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Highly diastereoselective Barbier allylation and iminium cyclization: a simple entry to bicyclic and tricyclic piperazinones

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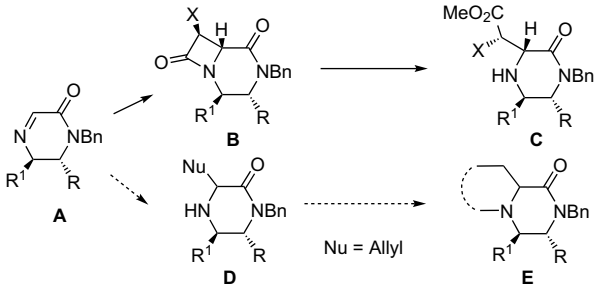
ABSTRACT

Barbier allylation of 5,6-dihydropyrazin-2(1*H*)-ones leads to a single isomer of 3-allylpiperazin-2-ones in high yields. Further Pictet–Spengler–Grieco cyclization of 3-allylpiperazin-2-ones with aldehydes provides bicyclic and tricyclic piperazinones with high diastereoselectivity.

1. Introduction

Developing synthetic methods to functionalize chiral piperazinones is a matter of current interest among chemists fueled by the number of applications of these compounds in synthetic and biological contexts.[1] The routes to prepare chiral piperazinones frequently rely on natural α-amino acids as starting materials and consequently further transformations to increase the structural diversity are limited by the functional groups existing in their side chains.[2]

In the past years, we have gained experience in the asymmetric synthesis of non-symmetrical vicinal diamino derivatives,[3] which prompted us to explore the reactivity of 5,6-dihydropyrazin-2(1*H*)-ones **A**, available by a six-step sequence from *p*-toluene sulfinimines (Scheme 1).[3a] We have previously focused on the diastereoselective Staudinger reaction that provides fused oxopiperazino-β-lactams **B** easily transformed into 2-oxopiperazine-3-acetic acid derivatives **C**.[4] Also we have studied the nucleophilic addition to produce **D**.[5] The diastereoselective addition of a simple allyl group takes places under Barbier conditions using $CeCl_3 \cdot 7H_2O$ as additive. In this work we describe our efforts on expanding the Barbier allylation to more complex allylic nucleophiles as well as examining the Pictet–Spengler–Grieco cyclization of 3-allylpiperazin-2-ones **D** with aldehydes to provide bicyclic and tricyclic piperazinones **E**.



Scheme 1. Transformations on enantiopure 5,6-dihydropyrazin-2(1*H*)-ones **A**.

2. Results and discussion

The synthesis of the 5,6-dihydropyrazin-2(1*H*)-ones **5a**,**b** and **6** was carried out from *N*-sulfinyl diamino alcohols protected as silyl ethers **1a**,**b** and **2** as we previously reported (Scheme 2).[3a,5] A more robust TBDPS protecting group (P) was introduced (**5b**) anticipating an eventual loss of the TBDMS moiety under acidic conditions during the iminium cyclization. The three-step sequence entails selective N-acylation with $ClCH_2COCl$, followed by cyclization of the chloroacetamide **3** via nucleophilic attack of the sulfinamide onto the chloromethylene group (Cs_2CO_3), and finally sulfinyl elimination (NaH). Pursuing to increase the efficiency of the route, we treated chloroacetamide **3b** with two sequential additions of NaH in THF to produce the one-pot cyclization/elimination and thus shortening the route toward **5b** in one step.

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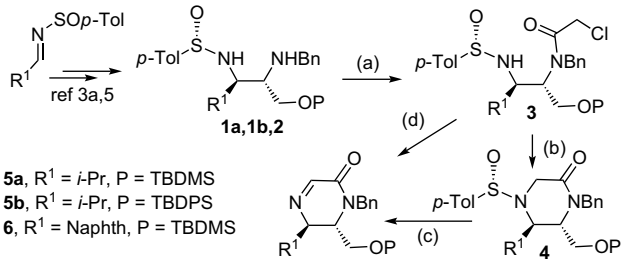


Scheme 2. Synthesis of enantiopure of 5,6-dihydropyrazin-2(1*H*)-ones. Reagents and conditions: (a) $ClCH_2COCl$, EtOAc/satd $NaHCO_3$ 50:50, 0 °C–rt, 93–85%; (b) 1.8 equiv Cs_2CO_3, DMF, 62 °C, 98–68%; (c) 4 equiv NaH, THF, 0 °C–rt, 86–69%; (d) 2.2 equiv NaH, THF, −40 °C to rt (4 h) then 4 equiv NaH, THF, −40 °C to rt (13 h) 86% for **3b**.

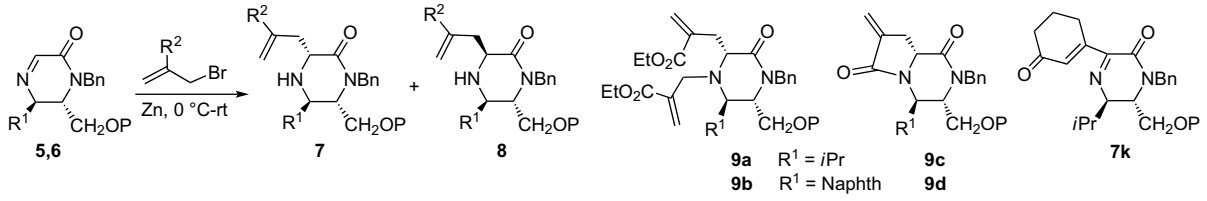
With the aim of expanding the scope of the diastereoselective allylation process, we initially tried the addition of bromomethyl acrylate/Zn (R^2=CO_2Et) and 3-bromo-2-methylprop-1-ene/Zn (R^2=Me) under the optimized conditions for allyl bromide using a cerium salt as additive in THF (Table 1, entry 1).[5] The addition takes place with complete diastereocontrol and good yield for the acrylate derivative (**7b**), however, only a 16% of allylation product **7c** was isolated as a single diastereomer along with recovered starting material after 38 h (Table 1, entries 2 and 3). In spite of the good diastereoselectivity, the low conversion for **7c** prompted us to search for different conditions and we found that TMSCl and DMF as solvent promoted the diastereoselective allylation of **5a** and **5b** to **7c** and **7d** in higher yields (entries 4 and 5). This enhancement in reactivity is probably due to the increase in solvent polarity (THF vs DMF) as well as the double role of TMSCl activating the C–N double bond and the Zn surface.[6]

Subsequently, we examined the behavior of other allylic bromides under these conditions. Thus, treatment of **5a** with (3-bromopropen-1-yl)benzene (R^2=Ph) and Zn/TMSCl in DMF provided a 79:21 mixture of **7e** and **8e** isolated in 63% and 14%, respectively (entry 6). The diastereoselective allylation was successfully extended to benzyl 2-(bromomethyl)prop-2-en-1-yl ether (R^2=CH_2OBn, entry 7) generated from 3-chloro-2(chloromethyl)prop-1-ene[7] affording a single piperazinone **7f** with a 70% yield. Interestingly, the more reactive acrylate that gave a good yield of **7b** with Zn/$CeCl_3$/THF in 22 h (entry 2) rendered lower yields of piperazinone with Zn/TMSCl/DMF even after prolonged reaction times and high excess of reagents, obtaining then small amounts of C- and N-allylation product **9a** (entry 8).

Finally, the influence of R^1 was examined and 5,6-dihydropyrazin-2(1*H*)-one **6** with a naphthyl group was submitted to Barbier allylation (entries 9–12). Treatment of **6** with Zn/TMSCl/DMF and allylic bromides (R^2=Me and Ph) provided good yields of piperazinones **7g** and **7h** as single diastereomers. Complete diastereoselectivity, albeit lower yield was obtained with bromomethyl acrylate (R^2=CO_2Et, **7i**, 64%) also isolating a 17% of bicyclic methylidene lactam **9d**. Interestingly, the efforts to obtain bicyclic γ-lactams **9c** and **9d** by forcing the allylation reaction were not entirely successful since variable amounts of **9a** and **9b** were always formed (entries 8 and 12).[8] Finally, 3-bromocyclohex-1-ene was used to generate the allylic nucleophile yielding a non-selective mixture of the four possible diastereoisomers **7j** (not shown) that evolved upon standing at room temperature and after 5–6 days to a compound tentatively assigned as cyclohexenone **7k** originated by spontaneous oxidation.

Having established the protocol for the diastereoselective Barbier allylation, we turned our attention toward the assembly of a bicyclic skeleton from allyl piperazinones **7**. The Pictet–Spengler–Grieco cyclization of double bonds onto iminium intermediates appeared an attractive method since structural diversity could be introduced through different aldehydes, precursors of the iminium ions, and up to two new stereocenters could be created from 3-allylic piperazin-2-ones **7** (Table 2).[9] Initially, we submitted piperazinone **7c** to reaction with an excess of aqueous formaldehyde in MeOH and after 2 days a 73% of bicyclic piperazinone **10a** was obtained as a single diastereomer. This highly diastereoselective remote stereocontrol observed for the addition of MeOH, confirmed by NOE experiments, was also found for ^{i}PrOH, although a lower conversion of **10b** was obtained even after increasing reaction temperature (82 °C) and time (5 days) (entries 1 and 2). Under similar conditions, piperazinone **7d** provided bicyclic piperazinone **10c** and **7f** rendered an 88:12 mixture of **10d** and its C-8 epimer **11d**, in moderate to good yields (entries 3 and 4). Subsequently, naphthyl piperazinone **7g** was

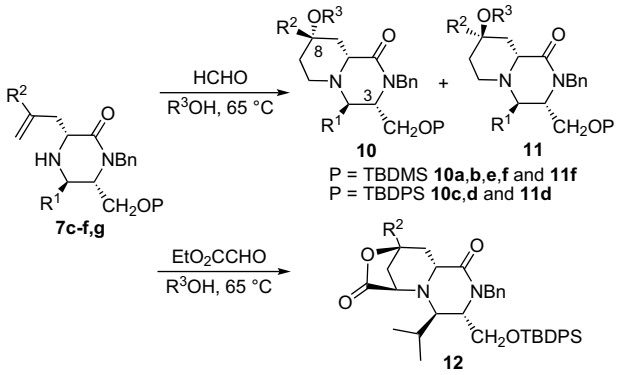
Table 1
Diastereoselective Barbier allylation of 5,6-dihydropyrazin-2(1*H*)-ones **5** and **6**



Entry	Compound	R^1	P	R^2	Conditions	**7** (yield[a] %)	**8** (yield[a] %)
1	**5a**	^{i}Pr	TBDMS	H	THF, $CeCl_3\cdot 7H_2O$, 23 h	**7a** (87)	
2	**5a**	^{i}Pr	TBDMS	CO_2Et	THF, $CeCl_3\cdot 7H_2O$, 22 h	**7b** (80)	
3	**5a**	^{i}Pr	TBDMS	Me	THF, $CeCl_3\cdot 7H_2O$, 38 h	**7c** (16)[b]	
4	**5a**	^{i}Pr	TBDMS	Me	DMF, TMSCl, 17 h	**7c** (94)	
5	**5b**	^{i}Pr	TBDPS	Me	DMF, TMSCl, 16 h	**7d** (84)	
6	**5a**	^{i}Pr	TBDMS	Ph	DMF, TMSCl, 18 h	**7e** (63)	**8e** (14)
7	**5b**	^{i}Pr	TBDPS	CH_2OBn	DMF, TMSCl, 46 h	**7f** (70)	
8	**5a**	^{i}Pr	TBDMS	CO_2Et	DMF, TMSCl, 88 h	**7b** (64)[c]	
9	**6**	Naphth	TBDMS	Me	DMF, TMSCl, 44 h	**7g** (78)	
10	**6**	Naphth	TBDMS	Ph	DMF, TMSCl, 28 h	**7h** (80)	
11	**6**	Naphth	TBDMS	CO_2Et	DMF, TMSCl, 14 h	**7i** (64)[d]	
12	**6**	Naphth	TBDMS	–CO–	DMF, TMSCl, 64 h	—[e]	

[a] Isolated yields.
[b] An 80% of starting material was recovered.
[c] An 87:13 mixture of **7b** and **9a** was observed in the crude (^{1}H NMR).
[d] An 80:20 mixture of **7i** and **9d** was observed in the crude (^{1}H NMR).
[e] A 61% of **9b** and 16% of **9d** was isolated.

Table 2
Pictet–Spengler–Grieco cyclization of 3-allyl piperazin-2-ones



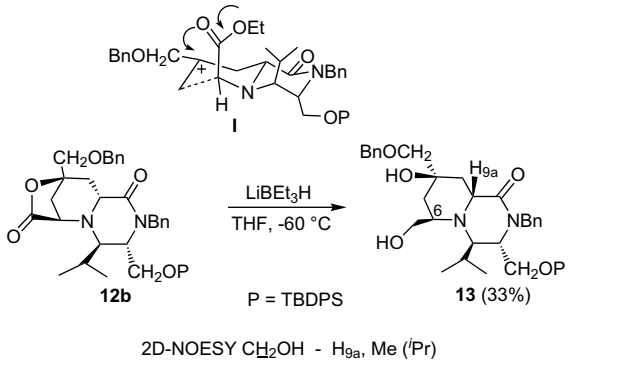
Entry	7	R^1	R^2	R^3	10[a] (%)	11[a] (%)	12[a] (%)
1	**7c**	^{i}Pr	Me	Me	**10a** (73)		
2	**7c**	^{i}Pr	Me	^{i}Pr	**10b** (50)[b]		
3	**7d**	^{i}Pr	Me	Me	**10c** (63)		
4	**7f**	^{i}Pr	CH_2OBn	Me	**10d** (61)	**11d**[c]	
5	**7g**	Naphth	Me	Me	**10e** (56)[d]		
6	**7e**	^{i}Pr	Ph	Me	**10f**[e]	**11f**[e]	
7	**7d**	^{i}Pr	Me	Me	—	—	**12a** (25)[f]
8	**7f**	^{i}Pr	CH_2OBn	Me	—		**12b** (50)[g]

[a] Isolated yields.
[b] 82 °C; a 15% of **7c** was isolated.
[c] An 88:12 ratio of **10d** and **11d** was detected in the crude (^{1}H NMR).
[d] A 12% of methylidene bicyclic piperazinone (not shown) was also isolated.
[e] 53% combined yield of a 64:36 mixture of diastereomers at C-8.
[f] A 40% of **7d** was recovered.
[g] A 25% of **7f** was recovered.

submitted to cyclization to afford a 56% of **10e** along with a small amount (<10%) of elimination product (not shown) (entry 5). On the other hand, a significant decrease in the diastereoselectivity is produced when R^2 is a phenyl group providing a 64:36 mixture of **10f** and **11f** (entry 6).

The alkene-iminium cyclization does not proceed in absence of a nucleophilic alcohol as solvent (THF, THF/BnOH) or when less reactive aldehydes (PhCHO) are employed. Further activation of the iminium formation induced by MS or acids (AcOH, TsOH), even when the more reactive acrolein was used, did not produce any cyclization product. In contrast, ethyl glyoxalate reacted with **7d** and **7f** producing tricyclic lactones **12a** and **12b** in moderate conversions along with starting material (entries 7 and 8). The presence of the ester moiety prevents the addition of MeOH at C-8. Instead, a remarkable cascade of processes would account for these results, stereoselective iminium formation, alkene addition onto the *re* face of the iminium species that places the carboxylate on the β-face (**I**, Scheme 3), and diastereoselective capture of the intermediate by the carboxylate group allowing for the stereocontrolled introduction of two new stereocenters in the molecules.

Finally, pursuing additional structural evidence for lactones **12** and seeking to illustrate further useful transformations of these substrates, we addressed the chemoselective reductive opening of lactone **12b** (Scheme 3). As a result, we found that lithium triethyl borohydride smoothly affected lactone reduction to provide diol **13** (33%) along with recovered starting material (45%). Diol **13** was fully characterized verifying previous structural assignments of **12**.



Scheme 3. Stereochemical outcome of the lactonization and chemoselective reduction of lactone **12b**.

3. Experimental

3.1. General

All reactions were carried out under a positive pressure of dry argon, using freshly distilled solvents under anhydrous conditions. Reagents and solvents were handled by using standard syringe techniques. Zn powder was washed with 2% aqueous HCl and dried prior to use. THF was distilled from sodium and benzophenone, and DMF was dried over CaH_2 and filtered before distillation under reduced pressure. Alternatively, anhydrous solvents were purified by filtration on a solvent purification system. Crude products were purified by flash chromatography on 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on silica gel plates. Through this section, the volume of solvents is reported in mL/mmol of starting material. ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz, 300 MHz, 400 MHz and 500 MHz spectrometers using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm) unless otherwise noted. Melting points are uncorrected. Optical rotations were measured on a polarimeter at 20 °C using a sodium lamp and in $CHCl_3$ solution. Low resolution mass spectra were recorded by direct injection using the electronic impact technique with an ionization energy of 70 eV (EI) or using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes. Elemental analyses were carried out at Instituto de Química Orgánica, CSIC.

3.2. Synthesis of (+)-(5*R*,6*S*,S_S)-1-benzyl-6-[(*tert*-butyldiphenylsilyloxy)methyl]-5-(*iso*-propyl)-4-(*p*-tolylsulfinyl)piperazin-2-one, 4b

3.2.1. (+)-(1R,2S,S_S)-N-[2-Benzylamino-3-(tert-butyldiphenylsilyloxy)-1-(iso-propyl)prop-1-yl] p-tolylsulfinamide, ***1b***

A solution of (+)-(2*S*,3*R*,S_S)-2-(benzylamino)-4-methyl-3-(*p*-tolylsulfinylamino)pentan-1-ol[3a] (72 mg, 0.2 mmol), 2 equiv of TBDPSCl (106 μL, 0.4 mmol), 2 equiv of imidazole (28 mg, 0.4 mmol), and 0.05 equiv of DMAP (1.2 mg, 0.01 mmol) in CH_2Cl_2 (5 mL/mmol) was stirred at room temperature and monitored by TLC until disappearance of the starting material (5 h 30 min). Then, water (10 mL/mmol) was added and the layers were separated. The aqueous layer was washed twice with CH_2Cl_2 (5 mL/mmol). The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and evaporated to give a crude product that was purified by chromatography on silica gel (30–60% Et_2O–hexane). Compound **1b** (86 mg, 0.144 mmol, 72%) was obtained as a colorless oil. Data for **1b**: R_f 0.30 (60% Et_2O–hexane). $[\alpha]_D^{20}$ +36.5 (*c* 1.51). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74 (d, 3H, *J*=6.6 Hz), 0.84 (d, 3H, *J*=6.8 Hz), 1.03 (s, 9H), 1.23 (br s, 1H), 1.77 (m, 1H), 2.36 (s, 3H), 2.71 (br s, 1H), 3.24 (m, 1H), 3.54 (d, 1H, *J*=12.7 Hz), 3.73 (m, 3H), 4.42 (d, 1H, *J*=9.1 Hz), 7.22 (m, 7H), 7.38 (m, 6H), 7.49 (dd, 2H, *J*=6.6, 1.7 Hz), 7.65 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 19.2, 19.8, 21.3, 26.8 (3C), 31.2, 52.2, 58.7, 59.8, 63.4, 125.6 (2C), 127.0, 127.7 (4C), 128.3 (4C), 129.3 (2C), 129.7 (2C), 133.3 (2C), 135.6 (2C), 135.7 (2C), 141.0 (2C), 142.5. IR (film): 3320, 3071, 3010, 2960, 2930, 2858, 1589, 1493, 1471, 1428, 1390, 1362, 1263,

1217, 1112, 1089, 1063, 811, 757, 702 cm^{-1}. MS (ES): 621 $[M+Na]^+$, 599 $[M+H]^+$.

3.2.2. (+)-(5R,6S,S_S)-1-Benzyl-6-[(tert-butyldiphenylsilyloxy)methyl]-5-(iso-propyl)-4-(p-tolylsulfinyl) piperazin-2-one, ***4b***

To a cold (0 °C) suspension of **1b** (434 mg, 0.726 mmol) in EtOAc (10 mL/mmol) and a saturated aqueous solution of $NaHCO_3$ (10 mL/mmol) was added 1.2 equiv of freshly distilled chloroacetyl chloride (70 μL, 0.871 mmol). The mixture was stirred and allowed to warm up to room temperature until disappearance of the starting material monitored by TLC (2 h 30 min). The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL/mmol). The combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, and filtered to give a crude chloroacetamide that was purified by chromatography (10–30% EtOAc–hexane). Data for (+)-*N*-benzyl-*N*-[(1*S*,2*R*,S_S)-1-(*tert*-butyldiphenylsilyloxymethyl)-3-methyl-2-(*p*-tolylsulfinylamino)but-1-yl]-2-chloroacetamide, **3b**: yield 85% (415 mg). R_f 0.40 (60% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ +55.8 (*c* 1.95). ^1H NMR ($CDCl_3$, 300 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 0.25+0.52 (2d, 3H, *J*=6.4 Hz), 0.44 (d, 3H, *J*=6.8 Hz), 0.94+0.98 (2s, 9H), 1.13 (m, 1H), 2.38+2.40 (2s, 3H), 3.58–3.88 (m, 4H), 4.00 (d, 1H, d, *J*=14.2 Hz), 4.30 (d, 1H, *J*=14.2 Hz), 4.38 (d, 1H, *J*=15.9 Hz), 4.96–5.14 (m, 2H), 7.01 (br s, 2H), 7.13 (t, 2H, *J*=7.4 Hz), 7.33 (m, 13H), 7.56 (d, 2H, *J*=8.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) (some signals appear broadened and display fine splittings due to the presence of rotamers) δ 14.2+14.8 (1C), 15.2+21.0 (1C), 18.8+20.6 (1C), 21.1+21.4 (3C), 26.9 (3C), 27.8, 43.2, 47.0, 57.0, 60.3, 61.9+62.2 (2C), 125.6 (2C), 125.8, 127.4, 127.6 (4C), 127.8, 127.9, 128.5, 129.1 (2C), 129.4 (2C), 129.6, 129.8, 130.0, 131.9 (2C), 135.4 (2C), 135.7, 135.9 (2C), 141.4, 168.2+169.9+171.1 (C=O). IR (film): 3307, 2959, 2928, 2857, 1654, 1467, 1427, 1111, 1067, 792, 740 cm^{-1}. MS (ES): 1374 $[2M+Na]^+$, 675 $[M+H]^+$. Subsequently, a solution of **3b** (80 mg, 0.12 mmol) in DMF (10 mL/mmol) and 1.8 equiv of solid Cs_2CO_3 (70 mg, 0.213 mmol) were stirred at 65 °C until disappearance of the starting material monitored by TLC (2 h 30 min). The mixture was cooled down to room temperature and was diluted with CH_2Cl_2 (10 mL/mmol) and H_2O (10 mL/mmol). The layers were separated and the organic phase was washed with cold water (3×10 mL/mmol) and a saturated solution of $NaHCO_3$ (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by chromatography (5–30% EtOAc–hexane). Compound **4b** (52 mg, 0.082 mmol, 68%) was obtained as a colorless oil. Data for **4b**: R_f 0.12 (30% EtOAc–hexane). $[\alpha]_D^{20}$ +31.0 (*c* 1.34). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.30 (d, 3H, *J*=6.6 Hz), 1.09 (s, 9H), 1.10 (d, 3H, *J*=6.8 Hz), 1.55 (m, 1H), 2.38 (s, 3H), 3.26 (d, 1H, *J*=17.6 Hz), 3.33 (m, 2H), 3.55–3.61 (m, 2H), 3.66 (d, 1H, *J*=18.1 Hz), 3.73 (dd, 1H, *J*=11.0, 3.2 Hz), 5.22 (d, 1H, *J*=14.2 Hz), 6.98 (m, 2H), 7.14 (d, 2H, *J*=8.1 Hz), 7.24 (m, 3H), 7.46 (m, 8H), 7.62 (m, 2H), 7.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), HSQC δ 19.1 (C ^tBu), 19.7 (CH_3), 21.1 (CH_3), 21.4 (CH_3 *p*-Tol), 26.8 (CH ^iPr), 26.9 ($3CH_3$ ^tBu), 40.5 (CH_2-3), 48.3 (NBn), 56.9 (CH-6), 62.4 (CH_2O), 63.7 (CH-5), 125.4 (2C), 128.0, 128.1 (4C), 128.6 (2C), 129.1 (2C), 129.6 (2C), 130.2 (2C), 132.9 (2C), 135.5 (4C), 136.4, 139.9, 141.7, 165.1. IR (film): 3051, 2931, 1659, 1470, 1428, 1361, 1264, 1192, 1089, 1013, 932, 813, 739, 702, 673 cm^{-1}. MS (ES): 1277 $[2M+1]^+$, 661 $[M+Na]^+$, 639 $[M+H]^+$.

3.3. (+)-(5*R*,6*S*)-1-Benzyl-6-(*tert*-butyldiphenylsilyloxymethyl)-5-(*iso*-propyl)-5,6-dihydro-1*H*-pyrazin-2-one, 5b

A solution of **4b** (44 mg, 0.069 mmol) in THF (5 mL/mmol) was added dropwise to a cold (0 °C) suspension of 4 equiv of NaH (4 mg, 0.152 mmol) in anhydrous THF (5 mL/mmol). The reaction mixture was stirred at room temperature until disappearance of starting material was observed by TLC (27 h), and water (5 mL/mmol) and CH_2Cl_2 (5 mL/mmol) were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL/mmol). The combined organic extracts were washed with a saturated solution of NaCl (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (8–30% EtOAc–hexane). Compound **5b** (24 mg, 0.048 mmol, 69%) was obtained as a colorless oil. Alternatively, **5b** was prepared by treating chloroacetamide **3b** (1 equiv) with 2.2 equiv of NaH in THF (10 mL/mmol) at −40 °C. The mixture was allowed to warm up to room temperature (4 h) and then temperature was lowered to −40 °C and was added 4 equiv of NaH stirring to room temperature for 13 h. After the previously described workup, **5b** was obtained in 86% yield. Data for **5b**: R_f 0.30 (30% EtOAc–hexane). $[\alpha]_D^{20}$ +164.3 (*c* 1.92). ^1H NMR ($CDCl_3$, 300 MHz), COSY δ 0.36 (3H, d, *J*=6.8 Hz, CH_3), 0.84 (3H, d, *J*=6.6 Hz, CH_3), 1.02 (9H, s, $3CH_3$ ^tBu), 1.37 (1H, m, CH ^iPr), 3.34 (1H, t, *J*=6.1 Hz, H-6), 3.57 (2H, d, *J*=6.1 Hz, CH_2O), 3.62 (1H, d, *J*=14.2 Hz, NBn), 3.73 (1H, d, *J*=8.1 Hz, H-5), 5.19 (1H, d, *J*=14.2 Hz, NBn), 7.10 (2H, m, Ar–H), 7.14 (3H, m, Ar–H), 7.42 (6H, m, Ar–H), 7.59 (4H, m, Ar–H), 7.77 (1H, br s, CH=N). ^{13}C NMR ($CDCl_3$, 75 MHz), HSQC δ 19.0 (2C, ^tBu, CH_3), 19.2 (CH_3), 26.8 ($3CH_3$ ^tBu), 32.0 (CH ^iPr), 48.1 (NBn), 53.9 (CH-6), 63.3 (CH-5), 63.6 (CH_2O), 127.9 (4C), 128.1, 128.7 (2C), 129.2 (2C), 130.0 (2C), 132.6, 132.8, 135.5 (4C), 135.9, 154.9 (CH=N), 155.1 (C=O). IR (film): 3071, 2960, 2931, 2859, 2247, 1674, 1471, 1454, 1428, 1362, 1264, 1113, 1047, 909, 823, 734, 702, 646 cm^{-1}. MS (ES): 1019 $[2M+Na]^+$, 499 $[M+H]^+$.

3.4. General procedure for the allylation of 5,6-dihydropyrazin-2(1*H*)-ones

Procedure A.[5] To a suspension of Zn powder (2 equiv) in THF (1.5 mL/mmol) at 0 °C was added $CeCl_3 \cdot 7H_2O$ (0.1 equiv), and a solution of 5,6-dihydropyrazin-2(1*H*)-one (1 equiv) and 1.5 equiv of allylic bromide. The mixture was stirred from 0 °C to room temperature monitored by TLC (22–23 h) and then was quenched with NH_4Cl (6 mL/mmol). This mixture was extracted with EtOAc (3×20 mL/mmol) and the combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the final products after purification by column chromatography.

Procedure B. To a solution of 5,6-dihydropyrazin-2(1*H*)-one in DMF (15 mL/mmol) was added 1.3–2.0 equiv of allylic bromide, 1.3–2.0 equiv of Zn powder, and 0.2–0.5 equiv of TMSCl. The mixture was stirred from 0 °C to room temperature until disappearance of the starting material monitored by TLC and then was quenched with NH_4Cl (15 mL/mmol). This mixture was extracted with Et_2O (3×20 mL/mmol) and the combined organic extracts were washed with a saturated solution of NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel.

3.4.1. (+)-(3R,5R,6S)-1-Benzyl-6-(tert-butyldimethylsilyloxymethyl)-5-(iso-propyl)-3-(2-methylprop-2-en-1-yl)piperazin-2-one, ***7c***

From **5a** (24 mg, 0.064 mmol), 3-bromo-2-methylpropene (97%, 18 mg, 13 μL, 0.132 mmol), Zn (8 mg, 0.128 mmol), and TMSCl (3 mg, 4 μL, 0.032 mmol) in DMF, following procedure B (17 h), **7c** (26 mg, 0.060 mmol, 94%) was obtained after chromatography (10–30% EtOAc–hexane) as a colorless oil. Data for **7c**: R_f 0.31 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +95.0 (*c* 1.02). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.34 (d, 3H, *J*=6.2 Hz), 0.83 (d, 3H, *J*=6.6 Hz), 0.87 (s, 9H), 1.58–1.62 (m, 2H), 1.74 (s, 3H), 2.19 (dd, 1H, *J*=13.5, 10.3 Hz),

2.41 (d, 1H, *J*=10.4 Hz), 2.84 (ap d, 1H, *J*=12.1 Hz), 3.24 (dd, 1H, *J*=7.0, 5.1 Hz), 3.53 (dd, 1H, *J*=10.3, 2.9 Hz), 3.73 (dd, 1H, *J*=9.8, 4.7 Hz), 3.79 (d, 1H, *J*=14.5 Hz), 3.84 (dd, 1H, *J*=9.8, 7.8 Hz), 4.78 (s, 1H), 4.83 (s, 1H), 5.46 (d, 1H, *J*=14.1 Hz), 7.28 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4, −5.3, 18.2, 19.2, 19.5, 21.8, 25.4, 25.9 (3C), 41.9, 48.7, 51.3, 56.8, 57.2, 63.7, 113.3, 127.6, 128.5 (2C), 128.8 (2C), 137.6, 142.5, 170.8. IR (film): 3372, 2955, 2929, 2854, 1646, 1471, 1461, 1453, 1387, 1375, 1361, 1257, 1101, 837, 776, 696 cm^{-1}. MS (ES): 453 $[M+Na]^+$, 431 $[M+1]^+$ (100%). Anal. Calcd for $C_{25}H_{42}N_2O_2Si$: C, 69.72; H, 9.83; N, 6.50. Found: C, 69.55; H, 9.41; N, 6.79.

3.4.2. (+)-(3R,5R,6S)-1-Benzyl-6-(tert-butyldiphenylsilyloxymethyl)-5-(iso-propyl)-3-(2-methylprop-2-en-1-yl)piperazin-2-one, **7d**

From **5b** (91 mg, 0.183 mmol), 3-bromo-2-methylpropene (97%, 24 μL, 0.245 mmol), Zn (16 mg, 0.238 mmol), and TMSCl (4 mg, 5 μL, 0.04 mmol) in DMF, following procedure B (16 h), **7d** (85 mg, 0.153 mmol, 84%) was obtained after chromatography (10–20% EtOAc–hexane) as a colorless oil. Data for **7d**: R_f 0.32 (20% AcOEt–hexane). $[\alpha]_D^{20}$ +57.1 (*c* 1.80). ^{1}H NMR ($CDCl_3$, 300 MHz), COSY δ 0.36 (3H, d, *J*=6.6 Hz, CH_3), 0.83 (3H, d, *J*=6.6 Hz, CH_3), 1.03 (9H, s, $3CH_3$ ^{t}Bu), 1.58 (1H, m, CH ^{i}Pr), 1.67 (1H, br s, NH), 1.71 (3H, s, CH_3 allyl), 2.10 (1H, dd, *J*=13.4, 10.5 Hz, CH_2 allyl), 2.53 (1H, d, *J*=10.5 Hz, H-5), 2.79 (1H, d, *J*=12.5 Hz, CH_2 allyl), 3.27 (1H, dd, *J*=8.2, 4.5 Hz, H-6), 3.49 (2H, dm, *J*=14.4 Hz, NBn and H-3), 3.77 (1H, dd, *J*=4.5, 9.9 Hz, CH_2O), 3.93 (1H, dd, *J*=9.9, 8.2 Hz, CH_2O), 4.74 (1H, s, CH_2=C), 4.81 (1H, s, CH_2=C), 5.35 (1H, d, *J*=14.2 Hz, NBn), 7.11 (2H, m, Ar–H), 7.25 (3H, m, Ar–H), 7.41 (6H, m, Ar–H), 7.64 (4H, m, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 19.2, 19.6, 21.8, 25.4 (3C), 26.8, 41.8, 48.6, 51.2, 56.4, 57.2, 63.8, 113.2, 127.5, 127.8 (4C), 128.4 (2C), 128.7 (2C), 129.8, 129.9, 133.1, 133.2, 135.5 (4C), 137.5, 142.4, 170.6. 2D-NOESY show cross-points between: CH_3 (0.83)/CH_3 (0.36), CH_3 (0.83)/^{i}Pr, CH_3 (0.83)/H-5, CH_3 (0.83)/H-3. IR (film): 3400, 3052, 2960, 1646, 1428, 1264, 1113, 896, 823, 740, 701 cm^{-1}. MS (ES): 555 $[M+H]^+$, 577 $[M+Na]^+$, 1131 $[2M+Na]^+$. Anal. Calcd for $C_{35}H_{46}N_2O_2Si\cdot HCl$: C, 71.09; H, 8.01; N, 4.74; Cl, 6.00. Found: C, 70.84; H, 8.25; N, 4.96.

3.4.3. (+)-(3R,5R,6S)-1-Benzyl-6-(tert-butyldimethylsilyloxymethyl)-5-(iso-propyl)-3-(2-phenylprop-2-en-1-yl)piperazin-2-one, **7e** and (3S,5R,6S)-1-benzyl-6-(tert-butyldimethylsilyloxymethyl)-5-(iso-propyl)-3-(2-phenylprop-2-en-1-yl)piperazin-2-one, **8e**

From **5a** (22 mg, 0.059 mmol), 3-bromo-2-phenylpropene[10] (15 mg, 0.076 mmol), Zn (4 mg, 0.076 mmol), and TMSCl (2 mg, 2 μL, 0.012 mmol) in DMF, following procedure B (18 h), a mixture (79:21) of **7e** and **8e** was obtained. After chromatography (5–10% EtOAc–hexane) **7d** (18 mg, 0.037 mmol, 63%) and **8e** (4 mg, 0.008 mmol, 14%) were isolated as colorless oils. Data for **7e**: R_f 0.34 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +37.0 (*c* 0.83). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 6H), 0.28 (d, 3H, *J*=6.6 Hz), 0.46 (d, 3H, *J*=6.6 Hz), 0.89 (s, 9H), 1.41–1.50 (m, 1H), 1.62 (br s, 1H), 2.36 (ap d, 1H, *J*=10.2 Hz), 2.48 (dd, 1H, *J*=14.1, 10.9 Hz), 3.20 (dd, 1H, *J*=7.4, 4.7 Hz), 3.40 (dd, 1H, *J*=10.9, 2.7 Hz), 3.61 (ap d, 1H, *J*=14.1 Hz), 3.75 (dd, 1H, *J*=9.8, 4.7 Hz), 3.80 (d, 1H, *J*=14.4 Hz), 3.89 (dd, 1H, *J*=9.8, 7.8 Hz), 5.19 (s, 1H), 5.49 (s, 1H), 5.47 (d, 1H, *J*=14.4 Hz), 7.25–7.37 (m, 8H), 7.48 (dd, 2H, *J*=8.0, 1.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4, −5.3, 18.2, 18.5, 19.4, 25.0, 25.9 (3C), 39.8, 48.5, 51.5, 56.8, 57.3, 63.7, 115.3, 126.5 (2C), 127.5, 127.7, 128.4 (2C), 128.5 (2C), 128.7 (2C), 137.6, 139.7, 145.6, 170.4. IR (film): 3473, 2949, 2925, 2854, 1647, 1470, 1438, 1251, 1236, 1092, 834, 776 cm^{-1}. MS (ES): 1007 $[2M+Na]^+$, 515 $[M+Na]^+$, 493 $[M+1]^+$ (100%). Anal. Calcd for $C_{30}H_{44}N_2O_2Si$: C, 73.12; H, 9.00; N, 5.68. Found: C, 72.95; H, 9.34; N, 5.41. Partial data for **8e**: R_f 0.20 (20% EtOAc–hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.09 (s, 3H), −0.08 (s, 3H), 0.69 (d, 3H, *J*=6.6 Hz), 0.72 (d, 3H, *J*=6.6 Hz), 0.77 (s, 9H), 1.53 (m, 2H), 2.56 (m, 2H), 3.13 (dt, 1H, *J*=6.5, 3.3 Hz), 3.23 (dd, 1H, *J*=10.4, 2.7 Hz), 3.35 (dd, 1H, *J*=10.7, 3.3 Hz), 3.59 (dd, 1H, *J*=10.5, 3.9 Hz), 3.60 (ap d, 1H, *J*=15.2 Hz), 4.03 (d, 1H, *J*=15.2 Hz), 5.19 (s, 1H), 5.29 (d, 1H, *J*=15.2 Hz), 5.35 (s, 1H), 7.21–7.33 (m, 8H), 7.43 (ap d, 2H). IR (film): 3353, 2949, 2925, 2855, 1653, 1462, 1449, 1254, 1106, 835, 776 cm^{-1}. MS (ES): 1007 $[2M+Na]^+$, 515 $[M+Na]^+$, 493 $[M+1]^+$ (100%).

3.4.4. (+)-(3R,5R,6S)-1-Benzyl-3-[2-(benzyloxymethyl)prop-2-en-1-yl]-6-(tert-butyldiphenylsilyloxymethyl)-5-(iso-propyl)piperazin-2-one, **7f**

From **5b** (90 mg, 0.181 mmol), benzyl 2-(bromomethyl)prop-2-en-1-yl ether[7] (23 μL, 0.235 mmol), Zn (16 mg, 0.235 mmol), and TMSCl (4 mg, 5 μL, 0.04 mmol) in DMF, following procedure B and after 16 h adding the same amounts of reagents (46 h total), **7f** (80 mg, 0.121 mmol, 70%) was obtained after chromatography (5–50% EtOAc–hexane) as a colorless oil. Data for **7f**: R_f 0.22 (20% AcOEt–hexane). $[\alpha]_D^{20}$ +49.1 (*c* 1.40). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.33 (d, 3H, *J*=6.4 Hz), 0.74 (d, 3H, *J*=6.8 Hz), 1.03 (s, 9H), 1.51 (m, 1H), 1.73 (br s, 1H), 2.14 (dd, 1H, *J*=13.9, 10.0 Hz), 2.50 (d, 1H, *J*=10.5 Hz), 2.87 (d, 1H, *J*=13.7 Hz), 3.24 (dd, 1H, *J*=8.1, 4.6 Hz), 3.47 (d, 1H, *J*=14.4 Hz), 3.55 (m, 1H), 3.75 (dd, 1H, *J*=4.5, 10.0 Hz), 3.91 (m, 3H), 4.48 (ap q, 2H, *J*=12.0 Hz), 4.99 (s, 1H), 5.16 (s, 1H), 5.33 (d, 1H, *J*=14.4 Hz), 7.10 (m, 2H), 7.27 (m, 8H), 7.41 (m, 6H), 7.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 19.2, 19.5, 25.3, 26.8 (3C), 38.0, 48.5, 52.0, 56.5, 57.1, 63.9, 72.3, 72.7, 114.5, 127.5, 127.6, 127.8 (5C), 128.3 (2C), 128.4 (2C), 128.7 (2C), 129.8 (2C), 129.9, 133.2 (2C), 135.5 (4C), 137.5, 138.2, 142.8, 170.3. IR (film): 3555, 3070, 2960, 2931, 2858, 1643, 1471, 1453, 1428, 1389, 1362, 1265, 1240, 1112, 823, 739, 701 cm^{-1}. MS (ES): 683 $[M+Na]^+$, 661 $[M+H]^+$.

3.4.5. Ethyl (+)-2-((2R,5S,6R)-4-benzyl-5-(tert-butyldimethylsilyloxymethyl)-6-(iso-propyl)-3-oxopiperazin-2-yl)methylacrylate, **7b** and ethyl 2-((2R,5S,6R)-4-benzyl-5-(tert-butyldimethylsilyloxymethyl)-1-(2-ethoxycarbonylallyl)-6-(iso-propyl)-3-oxopiperazin-2-yl)methylacrylate, **9a**

From **5a** (20 mg, 0.054 mmol), ethyl 2-(bromomethyl)acrylate (95%, 12 μL, 0.084 mmol), Zn (7 mg, 0.107 mmol), and $CeCl_3\cdot 7H_2O$ (2 mg, 0.005 mmol) following general procedure A (22 h), **7b** (21 mg, 0.043 mmol, 80%) was obtained after chromatography (5–10% EtOAc–hexane) as a colorless oil. Alternatively, from **5a** (13 mg, 0.035 mmol), ethyl 2-(bromomethyl)acrylate (95%, 14 mg, 10 μL, 0.073 mmol), Zn (5 mg, 0.070 mmol), and TMSCl (2 mg, 2 μL, 0.017 mmol) in DMF (procedure B) adding an equal amount of reagents after 16 h and 40 h (88 h total) a mixture (87:13) of **7b** and **9a** was obtained. After chromatography (2–5% EtOAc–CH_2Cl_2), **7b** (11 mg, 0.023 mmol, 64%) and **9a** (2 mg, 0.003 mmol, 10%) were isolated as colorless oils. Data for **7b**: R_f 0.26 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +86.6 (*c* 0.56). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6H), 0.32 (d, 3H, *J*=6.4 Hz), 0.79 (d, 3H, *J*=6.8 Hz), 0.86 (s, 9H), 1.28 (t, 3H, *J*=7.1 Hz), 1.47 (m, 1H), 1.67 (br s, 1H), 2.36 (d, 1H, *J*=10.4 Hz), 2.55 (dd, 1H, *J*=13.9, 7.5 Hz), 3.10 (dd, 1H, *J*=13.8, 3.6 Hz), 3.20 (dd, 1H, *J*=6.6, 4.9 Hz), 3.67 (dd, 1H, *J*=7.4, 4.3 Hz), 3.70 (dd, 1H, *J*=9.9, 4.6 Hz), 3.79 (d, 1H, *J*=14.5 Hz), 3.81 (dd, 1H, *J*=9.9, 7.5 Hz), 4.19 (qd, 2H, *J*=7.1, 2.2 Hz), 5.45 (d, 1H, *J*=14.5 Hz), 5.63 (s, 1H), 6.18 (s, 1H), 7.22–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4 (2C), 14.2, 18.2, 19.1, 19.5, 25.3, 25.9 (3C), 35.4, 48.6, 53.4, 57.0, 57.3, 60.7, 63.9, 126.8, 127.6, 128.5 (2C), 128.8 (2C), 137.6, 138.1, 167.4, 169.9. IR (film): 3355, 2961, 2929, 2853, 1716, 1647, 1450, 1387, 1248, 1176, 1096, 837, 774, 700 cm^{-1}. MS (ES): 999 $[2M+Na]^+$, 511 $[M+Na]^+$, 489 $[M+1]^+$ (100%). Anal. Calcd for $C_{27}H_{44}N_2O_4Si$: C, 66.35; H, 9.07; N, 5.73. Found: C, 66.02; H, 9.30; N, 5.84. Partial data for **9a**: R_f 0.26 (5% EtOAc–CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.02 (s, 3H, Me), 0.01 (s, 3H), 0.26 (d, 3H, *J*=6.6 Hz), 0.79 (d, 3H, *J*=6.8 Hz), 0.85 (s, 9H), 1.26 (t, 3H, *J*=7.1 Hz), 1.29 (t, 3H, *J*=7.2 Hz), 2.52 (d, 1H, *J*=10.5 Hz), 2.85 (m, 2H), 3.45 (m, 1H), 3.50 (m, 2H), 3.64 (d, 1H, *J*=13.2 Hz), 3.65 (m, 1H), 3.85 (d, 1H, *J*=13.7 Hz), 4.16 (m, 5H), 5.04 (d, 1H, *J*=14.4 Hz), 5.63 (s, 1H), 5.75 (s, 1H), 6.16 (d, 1H, *J*=1.7 Hz), 6.22 (s, 1H), 7.27 (m,

5H). IR (film): 2956, 2929, 2856, 1717, 1667, 1635, 1461, 1454, 1368, 1258, 1178, 1150, 1100, 1025, 838, 810, 755, 702 cm^{-1}. MS (ES): 601 $[M+1]^+$ (100%).

3.4.6. (+)-(3R,5R,6S)-1-Benzyl-6-(tert-butyldimethylsilyloxymethyl)-3-(2-methylprop-2-en-1-yl)-5-(1-naphthyl)piperazin-2-one, **7g**

From **6** (9 mg, 0.018 mmol), 3-bromo-2-methylpropene (97%, 5 mg, 4 μL, 0.041 mmol), Zn (3 mg, 0.039 mmol), and TMSCl (1 mg, 1 μL, 0.010 mmol) in DMF (procedure B) and adding 4 equiv of 3-bromo-2-methylpropene, 4 equiv Zn, and 1 equiv of TMSCl more after 20 h (44 h total), **7g** (8 mg, 0.016 mmol, 78%) was obtained after chromatography (10–15% EtOAc–hexane) as a colorless oil. Data for **7g**: R_f 0.33 (30% EtOAc–hexane). $[\alpha]_D^{20}$ +65.9 (*c* 0.83). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.93 (s, 9H), 1.66 (br s, 1H), 1.54 (s, 3H), 2.56 (dd, 1H, *J*=13.7, 10.8 Hz), 2.72 (dd, 1H, *J*=13.9, 2.6 Hz), 3.57 (dd, 2H, *J*=10.3, 2.7 Hz), 3.76 (m, 1H), 3.90 (dd, 1H, *J*=10.3, 6.3 Hz), 4.02 (d, 1H, *J*=14.8 Hz), 4.68 (s, 1H), 4.74 (s, 1H), 5.12 (d, 1H, *J*=4.4 Hz), 5.48 (d, 1H, *J*=14.7 Hz), 7.14 (m, 2H), 7.25 (m, 5H), 7.42 (d, 1H, *J*=6.3 Hz), 7.43 (d, 1H, *J*=6.4 Hz), 7.68 (d, 1H, *J*=8.2 Hz), 7.79 (dd, 1H, *J*=6.1, 3.4 Hz), 8.14 (dd, 1H, *J*=6.2, 3.7 Hz). 2D-NOESY show cross-points between: H-5/CH_2 allyl (2.56 ppm), H-5/H-6, H-5/Ar–H (8.14 ppm), H_{cys}-3 allyl/Me, H_{trans}-3 allyl/CH_2 allyl (2.56 ppm), H-6/CH_2O (3.57 and 3.90 ppm). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4 (2C), 18.2, 21.5, 25.9 (3C), 40.4, 47.5, 49.5, 53.7, 60.8, 61.2, 113.7, 123.1, 125.0, 125.2, 125.5, 126.1, 127.5, 128.3, 128.5 (2C), 128.6 (2C), 129.0, 131.2, 134.0, 136.3, 136.7, 142.2, 171.1. IR (film): 3375, 2950, 2925, 2856, 1648, 1446, 1252, 1106, 1069, 835, 777, 699 cm^{-1}. MS (ES): 1051 $[2M+Na]^+$, 537 $[M+Na]^+$, 515 $[M+1]^+$ (100%).

3.4.7. (+)-(3R,5R,6S)-1-Benzyl-6-(tert-butyldimethylsilyloxymethyl)-3-(2-phenylprop-2-en-1-yl)-5-(1-naphthyl)piperazin-2-one, **7h**

From **6** (11 mg, 0.025 mmol), (3-bromopropen-1-yl)benzene (9 mg, 0.048 mmol), Zn (3 mg, 0.048 mmol), and TMSCl (1 mg, 2 μL, 0.012 mmol) in DMF (procedure B) adding 2 equiv of (3-bromopropen-1-yl)benzene, 2 equiv Zn, and 1 equiv of TMSCl after 22 h (28 h total), **7h** (11 mg, 0.019 mmol, 80%) was obtained after chromatography (10–15% EtOAc–hexane) as a colorless oil. Data for **7h**: R_f 0.27 (40% Et_2O–hexane). $[\alpha]_D^{20}$ +50.6 (*c* 1.15). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 3H), 0.08 (s, 3H), 0.94 (s, 9H), 1.71 (br s, 1H), 2.87 (dd, 1H, *J*=14.7, 11.5 Hz), 3.40 (m, 2H), 3.55 (dd, 1H, *J*=10.4, 2.7 Hz), 3.72 (ddd, 1H, *J*=6.4, 4.6, 2.7 Hz), 3.89 (dd, 1H, *J*=10.4, 6.2 Hz), 4.01 (d, 1H, *J*=14.8 Hz), 5.06 (s, 1H), 5.11 (d, 1H, *J*=4.6 Hz), 5.23 (d, 1H, *J*=1.3 Hz), 5.48 (d, 1H, *J*=14.8 Hz), 7.00 (d, 1H, *J*=6.8 Hz), 7.12 (m, 4H), 7.23 (m, 7H), 7.42 (m, 2H), 7.62 (d, 1H, *J*=8.1 Hz), 7.77 (m, 1H), 8.09 (ap t, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4, −5.3, 18.2, 25.9 (3C), 38.1, 47.4, 49.5, 54.3, 60.8, 61.1, 115.3, 123.1, 124.9, 125.1, 125.5, 126.1, 126.3 (3C), 127.5 (2C), 128.2 (3C), 128.5 (3C), 129.0, 131.1, 134.0, 136.1, 136.8, 139.4, 145.4, 170.9. IR (film): 3384, 2950, 2918, 2856, 1648, 1461, 1446, 1253, 1103, 1069, 1026, 836, 777, 699 cm^{-1}. MS (ES): 1175 $[2M+Na]^+$, 599 $[M+Na]^+$, 577 $[M+1]^+$ (100%). Anal. Calcd for $C_{37}H_{44}N_2O_2Si$: C, 77.04; H, 7.69; N, 4.86. Found: C, 77.35; H, 7.87; N, 5.09.

3.4.8. Ethyl (+)-2-((2R,5S,6R)-4-benzyl-5-(tert-butyldimethylsilyloxymethyl)-6-(1-naphthyl)-3-oxopiperazin-2-yl)methylacrylate, **7i** (+)-(3R,4S,8aR)-2-benzyl-3-(tert-butyldimethylsilyloxymethyl)-7-methylene-4-(1-naphthyl)tetrahydropyrrolo[1,2-a]pyrazin-1,6-dione, **9d**, and ethyl (−)-(2′R,5′S,6′R)-2-[4′-benzyl-5′-(tert-butyldimethylsilyloxymethyl)-1′-(2-ethoxycarbonylallyl)-6′-(1-naphthyl)-3′-oxopiperazin-2′-yl]methylacrylate, **9b**

From **6** (10 mg, 0.022 mmol), ethyl 2-(bromomethyl)acrylate (95%, 9 mg, 6 μL, 0.046 mmol), Zn (3 mg, 0.044 mmol), and TMSCl (1 mg, 1 μL, 0.011 mmol) in DMF (procedure B, 14 h) a mixture (80:20) of **7i** and **9d** was obtained. After chromatography (0–5% EtOAc–CH_2Cl_2), **7i** (8 mg, 0.014 mmol, 64%) and **9d** (2 mg, 0.004 mmol, 17%) were isolated as colorless oils. Alternatively, from **6** (11 mg, 0.024 mmol), ethyl 2-(bromomethyl)acrylate (95%, 10 mg, 7 μL, 0.051 mmol), Zn (3 mg, 0.048 mmol), and TMSCl (1 mg, 1 μL, 0.012 mmol) in DMF, adding after 16 h and 48 h, 1.0 equiv of 2-(bromomethyl)acrylate, 1.0 equiv of Zn, and 0.25 equiv of TMSCl, an 82:18 mixture of **9b** and **9d** was obtained that after chromatography (0–5% EtOAc–CH_2Cl_2) rendered **9b** (10 mg, 0.015 mmol, 61%) and **9d** (2 mg, 0.004 mmol, 16%) as colorless oils. Data for **7i**: R_f 0.17 (5% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ +60.0 (*c* 0.64). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.11 (t, 3H, *J*=7.1 Hz), 1.63 (br s, 1H), 2.75 (dd, 1H, *J*=14.5, 8.6 Hz), 3.01 (dd, 1H, *J*=14.5, 4.2 Hz), 3.55 (dd, 1H, *J*=8.6, 4.2 Hz), 3.67 (ap d, 1H, *J*=10.3 Hz), 3.76 (m, 1H), 3.94 (dd, 1H, *J*=10.2, 6.9 Hz), 4.01 (qd, 2H, *J*=7.1, 1.5 Hz), 4.09 (d, 1H, *J*=14.5 Hz), 5.08 (d, 1H, *J*=2.6 Hz), 5.39 (d, 1H, *J*=14.5 Hz), 5.50 (s, 1H), 6.13 (s, 1H), 6.97 (d, 1H, *J*=8.1 Hz), 7.09 (t, 1H, *J*=7.8 Hz), 7.27 (m, 5H), 7.43 (t, 1H, *J*=4.3 Hz), 7.43 (d, 1H, *J*=8.6 Hz), 7.66 (d, 1H, *J*=8.1 Hz), 7.79 (m, 1H), 8.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4 (2C), 14.0, 18.2, 25.9 (3C), 34.4, 48.1, 49.7, 55.0, 60.7 (3C), 123.0, 124.7 (2C), 124.9, 125.6, 126.1, 127.0, 127.6, 128.2, 128.6 (2C), 128.9 (2C), 131.1, 134.0, 135.9, 136.8, 137.7, 165.7, 170.3. IR (film): 3367, 2950, 2925, 2856, 1716, 1649, 1449, 1252, 1156, 1106, 1066, 1025, 835, 777 cm^{-1}. MS (ES): 1167 $[2M+Na]^+$, 595 $[M+Na]^+$, 573 $[M+1]^+$ (100%). Data for **9d**: R_f 0.40 (5% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ +13.3 (*c* 0.15). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 2.91 (ddt, 1H, *J*=17.9, 5.5, 2.7 Hz), 3.05 (ddt, 1H, *J*=17.9, 9.3, 2.4 Hz), 3.68 (dd, 1H, *J*=10.1, 8.2 Hz), 3.82 (dd, 1H, *J*=9.2, 5.4 Hz), 3.88 (dd, 1H, *J*=10.1, 4.0 Hz), 4.05 (dd, 1H, *J*=8.2, 4.0 Hz), 4.14 (d, 1H, *J*=14.1 Hz), 5.38 (t, 1H, *J*=2.4 Hz), 5.48 (d, 1H, *J*=14.1 Hz), 6.06 (t, 1H, *J*=2.7 Hz), 6.27 (s, 1H), 6.73 (d, 1H, *J*=7.1 Hz), 6.90 (t, 1H, *J*=7.7 Hz), 7.38 (m, 3H), 7.45 (m, 3H), 7.52 (m, 1H), 7.68 (d, 1H, *J*=8.2 Hz), 7.78 (d, 1H, *J*=8.1 Hz), 8.39 (d, 1H, *J*=8.4 Hz). DNOE between H-8a/H-8 (3.05 ppm): 7.2%; H-8a/Ar–H (6.73 ppm): 5.7%; H-8 (2.91 ppm)/H-8 (3.05 ppm): 16.9%; H-8 (3.05 ppm)/H-8 (2.91 ppm) 33.5%; H-8 (3.05 ppm)/H_{cis}-7: 3.1%; H-8 (3.05 ppm)/H_{trans}-7: 5.6%. IR (film): 2925, 2850, 1695, 1661, 1442, 1252, 1109, 1066, 1023, 835, 777 cm^{-1}. MS (ES): 1075 $[2M+Na]^+$, 549 $[M+Na]^+$, 527 $[M+1]^+$ (100%). Data for **9b**: R_f 0.28 (5% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ −52.5 (*c* 0.57). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.96 (s, 9H), 1.18 (t, 3H, *J*=7.1 Hz), 1.32 (t, 3H, *J*=7.1 Hz), 2.61 (dd, 1H, *J*=13.8, 9.4 Hz), 3.13 (dd, 1H, *J*=13.7, 3.6 Hz), 3.56 (ap d, 1H, *J*=9.3 Hz), 3.61 (m, 1H), 3.64 (d, 1H, *J*=15.9 Hz), 3.74 (d, 1H, *J*=16.3 Hz), 3.86 (d, 1H, *J*=14.3 Hz), 4.08 (m, 3H), 4.24 (m, 2H), 4.31 (dd, 1H, *J*=9.3, 4.3 Hz), 4.80 (d, 1H, *J*=14.1 Hz), 5.24 (d, 1H, *J*=2.6 Hz), 5.62 (d, 1H, *J*=1.5 Hz), 5.63 (s, 1H), 6.16 (s, 1H), 6.24 (s, 1H), 6.61 (d, 2H, *J*=7.3 Hz), 6.71 (t, 2H, *J*=7.4 Hz), 6.79 (t, 1H, *J*=7.2 Hz), 7.10 (d, 1H, *J*=7.1 Hz), 7.27 (m, 2H), 7.36 (ap t, 1H), 7.67 (d, 1H, *J*=8.1 Hz), 7.72 (d, 1H, *J*=8.2 Hz), 7.89 (d, 1H, *J*=8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.4 (2C), 14.1, 14.2, 18.1, 25.8 (3C), 38.8, 49.2, 50.7, 51.9, 60.5, 60.7, 61.6, 61.8 (2C), 64.3, 122.5 (2C), 124.9, 125.0, 125.1, 125.7, 126.2, 126.9 (2C), 127.7 (2C), 128.1 (2C), 129.0, 131.2, 134.2, 134.7, 135.8, 137.5, 137.8, 166.4, 167.0, 169.1. IR (film): 2950, 2925, 2856, 1713, 1654, 1461, 1452, 1256, 1147, 1081, 1028, 836, 777 cm^{-1}. MS (ES): 1391 $[2M+Na]^+$, 707 $[M+Na]^+$, 685 $[M+1]^+$ (100%).

3.4.9. (+)-(5R,6S)-1-Benzyl-6-(tert-butyldimethylsilyloxymethyl)-5-(iso-propyl)-3-(3′-oxocyclohex-1′-enyl)-5,6-dihydropyrazin-2(1H)-one, **7k**

From **5a** (13 mg, 0.035 mmol), 3-bromocyclohex-1-ene (90%, 12 mg, 9 μL, 0.077 mmol), Zn (5 mg, 0.070 mmol), and TMSCl (2 mg, 2 μL, 0.017 mmol) in DMF, adding after 20 h, 3 equiv of 3-bromocyclohex-1-ene, 3 equiv of Zn, and 0.5 equiv of TMSCl (41 h total) was obtained an inseparable mixture of diastereomers from allylation at C-3 (12 mg, 75%) that evolved after 5–6 days at room

temperature (neat) to **7k** that was purified by chromatography (10–15% EtOAc–hexane) as a colorless oil. Data for **7k**: R_f 0.26 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +278.9 (*c* 0.17). ^{1}H NMR ($CDCl_3$, 400 MHz), COSY δ 0.00 (s, 6H, 2Me TBDMS), 0.37 (d, 3H, *J*=6.4 Hz, Me ^{i}Pr), 0.86 (s, 9H, ^{t}Bu TBDMS), 0.87 (d, 3H, *J*=7.0 Hz, Me ^{i}Pr), 1.32 (m, 1H, CH ^{i}Pr), 2.08 (dd, 2H, *J*=12.5, 6.2 Hz, 2H-5 cy), 2.46 (m, 3H, 2H-4 cy, H-6 cy), 2.84 (dtd, 1H, *J*=18.5, 7.1, 1.6 Hz, H-6 cy), 3.48 (m, 2H, H-6, CH_2O), 3.57 (dd, 1H, *J*=12.5, 8.6 Hz, CH_2O), 3.68 (d, 1H, *J*=8.8 Hz, H-5), 4.06 (d, 1H, *J*=14.1 Hz, CH_2Ph), 5.25 (d, 1H, *J*=14.1 Hz, CH_2Ph), 6.67 (t, 1H, *J*=1.6 Hz, H-2 cy), 7.31 (m, 5H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz), HSQC, HMBC δ −5.5 (2C, Me TBDMS), 18.2 (C-TBDMS), 19.3 (Me ^{i}Pr), 19.5 (Me ^{i}Pr), 22.5 (C-5 cy), 25.8 (3C, ^{t}Bu TBDMS), 26.4 (C-6 cy), 31.9 (CH ^{i}Pr), 37.8 (C-4 cy), 49.3 (CH_2Ph), 55.2 (C-6), 63.4 (2C, C-5, CH_2O), 128.2, 128.8 (2C), 129.3 (2C), 131.4 (C-2 cy), 136.3, 154.5, 154.8, 160.7 (C=N), 200.4 (CO). IR (film): 2950, 2929, 2856, 1730, 1660, 1461, 1453, 1256, 1109, 837, 773, 756, 699 cm^{-1}. MS (ES): 959 $[2M+Na]^+$, 491 $[M+Na]^+$, 469 $[M+1]^+$ (100%). Anal. Calcd for $C_{27}H_{40}N_2O_3Si$: C, 69.19; H, 8.60; N, 5.98. Found: C, 68.95; H, 8.31; N, 6.22.

3.5. General procedure for the Pictet–Spengler–Grieco cyclization

To a solution of **5** in methanol or isopropanol (45 mL/mmol), 5 equiv of aldehyde was added. The mixture was heated in a Kimble vial to 65 °C (unless otherwise is stated) and 5 equiv more of aldehyde was added every 30 min (20 equiv in total) until no further evolution was observed by TLC (reaction times indicated for each example). Then, the solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel.

3.5.1. (+)-(3S,4R,8S,9aR)-2-Benzyl-3-(tert-butyldimethylsilyloxymethyl)-8-methyl-8-methoxy-4-(iso-propyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, ***10a***

From **7c** (10 mg, 0.023 mmol) in methanol and HCHO (4 mg, 4 μL, 0.122 mmol) following the general procedure (48 h), **10a** (8 mg, 0.017 mmol, 73%) was obtained after chromatography (10–20% EtOAc–hexane) as a colorless oil. Data for **10a**: R_f 0.27 (30% EtOAc–hexane). $[\alpha]_D^{20}$ +81.1 (*c* 0.35). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 6H), 0.31 (d, 3H, *J*=6.6 Hz,), 0.86 (s, 9H), 0.87 (d, 3H, *J*=7.0 Hz), 1.20 (s, 3H), 1.34 (t, 1H, *J*=11.9 Hz), 1.56 (m, 2H), 1.60–1.77 (m, 1H), 2.34 (ap d, 1H, *J*=11.7 Hz), 2.46 (dd, 1H, *J*=8.6, 1.2 Hz), 2.70 (ddd, 1H, *J*=12.1, 4.7, 2.7 Hz), 2.96 (td, 1H, *J*=10.9, 4.5 Hz), 3.20 (ddd, 1H, *J*=8.6, 4.3, 1.2 Hz), 3.24 (s, 1H), 3.29 (dd, 1H, *J*=11.9, 2.9 Hz), 3.62 (dd, 1H, *J*=9.4, 4.7 Hz), 3.81 (t, 1H, *J*=9.0 Hz), 3.92 (d, 1H, *J*=14.1 Hz), 5.20 (d, 1H, *J*=14.1), 7.25–7.33 (m, 5H). DNOE between H-9a/H-9_{eq} (2.34 ppm): 6.2%; H-9a/CH ^{i}Pr: 6.3%; H-9a/Me: 6.9%; MeO/H-9_{eq} (2.34 ppm): 2.0%; MeO/Me: 2.2%; H-6 (2.96 ppm)/H-9a: 10.5%; H-6 (2.96 ppm)/H-6 (2.70 ppm): 43.0%; H-6 (2.96 ppm)/Me: 12.5%; H-6 (2.70 ppm)/H-4: 12.4%; H-3/H-4: 6.6%; H-3/CH_2O (3.81 ppm): 5.3%; H-3/Me ^{i}Pr (0.31 ppm): 6.2%; CH ^{i}Pr/H-9a: 4.5%; Me/H-9a: 2.6%; Me/MeO: 1.3%; Me/H-6 (2.96 ppm): 1.4%; Me/H-9_{eq} (2.34 ppm): 1.4%. ^{13}C NMR ($CDCl_3$, 75 MHz), HSQC δ −5.5, −5.4, 18.1, 19.5, 20.8, 22.3, 25.9 (3C), 27.4, 37.5, 40.6, 48.5, 49.3, 49.9, 55.8, 58.3, 62.7, 62.9, 73.9, 127.6, 128.5 (2C), 128.8 (2C), 137.5, 170.4. IR (film): 2950, 2926, 2854, 1651, 1464, 1452, 1387, 1254, 1100, 1071, 838, 776 cm^{-1}. MS (ES): 971 $[2M+Na]^+$, 497 $[M+Na]^+$, 474 $[M+1]^+$ (100%). Anal. Calcd for $C_{27}H_{46}N_2O_3Si$: C, 68.31; H, 9.77; N, 5.90. Found: C, 68.07; H, 9.52; N, 5.83.

3.5.2. (+)-(3S,4R,8S,9aR)-2-Benzyl-3-(tert-butyldimethylsilyloxymethyl)-8-methyl-4-(iso-propyl)-8-(iso-propoxy)-hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, ***10b***

From **7c** (14 mg, 0.032 mmol) in isopropanol and HCHO following the general procedure (82 °C, 5 days), **10b** (4 mg, 0.008 mmol, 50%) was obtained after chromatography (5–10% EtOAc–hexane) as a colorless oil along with 15% of recovered starting material **7c**. Data for **10b**: R_f 0.25 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +20.3 (*c* 0.32). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.31 (d, 3H, *J*=6.6 Hz), 0.87 (s, 9H), 0.87 (d, 3H, *J*=6.6 Hz), 1.11 (d, 6H, *J*=6.2 Hz), 1.20 (s, 3H), 1.38 (t, 1H, *J*=12.0 Hz), 1.60–1.80 (m, 2H), 1.65–1.75 (m, 1H), 2.32 (d, 1H, *J*=11.9 Hz), 2.46 (d, 1H, *J*=8.2 Hz), 2.70 (ddd, 1H, *J*=12.0, 4.7, 2.5 Hz), 2.96 (m, 1H), 3.20 (dd, 1H, *J*=7.8, 4.5 Hz), 3.29 (dd, 1H, *J*=11.6, 3.2 Hz), 3.65 (dd, 1H, *J*=9.3, 4.6 Hz), 3.83 (t, 1H, *J*=9.2 Hz), 3.92 (m, 1H), 3.92 (d, 1H, *J*=14.3 Hz), 5.21 (d, 1H, *J*=14.1 Hz), 7.24–7.33 (m, 5H). IR (film): 2955, 2929, 2854, 1651, 1462, 1453, 1375, 1361, 1252, 1104, 1030, 835, 776 cm^{-1}. MS (ES): 1027 $[2M+Na]^+$, 503 $[M+1]^+$ (100%).

3.5.3. (+)-(3S,4R,8S,9aR)-2-Benzyl-3-(tert-butyldiphenyl silyloxymethyl)-8-methyl-8-methoxy-4-(iso-propyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, ***10c***

From **7d** (9 mg, 0.016 mmol) in methanol and HCHO following the general procedure (5 h) was obtained a crude mixture of **10c** (85%) along with other minor non-identified byproducts (15%). After chromatography (4–20% EtOAc–hexane), **10c** (6 mg, 0.010 mmol, 63%) was isolated as a colorless oil. Data for **10c**: R_f 0.20 (70% Et_2O–hexane). $[\alpha]_D^{20}$ +42.1 (*c* 0.73). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.34 (d, 3H, *J*=6.5 Hz), 0.89 (d, 3H, *J*=6.8 Hz), 1.02 (s, 9H), 1.17 (s, 3H), 1.23 (m, 1H), 1.45 (m, 2H), 1.70 (m, 1H), 2.27 (d, 1H, *J*=11.7 Hz), 2.60 (m, 2H), 2.93 (dt, 1H, *J*=11.0, 4.4 Hz), 3.20 (s, 3H), 3.25 (m, 2H), 3.69 (dm, 2H, *J*=14.2 Hz), 3.95 (t, 1H, *J*=9.2 Hz), 5.09 (d, 1H, *J*=14.2 Hz), 7.15 (m, 2H), 7.23 (m, 4H), 7.40 (m, 5H), 7.61 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 19.5, 20.8, 22.3, 26.8 (3C), 27.4, 37.4, 40.3, 48.5, 49.2, 49.9, 55.7, 58.1, 62.8, 63.1, 73.8, 127.6, 127.8 (4C), 128.4 (2C), 129.1 (2C), 129.9 (2C), 133.3 (2C), 135.5 (4C), 137.3, 170.3. IR (film): 2931, 1651, 1452, 1256, 1114, 823, 701 cm^{-1}. MS (ES): 599 $[M+H]^+$.

3.5.4. (+)-(3S,4R,8S,9aR)-2-Benzyl-8-[(benzyloxy)methyl]-3-(tert-butyldiphenylsilyloxymethyl)-4-(iso-propyl)-8-methoxyhexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, ***10d*** *and (3S,4R,8R,9aR)-2-benzyl-8-[(benzyloxy)methyl]-3-(tert-butyldiphenyl silyloxymethyl)-4-(iso-propyl)-8-methoxyhexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one,* ***11d***

From **7f** (9 mg, 0.014 mmol) in methanol and HCHO following the general procedure (5 h), a mixture (88:12) of the isomers **10d** and **11d** was obtained. After chromatography (8–20% EtOAc–CH_2Cl_2), **10d** (6 mg, 0.008 mmol, 61%) and **11d** (1 mg, 0.002 mmol, 10%) were isolated as colorless oils. Data for **10d**: R_f 0.28 (10% AcOEt–CH_2Cl_2). $[\alpha]_D^{20}$ +50.1 (*c* 0.81). ^{1}H NMR ($CDCl_3$, 300 MHz), COSY δ 0.28 (d, 3H, *J*=6.4 Hz, CH_3), 0.69 (d, 3H, *J*=6.8 Hz, CH_3), 1.01 (s, 9H, CH_3 ^{t}Bu), 1.24 (m, 1H, H-9_{ax}), 1.36 (dd, 1H, *J*=12.2, 4.9 Hz, H-7), 1.55 (m, 1H, CH ^{i}Pr), 1.90 (dd, 1H, *J*=12.2, 2.2 Hz, H-7), 2.32 (dt, 1H, *J*=12.5, 2.7 Hz, H-9_{eq}), 2.49 (dm, 2H, *J*=8.1 Hz, H-6, H-4), 2.68 (dd, 1H, *J*=10.0, 12.0 Hz, H-6), 3.11 (dd, 1H, *J*=12.0, 2.9 Hz, H-9a), 3.18 (m, 1H, H-3), 3.22 (s, 3H, OCH_3), 3.45 (dd, 2H, *J*=13.9, 11.0 Hz, CH_2OBn), 3.65 (dm, 2H, *J*=14.2 Hz, NBn, CH_2O), 3.92 (t, 1H, *J*=9.3 Hz, CH_2O), 4.45 (d, 1H, *J*=12.5 Hz, OBn), 4.62 (d, 1H, *J*=12.5 Hz, OBn), 5.08 (d, 1H, *J*=14.2 Hz, NBn), 7.13 (m, 2H), 7.33 (m, 14H), 7.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz), HSQC δ 19.2, 20.9, 22.3, 26.8 (3C), 27.3, 32.2, 36.2, 49.2, 49.3, 49.5, 55.4, 58.1, 62.7, 63.2, 67.8, 73.2, 75.3, 127.6, 127.7, 127.8 (4C), 128.2 (2C), 128.4 (4C), 129.1 (2C), 129.9 (2C), 133.4 (2C), 135.5 (4C), 137.3, 138.0, 170.0. 2D-NOESY: CH_3 (0.28)/CH_3 (0.69), CH_3 (0.28)/^{i}Pr, CH_3 (0.28)/CH_2OBn, CH (^{i}Pr)/CH_3, CH (^{i}Pr)/CH_3, CH (^{i}Pr)/H-4, CH (^{i}Pr)/H-9a, CH_3 (0.69)/H-6 (2.68), H-9a/CH_2OBn. IR (film): 3070, 2931, 2858, 2245, 1646, 1453, 1428, 1362, 1264, 1113, 910, 823, 737, 701, 646 cm^{-1}. MS (ES): 727 $[M+Na]^+$, 705 $[M+H]^+$. Partial data for **11d**: R_f 0.33 (10% EtOAc–CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.43 (d, 3H, *J*=6.4 Hz), 0.88 (d, 3H, *J*=6.3 Hz), 1.00 (s, 9H), 1.20–1.70 (m, 4H), 1.77 (m, 1H),

1.94 (m, 1H), 2.23 (d, 1H, *J*=5.6 Hz), 2.35 (m, 1H), 2.65 (dd, 1H, *J*=2.4, 11.2 Hz), 2.77 (m, 1H), 3.26 (s, 3H), 3.32 (m, 4H), 4.24 (d, 1H, *J*=14.4 Hz), 4.49 (2H, AB system), 4.81 (d, 1H, *J*=14.2 Hz), 7.17–7.31 (m, 10H), 7.35–7.44 (m, 6H), 7.51–7.58 (m, 4H). MS (ES): 727 $[M+Na]^+$, 705 $[M+H]^+$.

3.5.5. (+)-(3S,4R,8S,9aR)-2-Benzyl-3-(tert-butyldimethylsilyloxymethyl)-8-methyl-8-methoxy-4-(1-naphthyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, **10e**

From **7g** (8 mg, 0.016 mmol) in methanol and HCHO following the general procedure (91 h), **10e** (5 mg, 0.009 mmol, 56%) was obtained after chromatography (10–20% EtOAc–hexane) as a colorless oil along with a 12% of a compound tentatively assigned as (3*S*,4*R*,8*S*,9a*R*)-2-benzyl-3-(*tert*-butyldimethylsilyloxymethyl)-8-methylene-4-(1-naphthyl) hexahydropyrido[1,2-*a*]pyrazin-1-one (**10e′**). Data for **10e**: R_f 0.20 (40% EtOAc–hexane). $[\alpha]_D^{20}$ +15.0 (*c* 0.40). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.12 (s, 3H), 0.94 (s, 9H), 1.11 (s, 3H), 1.24 (m, 1H), 1.43 (m, 1H), 1.71 (td, 1H, *J*=12.5, 5.1 Hz), 2.37 (m, 2H), 2.77 (ap d, 1H, *J*=10.5 Hz), 3.25 (s, 3H), 3.49 (ap d, 1H, *J*=11.3 Hz), 3.63 (m, 2H), 3.96 (d, 1H, *J*=14.5 Hz), 3.98 (m, 1H), 5.16 (br s, 1H), 5.25 (d, 1H, *J*=13.3 Hz), 7.07 (m, 5H), 7.14 (m, 2H), 7.40 (m, 2H), 7.68 (dd, 1H, *J*=7.0, 2.0 Hz), 7.78 (dd, 1H, *J*=7.4, 2.3 Hz), 8.20 (m, 1H). DNOE between H-9a/Ar–H (7.14 ppm): 14.8%; H-9a/Me: 5.9%; OMe/Me: 2.2%; H-6 (2.77 ppm)/H-6 (2.37 ppm): 17.4%; H-6 (2.37 ppm)/H-4: 10.4%; H-7 (1.71 ppm)/OMe: 1.9%; H-7 (1.71 ppm)/H-6 (2.77 ppm): 3.3%; H-7 (1.71 ppm)/H-7 (1.43 ppm): 6.4%, Me/H-9a: 5.4%. Me/OMe: 5.4%. ^{13}C NMR ($CDCl_3$, 100 MHz), HSQC δ −5.5, −5.4, 18.2, 19.8, 25.9 (3C), 36.1, 39.7, 48.4 (2C), 49.2, 53.3, 56.9, 62.1 (2C), 73.8, 124.9, 125.4, 125.9, 127.4, 128.3 (2C), 128.4, 129.0, 132.0, 134.0, 134.2, 136.4, 170.0. IR (film): 2925, 1651, 1449, 1256, 1156, 1069, 835, 777 cm^{-1}. MS (ES): 1139 $[2M+Na]^+$, 581 $[M+Na]^+$, 559 $[M+1]^+$ (100%). Partial data of **10e′**: R_f 0.57 (40% EtOAc–hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.95 (s, 9H), 2.07 (m, 1H), 2.34 (m, 3H), 2.87 (m, 2H), 3.64 (m, 3H), 3.92 (d, 1H, *J*=14.6 Hz), 4.04 (m, 1H), 4.67 (s, 1H), 4.78 (s, 1H), 5.20 (m, 2H), 6.98 (m, 5H), 7.16 (m, 2H), 7.39 (m, 2H,), 7.66 (m, 1H), 7.76 (m, 1H), 8.14 (m, 1H). IR (film): 2928, 2856, 1649, 1470, 1452, 1358, 1257, 1108, 1028, 885, 838, 798, 778, 699, 664 cm^{-1}. MS (ES): 1075 $[2M+Na]^+$, 527 $[M+1]^+$ (100%).

3.5.6. (+)-(3S,4R,8S,9aR)-2-Benzyl-3-(tert-butyldimethylsilyloxymethyl)-8-methoxy-8-phenyl-4-(iso-propyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, **10f** and (+)-(3S,4R,8R,9aR)-2-benzyl-3-(tert-butyldimethylsilyloxymethyl)-8-methoxy-8-phenyl-4-(iso-propyl)hexahydro-2H-pyrido[1,2-a]pyrazin-1(6H)-one, **11f**

From **7e** (18 mg, 0.036 mmol) in methanol and HCHO following the general procedure (7 days), a mixture (64:36) of **10f** and **11f** was obtained. After chromatography (5–20% EtOAc–hexane), **10f** (4 mg, 0.008 mmol, 22%), **11f** (6 mg, 0.012 mmol, 31%), and **7e** (22%) were isolated as colorless oils. Data for **10f**: R_f 0.38 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +56.9 (*c* 0.13). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6H), 0.25 (d, 3H, *J*=6.6 Hz), 0.64 (d, 3H, *J*=6.8 Hz), 0.87 (s, 9H), 1.61 (t, 1H, *J*=12.5 Hz), 1.61 (m, 1H), 1.87 (td, 1H, *J*=12.5, 5.1 Hz), 2.36 (ap d, 1H, *J*=14.9 Hz), 2.43 (d, 1H, *J*=8.4 Hz), 2.71 (m, 2H), 2.88 (s, 3H), 3.20 (dd, 1H, *J*=8.2, 4.6 Hz), 3.24 (d, 1H, *J*=13.0 Hz), 3.43 (d, 1H, *J*=9.5 Hz), 3.67 (dd, 1H, *J*=9.7, 4.6 Hz), 3.87 (t, 1H, *J*=9.0 Hz), 3.95 (d, 1H, *J*=14.3 Hz), 5.22 (d, 1H, *J*=14.1 Hz), 7.25–7.39 (m, 8H), 7.51 (d, 2H, *J*=7.5 Hz). DNOE between CH ^{i}Pr/H-9a: 6.3%; H-9 (1.61 ppm)/H-9 (3.43 ppm): 1.8%; H-9 (3.43 ppm)/H-9a: 3.2%; H-9 (3.43 ppm)/Ar–H (7.51 ppm): 12.3%; H-9a/Ar–H (7.51 ppm): 5.3%. IR (film): 2950, 2929, 2856, 1647, 1461, 1450, 1253, 1089, 1069, 1028, 837, 777, 6998 cm^{-1}. MS (ES): 1095 $[2M+Na]^+$, 559 $[M+Na]^+$, 537 $[M+1]^+$ (100%). Data for **11f**: R_f 0.23 (5% EtOAc–CH_2Cl_2). $[\alpha]_D^{20}$ +61.7 (*c* 0.06). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.37 (d, 3H, *J*=6.8 Hz), 0.86 (s, 9H), 0.96 (d, 3H, *J*=6.6 Hz), 1.69 (m, 2H), 1.85 (m, 1H), 1.98 (m, 1H), 2.51 (d, 1H, *J*=8.8 Hz), 2.58 (ap d, 1H), 2.78 (dm, 1H, *J*=13.0 Hz), 2.99 (s, 3H), 3.23 (dd, 1H, *J*=8.6, 4.2 Hz), 3.38 (ap t, 1H), 3.64 (dd, 1H, *J*=9.2, 4.2 Hz), 3.68 (ap dd, 1H), 3.84 (t, 1H, *J*=9.0 Hz), 3.98 (d, 1H, *J*=14.1 Hz), 5.20 (d, 1H, *J*=14.1 Hz), 7.24–7.40 (m, 10H). DNOE between CH ^{i}Pr/H-9a: 6.4%; CH ^{i}Pr/Me ^{i}Pr (0.37 ppm): 3.3%; H-6 (3.38 ppm)/H-6 (2.58 ppm): 27.1%; H-6 (3.38 ppm)/Me ^{i}Pr (0.96 ppm): 7.9%. IR (film): 2925, 2850, 1648, 1446, 1253, 1156, 1069 cm^{-1}. MS (ES): 559 $[M+Na]^+$, 537 $[M+1]^+$ (100%).

3.5.7. (+)-(3S,4R,6S,9R,10aR)-2-Benzyl-3-(tert-butyldiphenylsilyloxymethyl)-4-(iso-propyl)-9-methyltetrahydro-2H-6,9-methanopyrazino[1,2-d][1,4]oxazepine-1,7(9H)-dione, **12a**

From **7d** (11 mg, 0.02 mmol) in methanol and a 50% toluene solution of EtOOCCHO (20 μL, 0.1 mmol, previously depolymerized by heating at 60 °C, 1 min) following the general procedure (3 days), **12a** (3 mg, 0.005 mmol, 25%) was obtained after chromatography (10–20% EtOAc–hexane) as a colorless oil along with 40% of **7c**. Data for **12a**: R_f 0.40 (80% Et_2O–hexane). $[\alpha]_D^{20}$ +34.3 (*c* 0.35). ^{1}H NMR ($CDCl_3$, 500 MHz), COSY δ 0.41 (d, 3H, *J*=6.8 Hz), 0.85 (d, 3H, *J*=6.8 Hz), 1.02 (s, 9H), 1.40 (m, 1H, H-10_{ax}), 1.41 (s, 3H), 1.51 (d, 1H, *J*=11.2 Hz, CH_{2ax} bridge), 1.82 (ddd, 1H, *J*=11.2, 4.2, 2.4 Hz, CH_{2eq} bridge), 2.07 (dq, 1H, *J*=6.8, 4.9 Hz, CH ^{i}Pr), 2.38 (ddd, 1H, *J*=13.7, 4.9, 2.4 Hz, H-10_{eq}), 2.87 (d, 1H, *J*=4.6 Hz, H-4), 3.19 (d, 1H, *J*=4.2 Hz, H-6), 3.31 (dd, 1H, *J*=7.3, 5.4 Hz, H-3), 3.68 (m, 2H, CH_2O), 3.70 (dd, 1H, *J*=11.0, 4.9 Hz, H-10a), 3.95 (d, 1H, *J*=14.2 Hz, NBn), 4.88 (d, 1H, *J*=14.2 Hz, NBn), 7.17 (m, 2H), 7.24 (m, 2H), 7.42 (m, 7H), 7.59 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz), HSQC δ 19.2, 19.8, 22.5, 25.0, 26.9 (3C), 27.9, 39.0, 44.2, 49.5, 52.9, 57.4, 62.8, 62.9, 63.5, 84.4, 127.9 (5C), 128.6 (2C), 129.3 (2C), 130.0 (2C), 133.0, 133.1, 135.6 (4C), 136.9, 168.5, 174.7. 2D-NOESY: CH_3 (0.41)/CH_3 (0.85), CH_3 (0.41)/CH ^{i}Pr, CH_3 (0.41)/H-3, CH_3 (0.41)/H-10a, H-10_{ax}/H-10_{eq}, H-10_{ax}/CH_2O, H-10_{ax}/CH_{2ax} bridge, H-6/H-4. IR (film): 3017, 2932, 2859, 1771, 1645, 1471, 1453, 1428, 1385, 1256, 1217, 1113, 920, 823, 755, 702, 667 cm^{-1}. MS (ES): 611 $[M+H]^+$.

3.5.8. (+)-(3S,4R,6S,9R,10aR)-2-Benzyl-9-(benzyloxy)methyl-3-(tert-butyldiphenylsilyloxymethyl)-4-(iso-propyl)tetrahydro-2H-6,9-methanopyrazino[1,2-d][1,4]oxazepine-1,7(9H)-dione, **12b**

From **7f** (12 mg, 0.018 mmol) in methanol and 50% toluene solution of EtOOCCHO (18 μL, 0.09 mmol, previously depolymerized by heating at 60 °C, 1 min) following the general procedure (3 days), **12b** (7 mg, 0.009 mmol, 50%) was obtained after chromatography (5–20% EtOAc–hexane) as a colorless oil along with recovered starting material **7f** (25%). Data for **12b**: R_f 0.24 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +30.7 (*c* 0.31). ^{1}H NMR ($CDCl_3$, 500 MHz), COSY δ 0.44 (d, 3H, *J*=6.8 Hz, CH_3), 0.87 (d, 3H, *J*=6.8 Hz, CH_3), 1.04 (s, 9H), 1.46 (dd, 1H, *J*=13.4, 10.8 Hz, H-10_{ax}), 1.49 (d, 1H, *J*=11.2 Hz, CH_{2ax} bridge), 2.08 (m, 2H, CH_{2eq} bridge, CH ^{i}Pr), 2.48 (dm, 1H, *J*=11.2 Hz, H-10_{eq}), 2.90 (d, 1H, *J*=4.6 Hz, H-4), 3.21 (d, 1H, *J*=4.2 Hz, H-6), 3.33 (dd, 1H, *J*=7.8, 4.9 Hz, H-3), 3.49 (d, 1H, *J*=10.8 Hz, CH_2OBn), 3.58 (d, 1H, *J*=11.0 Hz, CH_2OBn), 3.70–3.72 (m, 2H, CH_2O), 3.75 (dd, 1H, *J*=4.9, 11.0 Hz, H-10a), 3.97 (d, 1H, *J*=13.9 Hz, NBn), 4.58 (s, 2H, BnO), 4.90 (d, 1H, *J*=13.9 Hz, NBn), 7.18 (m, 2H), 7.27 (m, 2H), 7.38 (m, 12H), 7.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz), HMBC δ 19.1, 19.8, 22.5, 26.9 (3C), 27.9, 35.0, 39.8, 49.5, 52.7, 57.4, 62.7, 62.8, 63.0, 72.5, 73.7, 85.8, 127.7 (2C), 127.9 (6C), 128.4 (2C), 128.5 (2C), 129.3 (2C), 129.9, 130.0, 133.0, 133.1, 135.6 (4C), 136.8, 137.6, 168.4, 174.2. 2D-NOESY: H-6/H-4, H-6/CH_{2eq} bridge, H-6/CH_{2ax} bridge, H-10a/H-10, H-10a/CH ^{i}Pr, H-10a/NBn, CH_3 (0.44)/H-10a, H-10_{ax}/CH_2O, H-10_{ax}/H-10_{eq}, H-10_{eq}/CH_2OBn, H-10_{eq}/H-10a. IR (film): 2930, 2858, 1778, 1651, 1453, 1428, 1258, 1112, 924, 823, 752, 702 cm^{-1}. MS (ES): 717 $[M+H]^+$.

3.6. (+)-(3*S*,4*R*,6*R*,8*R*,9a*R*)-2-Benzyl-8-[(benzyloxy)methyl]-3-(*tert*-butyldiphenylsilyloxymethyl)-8-hydroxy-6-(hydroxymethyl)-4-*iso*-propylhexahydro-2*H*-pyrido[1,2-*a*]pyrazin-1(6*H*)-one, 13

To a suspension of $LiEt_3BH$ (1 M solution in THF, 34 μL, 0.034 mmol) in THF (10 mL/mmol), a solution of **12b** (6 mg, 0.008 mmol) in THF (10 mL/mmol) was added at −78 °C. The mixture was stirred (1 h) monitored by TLC and then a saturated solution of $NaHCO_3$ (25 mL/mmol) was added and was warmed at room temperature. The mixture was acidified with 1 N HCl to pH=4 and the layers were separated. The aqueous layer was washed with Et_2O (3×25 mL/mmol), basified with 1 M solution of NaOH (pH≈9), and then was extracted with CH_2Cl_2 (3×25 mL/mmol). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude product that was purified by column chromatography (50–90% EtOAc–CH_2Cl_2). Compound **13** (3 mg, 0.004 mmol, 33%) was obtained as a colorless oil along with recovered starting material **12b** (45%). Data for **13**: R_f 0.20 (20% MeOH–CH_2Cl_2). $[\alpha]_D^{20}$ +21.0 (*c* 0.31). ^{1}H NMR ($CDCl_3$, 500 MHz), COSY δ 0.58 (d, 3H, *J*=6.8 Hz, CH_3), 0.80 (d, 3H, *J*=6.8 Hz, CH_3), 1.00 (s, 9H), 1.17 (dd, 1H, *J*=13.4, 10.8 Hz, H-9_{ax}), 1.42 (dd, 1H, *J*=7.1, 13.9 Hz, H-7_{ax}), 1.64 (d, 1H, *J*=13.9 Hz, H-7_{eq}), 2.09 (m, 1H, CH ^{i}Pr), 2.20 (dt, 1H, *J*=2.7, 13.2 Hz, H-9_{eq}), 2.80 (m, 1H, H-6), 2.86 (d, 1H, *J*=3.7 Hz, H-4), 3.19 (dd, 2H, *J*=9.0, 15.7 Hz, CH_2OBn), 3.33 (dd, 1H, *J*=2.9, 9.1 Hz, H-3), 3.51 (dd, 1H, *J*=3.9, 9.5 Hz, CH_2O), 3.62 (m, 2H, CH_2O, CH_2OH), 3.84 (m, 1H, CH_2OH), 4.21 (d, 1H, *J*=11.7, 3.2 Hz, H-9a), 4.22 (d, 1H, *J*=14.2 Hz, NBn), 4.51 (dd, 2H, *J*=16.6, 12.0 Hz, BnO), 4.62 (d, 1H, *J*=14.2 Hz, NBn), 7.17 (m, 2H), 7.23 (m, 3H), 7.28 (m, 3H), 7.37 (m, 8H), 7.55 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz), HSQC δ 18.9, 19.1, 21.6, 26.8 (3C), 31.1, 35.4, 39.3, 49.9, 52.1, 57.4, 58.1, 61.0, 63.1, 65.5, 69.9, 73.5, 78.0, 127.6 (2C), 127.8 (6C), 128.4 (4C), 129.3 (2C), 129.9 (2C), 133.1 (2C), 135.5 (4C), 137.1, 137.7, 171.7. 2D-NOESY: CH_3 (0.58)/H-9a, H-9a/H-9_{eq}, H-9a/H-9_{ax}, H-9a/CH_2OH, CH_2OBn/BnO, H-6/H-7_{ax}, H-6/H-4, H-6/CH_2OH, CH_3 (0.80)/CH_2OH. IR (film): 3359, 2930, 2858, 1778, 1651, 1453, 1428, 1258, 1112, 924, 823, 752, 702 cm^{-1}. MS (ES): 721 $[M+H]^+$.

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