Synthesis of 1,4-Oxazepin-7-ones Using Baylis–Hillman Products as Key Intermediates

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Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday.

Abstract: Baylis–Hilman adducts derived from aromatic aldehydes and methyl acrylate can be readily converted to 1,4-oxazepin-7-ones substituted in 2-, 3-, or 4-position by condensation with amino alcohols.

Key words: Baylis–Hillman reaction, 1,4-oxazepin-7-ones, amino alcohols, aromatic aldehydes, lactonization, hydrogenation

Azepines play an important role in the chemistry of biologically active substances. At present there exist a large number of drugs that are currently in medicinal use, either containing a benzo-1,4-diazepine[1] or a benzo-1,4-oxazepine ring.[2] The synthesis of alkaloids such as calvine (**1a**) and 2-epicalvine (**1b**) containing a 1,7-tetramethylene-1,4-oxazepine-5-one was recently reported.[3] Moreover, 1,4-oxazepine-5,7-diones such as **2** have been efficiently used, most notably by Tietze et al.,[4b–d] as chiral templates for stereoselective synthesis[4] (Figure 1).

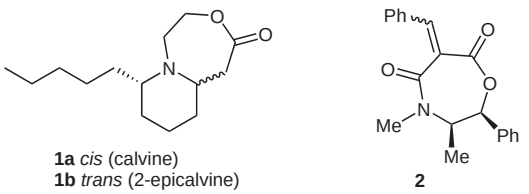
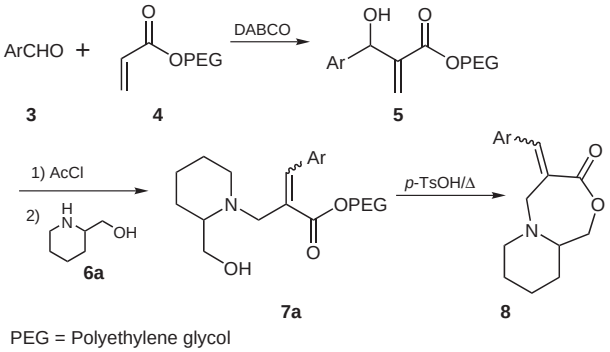


Figure 1 The structures of calvine (**1a**), epicalvine (**1b**) and a 1,4-oxazepine **2**

We recently explored the polymer-supported synthesis of 1,4-oxazepin-7-ones[5] **8** by condensation of Baylis–Hillman adducts **5** with amino alcohols, e.g. **6a** (Scheme 1). The critical step of this sequence is the final ring closure of **7** which is challenging since **8** does not only contain a seven-membered ring but also two exocyclic double bonds.

Our initial strategy made use of an acid-catalyzed transesterification of **7**. Only **7a**, however, which has the cyclic amino alcohol **6a** incorporated and which is predisposed for the desired cyclization, was successfully employed for the synthesis of **8**. Other cyclic amino alcohols like prolinol gave low yields of oxazepineones **8**, while acyclic



Scheme 1

amino alcohols failed completely in the final cyclization step, limiting substantially the scope of this synthetic method.

We report here a different protocol that allows the synthesis of **8** even with acyclic amino alcohols as coupling partners. On the outset of this study, we verified that the difficulties encountered in the cyclization were not due to the fact that the substrates **7** were immobilized on a polymer. Thus, a number of methyl esters **9** (Table 1) were reacted with *p*-TsOH under refluxing conditions. Again, only adducts derived from **6a** gave satisfactory results in the synthesis of **8** (entries 1,5). However, the fact that **9ab** resulted at least in small amounts of the desired oxazepinones (entry 2) in contrast to **9ad** or even **9ae** (entries 3,4), which should have benefited from the Thorpe–Ingold effect,[6] suggested, that a tertiary amine structure might be necessary to facilitate the formation of the desired seven-membered ring products.

Rather than attempting the direct cyclization, we therefore investigated a two-step protocol involving first the saponification of the esters **9** followed by activation of the resulting carboxylic acids **10**.

Using **10aa** and **10ab** as model systems, obtained by saponification of **9aa** and **9ab**, respectively, with LiOH, cyclization to **8** initiated by carbodiimides (DIC[7] or DCC[8]), mixed anhydrides (ethyl chloroformate[9]) or 2,4,6-trichlorobenzoyl chloride[10] (TCBC) was investigated (Table 2). From this study it was concluded that DCC/DMAP was the most promising method, giving even with **10ab** at least moderate yields of the oxazepinone **8ab**.

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Table 1 Cyclization under TsOH/Δ Conditions

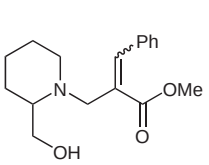
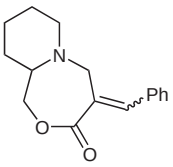
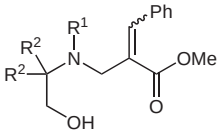
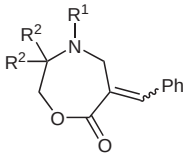
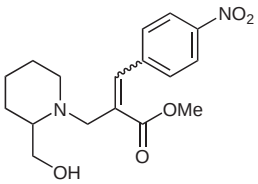
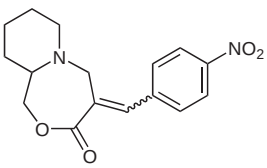
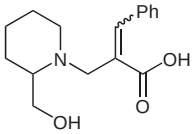
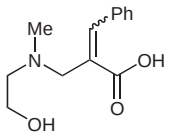
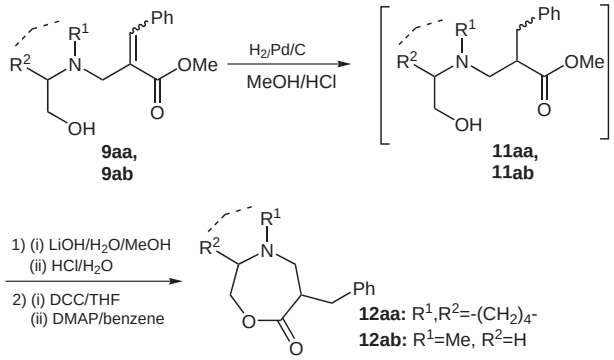
Entry	Ester **9**	1,4-oxazepinones **8**	Yield (%)
1	 **9aa**	 **8aa**	45
2	 **9ab**: R^1 = Me, R^2 = H	 **8ab**: R^1 = Me, R^2 = H	8
3	**9ad**: R^1 = H, R^2 = H	**8ad**: R^1 = H, R^2 = H	0
4	**9ae**: R^1 = H, R^2 = Me	**8ae**: R^1 = H, R^2 = Me	0
5	 **9ba**	 **8ba**	60

Table 2 Optimization of Cyclization via Saponification

Acid **10**	Activators[a] and Products **8aa**, **8ab**; Yields (%) DIC/DMAP	$ClCO_2Et/Et_3N$	DCC/DMAP	TCBC/DMAP
 **10aa**	21	49	75	21
 **10ab**	–	0[b]	47	23

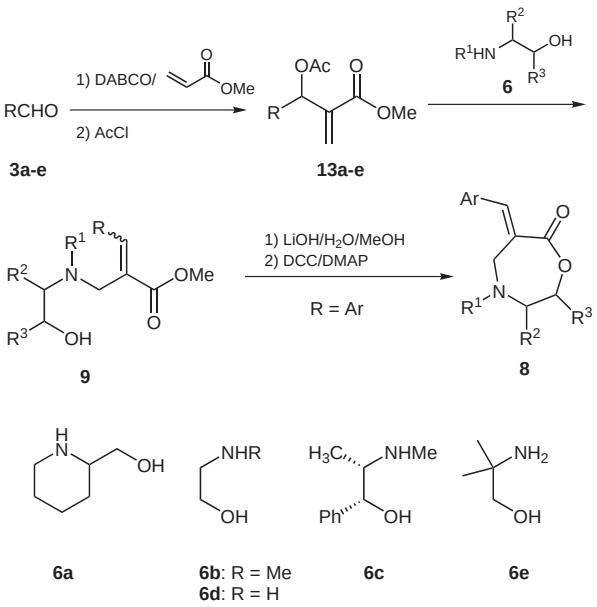
[a] TCBC: 2,4,6-Trichlorobenzoyl chloride; DIC: diisopropylcarbodiimide; DCC: dicyclohexylcarbodiimide; DMAP: 4-dimethylaminopyridine.
[b] Mixture of products.

Using this protocol, we further investigated if the cyclization can be improved by removing the olefinic double bond in **9**, since switching the sp^2 to a sp^3 center should facilitate the ring closure. Therefore, **11** was synthesized by hydrogenation of **9** under standard conditions using palladium on charcoal as catalyst. It was necessary to carry out the reaction in the presence of HCl, thus converting **9** into the corresponding tertiary ammonium salt, in order to avoid elimination of the allylic amine under the reaction conditions. Without further purification, **11** was directly converted into **12** by saponification and DCC activation as described above. Both, **12aa** and **12ab** were obtained in moderate yields (48 and 52%) giving access to fully saturated oxazepinones (Scheme 2). However, there seemed to be no advantage in the cyclization of **11** compared to the unsaturated substrates **10**.



Scheme 2

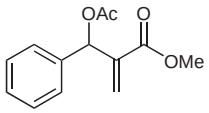
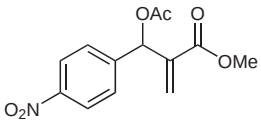
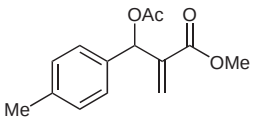
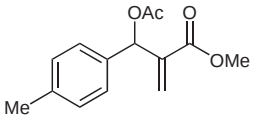
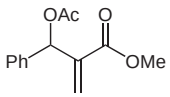
With the improved cyclization procedure in hand, we were able to efficiently synthesize oxazepinones **8** in a three-step sequence (Scheme 3, Table 3). The acylated adducts **13** can be obtained with excellent purity in a one-pot procedure via the Baylis–Hillman reaction[11] between aldehydes **3** and methyl acrylate, followed by direct acetylation of the resulting allylic alcohols with acetyl chloride.



Scheme 3

Nucleophilic substitution[12] with amino alcohols **6** proceeded exclusively in an S_N2' fashion to afford **9**. For substrates **13a–d** derived from aromatic aldehydes, **9** was formed in high (*E*)-selectivity, while the aliphatic **9e** was obtained as an equimolar mixture of *E*/*Z*-isomers.

Table 3 Synthesis of **8** via Optimized Conditions

Entry	Aldehyde, R		**13**	Yield **13** (%)	β-Amino Alcohol **6**	**9**	Yield **9** (%)	*E*/*Z* Ratio (%)	**8**	Yield **8** (%)
1	Ph	**3a**		**13a**	**6a**	**9aa**	94	-	**8aa**	75
2				80	**6b**	**9ab**	81	94:6	**8ab**	47
3					**6c**	**9ac**	94	88:12	**8ac**	35
4					**6d**	**9ad**	62	92:8	-	-
5	4-$NO_2C_6H_4$	**3b**		**13b**	**6a**	**9ba**	75	88:12	**8ba**	60
6				70	**6b**	**9bb**	93	90:10	-	-
7	4-MeC_6H_4	**3c**		**13c**	**6a**	**9ca**	90	90.10	**8ca**	75
8				80	**6b**	**9cb**	97	100:0	**8cb**	56
9					**6e**	**9ce**	90	92:8	-	-
10	3-$MeOC_6H_4$	**3d**		**13d**	**6a**	**9da**	86	86:14	**8da**	60
11				78	**6b**	**9db**	91	92:8	**8db**	50
12					**6c**	**9dc**	94	91:9	**8dc**	61
13	Et	**3e**		**13e**	**6a**	**9ea**	71	60:40	-	-
14				73	**6c**	**9ec**	89	50:50		-

Saponification and cyclization initiated by DCC/DMAP as described above resulted in the target compounds **8**. While the adducts **9a**–**d** derived from aromatic aldehydes successfully underwent the final cyclization step, the aliphatic derivative **9e** failed to yield the desired oxazepinone. Although prior to the cyclization small amounts of *Z*-isomers were detected (cf. Table 3), all oxazepinones **8** were obtained as pure *E*-isomers. We can not unambiguously rule out that the minor *Z*-isomer was lost during workup, but since it could not be detected in a single case we assume that isomerization to the more stable *E*-isomer had taken place.

NMR and mass spectral data of compounds **9** are listed in Table 4 and the analytical and spectroscopical data for compounds **8** and **12** are listed in Table 5.

In conclusion, we have developed an efficient three-step protocol for the synthesis of 1,4-oxazepin-7-ones from aromatic aldehydes, methyl acrylate and N-alkylated amino alcohols. It is noteworthy that only the final products of this sequence required chromatographic workup, for all other steps simple filtration/extraction procedures were sufficient.

Table 4 NMR and Mass Spectral Data of **9**

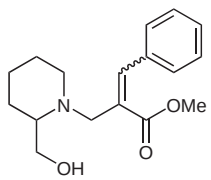
Product		^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS, *m*/*z*
9ab		*E*-isomer: 2.15 (s, 3 H), 2.52–2.57 (m, 2 H), 2.82 (br s, 1 H, 3.48 (s, 2 H), 3.58–3.62 (m, 2 H), 3.84 (s, 3 H), 7.27–7.44 (m, 5 H) *Z*-isomer: 2.31 (s, 3 H), 2.52–2.57 (m, 2 H), 2.82 (br s, 1 H), 3.38 (s, 2 H), 3.58–3.62 (m, 2 H), 3.68 (s, 3 H), 6.73 (s, 1 H), 7.27–7.44 (m, 5 H), 7.83 (s, 1 H)	*E*-isomer: 41.7 (+, CH_3), 52.1 (–, CH_2), 52.1 (+, CH_3), 58.6 (–, CH_2), 58.7 (–, CH_2), 128.4 (+, 2 CH), 128.7 (+, CH), 129.5 (+, 2 CH), 130.6 (C_{quat},), 135.1 (C_{quat}), 142.2 (+, CH), 168.9 (C_{quat}) *Z*-isomer: 41.8 (+, CH_3), 51.8 (–, CH_2), 58.5 (+,CH_3), 58.6 (–, CH_2), 62.1 (–, CH_2), 128.3, 128.4 (+, 2 CH), 130.3 (C_{quat}), 132.4 (C_{quat}), 134.6 (+, CH), 168.9 (C_{quat})	250.1 [MH^+], 218.1, 194.1

Table 4 NMR and Mass Spectral Data of **9** (continued)

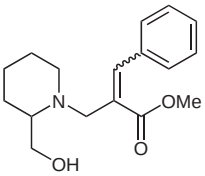
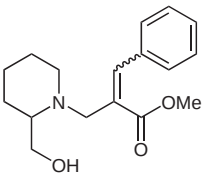
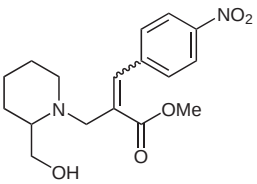
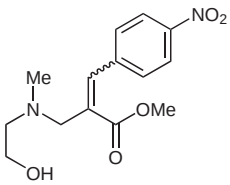
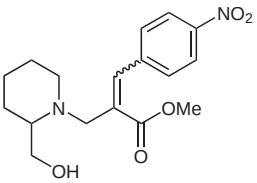
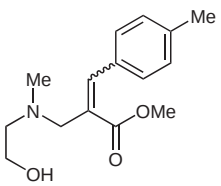
Product		^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS, *m*/*z*
9ac		*E*-isomer: 0.87 (d, 3 H *J* = 6.8), 2.02 (s, 3 H), 2.73–2.89 (m, 1 H), 3.48–3.60 (m, 2 H), 3.83 (s, 3 H), 4.83–4.87 (m, 1 H), 7.13–7.36 (m, 10 H), 7.80 (s, 1 H) *Z*-isomer: 70.93 (d, 3 H, *J* = 6.9), 2.26 (s, 3 H), 2.73–2.89 (m, 1 H), 3.48–3.60 (m, 2 H), 3.65 (s, 3 H), 4.83–4.87 (m, 1 H), 6.66 (s, 1 H), 7.13–7.36 (m, 10 H)	*E*-isomer: 9.4 (+, CH_3), 38.3 (+, CH_3), 50.4 (–, CH_2), 52.2 (+, CH_3), 63.8 (+, CH), 74.2 (+, CH), 126.2, 127.9, (+, 2 × 2 CH), 128.4, 129.6 (+, 2 × 2 CH), 126.8, 128.6 (+, 2 × 1 CH), 131.4 (C_{quat}), 135.2 (C_{quat}), 142.0 (+, CH), 142.6 (C_{quat}), 169.1 (C_{quat}) *Z*-isomer: 9.6 (+, CH_3), 38.6 (+, CH_3), 51.8 (+, CH_3), 60.4 (–, CH_2), 64.0 (+, CH), 73.2 (+, CH), 126.2, 128.0, 128.3, 128.3 (+, 4 × 2 CH), 126.9, 128.2 (+, 2 × 1 CH), 133.1 (C_{quat}), 134.1 (+, CH), 135.5 (C_{quat}), 169.9 (C_{quat})	340.4 [MH^+], 308.2 232.2, 194.1, 166.1
9ad		*E*-isomer: 2.70–2.74 (m, 2 H), 2.83 (br s, 2 H), 3.55–3.61 (m, 4 H), 3.80 (s, 3 H), 7.23–7.43 (m, 5 H), 7.80 (s, 1 H) *Z*-isomer: 2.70–2.74 (m, 2 H), 2.83 (br s, 2 H), 3.55–3.61 (m, 4 H), 3.71 (s, 3 H), 6.79 (s, 1 H), 7.23–7.43 (m, 5 H, C_6H_5)	*E*-isomer: 45.2 (–, CH_2), 50.6 (–, CH_2), 52.2 (+, CH_3), 60.7 (–, CH_2), 128.6, 129.37 (+, 2 CH), 129.0 (+, CH), 130.4 (C_{quat}), 135.0 (C_{quat}), 142.1 (+, CH), 168.5 (C_{quat}), 169.5 (C_{quat}) *Z*-isomer: 50.1 (–, CH_2), 51.7 (–, CH_2), 53.3 (+, CH_3), 60.8 (–, CH_2), 128.2, 128.7 (+, 2 CH), 128.4 (+, CH), 132.2 (C_{quat}), 135.3 (+, CH), 135.5 (C_{quat})	236.2 [MH^+], 204.1 [M^+ – OMe], 194.1
9ba		*E*-isomer: 1.17–1.70 (m, 6 H), 1.79–1.89 (m, 1 H), 2.18–2.26 (m, 1 H), 2.35–2.38 (m, 1 H), 2.73–2.81 (m, 1 H), 3.15 (d, 1 H, *J* = 13.0), 3.40 (dd, 1 H, *J* = 3.5, 11.8), 3.68–3.74, 3.87–4.06 (2 m, 1 H + 1 H), 3.85 (s, 3 H), 7.49–7.54 (m, 2 H), 7.76 (s, 1 H), 8.22–8.27 (m, 2 H) *Z*-isomer: 1.17–1.70 (m, 6 H), 1.97–2.04 (m, 1 H), 2.83–2.95 (m, 1 H), 3.03 (d, 1 H, *J* = 13.3), 3.50 (dd, 1 H, *J* = 3.9, 13.5), 3.67 (s, 3 H), 3.68–3.74, 3.87–4.06 (2 m, 1 H + 1 H), 6.80 (s, 1 H), 7.37–7.40 (m, 2 H), 8.14–8.21 (m, 2 H)	*E*-isomer: 23.6, 24.3, 27.4 (–, 3CH_2), 48.1 (–, CH_2), 51.2 (–, CH_2,), 52.6 (+, CH_3), 62.2 (+, CH), 62.6 (–, CH_2), 123.7 (+, 2 CH), 130.1 (+, 2 CH), 134.6 (C_{quat}), 138.5 (+, CH), 141.9, 147.5, 168.3 (C_{quat}) *Z*-isomer: 23.6, 24.3 (–, 2 CH_2), 51.6 (–, CH_2), 52.1 (+, CH_3), 57.5 (–, CH_2), 61.5 (+, CH), 123.5 (+, 2 CH), 129.0 (+, 2 CH), 131.8 (+, CH), 137.1, 142.2, 147.2, 169.0 (C_{quat})	335.3 [MH^+], 305.3, 303.3 [M^+ – OMe], 273.2, 116.1
9bd		*E*-isomer: 2.11 (s, 3 H), 2.49–2.53 (m, 2 H), 2.61 (br m, 1 H), 3.40 (s, 2 H), 3.56–3.60 (m, 2 H), 3.82 (s, 3 H), 7.56–7.60, 8.19–8.24 (2 m, 2 H + 2 H), 7.78 (s, 1 H) *Z*-isomer: 2.29 (s, 3 H), 2.49–2.53 (m, 2 H), 2.61 (br m, 1 H), 3.56–3.60 (m, 2 H), 3.66 (s, 3 H), 6.78 (s, 1 H), 7.37–7.42, 8.11–8.17 (2 m, 2 H 2 H)	*E*-isomer: 41.7 (+, CH_3), 52.3 (–, CH_2), 52.5 (+,CH_3), 58.7 (–, CH_2), 58.9 (–, CH_2), 123.7, 130.4 (+, 2 CH + 2 CH), 134.0 (C_{quat}), 139.4 (+, CH), 141.7, 147.6, 168.1 (C_{quat}) *Z*-isomer: 42.0 (+, CH_3), 52.1 (+, CH_3), 60.4 (–, CH_2), 61.8 (–, CH_2), 123.5, 129.0 (+, 2 CH + 2 CH), 132.2 (+, CH), 136.3 (C_{quat})	294.2 [M^+], 263.2 [M^+ – OMe], 174.2, 149.2, 115.2
9ca		*E*-isomer: 1.17–1.73 (m, 6 H), 1.84–1.94 (m, 1 H), 2.21–2.29 (m, 1 H), 2.37 (s, 3 H), 2.79–2.87 (m, 1 H), 3.28 (d, 1 H, *J* = 12.9), 3.40 (dd, 1 H, *J* = 3.5, 11.7), 3.83 (s, 3 H), 3.84–4.10 (m, 1 H + 1 H), 7.09–7.29 (m, 4 H), 7.77 (s, 1 H) *Z*-isomer: 1.17–1.73 (m, 6 H), 1.84–1.94 (m, 1 H), 2.21–2.29 (m, 1 H), 2.33 (s, 3 H), 2.96 (d, 1 H, *J* = 13.9), 3.04–3.11 (m, 1 H), 3.40 (dd, 1 H, *J* = 3.5, 11.7), 3.68 (s, 3 H), 3.84–4.10 (m, 1 H + 1 H), 6.70 (s, 1 H), 7.09–7.29 (m, 4 H)	*E*-isomer: 21.3 (+, CH_3), 23.8, 24.2, 27.4 (–, 3 CH_2), 47.7 (–, CH_2), 51.0 (–, CH_2), 52.2 (+, CH_3), 62.0 (+, CH), 62.6 (–, CH), 129.2 (+, 2 CH), 129.4 (+, 2 CH), 130.5, 132.3, 138.7 (C_{quat}), 141.9 (+, CH), 169.2 (C_{quat}) *Z*-isomer: 14.2 (+, CH_3), 21.3, 23.7, 24.3 (–, 3 CH_2), 51.3 (–, CH_2), 51.7 (+, CH_3), 57.8 (–, CH_2), 61.4 (+, CH), 62.5 (–, CH_2), 128.3 (+, 2 CH), 129.0 (+, 2 CH), 132.0, 132.5, 138.2 (C_{quat}), 134.4 (+, CH), 170.3 (C_{quat})	304.2 [MH^+], 272.1, [M^+ – OMe], 208.1, 116.0
9cb		*E*-isomer: 2.13 (s, 3 H), 2.33 (s, 3 H), 2.49–2.53 (m, CH_2), 2.96 (br s, 1 H), 3.46 (s, 2 H), 3.56–3.60 (m, 2 H), 3.79 (s, 3 H), 7.15–7.18, 7.31–7.35 (2 m, 2 H + 2 H), 7.77 (s, 1 H)	*E*-isomer: 21.3 (+, CH_3), 41.6 (+, CH_3), 52.1 (+, CH_3), 52.2 (–, CH_2), 58.7 (–, CH_2), 58.7 (–, CH_2), 129.2 (+, 2 CH), 129.6 (C_{quat}), 129.8 (+, 2 CH), 132.2, 139.0 (C_{quat}), 142.5 (+, CH), 169.0 (C_{quat})	264.2 [MH^+], 232.1 [M^+ – OMe], 208.2

Table 4 NMR and Mass Spectral Data of **9** (continued)

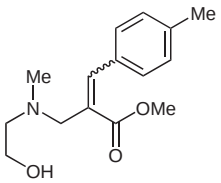
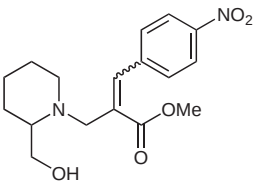
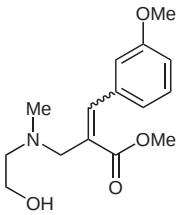
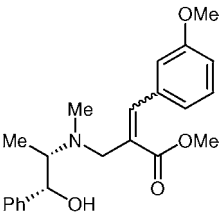
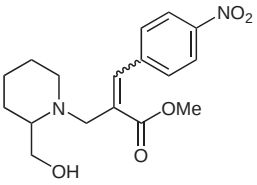
Product	^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS, *m*/*z*
9ce 	*E*-isomer: 1.10 (s, 6 H), 1.68 (br s, 1 H), 2.37 (s, 3 H), 3.39 (s, 2 H), 3.49 (s, 2 H), 3.83 (s, 3 H), 7.12–7.27 (m, 2 H), 7.44–7.54 (m, 2 H), 7.77 (s, 1 H) *Z*-isomer: 0.99 (s, 6 H), 1.68 (br s, 1 H), 2.33 (s, 3 H), 3.33 (s, 2 H), 3.48 (s, 2 H), 3.68 (s, 3 H), 6.80 (s, 1 H), 7.12–7.27 (m, 2 H), 7.44–7.54 (m, 2 H)	*E*-isomer: 21.4 (+, CH_3), 24.1 (+, 2 CH_3), 39.0 (–, CH_2), 52.1 (+, CH_3), 54.2 (C_{quat}), 68.0 (–, CH_2), 129.3, 129.5 (+, 2 CH + 2 CH), 129.7, 132.2, 139.4 (C_{quat}), 142.2 (+, CH), 169.0 (C_{quat}) *Z*-isomer: 20.2 (+, CH_3), 24.3 (+, 2 CH_3), 51.7 (+, CH_3), 53.9 (C_{quat}), 60.4 (–, CH_2), 68.2 (–, CH_2), 128.4, 128.9 (+, 2 CH + 2 CH), 130.9, 132.5 (C_{quat}), 134.8 (+, CH), 141.6 (C_{quat})	278.2 [MH^+], 246.2 [M^+ – OMe]
9da 	*E*-isomer: 1.21–1.71 (m, 6 H), 1.85–1.95 (m, 1 H), 2.23–2.27 (m, 1 H), 2.34–2.36 (m, 1 H), 2.80–2.88 (m, 1 H), 3.25 (d, 1 H, *J* = 12.9), 3.40 (dd, 1 H, *J* = 3.5, 11.8), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.87–4.16 (m, 1 H + 1 H), 6.84–6.94 (m, 3 H), 7.22–7.34 (m, 1 H), 7.76 (s, 1 H) *Z*-isomer: 1.21–1.71 (m, 6 H), 1.85–1.95 (m, 1 H), 2.98 (d, 1 H, *J* = 14.3), 3.04–3.15 (m, 1 H), 3.40 (dd, 1 H, *J* = 3.5, 11.8), 3.68 (s, 3 H), 3.79 (s, 3 H), 3.87–4.16 (m, 1 H + 1 H), 6.81 (s, 1 H), 6.84–6.94 (m, 3 H), 7.22–7.34 (m, 1 H)	*E*-isomer: 23.8, 24.2, 27.4 (–, 3 CH_2), 47.8 (–, CH_2), 51.1 (–, CH_2), 52.3 (+, CH_3), 55.3 (+, CH_3), 62.0 (+, CH), 62.6 (–, CH_2), 113.2, 114.8, 121.7, 129.5 (+, CH), 131.6, 136.6, 159.5 (C_{quat}), 141.6 (+, CH), 169.0 (C_{quat}) *Z*-isomer: 21.0, 23.7, 24.3 (–, 3 CH_2), 51.4 (–, CH_2), 51.8 (+, CH_3), 55.2 (+, CH_3), 57.7 (–, CH_2), 61.4 (+, CH), 62.5 (–, CH_2), 113.5, 114.1, 120.8, 129.3 (+, CH), 133.4 (C_{quat}), 133.9 (+, CH), 136.7, 170.2 (C_{quat})	320.3 [MH^+], 288.2, [M^+ – OMe], 116.1
9db 	*E*-isomer: 2.14 (s, 3 H), 2.50–2.54 (m, 2 H), 2.83 (br s, 1 H), 3.45 (s, 2 H), 3.56–3.60 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 6.85–6.89, 6.96–6.99, 7.25–7.31 (3 m, 4 H), 7.77 (s, 1 H) *Z*-isomer: 2.01 (s, 3 H), 2.83 (br s, 1 H) 3.56–3.60 (m, 2 H), 3.68 (s, 3 H), 3.81 (s, 3 H) 6.85–6.89, 6.96–6.99, 7.25–7.31 (3 m, 4 H)	*E*-isomer: 41.8 (+, CH_3), 52.2 (+, CH_3), 52.2 (–, CH_2), 55.3 (+, CH_3), 58.7 (–, CH_2), 58.7 (–, CH_2), 114.3, 115.1, 122.1, 129.5 (+, CH), 130.8, 136.5, 159.6 (C_{quat}), 142.2 (+, CH), 168.9 (C_{quat}) *Z*-isomer: 125.0, 126.3, 128.7 (+, CH), 129.0, 135.2, 172.5 (C_{quat})	280.2 [MH^+], 248.2, [M^+ – OMe], 224.2
9dc 	*E*-isomer: 0.88 (d, 3 H, *J* = 6.8), 2.07 (s, 3 H), 2.75–2.90 (m, 1 H), 3.48–3.70 (m, 2 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 4.84–4.88 (m, 1 H), 6.81–6.95, 7.15–7.38 (2 m, 9 H), 7.78 (s, 1 H) *Z*-isomer: 0.95 (d, 3 H, *J* = 6.8), 2.27 (s, 3 H), 2.75–2.90 (m, 1 H), 3.48–3.70 (m, 2 H), 4.84–4.88 (m, 1 H), 6.63 (s, 1 H), 6.81–6.95, 7.15–7.38 (2 m, 9 H)	*E*-isomer: 9.4 (+, CH_3), 38.4 (+, CH_3), 50.5 (–, CH_2,), 52.2 (+, CH_3), 55.3 (+, CH_3), 63.6 (+, CH), 74.3 (+, CH), 126.2, 127.9 (+, 2 × 2 CH), 114.2, 115.0, 122.0, 126.7, 129.4, (+, 5 × 1 CH), 131.6, 136.5 (C_{quat}), 141.8 (+, CH), 142.5, 142.5, 170.0 (C_{quat}) *Z*-isomer: 9.6 (+, CH_3), 38.7 (+, CH_3), 51.8 (+, CH_3), 55.2 (+, CH_3), 59.7 (–, CH_2), 64.0 (+, CH), 74.2 (+, CH), 113.6, 114.0, 120.8, 126.9, 128.0, 129.3 (+, CH), 133.5 (C_{quat}), 133.6 (+, CH), 136.8, 169.1 (C_{quat})	370.2 [MH^+], 338.2 [M^+ – OMe], 262.2, 224.1, 166.1
9ea 	*E*-isomer: 0.95–1.04 (m, 3 H), 1.15–1.48 (m, 6 H), 1.89–2.01 (m, 1 H), 2.16–2.28, 2.33–2.41 (2 m, 2 H + 1 H), 2.83 (d, 1 H, *J* = 12.71), 3.33 (dd, 1 H, *J* = 2.8, 11.9), 3.65–3.69, 3.80–3.89, 3.94–4.00 (3 m, 1 H + 1 H), 3.70 (s, 3 H), 6.84 (t, 1 H, *J* = 7.6) *Z*-isomer: 0.95–1.04 (m, 3 H), 1.15–1.48 (m, 6 H), 1.89–2.01 (m, 1 H), 2.16–2.28, 2.33–2.41 (2 m, 2 H + 1 H), 2.62 (d, 1 H, *J* = 13.1), 3.33 (dd, 1 H, *J* = 2.8, 11.9), 3.65–3.69, 3.80–3.89, 3.94–4.00 (3 m, 1 H + 1 H), 3.71 (s, 3 H), 5.91 (t, 1 H, *J* = 7.4)	*E*-isomer: 13.2 (+, CH_3), 22.0 (–, CH_2), 24.1, 24.5, 27.8 (–, 3 CH_2), 47.3 (–, CH_2), 51.1 (–, CH_2), 51.9 (+, CH_3), 62.2 (+, CH), 62.8 (–, CH_2), 128.7 (C_{quat}), 147.3 (+, CH), 168.4 (C_{quat}) *Z*-isomer: 13.8 (+, CH_3), 23.0 (–, CH_2), 23.8, 24.2, 27.6 (–, 3 CH_2), 50.8 (–, CH_2), 51.4 (+, CH_3), 56.6 (–, CH_2), 61.6 (+, CH), 62.5 (–, CH_2), 129.2 (C_{quat}), 145.7 (+, CH), 168.4 (C_{quat})	241.4 [M^+] 210.2 [M^+ – OMe], 196.4, 97.3, 84.3

Table 4 NMR and Mass Spectral Data of **9** (continued)

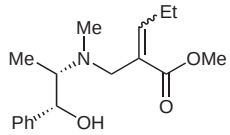
Product	^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS, *m*/*z*
9ec 	*E* + *Z*-isomers: 0.88 (d, 3 H, *J* = 5.1), 0.89 (d, 3 H, *J* = 5.1), 1.02–1.07 (m, 3 H + 3 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.22–2.29 (m, 2 H), 2.39–2.47 (m, 2 H), 2.77–2.83 (m, 1 H + 1 H), 3.23–3.40 (m, 2 H + 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.84 (d, 1 H, *J* = 4.1), 4.92 (d, 1 H, *J* = 3.8), 5.93 (t, 1 H, *J* = 7.5), 6.89 (t, 1 H, *J* = 7.6), 7.19–7.35 (m, 5 H + 5 H)	*E* + *Z*-isomers: 9.2, 9.5 (+, CH_3), 13.2, 13.7 (+,CH_3), 21.8, 22.8 (–, CH_2), 38.2, 38.5 (+,CH_3), 49.9, 59.0 (–, CH_2), 51.3, 51.8 (+, CH_3), 63.9, 64.1 (+, CH), 73.8, 73.9 (+, CH), 126.0, 126.0 (+, 2 × 2 CH), 126.6, 126.7 (2 × 1 CH), 127.8, 127.8 (+, 2 × 2 CH), 129.1, 129.5, 142.3, 142.3 (C_{quat}), 145.3, 147.3 (+, CH), 168.2, 168.5 (C_{quat})	292.2 [M^+], 273.1, 260.1, 246.1, 184.1

Table 5 Spectroscopic Data for Compounds **8** (Pure *E*-isomers) and **12**

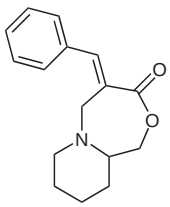
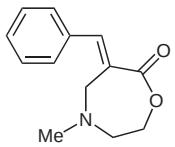
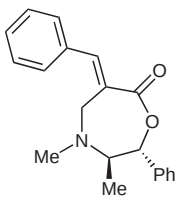
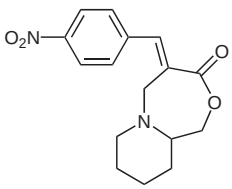
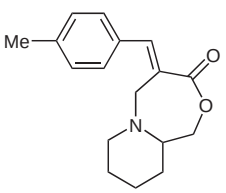
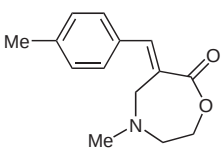
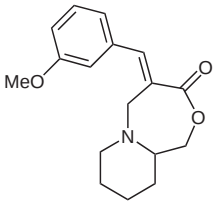
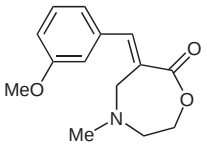
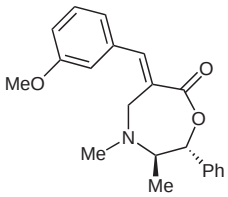
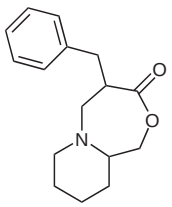
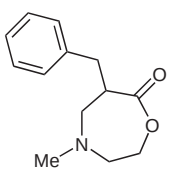
Product	R_f (Eluent)	mp (°C)	Method	^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS *m*/*z*
8aa[a] 	0.73 (hexanes–EtOAc 1:1)	-	GP3, GP4	1.25–1.90 (m, 6 H), 2.20–2.40 (m, 2 H), 2.87–2.96 (m, 1 H), 3.02–3.40 (m, 1 H), 3.52 (d, 1 H, *J* = 14.5), 3.98–4.10 (m, 1 H), 4.12–4.33 (m, 1 H), 7.23 (s, 1 H), 7.29–7.54 (m, 5 H)	24.0 (–, CH_2), 25.6 (–, CH_2), 28.9 (–, CH_2), 55.2 (–, CH_2), 55.5 (–, CH_2), 63.7 (+, CH), 71.9 (–, CH_2), 128.5, 128.77, 129.7 (+, CH), 133.6, 134.7 (C_{quat}), 137.8 (+, CH), 173.2 (C_{quat})	
8ab 	0.30 (hexanes–EtOAc 1:1)	75–77	GP3, GP4	2.43 (s, 3 H), 2.81–2.84 (m, 2 H), 3.27 (s, 2 H), 4.30–4.34 (m, 2 H), 7.25 (s, 1 H), 7.35–7.51 (m, 5 H)	45.5 (+, CH_3), 54.7 (–, CH_2), 58.0 (–, CH_2), 67.6 (–, CH_2), 128.6 (+, 2 CH), 128.9 (+, CH), 129.6 (+, 2 CH), 133.1, 134.6 (C_{quat}), 138.7 (+, CH), 173.2 (C_{quat})	218.1 [MH^+], 175.0, 131.0, 114.9, 90.9
8ac 	0.60 (hexanes–EtOAc 1:5)	114–118	GP4	0.92 (d, 3 H, *J* = 6.5), 2.49 (s, 3 H), 2.74–2.83 (m, 1 H), 3.69 (dq, 2 H, *J* = 1.4, 15.9), 5.71 (d, 1 H, *J* = 2.4), 7.23–7.26 (m, 10 H), 7.24 (s, 1 H)	9.3 (+, CH_3), 43.3 (+, CH_3), 52.5 (–, CH_2), 64.4 (+, CH), 80.1 (+, CH), 125.8, 128.4, 128.7, 129.8 (+, 2 CH), 127.7, 128.9 (+, CH), 133.8, 134.8, 137.4 (C_{quat}), 137.3 (+, CH), 171.4 (C_{quat})	308.4 [MH^+], 264.4, 166.2
8ba 	0.64 (hexanes–EtOAc 1:1)	111–115	GP3, GP4	1.12–1.89 (m, 6 H), 2.23–2.38 (m, 1 H + 1 H), 2.92 (d, 1 H, *J* = 11.1), 3.19 (br d, 1 H, *J* = 14.1), 3.38–3.48 (m, 1 H), 4.04–4.16 (m, 1 H), 4.19–4.24 (m, 1 H), 7.25 (s, 1 H), 7.66 (d, 2 H, *J* = 8.7), 8.22–8.32 (m, 2 H)	24.0, 25.7, 28.8 (–, CH_2), 55.1 (–, CH_2), 55.6 (–, CH_2), 63.7 (+, CH), 72.3 (–, CH_2), 123.8, 130.4 (+, 2 CH + 2 CH), 135.2 (+, CH), 137.6, 141.0, 147.5, 172.3 (C_{quat})	303.2 [MH^+], 273.2, 168.1, 98.0
8ca 	0.55 (hexanes–EtOAc 1:1)	118–120	GP4	1.23–1.86 (m, 6 H), 2.22–2.34 (m, 1 H + 1 H), 2.38 (s, 3 H), 2.92 (d, 1 H, *J* = 10.9), 3.19 (br d, 1 H, *J* = 13.3), 3.53 (dd, 1 H, *J* = 0.7, 14.6), 3.99–4.06 (m, 1 H), 4.20 (d, 1 H, *J* = 13.0), 7.21 (d, 2 H, *J* = 7.8), 7.26 (s, 1 H), 7.37 (d, 2 H, *J* = 8.0)	21.4 (+, CH_3), 24.2, 25.7, 29.0 (–, CH_2), 55.4 (–, CH_2), 55.6 (–, CH_2), 63.8 (+, CH), 71.8 (–, CH_2), 129.4, 129.8 (+, 2 C + 2 C), 132.0, 132.7, 139.0 (C_{quat}), 137.9 (+, CH), 173.4 (C_{quat})	272.3 [MH^+]
8cb 	0.22 (hexanes–EtOAc 1:3)	56–58	GP4	2.35 (s, 3 H), 2.40 (s, 3 H), 2.77–2.81 (m, 2 H), 3.25 (s, 2 H), 4.26–4.30 (m, 2 H), 7.17 (s, 1 H), 7.20 (d, 2 H, *J* = 2.3), 7.35 (d, 2 H, *J* = 8.1)	21.4 (+, CH_3), 45.5 (+, CH_3), 54.8 (–, CH_2), 58.0 (–, CH_2), 67.4 (–, CH_2), 129.4 (+, 2 CH), 129.7 (+, 2 CH), 131.8, 132.2 (C_{quat}), 138.7 (+, CH), 139.1, 173.4 (C_{quat})	232.2 [MH^+], 225.2

Table 5 Spectroscopic Data for Compounds **8** (Pure *E*-isomers) and **12** (continued)

Product	R_f (Eluent)	mp (°C)	Method	^{1}H NMR (250 MHz, $CDCl_3$) δ, *J* (Hz)	^{13}C NMR (62.9 MHz, $CDCl_3$) δ	MS *m/z*
8da 	0.55 (hexanes–EtOAc 1:1)	64–67	GP4	1.30–1.86 (m, 6 H), 2.20–2.36 (m, 1 H + 1 H), 2.92 (d, 1 H, *J* = 11.2), 3.11–3.19 (m, 1 H), 3.53 (dd, 1 H, *J* = 0.8, *J* = 14.3), 3.83 (s, 3 H), 3.99–4.21 (m, 2 H), 6.88–6.93, 7.03–7.06, 7.28–7.35 (3 m, 4 H), 7.20 (s, 1 H)	24.1, 25.7, 28.9 (–, CH_2), 55.2 (+, CH_3), 55.3 (–, CH_2), 55.6 (–, CH_2), 63.9 (+, CH), 72.1 (–, CH_2), 114.8 (+, 2 CH), 122.3, 129.6 (+, CH), 133.8, 136.0, 159.6 (C_{quat}), 138.0 (+, CH), 173.2 (C_{quat})	288.2 [MH^+]
8db 	0.55 (hexanes–EtOAc 1:2)	71–73	GP4	2.43 (s, 3 H), 2.81–2.85 (m, 2 H), 3.27 (s, 2 H), 3.83 (s, 3 H), 4.30–4.34 (m, 2 H), 6.89–6.93, 7.05–7.08, 7.28–7.36 (m, 4 H), 7.22 (s, 1 H)	45.6 (+, CH_3), 54.7 (–, CH_2), 55.3 (+, CH_3), 58.0 (–, CH_2), 67.6 (–, CH_2), 114.7, 114.9, 122.1, 129.6 (+, CH), 133.3, 135.9, 159.7 (C_{quat}), 138.7 (+, CH), 173.2 (C_{quat})	248.1 [MH^+], 225.1
8dc 	0.52 (hexanes–EtOAc 3:2)	-	GP4	0.92 (d, 3 H, *J* = 6.5), 2.49 (s, 3 H), 2.75–2.82 (m, 1 H), 3.54–3.81 (m, 2 H), 3.84 (s, 3 H), 5.71 (d, 1 H, *J* = 2.3), 6.89–7.20 (m, 4 H), 7.26 (s, 1 H), 7.27–7.44 (m, 5 H)	9.2 (+, CH_3), 43.3 (+, CH_3), 52.4 (–, CH_2), 55.4 (+,CH_3), 64.4 (+, CH), 80.1 (+, CH), 114.3, 115.4, 122.2, 127.7, 129.7 (+, CH), 125.8, 128.4 (+, 2 CH), 134.1, 136.1, 137.4, 159.7 (C_{quat}), 137.2 (+, CH), 171.4 (C_{quat})	338.3 [MH^+], 294.2
12aa 	0.40 (hexanes–EtOAc 1:10)	96–98	GP5	Diastereomeric mixture (1:1.5): 1.10–1.78 (m, 12 H, piperidine-CH_2, both isomers), 2.04 (dt, 1 H, *J* = 3.3, 11.6, NC$H_2$$CH_2$, major isomer), 2.22–2.40 (m, 4 H, NCH + NCH both isomers, NC$H_2$$CH_2$ major isomer, CHCH_2N minor isomer), 2.54–2.64 (m, 2 H, PhCH_2 major isomer, NC$H_2$$CH_2$ minor isomer), 2.70–2.79 (m, 2 H, NC$H_2$$CH_2$ major isomer, CHCH_2N major isomer), 2.88 (dd, 1H, *J* = 11.1, 15.5, PhCH_2 minor isomer), 3.21–3.32 (m, 4 H, PhCH_2 + $PhCH_2$C*H*, both isomers), 3.90 (d, 1 H, *J* = 13.2, OCH_2 major isomer), 4.02 (dd, 1 H, *J* = 3.3, 13.2 Hz, OCH_2 minor isomer), 4.25 (dd, 1 H, *J* = 8.6, 13.3 Hz, OCH_2 major isomer), 4.34 (d, 1 H, *J* = 16.1, CH_2 minor isomer), 7.18–7.33 (m, 5 H, C_6H_5, both isomers)	Major diastereomer: 23.80, 25.33, 28.81 (–, piperidine-C), 36.25 (–, *C*H_2Ph), 44.91 (+, $PhCH_2$*C*H), 56.06 (–, NC$H_2$$CH_2$), 58.12 (–, CHC$H_2$N), 63.34 (+, NCH), 72.73 (–, CH_2O), 126.48 (+, 1 C, CH_{arom}), 128.52, 129.40 (+, 2 C, CH_{arom}), 138.88 (C_{quat}, C_{arom}), 176.12 (C_{quat}, C=O) Minor diastereomer: 24.20, 24.20, 28.10 (–, piperidine-C), 36.70 (–, *C*H_2Ph), 46.27 (+, $PhCH_2$*C*H), 54.47 (–, NC$H_2$$CH_2$), 56.15 (–, CHC$H_2$N), 61.91 (+, NCH), 70.44 (–, CH_2O), 126.51 (+, 1C, CH_{arom}), 128.55, 129.18 (+, 2 C, CH_{arom}), 138.88 (C_{quat}, C_{arom}), 175.12 (C_{quat}, C=O)	260.2 [MH^+]
12ab 	0.30 (hexanes–EtOAc 1:10)	-	GP5	2.22 (ddd, 1 H_{ax}, *J* = 9.8, 12.5, CHCH_2N), 2.26 (s, 3 H, NCH_3), 2.50 (ddd, 1 H_{ax}, *J* = 1.4, 9.9, 14.1, NC$H_2$$CH_2$), 2.63 (dd, 1 H, *J* = 8.8, 14.2, CH_2Ph), 2.92 (br dd, 1 H_{eq}, *J* = 4.9, 14.1, NC$H_2$$CH_2$), 3.17 (dddq, 1 H_{ax}, *J* = 0.6, 1.9, 5.5, 8.8, 9.8 Hz, CH), 3.25 (dd, 1 H, *J* = 5.5, 14.2, CH_2Ph), 4.22 (ddd, 1 H_{eq}, *J* = 1.4, 4.9, 13.5, OCH_2), 4.43 (ddq, 1 H_{ax}, *J* = 0.71, 0.73, 9.9, 13.5, OCH_2), 7.18–7.34 (m, 5 H, C_6H_5)	36.0 (–, *C*H_2Ph), 45.5 (+, $PhCH_2$*C*H), 46.2 (+, NCH_3), 57.0 (–, H*C*H_2N), 58.0 (–, NC$H_2$$CH_2$), 67.6 (–, CH_2O), 126.5 (+, CH_{arom}), 128.6, 129.2 (+, 2 C, CH_{arom}), 138.8 (C_{quat}, C_{arom}), 176.0 (C_{quat}, C=O)	220.1 [MH^+]

[a] NMR data for **8aa** were taken from literature.[5]

NMR spectra were recorded on Bruker AC 250 and AC 400 spectrometers in $CDCl_3$ (internal standard: tetramethylsilane). Mass spectra were carried out on a Finnigan MAT 95 mass spectrometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Melting points were determined on a Reichert hot plate apparatus and are uncorrected. Column chromatography was performed on Merck Kieselgel 60. Solvents for chromatography were distilled prior to use. TLC was performed on Merck $60F_{254}$ plates. Visualization of TLC spots was effected using phosphomolybdic acid hydrate solution in EtOH. ^{1}H NMR: *ax* = axial proton, *eq* = equatorial proton. ^{13}C NMR: + = positive DEPT 135 signal, – = negative DEPT 135 signal, C_{quat} = quaternary carbon.

One-Pot Baylis–Hillman Reaction and Acylation; General Procedure (GP1)

A mixture of aldehyde **3** (1.0 equiv, 100 mmol), acrylic acid methyl ester (12.91 g, 1.5 equiv, 150 mmol, 13.6 mL) and DABCO (1.68 g, 0.2 equiv, 20 mmol) was stirred at r.t. for the number of days indicated below. Subsequently, pyridine (23.7 g, 3.0 equiv, 300 mmol, 24.2 mL) and CH_2Cl_2 (200 mL) were added. The solution was cooled to 0 °C and AcCl (15.7 g, 2.0 equiv, 200 mmol, 14.2 mL) was added dropwise and the stirring was continued for 4 h at 0 °C. Aq 1 N HCl (200 mL) was added slowly, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (2 × 150 mL), dried (Na_2SO_4) and concentrated in vacuo. All products obtained this way were about 95% pure as confirmed by NMR spectroscopy and were used for subsequent reactions without further purification.

2-(Acetoxyphenylmethyl)acrylic Acid Methyl Ester (13a)

Benzaldehyde (**3a**; 10.61 g, 100 mmol) was reacted according to GP1 to yield **13a (**18.7 g, 80%) as a brown-yellow viscous oil. Baylis–Hillman reaction time was 7 d. Analytical data were identical to those given in the literature.[12a]

2-(Acetoxy-4-nitrophenylmethyl)acrylic Acid Methyl Ester (13b)

4-Nitrobenzaldehyde (**3b**; 7.56 g, 50 mmol) was reacted according to GP1 to afford **13b (**9.7 g, 70%) as a yellow viscous oil. Baylis–Hillman reaction time was 3 d. An analytically pure sample **13b** was obtained by column chromatography on silica gel (hexanes–EtOAc, 1:1, R_f 0.34) and subsequent filtration through a 2 cm Celite pad.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.12 (s, 3 H, $COCH_3$), 3.70 (s, 3 H, CO_2CH_3), 5.96 (d, 1 H, *J* = 1.0 Hz, C*H*OCH_3), 6.45 (s, 1 H, C=CH_2), 6.70 (s, 1 H, C=CH_2), 7.54–7.57 (m, 2 H_{arom}), 8.17–8.20 (m, 2 H_{arom}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.0 (+, $COCH_3$), 52.2 (+, CO_2CH_3), 72.2 (+, CH), 123.7 (+, 2 CH_{arom}), 126.8 (–, CH_2), 128.5 (+, 2 CH_{arom}), 138.6 (C_{quat}), 145.2 (C_{quat}), 147.8 (C_{quat}), 164.9 (C_{quat}, $COCH_3$), 169.2 (C_{quat}, CO_2CH_3).

MS: *m*/*z* = 279.3 [M^+].

Anal. calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69; N, 5.02. Found: C, 56.11; H, 4.78; N, 5.22.

2-(Acetoxy-4-methylphenylmethyl)acrylic Acid Methyl Ester (13c)

4-Methylbenzaldehyde (**3c**; 6.01 g, 50 mmol) was reacted according to GP1 to yield **13c (**9.9 g, 80%) as a brown-yellow viscous oil. Baylis–Hillman reaction time was 30 d. Analytical data were identical to those given in the literature.[13]

2-(Acetoxy-3-methoxyphenylmethyl)acrylic Acid Methyl Ester (13d)

3-Methoxybenzaldehyde (**3d**;0 6.76 g, 50 mmol) was reacted according to GP1 to give **13d (**10.4 g, 78%) as a brown-yellow viscous oil. Baylis–Hillman reaction time was 20 d. An analytically pure sample **13d** was obtained by column chromatography on silica gel (hexanes–EtOAc 1:1, R_f 0.38) and subsequent filtration through a 2 cm Celite pad.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, $COCH_3$), 3.71 (s, 3 H CO_2CH_3), 3.78 (s, 3 H, ArOC*H*$_3$), 5.85 (dd, 1 H, *J* = 0.92, 1.46 Hz, C*H*OCH_3), 6.40 (dd, 1 H, *J* = 0.87, 0.92 Hz, C=CH_2), 6.66 (dd, 1 H, *J* = 1.46, 0.86 Hz, C=CH_2), 6.81–6.98 (m, 3 H_{arom}), 7.22–7.28 (m, 1 H_{arom}).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.1 (+, $COCH_3$), 52.2 (+, CO_2CH_3), 55.2 (+, ArO*C*H_3), 72.9 (+, CH), 113.4 (+, Ar), 113.7 (+, Ar), 119.9 (+, Ar),126.0 (–, CH_2), 129.5 (+, Ar), 139.4 (C_{quat}), 139.6 (C_{quat}), 159.7 (C_{quat}), 165.4 (C_{quat}, $COCH_3$), 169.4 (C_{quat}, CO_2CH_3).

MS: *m*/*z* = 264.3 [M^+].

Anal. calcd for $C_{14}H_{13}O_5$: C, 63.62; H, 6.10. Found: C, 63.53; H, 6.06.

2-(Acetoxyethylmethyl)acrylic Acid Methyl Ester (13e)

4-Propionaldehyde (**3e**; 2.90 g, 50 mmol) was reacted according to GP1 to yield **13e** 6.7 g (80%) as a yellow viscous oil. Baylis–Hillman reaction time was 12 d. Analytical data were identical to those given in the literature.[14]

Reaction of 13 with β-Amino Alcohols 6; General Procedure (GP2)

To a solution of **13** (1.0 equiv, 4 mmol) and the corresponding β-amino alcohol **6a**–**e** (1.0 equiv, 4 mmol) in CH_2Cl_2 (30 mL) was added K_2CO_3 (2.0 equiv, 1.106 g, 8 mmol) and the resulting suspension was stirred at r.t. for 10 h. The reaction mixture was quenched by addition of H_2O (30 mL). The organic layer was washed with brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. All products **9** were about 90–95% pure as confirmed by NMR-spectroscopy and were used for subsequent reactions without further purification. Spectroscopic data are given in Table 4. Analytically pure compounds **9** were obtained by column chromatography on silica gel (hexanes–EtOAc, 1:1).

2-{[(2-Hydroxyethyl)methylamino]methyl}-3-phenylacrylic Acid Methyl Ester (9ab)

According to GP2, compound **9ab** was prepared from **13a** (2.49g, 10.6 mmol) and 2-(methylamino)ethanol (**6b**; 0.8 g, 10.6 mmol) and isolated as a light-yellow viscous oil; yield: 2.14 g (81%).

Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.46; H, 7.68; N, 5.62. Found: C, 67.25; H, 7.63; N, 5.69.

2-[(2-Hydroxy-1-methylphenylethylmethylamino)methyl]-3-phenylacrylic Acid Methyl Ester (9ac)

According to GP2, compound **9ac** was prepared from **13a** (0.47 g, 2.0 mmol) and L-(–)-ephedrine **(6c**; 0.33 g, 2 mmol) and isolated as a light-yellow viscous oil; yield: 0.64 g (94%).

Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.43; N, 4.13. Found: C, 74.04; H, 7.20; N, 4.07.

2-{[(2-Hydroxyethyl)amino]methyl}-3-phenylacrylic Acid Methyl Ester (9ad)

According to GP2, compound **9ad** was prepared from **13a** (0.50 g, 2.14 mmol) and 2-aminoethanol **6d** (0.13 g, 2.14 mmol) and isolated as a light-yellow viscous oil; yield: 0.31 g (62%).

Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.37; H, 7.28; N, 5.63.

2-[(2-Hydroxymethylpiperidin-1-ylmethyl)-3-(4-nitrophenyl)acrylic Acid Methyl Ester (9ba)
According to GP2, compound **9ba** was prepared from **13b** (0.43 g, 1.54 mmol) and 2-piperidinemethanol (**6a**; 0.18 g, 1.54 mmol) and isolated as a yellow viscous oil; yield: 0.38 g (75%).

HRMS: *m*/*z* calcd for $C_{17}H_{22}N_2O_5$: 334.15287. Found 334.15263.

2-{[(2-Hydroxyethyl)methylamino]methyl}-3-(4-nitrophenyl)acrylic Acid Methyl Ester (9bb)
According to GP2, compound **9bb** was prepared from **13b** (0.56 g, 2.0 mmol) and 2-(methylamino)ethanol (**6b**; 0.15 g, 2.0 mmol) and isolated as a yellow viscous oil; yield: 0.55 g (93%).

HRMS: *m*/*z* calcd for $C_{14}H_{18}N_2O_5$: 294.12157. Found: 294.12178.

2-[(2-Hydroxymethylpiperidin-1-ylmethyl)-3-(4-methylphenyl)acrylic Acid Methyl Ester (9ca)
According to GP2, compound **9ca** was prepared from **13c** (0.70 g, 2.82 mmol) and 2-piperidinemethanol (**6a**; 0.33 g, 2.82 mmol) and isolated as a light-yellow viscous oil; yield: 0.77 g (90%).

Anal. calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 70.96; H, 8.31; N, 4.53.

2-{[(2-Hydroxyethyl)methylamino]methyl}-3-(4-methylphenyl)acrylic Acid Methyl Ester (9cb)
According to GP2, compound **9cb** was prepared from **13c** (0.90 g, 3.63 mmol) and 2-(methylamino)ethanol (**6b**; 0.27 g, 3.63 mmol) and isolated as a light-yellow viscous oil; yield: 0.93 g (97%).

Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.07; H, 8.26; N, 5.64.

2-{[(2-Hydroxy-1,1-dimethylethyl)methylamino]methyl}-3-(4-methylphenyl)acrylic Acid Methyl Ester (9ce)
According to GP2, compound **9ce** was prepared from **13c** (0.38 g, 1.52 mmol) and 2-amino-2-methylpropan-1-ol (**6e**; 0.14 g, 1.52 mmol) and isolated as a light-yellow viscous oil; yield: 0.36 g (90%).

HRMS: *m*/*z* calcd for $C_{16}H_{24}NO_3$: 278.17562. Found: 178.17500 [MH^+].

2-[(2-Hydroxymethylpiperidine-1-ylmethyl)-3-(3-methoxyphenyl)acrylic Acid Methyl Ester (9da)
According to GP2, compound **9da** was prepared from **13d** (0.99 g, 3.75 mmol) and 2-piperidinemethanol (**6a**; 0.43 g, 3.75 mmol) and isolated as a light-yellow viscous oil; yield 1.03 g (86%).

Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.68; H, 7.89; N, 4.39. Found: C, 68.14; H, 7.92; N, 4.39.

2-{[(2-Hydroxyethyl)methylamino]methyl}-3-(3-methoxyphenyl)acrylic Acid Methyl Ester (9db)
According to GP2, compound **9db** was prepared from **13d** (1.08 g, 3.90 mmol) and 2-(methylamino)ethanol (**6b**; 0.29 g, 3.90 mmol) and isolated as a light-yellow viscous oil; yield: 0.93 g (91%).

Anal. calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.02. Found: C, 64.71; H, 7.57; N, 5.10.

2-[(2-Hydroxy-1-methylphenylethylmethylamino)methyl]-3-(3-methoxyphenyl)acrylic Acid Methyl Ester (9dc)
According to GP2, compound **9dc** was prepared from **13d** (0.56 g, 2.1 mmol) and L-(–)-ephedrine (**6c**; 0.35 g, 2.1 mmol) and isolated as a light-yellow viscous oil; yield: 0.71 g (94%).

Anal. calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.26; H, 7.45; N, 3.69.

2-[(2-Hydroxymethylpiperidin-1-ylmethyl)-3-ethylacrylic Acid Methyl Ester (9ea)
According to GP2, compound **9ea** was prepared from **13e** (0.35 g, 1.87 mmol) and 2-piperidinemethanol (**6a**; 0.22 g, 1.87 mmol) and isolated as a colorless viscous oil; yield: 0.32 g (71%).

HRMS: *m*/*z* calcd for $C_{13}H_{23}NO_3$: 241.16779. Found 241.16804

2-[(2-Hydroxy-1-methylphenylethylmethylamino)methyl]-3-ethylacrylic Acid Methyl Ester (9ec)
According to GP2, compound **9ec** was prepared from **13e** (0.88 g, 4.73 mmol) and L-(–)-ephedrine (**6c**; 0.78 g, 4.73 mmol) and isolated as a colorless viscous oil; yield: 1.23 g (89%).

HRMS: *m*/*z* calcd for $C_{17}H_{25}NO_3$: 292.19127. Found 292.19088 [MH^+].

Cyclization of 9 (*p*-TsOH Protocol) (GP3); General Procedure
To a solution of **9** (1.0 equiv, 0.835 mmol) in toluene (7 mL) was added *p*-toluenesulfonic acid monohydrate (175 mg, 1.1 equiv, 0.919 mmol) and the mixture was refluxed for 24 h. The mixture was washed with sat. aq $NaHCO_3$ (2 × 10 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatorgaphy on silica gel (the type of eluent and R_f are given in Table 5) to provide the products **8**. Spectroscopic data are given in Table 5.

3,4-Tetramethylene-6-(2-phenyl-1-ylmethylidene)[1,4]oxazepin-7-one (8aa)
According to GP3, compound **8aa** was prepared from **9aa** (0.99 g, 3.45 mmol) and isolated as a colorless viscous oil; yield: 0.4 g (45%). Analytical data were identical to those given in the literature.[5]

4-Methyl-6-(2-phenyl-1-ylmethylidene)[1,4]oxazepin-7-one (8ab)
According to GP3, compound **8ab** was prepared from **9ab** (0.36 g, 1.44 mmol) and isolated as a white solid; yield 0.03 g (8%).

Anal. calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.81; H, 6.96; N, 6.44.

3,4-Tetramethylene-6-[2-(4-nitrophenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8ba)
According to GP3, compound **8ba** was prepared from **9ba** (0.39 g, 1.16 mmol) and isolated as a yellow solid; yield 0.21 g (60%).

Anal. calcd for $C_{16}H_{18}N_2O_4$: C, 63.45; H, 6.00; N, 9.27. Found: C, 63.45; H, 6.22; N, 9.07.

Cyclization of 9 via Saponifiacation (Optimized DCC/DMAP-Protocol) (GP4); General Procedure
To a solution of **9** (1.0 equiv, 0.5 mmol) in MeOH (5 mL) was added a solution of LiOH (24 mg, 2.0 equiv, 1.0 mmol) in H_2O (1 mL). The mixture was stirred at r.t. until complete disappearance of the starting material (TLC monitoring) (8–16 h). Conc. HCl was added dropwise to neutralize the excess of LiOH (pH about 4–7).The solvent was concentrated in vacuo and the residue was coevaporated with MeOH, then with benzene and dried in vacuo at 60–70 °C to yield solid **10**. Subsequently, the solid residue **10** was dissolved in THF (7 mL), DCC (103 mg, 1.0 equiv, 0.5 mmol) was added and the mixture was stirred for 12 h at r.t. During this time, in most cases a white precipitate had formed. This mixture was added via a syringe pump over a period of 20–30 min to a boiling solution of DMAP (122 mg, 2.0 equiv, 1 mmol) in benzene (5 mL) and was heated further 4 h under reflux. The solvent was concentrated in vacuo, the residue was diluted with CH_2Cl_2 (10 mL), the precipitate was filtered and washed with CH_2Cl_2. Concentration in vacuo of the combined organic layers and purification of the residue by column chromatography on silica gel (the type of eluent and R_f are given in

Table 5) provided pure 1,4-oxazepin-7-ones **8**. Spectroscopic data are given in Table 5.

3,4-Tetramethylene-6-(2-phenyl-1-ylmethylidene)[1,4]oxazepin-7-one (8aa)
According to GP4, compound **8aa** was prepared from **9aa** (1.59 g, 5.61 mmol) and isolated as a colorless viscous oil; yield: 1.08 g (75%). Analytical data were identical to those given in the literature.[5]

4-Methyl-6-(2-phenyl-1-ylmethylidene)[1,4]oxazepin-7-one (8ab)
According to GP4, compound **8ab** was prepared from **9ab** (0.39 g, 1.56 mmol) and isolated as a white solid; yield: 0.16 g (47%). The product had identical spectroscopic properties to the material obtained by GP3**.**

2-Phenyl-3,4-dimethyl-6-(2-phenyl-1-ylmethylidene)[1,4]oxazepin-7-one (8ac)
According to GP4, compound **8ac** was prepared from **9ac** (0.47 g, 1.38 mmol) and isolated as a white solid; yield: 0.15 g (35%); $[\alpha]_D^{25}$ –253 (c = 1.0, CH_2Cl_2).

Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89; N, 4.56. Found: C, 77.82 H, 6.99; N, 4.53.

3,4-Tetramethylene-6-[2-(4-nitrophenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8ba)
According to GP4, compound **8ba** was prepared from **9ba** (0.15 g, 0.45 mmol) and isolated as a yellow solid; yield: 0.03 g (24%). The product had identical spectroscopic properties to the material obtained by GP3.

3,4-Tetramethylene-6-[2-(4-methylphenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8ca)
According to GP4, compound **8ca** was prepared from **9ca** (0.38 g, 1.38 mmol) and isolated as a white solid; yield: 0.25 g (75%).

Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.17; H, 7.76; N, 5.17.

4-Methyl-6-[2-(4-methylphenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8cb)
According to GP4, compound **8cb** was prepared from **9cb** (0.43 g, 1.65 mmol) and isolated as a white solid; yield: 0.13 g (56%).

Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41; N, 6.06. Found: C, 72.49; H, 7.41; N, 6.06.

3,4-Tetramethylene-6-[2-(3-methoxyphenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8da)
According to GP4, compound **8da** was prepared from **9da** (0.37 g, 1.15 mmol) and isolated as a white solid; yield: 0.2 g (60%).

Anal. calcd for $C_{17}H_{21}NO_2$: C, 71.06; H, 7.36; N, 4.88. Found: C, 70.89; H, 7.62; N, 4.82.

4-Methyl-6-[2-(3-methoxyphenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8db)
According to GP4, compound **8db** was prepared from **9db** (0.24 g, 0.86 mmol) and isolated as a white solid; yield: 0.11 g (50%).

HRMS: calcd for $C_{14}H_{17}NO_3$ 247.12084. Found 247.12122

2-Phenyl-3,4-dimethyl-6-[2-(3-methoxyphenyl)-1-ylmethylidene][1,4]oxazepin-7-one (8dc)
According to GP4, compound **8dc** was prepared from **9dc** (0.21 g, 0.56 mmol) and isolated as a colorless viscous oil; yield: 0.11 g (61%); $[\alpha]_D^{25}$ –192 (c = 1.0, CH_2Cl_2).

HRMS: m/z calcd for $C_{21}H_{23}NO_3$ 337.16645. Found 337.16791.

Hydrogenation of [1,4]oxazepin-7-ones (GP5); General Procedure
The compound **9aa** or **9ab** (1.0 equiv, 1 mmol) was dissolved in absolute MeOH (7 mL). Aq sat. solution of HCl in EtOAc (1 mL) was added followed by a catalytic amount (ca. 5%) of Pd/C. The mixture was stirred under H_2 for 3–4 h, filtered through a Celite pad and the solvent was concentrated in vacuo thoroughly. The residue was used for further transformations according to the GP4 protocol.

3,4-Tetramethylene-6-benzyl[1,4]oxazepin-7-one (12aa)
According to GP5, compound **12aa** was prepared from **9aa** (0.29 g, 1.0 mmol) and isolated as a white solid: yield: 0.14 g (52%).

HRMS: m/z calcd for $C_{16}H_{21}NO_2$ 259.15723. Found 259.15741.

4-Methyl-6-benzyl[1,4]oxazepin-7-one (12ab)
According to GP5, compound **12ab** was prepared from **9ab** (0.28 g, 1.12 mmol) and isolated as a colorless viscous oil; yield: 0.12 g (48%).

Anal. calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.06; H, 7.98; N, 6.38.

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