmol) were then added *via* syringe. The resulting mixture was stirred for 3 days at 55 °C (oil bath temperature) and allowed to cool. Water was co-evaporated with toluene under vacuum. The crude mixture was then filtered over celite with dichloromethane and concentrated *in vacuo*. Purification by three columns chromatography (AcOEt/EtOH 8:2, R_f = 0.30) afforded **7** (632 mg, 82%) as a colourless liquid.

^{1}H NMR: 5.52 (s, 1H, =CH_2), 5.23 (s, 1H, =CH_2), 4.29 (d, 2H, J = 6 Hz, HO-CH_2), 3.10 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3), 2.96 (t, 1H, J = 6 Hz, OH).

^{13}C NMR: 171.2, 143.8, 115.8, 64.0, 39.1, 34.9.

IR (KBr): 3373, 2932, 2873, 1647, 1611, 1060.

MS (70 eV, EI) *m/z* (%): 130 (22, M^++1), 112 (100), 98 (9), 85 (30), 72 (32), 55 (23), 44 (52).

HRMS Calcd for $C_6H_{11}NO_2$ (MH+): 130.0868. Found: 130.0872.

N,*N*-Dimethyl-2-(bromomethyl)-acrylamide 8 (small scale from the alcohol 7).

The alcohol **7** (100 mg, 0.77 mmol) was dissolved in dry diethyl ether (620 µL) in a 5 mL flask under nitrogen pressure. Dimethylformamide (0.3 mL, 3.87 mmol) was added and the mixture was cooled to –5 °C. A solution of PBr_3 (36 µL, 0.39 mmol) in dry diethyl ether (140 µL) was then added dropwise. A white precipitate appeared. The reaction was stirred at room temperature and monitored by TLC (AcOEt/EtOH 4:1). After 20 h, the mixture was quenched by hydrolysis with water (1 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The organic layers were combined and washed with water (2 × 20 mL) to remove dimethylformamide. Then, the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt/pentane 4:1, R_f = 0.37) afforded **8** (90 mg, 61%) as a colorless liquid. For the analyses see below.

N,*N*-Dimethyl-2-(bromomethyl)-acrylamide 8 (Larger scale from dimethylacrylamide).

Paraformaldehyde (9.76 g, 325 mmol), DABCO (7.52 g, 65 mmol) and phenol (1.53 g, 16.25 mmol) were introduced into a 100 mL flask equipped with a stirring bar. The vessel was fitted with a septum and gently flushed with argon. A *t*-BuOH/H_2O (3:7) solvent mixture (4.05 mL) and *N*,*N*-dimethylacrylamide (6.71 mL, 65 mmol) were then added with a syringe. The resulting mixture was stirred for 24 h at 80 °C (oil bath temperature) and allowed to cool. Water was co-evaporated with toluene under vacuum. The crude mixture was then filtered over celite with dichloromethane and concentrated *in vacuo*. Filtration on a short pad of silica by a column chromatography (AcOEt/EtOH 8:2, R_f = 0.30) afforded as intermediate the crude alcohol (11.00 g, 65 mmol on regard to a theorically 100% conversion). This crude alcohol was subsequently dissolved in dry diethyl ether (50 mL) in a 250 mL flask equipped with mechanic stirring under nitrogen pressure. Dimethylformamide (50 mL, 650 mmol) was added and the mixture was cooled to –5 °C. A solution of PBr_3 (3.06 mL, 32.5 mmol) in dry diethyl ether (10 mL) was then added dropwise. There was a white fume and a white precipitate appeared. It was stirred at room temperature and the reaction was monitored by TLC (AcOEt/EtOH 8:2). As alcohol remained after 15 h, another solution of PBr_3 (3.06 mL, 32.5 mmol) in dry diethyl ether (10 mL) was added. The mixture became orange. The reaction was quenched by hydrolysis with water (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and washed with water (2 × 200 mL) to remove dimethylformamide. Then, the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (AcOEt/pentane 4:1, R_f = 0.37) afforded **8** (3.42 g, 27%) as a colourless liquid.

^{1}H NMR: 5.54 (s, 1H, =CH_2), 5.19 (s, 1H, =CH_2), 4.22 (s, 2H, Br-CH_2), 3.14 (s, 3H, N-CH_3), 3.03 (s, 3H, N-CH_3).

^{13}C NMR: 169.4, 140.3, 118.3, 39.1, 35.1, 33.4.

IR (neat): 2933, 1643, 1613, 1500, 1390, 1212, 1144, 1102, 935.

MS (70 eV, EI) *m/z* (%): 193 (10), 191 (9, M^+), 149 (15), 147 (14), 121 (20), 119 (20), 112 (100), 72 (33), 55 (14), 42 (20).

HRMS calcd for $C_6H_{10}NOBr$ (MH^+): 192.0024, found: 192.0011.

N,*N*-Dimethyl-2-(iodomethyl)-acrylamide 9.

To a solution of **8** (92 mg, 0.48 mmol) in acetone (1.5 mL) was added portionwise sodium iodide (145 mg, 0.97 mmol) at room temperature. The suspension was stirred for 6.5 h (protected from light). The mixture was filtered over celite and concentrated *in vacuo*. Purification by column chromatography (AcOEt/heptane 5:1, R_f = 0.35) afforded **9** (100 mg, 87%) as an orange oil.

^{1}H NMR: 5.52 (s, 1H, =CH_2), 5.07 (s, 1H, =CH_2), 4.15 (s, 2H, I-CH_2), 3.17 (s, 3H, N-CH_3), 3.03 (s, 3H, N-CH_3).

^{13}C NMR: 169.5, 141.1, 117.0, 38.7, 35.1, 5.8.

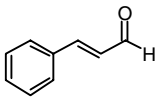
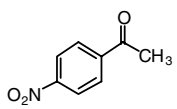
IR (neat): 2931, 1637, 1608, 1497, 1384, 1158, 1135.

MS (70 eV, EI) *m/z* (%): 239 (47, M^+), 195 (8), 167 (23), 127 (13), 112 (100), 72 (64), 55 (11), 42 (16).

HRMS Calcd for $C_6H_{10}NOI$ (MH+): 239.9885. Found: 239.9885.

II. Epoxidation reaction of various carbonyl compounds

General procedure. To a solution of the allylic bromide **8** (62 mg, 0.33 mmol, 1.3 eq.), aldehyde (0.25 mmol) and sodium iodide (7.5 mg, 0.05 mmol, 0.2 eq.) in acetonitrile (0.5 mL) was added tetrahydrothiophene (4.5 µL, 0.05 mmol, 0.2 eq.). The reaction mixture was stirred for 5 min, then, cesium carbonate (147 mg, 0.45 mmol, 1.8 eq.) was added. The resulting mixture was stirred at 20 °C for 24 h. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo*. Purification by column chromatography afforded the desired epoxide as an unseparable mixture of *trans* and *cis* diastereoisomers.

carbonyl compounds	epoxide	Time (h)	Yield (%)	dr (*trans*/*cis*)	-	stability	eluent AcOEt/pent.	R_f
Ph	**11a**	24	90	>95:5	Orange oil	silica	3:1	0.43
4-$CF_3C_6H_4$	**11b**	24	92	93:7	Yellow oil	silica	2:1	0.41
4-$NO_2C_6H_4$	**11c**	24	83	94:6	yellow cristals	silica	3:1	0.23
4-$MeOC_6H_4$	**11d**	48	73[a] (33)	>95:5	Orange liquid	neutral alumina	1:2	0.28
	**11f**	24	85[a] (67)	92:8	Brown oil	neutral alumina	1:2 then 2:1	0.26
n-Butyl	**11g**	24	<90	77:23	colorsless liquid	silica	4:1	0.36
2-furyl	**11e**	24	75[a]	95:5	Orange oil	unstable	/	/
	**11h**	1 week	32[a] (32)	41:59	Orange oil	silica	1:1	0.18

a : determined by internal standard (DMSO) on the NMR ^1H spectra

N,*N*-Dimethyl-2-(3-phenyl-2-oxiranyl)-acrylamide 11a

^{1}H NMR: *trans* 7.38-7.27 (m, 5H, Ph), 5.59 (s, 1H, =CH_2), 5.36 (s, 1H, =CH_2), 3.99 (d, J = 1.8 Hz, 1H, CHO-), 3.54 (d, J = 1.8 Hz, 1H, CHO-), 3.08 (s, 3H, N-CH_3), 3.01 (s, 3H, N-CH_3). *cis* 7.38-7.27 (m, 5H, Ph), 5.52 (s, 1H, =CH_2), 5.16 (s, 1H, =CH_2), 4.29 (d, J = 4.1 Hz, 1H, CHO-), 4.16 (d, J = 4.1 Hz, 1H, CHO-), 2.83 (s, 3H, N-CH_3), 2.27 (s, 3H, N-CH_3).

^{13}C NMR: *trans* 168.6, 141.9, 136.6, 128.6, 128.5, 125.7, 117.4, 62.0, 60.2, 38.9, 34.7.

IR (neat): 3478, 3032, 2931, 1642, 1497, 1457, 1400, 1262, 1133, 759, 700.

MS (70 eV, EI) *m/z* (%): 218 (64, M^++1), 188 (83), 174 (37), 145 (42), 115 (70), 105 (39), 96 (100), 72 (64), 42 (25).

HRMS calcd for $C_{13}H_{16}NO_2$ (MH^+): 218.1181, found: 218.1178.

N,*N*-dimethyl-2-[3-(4-trifluoromethylphenyl)-2-oxiranyl]-acrylamide 11b

^{1}H NMR: *trans* 7.60 (d, J = 8.2 Hz, 2H, Ar), 7.41 (d, J = 8.2 Hz, 2H, Ar), 5.62 (s, 1H, =CH_2), 5.38 (s, 1H, =CH_2), 4.07 (d, J = 1.7 Hz, 1H, CHO-), 3.50 (d, J = 1.7 Hz, 1H, CHO-), 3.08 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3). *cis* 5.50 (s, 1H, =CH_2), 5.18 (s, 1H, =CH_2), 4.32 (d, J = 5.2 Hz, 1H, CHO-), 4.15 (d, J = 5.2 Hz, 1H, CHO-). Only epoxide and vinyl protons for the *cis* diastereoisomer were observed beside the *trans* epoxide.

^{13}C NMR: *trans* 168.2, 141.3, 140.70, 140.71, 125.90, 125.91, 125.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 118.0, 62.2, 59.4, 38.9, 34.7.

IR (neat): 2936, 1644, 1619, 1322, 1110, 1065, 835.

MS (70 eV, EI) *m/z* (%): 286 (25, M^++1), 256 (100), 221 (13), 202 (19), 173 (27), 145 (31), 127 (14), 96 (69), 72 (40), 44 (28).

HRMS calcd for $C_{14}H_{15}NO_2F_3$ (MH^+): 286.1055, found: 286.1051.

N,*N*-dimethyl-2-[3-(4-nitrophenyl)-2-oxiranyl]-acrylamide 11c

^{1}H NMR: *trans* 8.20 (d, J = 8.8 Hz, 2H, Ar), 7.46 (d, J = 8.8 Hz, 2H, Ar), 5.65 (s, 1H, =CH_2), 5.41 (s, 1H, =CH_2), 4.13 (d, J = 1.7 Hz, 1H, CHO-), 3.51 (d, J = 1.7 Hz, 1H, CHO-), 3.09 (s, 3H, N-CH_3), 3.01 (s, 3H, N-CH_3). *cis* 5.50 (s, 1H, =CH_2), 5.20 (s, 1H, =CH_2), 4.36 (d, J = 4.5 Hz, 1H, CHO-), 4.15 (d, J = 4.5 Hz, 1H, CHO-). Only epoxide and vinyl protons for the *cis* diastereoisomer were observed beside the *trans* epoxide.

^{13}C NMR: *trans* 168.0, 147.9, 144.0, 140.9, 126.4, 123.8, 118.5, 62.4, 59.0, 38.9, 34.7.

IR (neat): 2950, 1725, 1616, 1517, 1345, 1091, 947, 845.

MS (70 eV, EI) *m/z* (%): 263 (4, M^++1), 247 (6), 233 (100), 219 (27), 207 (5), 190 (6), 174 (13), 161 (6), 144 (16), 133 (9), 115 (21), 96 (56), 72 (39), 44 (31).

HRMS calcd for $C_{13}H_{15}N_2O_4$ (MH^+): 263.1032, found 263.1029.

N,*N*-dimethyl-2-[3-(4-methoxyphenyl)-2-oxiranyl]-acrylamide 11d

^{1}H NMR: *trans* 7.21 (d, *J* = 8.7 Hz, 2H, Ar), 6.87 (d, *J* = 8.7 Hz, 2H, Ar), 5.58 (s, 1H, =CH_2), 5.34 (s, 1H, =CH_2), 3.93 (d, *J* = 1.8 Hz, 1H, CHO-), 3.80 (s, 3H, OMe), 3.53 (d, *J* = 1.8 Hz, 1H, CHO-), 3.08 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3).

^{13}C NMR: *trans* 168.6, 159.8, 142.0, 128.4, 126.9, 117.1, 114.0, 61.7, 60.1, 55.3, 38.8, 34.6.

IR (neat): 2936, 1612, 1515, 1397, 1247, 1173, 1030, 831.

MS (70 eV, ESI) *m/z* (%): 248 (31, M^++1), 230 (39), 203 (100), 202 (13), 187 (6), 175 (33), 147 (37), 121 (20).

HRMS calcd for $C_{14}H_{18}NO_3$ (MH^+): 248.1274, found 248.1287.

N,*N*-Dimethyl-2-[3-(2-furyl)-2-oxiranyl]-acrylamide 11e

This compound was unstable on silica and alumina. Thus, it was described from the crude product.

^{1}H NMR : *trans* 7.32 (d, *J* = 1.6 Hz, 1H, H_{arom1}), 6.42-6.41 (m, 1H, H_{arom3}), 6.31-6.29 (m, 1H, H_{arom2}), 5.59 (s, 1H, =CH_2), 5.32 (s, 1H, =CH_2), 4.00 and 3.97 (AB, *J* = 2.0 Hz, 2H, CHO-), 3.01 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3). *cis* 4.14 (d, *J* = 4.0 Hz, 1H, CHO-), 4.05 (d, *J* = 4.0 Hz, 1H, CHO-). Only epoxide protons for the *cis* diastereoisomer were observed beside the *trans* epoxide.

^{13}C NMR: *trans* 168.3, 149.0, 143.0, 141.2, 118.0, 110.8, 110.6, 58.8, 53.9, 38.9, 34.7.

IR (neat): 2926, 1615, 1501, 1399, 1131, 743.

MS (70 eV, ESI) *m/z* (%): 208 (71, M^++1), 190 (6), 181 (8), 180 (13), 163 (100), 145 (15), 135 (41), 126 (84), 109 (12), 107 (13), 95 (11).

HRMS calcd for $C_{13}H_{16}NO_2$ (MH^+): 218.1181, found: 218.1178.

N,*N*-dimethyl-2-[3-(2-phenylethenyl)-2-oxiranyl]-acrylamide 11f

^{1}H NMR: *trans* 7.38-7.23 (m, 5H, Ar), 6.80 (d, *J* = 16.0 Hz, 1H, =CH), 5.93 (dd, *J* = 7.7 and 16.0 Hz, 1H, =CH), 5.58 (s, 1H, =CH_2), 5.31 (s, 1H, =CH_2), 3.64 (dd, *J* = 1.9 and 7.7 Hz, 1H, CHO-), 3.55 (d, *J* = 1.9 Hz, 1H, CHO-), 3.06 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3). *cis* 6.83 (d, *J* = 16.0 Hz, 1H, =CH), 6.01 (dd, *J* = 7.9 and 16.0 Hz, 1H, =CH), 5.61 (s, 1H, =CH_2), 5.43 (s, 1H, =CH_2),

3.99 (d, J = 4.2 Hz, 1H, CHO-), 3.77 (dd, J = 4.2 and 7.9 Hz, 1H, CHO-). The other protons could not be observed for the *cis* diastereoisomer.

^{13}C NMR: *trans* 168.7, 141.9, 136.1, 135.1, 128.7, 128.3, 126.6, 125.5, 117.3, 60.7, 60.2, 39.0, 34.8.

IR (neat): 2932, 1616, 1495, 1450, 1398, 1131, 692.

MS (70 eV, ESI) *m/z* (%): 244 (100, M^++1), 226 (8), 199 (23), 171 (4), 143 (1), 91 (3).

HRMS calcd for $C_{15}H_{18}NO_2$ (MH^+): 244.1338, found: 244.1345.

N,*N*-dimethyl-2-(3-butyl-2-oxiranyl)-acrylamide 11g

^{1}H NMR: *trans* 5.49 (s, 1H, =CH_2), 5.21 (s, 1H, =CH_2), 3.25 (d, J = 2.1 Hz, 1H, CHO-), 3.15-2.96 (m, 1H, CHO-), 3.00 (s, 3H, N-CH_3), 2.96 (s, 3H, N-CH_3), 1.66-1.33 (m, 6H, CH_2), 0.88 (t, J = 7.0 Hz, 3H, CH_3). *cis* 5.42-5.41 (m, 1H, =CH_2), 5.35 (s, 1H, =CH_2), 3.67 (dd, J = 0.9 and 4.3 Hz, 1H, CHO-). The other protons could not be observed for the *cis* diastereoisomer.

^{13}C NMR: *trans* 168.9, 142.7, 116.8, 60.8, 58.1, 38.9, 34.7, 31.8, 28.0, 22.6, 14.0. *cis* 169.5, 138.8, 117.5, 59.9, 56.4, 38.9, 34.7, 28.4, 26.4, 22.7, 14.1.

IR (neat): 2931, 2872, 1644, 1618, 1398, 1110, 920.

MS (70 eV, EI) *m/z* (%): 198 (100, M^++1), 168 (12), 142 (6), 96 (31), 72 (16), 44 (10).

HRMS calcd for $C_{11}H_{20}NO_2$ (MH^+): 198.1494, found: 198.1496.

N,*N*-dimethyl-2-[3-methyl-3-(4-nitrophenyl)-2-oxiranyl]-acrylamide 11h

^{1}H NMR: *trans* 8.19 (d, J = 8.4 Hz, 2H, Ar), 7.57 (d, J = 8.4 Hz, 2H, Ar), 5.62 (s, 1H, =CH_2), 5.50 (s, 1H, =CH_2), 3.49 (s, 1H, CHO-), 3.14 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3), 1.67 (s, 3H, Me). *cis* 8.16 (d, J = 8.7 Hz, 2H, Ar), 7.56 (d, J = 8.7 Hz, 2H, Ar), 5.27 (s, 1H, =CH_2), 5.03 (s, 1H, =CH_2), 3.91 (s, 1H, CHO-), 2.89 (s, 3H, N-CH_3), 2.66 (s, 3H, N-CH_3), 1.76 (s, 3H, Me).

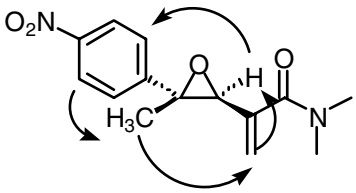
^{13}C NMR: *trans* 168.8, 149.2, 147.3, 138.2, 126.4, 123.7, 118.5, 65.4, 63.2, 39.0, 35.0, 16.5. *cis* 168.6, 147.3, 145.6, 136.7, 128.2, 123.1, 118.3, 65.6, 64.5, 39.0, 35.0, 24.3.

IR (neat): 2931, 1615, 1518, 1344, 1113, 856.

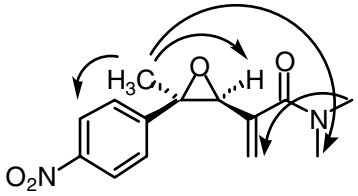
MS (70 eV, EI) *m/z* (%): 277 (33, M^++1), 259 (20), 247 (80), 233 (54), 216 (8), 203 (17), 192 (44), 175 (14), 150 (41), 128 (55), 112 (13), 96 (100) 72 (78), 58 (34), 44 (61).

HRMS calcd for $C_{14}H_{17}N_2O_4$ (MH^+): 277.1188, found: 277.1181.

Nuclear Overhauser Effect Spectroscopy 2D: correlation assignments



trans



cis