Combinatorial Liquid-Phase Synthesis of [1,4]Oxazepine-7-ones via the Baylis−Hillman Reaction

Reinhard Räcker, Klaus Döring, and Oliver Reiser*

Department of Organic Chemistry, University of Regensburg, Universitätsstrasse 31, D-93053 Regensburg, Germany

oliver.reiser@chemie.uni-regensburg.de

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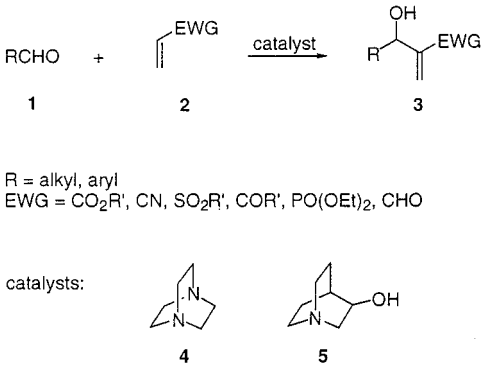
A new method for the synthesis of [1,4]oxazepin-7-ones from readily available aldehydes and α-amino alcohols was developed using the Baylis−Hillman reaction as the key step. To determine the scope and limitations of the method, a mixture library was synthesized from six aldehydes and six α-amino alcohols on the soluble polymer support poly(ethylene glycol) 5000 monomethyl ether (MeOPEG) via split synthesis and analyzed by GC−EIMS. Those oxazepines that were formed predominantly were resynthesized in a parallel synthesis and fully characterized. Thus, we have shown that split synthesis on MeOPEG can be an efficient method to rapidly screen the substrate spectrum of a newly developed reaction sequence.

Introduction

The Baylis−Hillman reaction is a valuable C−C bond-forming reaction in organic synthesis,[1] which has found widespread application in recent times.[2] In general, an aldehyde **1** is treated with an activated alkene **2** in the presence of a catalyst to yield allylic alcohols **3** (Scheme 1).

Most commonly, tertiary amines such as 1,4-diazabicyclo[2.2.2]octane (**4**, DABCO) or 3-quinuclidinol (**5**, 3-QDL) are used as catalysts, although many other compounds have been shown to catalyze the Baylis−Hillman reaction as well.[3] Alkyl as well as aryl aldehydes in combination with electron-deficient terminally substituted alkenes generally undergo the reaction at atmospheric pressure and room temperature. In contrast, reasonable reaction rates with 1,2-disubstituted alkenes can only be observed under high-pressure conditions.[4]

Scheme 1. Baylis−Hillman Reaction



Several groups have shown that allylic acetates derived from **3** undergo S_N2'-type reactions in the absence of transition metal catalysts when nucleophiles such as *β*-dicarbonyl compounds,[5] nitroalkanes,[5b] *O*-methyl (*S*)-prop-2-ynyl dithiocarbonate,[6] *tert*-butyl hydroperoxide,[7] phenol,[8] silylenol ethers in the presence of $TiCl_4$,[9] Grig-

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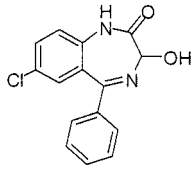
nard reagents,[10] hydride,[11] triethyl phosphite,[12] allylic sulfones,[13] oxosulfonium ylides,[14] azide[15b] or—for our study most relevant—amines[15] are employed.

Seven-membered heterocycles with two heteroatoms in 1,4-distance are known to possess manifold biological activities. In particluar, aryl-annelated [1,4]diazepine and [1,4]oxazepine[16] units are crucial moieties in several psychoactive pharmaceuticals, e.g., oxazepam **6** (tranquilizer).[17] Moreover, Mukaiyama[18] and Tietze[19] have shown that 6-bezylidene-oxazepane-5,7-dione **7** is a valuable chiral template for stereoselective syntheses.



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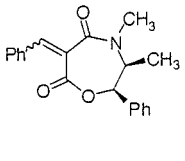

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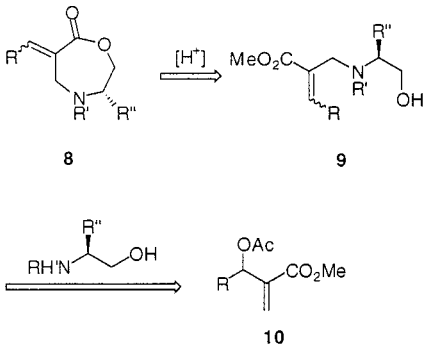
We were intrigued by the question if allylic acetates **10** could be reacted with α-amino alcohols in a S_N2'-type reaction and subsequently cyclized under acidic conditions to yield [1,4]oxazepin-7-ones **8**, a class of compounds which has been only scarcely explored to date (Scheme 2).[20]

To rapidly determine the scope and limitations of this reaction sequence toward the [1,4]oxazepin-7-ones, we decided to generate a mixture library of compounds using a "split synthesis"[21] approach on a soluble polymer support and to analyze the mixture via GC−EIMS.[22] Split synthesis is an important methodology in combinatorial

Scheme 2. Disconnection Approach to [1,4]Oxazepines



8 **9** **10**

chemistry[23] to generate molecular diversity. It is usually carried out on solid polymer supports[24] and allows the generation of libraries with spatially separated compounds on individual resin beads. Split synthesis on *soluble* polymer supports leads always to compound mixtures and thus makes deconvolution necessary.[25] This fact should be the main reason—to the best of our knowledge—only a few articles have been published so far which describe a split synthesis using a soluble polymer support.[26] We demonstrate here that a split synthesis approach on soluble polymers is a valuable method to rapidly screen the scope and limitations of a new reaction sequence.

We chose to perform our reactions on the soluble polymer support[27] poly(ethylene glycol) 5000 monomethyl ether (MeOPEG). This polymer is soluble in many solvents, e.g., THF, CH_2Cl_2, or H_2O at room temperature,[28] but can be precipitated from a solution and thus

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Table 1. Results of the Baylis−Hillman Reactions of the MeOPEG-acrylate 12 with Benzaldehyde (13a) under Various Conditions[a]

entry	catalyst	solvent	c[b]/g mL^{-1}	T/°C	time/h	**14a**/%	**12**/%	**11**/%
1	DABCO	THF	0.10	66	24	0	100	0
2	DABCO	CH_2Cl_2	0.33	0	44	0	100	0
3	DABCO	CH_3CN	0.33	23	120	27	73	0
4	DABCO	$MeOH/CH_2Cl_2$	0.083	23	120	21	13	66
5	DABCO	$EtOH/CH_2Cl_2$	0.083	23	120	23	54	23
6	DABCO	$iPrOH/CH_2Cl_2$	0.083	23	120	18	82	0
7	DABCO	t-$BuOH/CH_2Cl_2$	0.083	23	120	17	83	0
8	3-QDL	EtOH	0.33	30	120	93	0	7
9	DABCO	EtOH	0.33	30	96	87	13	0

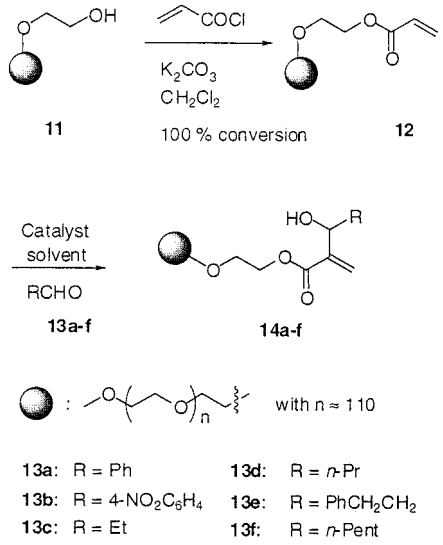
[a] The recovery of the polymer was >95% (see the Supporting Information for details). [b] Grams of the MeOPEG-acrylate **12** divided by milliliters of solvent. The ratio of the acrylate, the aldehyde, and the catalyst was constant for all experiments: **12**/**13a**/catalyst = 1:100:10.

purified by addition of diethyl ether, hexane, or 2-propanol.[29] Soluble polymers have several advantages over polystyrene-derived resins. Reactions of soluble polymer-bound and the corresponding non polymer-bound substrates generally show the same kinetics,[30] insoluble byproducts or reagents can easily be separated from the polymer solution by filtration and the polymer is significantly less expensive than polystyrene-resins. Furthermore, each reaction can be easily monitored by solution-phase ^{1}H NMR of a polymer sample in $CDCl_3$. Hegedus described the use of MeOPEG in a two-phase reaction as advantageous compared to the use of Merrifield resin.[31] Kahn and Blaskovich have successfully demonstrated the optimization of a multistep sequence using MeOPEG-bound substrates.[32] For their synthesis they showed that the optimized reaction conditions could be transferred to a polystyrene-based resin (Wang-resin). Polystyrene resins have advantages over poly(ethylene glycol)-derived polymers especially when it comes to automation. Our work presented here shows that the use of MeOPEG-bound substrates can help to rapidly evaluate the substrate spectrum of a multistep sequence.

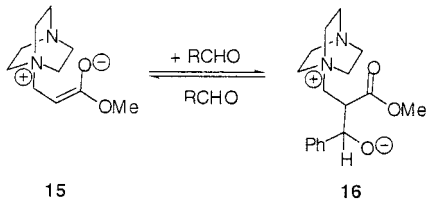
Results and Discussion

As the first step, the MeOPEG-bound equivalents of the allylic acetates of type **10** had to be prepared. A few groups have already described Baylis−Hillman reactions on polystyrene-derived resins.[33] These groups have observed that complete conversion occurs only with very electrophilic aldehydes such as 4-trifluoromethylbenzaldehyde or 4-nitrobenzaldehyde. Baylis−Hillman reactions with substrates attached to *soluble* polymer supports have not been carried out so far. Thus, we have optimized the Baylis−Hillman reaction of the MeOPEG-bound acrylate **12** with benzaldehyde (**13a**) (Scheme 3).

Scheme 3. Baylis−Hillman Reaction of Various Aldehydes with the MeOPEG-Bound Acrylate 12



Scheme 4 Assumed Rate-Determining Step of the Baylis−Hillman Reaction



Esterification of MeOPEG **11** with acryloyl chloride readily gave rise to the acrylate **12** in quantitative yield, which was then subjected to Baylis−Hillman reactions with benzaldehyde (**13a**) under different reaction conditions (Table 1).

No reaction took place at all when **12** was reacted with benzaldehyde (**13a**) and DABCO in THF or dichloromethane (entries 1 and 2). Changing to acetonitrile as the solvent, **14a** was formed in 27% yield as determined by ^{1}H NMR (entry 3). Drewes et al. first described the beneficial use of alcohols as solvent or additive in Baylis−Hillman reactions.[34] The increased reaction rates caused by protic solvents are attributed to the stabilization of zwitterionic intermediates such as **15** and **16** through hydrogen-bonding. Scheme 4 shows the assumed rate-determining step of the Baylis−Hillman reaction.[35]

(28) MeOPEG is not soluble in THF or dichloromethane at −78 °C. To circumvent this problem Janda et al. have successfully used non-cross-linked chloromethylated polystyrene (NCPS) as a soluble polymer support. Chen, S., Janda, K. D., *J. Am.Chem. Soc.* **1997**, *119*, 8724−8725.

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Table 2. Baylis−Hillman Reactions of the Acrylate 12 and Six Different Aldehydes under Optimized Conditions (3-QDL, EtOH, 30 °C, 120 h)

aldehyde	**14**/%	**12**/%	**11**/%
13a	93	0	7
13b	56	0	44
13c	65	0	35
13d	89	0	11
13e	51	0	49
13f	55	0	45

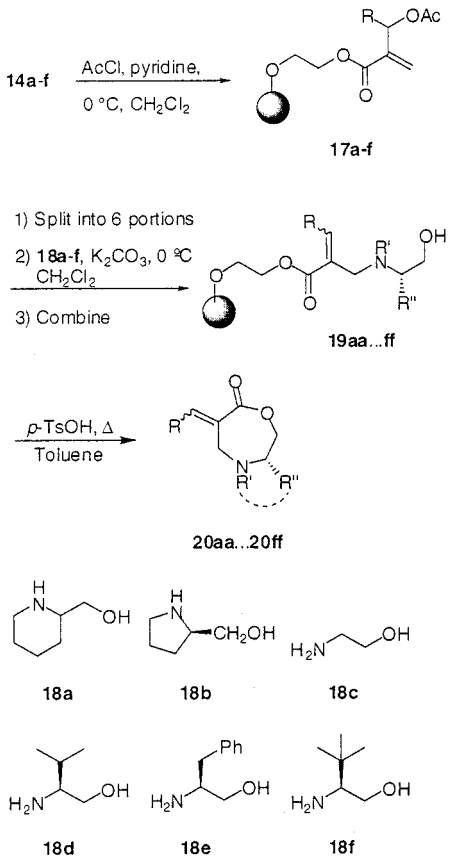
Indeed, using alcohols as additives also was beneficial for the Baylis−Hillman reaction of the MeOPEG-bound acrylate **12**. Comparison of entries 4−7 shows, however, the dilemma we were facing in optimizing the Baylis−Hillman reaction on the MeOPEG-bound acrylate **12**: while the use of alcohols such as methanol and ethanol resulted in the greatest rate acceleration, also substantial cleavage from the polymer was observed. The latter could be completely suppressed by the use of 2-propanol or *tert*-butyl alcohol, however, at the same time the reaction rate was also substantially reduced. Optimal conditions were finally found in the use of pure ethanol as the solvent and conducting the reaction at the highest possible concentration of reactants without precipitation of the polymer. Both DABCO (**4**) as well as 3-QDL (**5**) were effective as amine catalysts (entries 8 and 9). We decided to carry on with 3-QDL (**5**) since an incomplete conversion of the starting material would probably give rise to side products further along the reaction sequence (1,4-addition of amines to **12**), while free MeOPEG **11** generated by cleavage should be acylated in the next reaction step and therefore cause no further interference.

Subsequently, the aldehydes **13a**−**f** were subjected to the Baylis−Hillman protocol with the acrylate **12** using the conditions previously optimized in six parallel reactions. Samples were taken and analyzed by ^{1}H NMR, revealing that **14a**−**f** had formed in all cases (51−93%) along with cleavage from the polymer support resulting in the formation of **11** (7−49%, Table 2).

Since in the next step of the reaction sequence no diversity is introduced, this transformation can be carried out in a single operation for all allylic alcohols **14** combined. Therefore, the Baylis−Hillman adducts **14a**−**f** were combined[36] in a single flask and treated with an excess (20 equiv) of acetyl chloride to yield a mixture of allylic acetates **17** (Scheme 5).

The mixture of **17a**−**f** was subsequently devided into six equal portions, and each of them was reacted with one of the α-amino alcohols **18a**−**f** in dichloromethane. Again, the following lactonization step along with concurrent cleavage of the products **20** from the polymer can be carried out for all compounds simultaneously. Consequently, the six polymer portions were combined once more and lactonization and cleavage from the polymer were effected at the same time by refluxing the polymer in toluene in the presence of *p*-toluenesulfonic acid. The obtained mixture of [1,4]oxazepin-7-ones **20aa**−**ff** was examined by GC−EIMS to find out which of the desired products had actually been formed (Figure 1).

Scheme 5. Split Synthesis of the [1,4]Oxazepin-7-ones 20aa−20ff



The evaluation of the mass spectra showed that 53 out of 72[37] expected products were formed, however, to a very different extent. All compounds could be identified unambiguously by their molecular peaks as well as by their fragmentation patterns. This was especially true for products having the same molecular mass. The characteristic fragmentation reactions of the different amino alcohol moieties could be used for identification, since within a group of substances derived from the same α-amino alcohol none had equal masses. Moreover, the *E*- and *Z*-isomers of **20** could also be identified by their significantly different fragmentation patterns; only the *E*-isomers gave [M^+ − R] as a major fragment. The correctness of this assignment was later confirmed by the individual synthesis of **20aa**−**fa** (vide infra). Since no heterocycles derived from ethanolamine (**18c**) were detected no statements can be made about the major fragmentation pathways in those cases (Scheme 6).

The most intensive peaks could be attributed (Figure 1) to the heterocycles **20aa**−**fa** derived from cyclization of **17a**−**f** with 2-piperidinylmethanol (**18a**).[38] Clearly, the conformational restrains in **18a** favor the *cisoid* confor-

(35) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611.

(36) Each Baylis−Hillman reaction started from 1.00 g of the MeOPEG-acrylate **12**. After workup, 0.90−0.97 g of the corresponding polymers could be recovered. To minimize the influence of unavoidably varying mass recovery on the compound ratios in the library, equal masses (0.80 g) of the polymer-bound allylic alcohols **14** were combined for the subsequent acylation.

(37) With 6 aldehydes and 6 amino alcohols 36 combinations are possible. As each of the oxazepinones may be formed as (*E*)-or (*Z*)-isomer all in all 72 heterocyclic products can be expected.

(38) It should be noted that ratios of peak areas derived from GC-EIMS do not, in general, directly provide ratios of compound concentrations. However, for the purpose of evaluation of a multistep sequence the ratios of peak areas provide a good estimate of which products are formed preferentially and which only to a minor extent. GC of the product mixture carried out by FI detection showed the same 12predominant peaks. Furthermore, we have verified the correctness of this assumption for our sequence by carrying out control experiments in solution by reacting the methyl ester corresponding to **17a** with **18** followed by intramolecular cyclization.

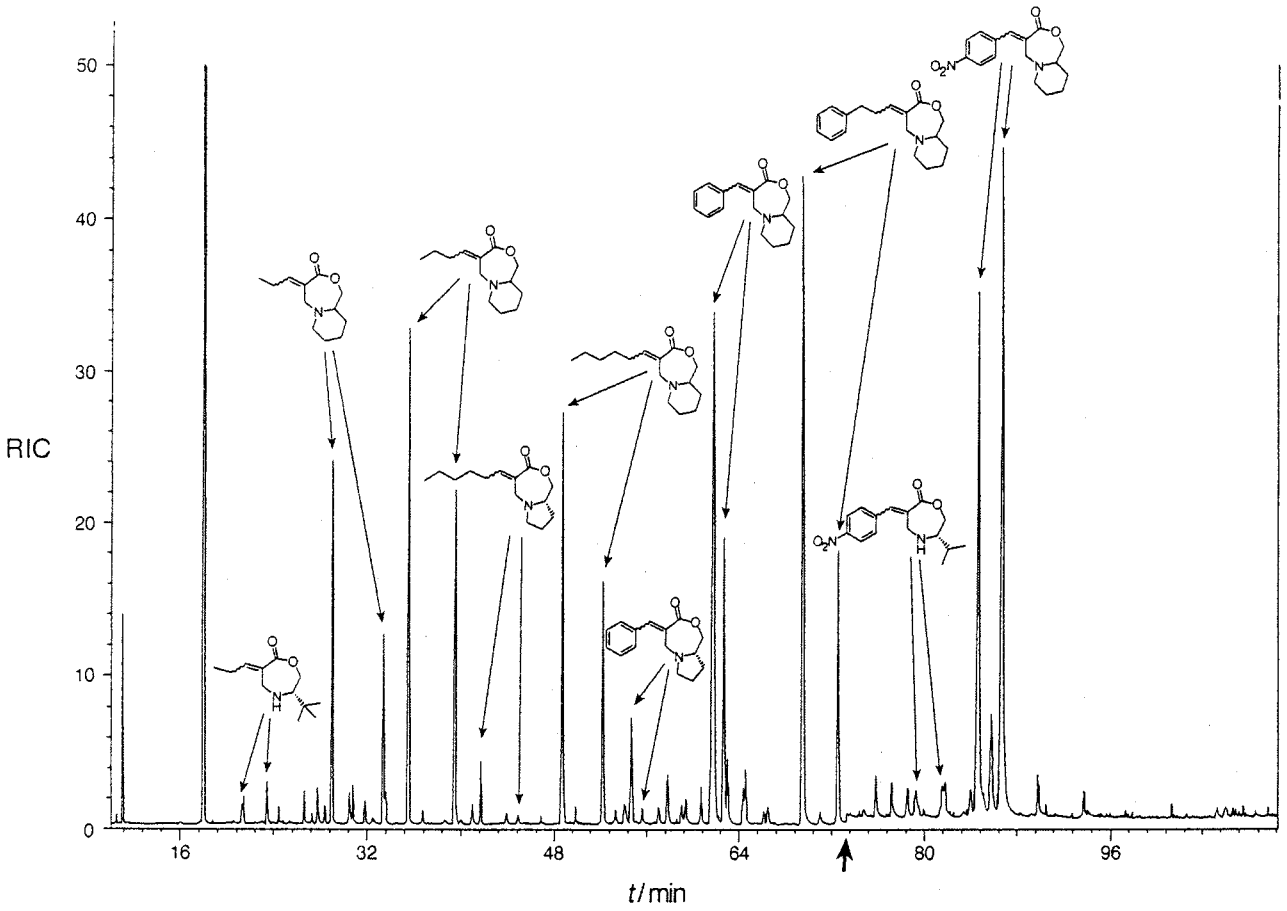
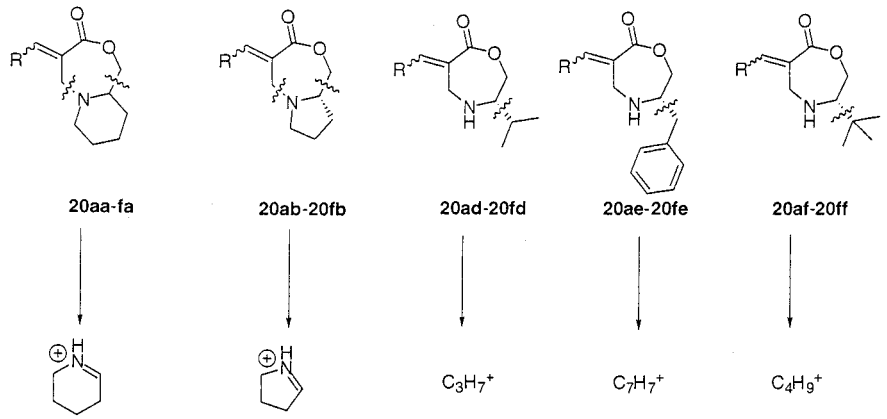


Figure 1. GC of the mixture of [1,4]oxazepin-7-ones with EIMS detection. The signals in the area to the right of the bold arrow pointing at the time axis were magnified by a factor of 3.8 for better visibility. *2,6-Di-*tert*-butyl-4-methylphenol (contained in diethyl ether as stabilizing agent). RIC = relative ion current.

Scheme 6. Major Fragmentation Reactions (EI) of the Oxazepines as a Function of the α-Amino Alcohol Moiety



mation necessary for the cyclization to **20**. Following this argument, however, it was most surprising to see that prolinol (**18b**) gave rise to the oxazepines **20ab**−**fb** only in low yields at best. No [1,4]oxazepin-7-ones were formed from ethanolamine (**18c**), apparently an α-substituent is necessary for the cyclization to proceed (Thorpe−Ingold effect[39]). Furthermore, the *E*/*Z* selectivity strongly varied with the employed aldehyde **13**. While with benzaldehyde **13a** predominately the *E*-configurated oxazepinones **20ax** are obtained, alkyl substituted aldehydes **13c**−**f** gave predominately rise to the *Z*-configured oxazepinones.

On the basis of our screening, it was clear that best results toward [1,4]oxazepin-7-ones **20** will be achieved with **18a**.[40] Consequently, **20aa**−**fa** were resynthesized

(39) (a) Eliel, E. E.; Wilen, S. H. *Sterochemistry of Organic Compounds*; Wiley: New York, 1994; p. 682. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102. (c) Verevkin, S. P.; Kümmerlin, M.; Beckhaus, H.-D.; Galli, C.; Rüchardt, C. *Eur. J. Org. Chem.* **1998**, *579*, 9−584. (d) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Soc. Chim. Fr.* **1995**, *132*, 808−814.

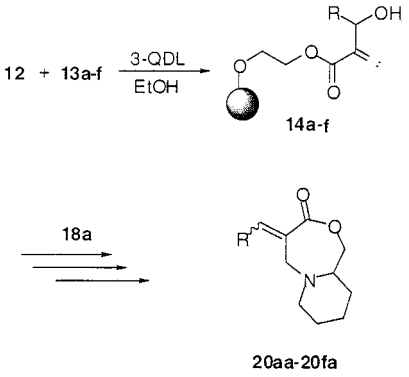
(40) One of the referees raised the question if 2-aminophenol would work in the sequence described here. Therefore, we performed independent experiments with benzaldehyde and this amino alcohol. The sequence proceeded well to the substitution product corresponding to **19**, however, the final cyclization could not be achieved under the conditions described for the synthesis of **20**.

Table 3. Conversion of the Baylis−Hillman Reactions to 14 and Total Yield of 20aa−fa as a Function of the Employed Aldehyde

aldehyde	**14**[a]/%	**20**[b]/%	*E*/*Z* ratio of **20**[c]
13a	79	27	75:25
13b	66	14	42:58
13c	51	17	45:55
13d	74	32	37:63
13e	71	41	42:58
13f	61	27	33:67

[a] As determined by ^{1}H NMR. [b] Overall isolated yield (four steps) starting from **12**. With the exception of **20ca** all compounds could be obtained as geometrically pure isomers after column chromatography. [c] There were very small changes in the *E*/*Z* ration of **19** and after cyclization to **20**. E.g., **19da** was obtained with a *E*/*Z* ratio of 35:65, as determined by ^{1}H NMR (see the Supporting Information for details).

Scheme 7. Parallel Synthesis of the [1,4]Oxazepin-7-ones 20aa−20fa



in parallel on MeOPEG **11**. These examples were also used to investigate the individual reaction steps of the sequence in more detail.

Starting with four times the amount of the acrylate **12** that was used previously in the library synthesis, the [1,4]oxazepine-7-ones **20aa−fa** could be obtained in overall yields of 14−41% starting from **12** (Scheme 7 and Table 3). Gratifyingly, on this scale the conversion for the Baylis−Hillman reactions was nearly as good and in some cases even better as compared to the results obtained during the screening (Table 3, cf. Table 2). The following acylation proceeded quantitatively, as was revealed by comparing the chemical shifts of the olefinic and allylic protons in the ^{1}H NMR spectra of the allylic alcohols **14** and the allylic acetates **17**. From this analysis it could also be concluded that the portion of MeOPEG **11** present as an impurity in **14** due to partial cleavage in the preceding Baylis−Hillman reaction was acylated quantitatively to yield MeOPEG-OAc. The complete disappearance of the olefinic signals for the allylic acetates **17a−f** in the course of the S_N2'-reaction and the occurrence of a new olefinic signal was taken as evidence that these reactions have proceeded quantitatively.

Except for **20ca**, it was possible to separate the diasteromers by column chromatography and obtain sufficient analytical data (^{1}H NMR, ^{13}C NMR, HRMS) in all cases. The assignment of the (*E*)- and (*Z*)-isomers of **20aa**, **20ba**, and **20da** was possible unambiguously by ^{1}H NMR NOESY experiments. **20ca**, **20ea**, and **20fa** were assigned in analogy to **20da** based on the chemical shifts of their olefinic protons (*E*-**20ca−fa**: $\delta = 6.26 \pm 0.02$ ppm; *Z*-**20ca−fa**: $\delta = 6.05 \pm 0.03$ ppm). Moreover, all (*E*)-configured products had significantly higher R_f values on silica gel which further corroborates our assignment.

Conclusion

The scope and limitation of a new reaction sequence toward [1.4]-oxazepine-7-ones was rapidly screened by a split synthesis approach using MeOPEG as a soluble polymer support. The synthesis of a model library of 72 oxazepines (36 structural isomers with two diasteromers for each) was attempted by this strategy, making only 14 different transformations necessary compared to 84 in a parallel synthesis approach. This way, the most promising building blocks toward the title compounds could be identified, which were consequently used in parallel synthesis to yield the new [1,4]oxazepione-7-ones **20aa−fa** as single compounds. Thus, we have shown that split synthesis on a soluble support is an efficient method to evaluate a multistep reaction sequence.

Experimental Section

Preparation of the Library Using Split Synthesis MeOPEG Acrylate (12). To a solution of MeOPEG-OH **11** (50.00 g, 10.00 mmol) in 300 mL of dichloromethane were added potassium carbonate (6.91 g, 50.00 mmol), and the mixture was cooled to 0 °C. Subsequently, acryloyl chloride (4.53 g, 3.97 mL, 50.00 mmol) was added dropwise within 15 min. After the mixture was stirred for 1 h at 0 °C and 48 h at room temperature, the polymer was precipitated by addition of 1.5 l of diethyl ether. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The polymer was filtered, rinsed with 0.5 l of diethyl ether, and dried for 5 h at 0.5 Torr in vacuo. Thus, 48.97 g (97%) of the acrylate **12** was obtained as a colorless powder: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.38 (s, 3H, OCH_3), 3.45−3.75 (m, PEG), 4.32 (m, 2H, PEG), 5.84 (dd, J = 10.3, 1.6 Hz, 1H), 6.16 (dd, J = 17.3, 10.3 Hz, 1H), 6.43 (dd, J = 17.3, 1.6 Hz, 1H).

General Procedure for the Baylis−Hillman Reaction with the MeOPEG-acrylate 12. A solution of the MeOPEG-acrylate **12** (1.00 g, 0.198 mmol), an aldehyde **13a−f** (19.8 mmol; exception: 4-nitrobenzaldehyde (3.96 mmol)), and 3-quinuclidinol (**5**, 0.25 g, 1.98 mmol) in ethanol or ethanol/dichloromethane was stirred for 96 h at 30 °C. Afterward, the polymer was precipitated by the addition of 60 mL of diethyl ether. The suspension was kept at 0 °C for another 30 min to ensure complete precipitation. The polymer was filtered, rinsed with 60 mL of diethyl ether and dried in vacuo. Each of the recovered polymers contained varying amounts of MeOPEG-OH due to cleavage of the ester functionality. The portion of MeOPEG-OH in each sample was determined by ^{1}H NMR spectroscopy.

Baylis−Hillman adduct with benzaldehyde, 14a: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.24−4.30 (m, 2H), 5.59 (s, 1H), 5.82 (t, J = 1.2 Hz, 1H), 6.36−6.39 (m, 1H), 7.26−7.42 (m, 5H).

Baylis−Hillman adduct with 4-nitrobenzaldehyde, 14b: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.25−4.30 (m, 2H), 5.67 (s, 1H), 5.89 (t, J = 1.1 Hz, 1H), 6.42−6.44 (m, 1H), 7.61 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H).

Baylis−Hillman adduct with propionic aldehyde, 14c: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.60−1.76 (m, 2H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.29−4.36 (m, 3H), 5.79 (t, J = 1.2 Hz, 1H), 6.27 (d, J = 1.2 Hz, 1H).

Baylis−Hillman adduct with *n*-butanoic aldehyde, 14d: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.27−1.70 (m, 4H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.31−4.36 (m, 2H), 4.36−4.41 (m, 1H), 5.81 (t, J = 1.2 Hz), 6.26 (d, J = 1.2 Hz, 1H).

Baylis−Hillman adduct with hydrocinnamic aldehyde, 14e: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.90−2.02 (m, 2H),

2.61−2.88 (m, 2H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.29−4.35 (m, 2H), 4.39−4.46 (m, 1H), 5.81 (t, J = 1.1 Hz, 1H), 6.27 (d, J = 1.1 Hz, 1H), 7.11−7.31 (m, 5H).

Baylis−Hillman adduct with *n*-hexanoic aldehyde, 14f: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.22−1.38 (m, 6H), 1.57−1.69 (m, 2H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.30−4.35 (m, 2H), 4.36−4.43 (m, 1H), 5.79 (t, J = 1.2 Hz, 1H), 6.25 (d, J = 1.2 Hz, 1H).

Acylation of a Mixture of MeOPEG-Bound Baylis−Hillman Adducts. To a solution of equimolar amounts of the MeOPEG-bound Baylis−Hillman adducts **14a−f** (total: 4.80 g, 0.931 mmol) and pyridine (0.37 mL, 0.37 g, 4.62 mmol) in 35 mL of dichloromethane was added acetyl chloride (1.31 mL, 1.45 g, 18.5 mmol) at 0 °C, and the mixture was allowed to warm to room temperature with stirring overnight. After filtration through Celite the polymer was precipitated from the solution by addition of 300 mL of diethyl ether. The suspension was kept at 0 °C for another 30 min, and the polymer was filtered, rinsed with 100 mL of diethyl ether, 50 mL of ethanol, and 100 mL of diethyl ether, and dried in vacuo. Thus, 4.40 g of a colorless mixture of the MeOPEG-bound allylic acetates **17a−f** were obtained.

Allylic Substitution Reactions with a Mixture of MEOPEG-Bound Baylis−Hillman Allylic Acetates 17a−f and Six α-Amino Alcohols 18a−f. The mixture of the MeOPEG-bound allylic acetates **14a−f** was split into six portions of 0.70 g (0.14 mmol),[41] each of them in a separate reaction vessel. To each vessel were added 3 mL of dichloromethane to dissolve the polymer, potassium carbonate (93 mg, 0.67 mmol), and afterward 1.35 mmol of an α-amino alcohol **18a−f** was added to each solution, i.e., 0.16 g of (*rac*)-piperidine-2-methanol (**18a**) to vessel 1, 82 mg of ethanolamine (**18c**) to vessel 2, 0.14 g of (*S*)-valinol (**18d**) to vessel 3, 0.20 g of (*S*)-phenyl alaninol (**18e**) to vessel 4, 0.14 g of (*S*)-prolinol (**18b**) to vessel 5 and 0.16 g of (*S*)-*tert*-leucinol (**18f**) to vessel 6. Each mixture was stirred for 4 h and filtered through Celite. The polymer was precipitated by addition of 70 mL of diethyl ether to the filtrate. The suspension was kept at 0 °C for another 30 min to ensure complete precipitation and finally the polymer was filtered, rinsed with 70 mL of diethyl ether and dried in vacuo. The mass recovery was 0.50 g (71%) in vessel 1, 0.35 g (50%) in vessel 2, 0.53 g (76%) in vessel 3, 0.47 g (67%) in vessel 4, 0.49 g (70%) in vessel 5 and 0.46 g (66%) in vessel 6.[42]

Cleavage of a Library of [1,4]Oxazepin-7-ones 20aa−ff. From each of the polymer portions in the preceding procedure were taken 0.35 g and mixed together. To the resulting polymer mixture (2.10 g, 0.404 mmol)[41] were added 20 mL of toluene and *p*-toluenesulfonic acid monohydrate (0.15 g, 0.808 mmol). The mixture was stirred at reflux for 18 h. Afterward, it was diluted with 50 mL of diethyl ether and extracted with 3 × 10 mL of saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and evaporated. The polymer was removed from the crude residue by filtration through silica gel with ethyl acetate as eluent. A 9.7 mg portion of a mixture of [1,4]oxazepine-7-ones was obtained and analyzed by GC−EIMS (cf. Figure 1).

Preparation of Single Compounds. General Procedure for the Baylis−Hillman Reaction with MeOPEG-acrylate 12. The 4-fold amounts of polymer and reagents used in the library procedure were employed. For details see the Supporting Information.

General Procedure for the Acylation of MeOPEG-Bound Baylis−Hillman Adducts 14a−f. To a solution of a MeOPEG-bound Baylis−Hillman adduct (3.50 g, 0.672−0.685 mmol) and pyridine (0.27 mL, 0.27 g, 3.4 mmol) in 25 mL of dichloromethane was added acetyl chloride (1.0 mL, 1.1 g, 13 mmol) dropwise during 15 min at 0 °C. The mixture was stirred overnight and allowed to warm to room temperature (total reaction time: 24 h). Afterward, the reaction mixture was filtered through a 2 cm pad of Celite, which was subsequently rinsed with 10 mL of dichloromethane. The polymer was precipitated from the combined washings through addition of 250 mL of diethyl ether, and the suspension was kept at 0 °C for 30 min to effect complete precipitation. The polymer was filtered and rinsed with 60 mL of diethyl ether, 20 mL of ethanol, and 80 mL of diethyl ether. It was dried in vacuo to yield a colorless powder. Each sample contained MeOPEG-OAc to the extent that the educt contained MeOPEG-OH. Mass recoveries and ^{1}H NMR data for the different polymers were as follows. The signals of MeOPEG-OAc are not listed.

MeOPEG-2-(1-acetoxyphenylmethyl)acrylate 17a: yield 3.31 g (95%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.18−4.27 (m, 2H), 5.84−5.87 (m, 1H), 6.42 (t, J = 0.9 Hz, 1H), 6.67 (t, J = 1.2 Hz, 1H), 7.29−7.40 (m, 5H).

MeOPEG-2-(1-acetoxy-*p*-nitrophenylmethyl)acrylate 17b: yield 3.23 g (92%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.20−4.28 (m, 2H), 5.96−5.98 (m, 1H), 6.48−6.50 (m, 1H), 6.69−6.71 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H).

MeOPEG-3-acetoxy-2-methylenepentanoate 17c: yield 3.12 g (89%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.60−1.91 (m, 2H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.26−4.34 (m, 2H), 5.53−5.60 (m, 1H), 5.77 (t, J = 1.1 Hz, 1H), 6.30−6.32 (m, 1H).

MeOPEG-3-acetoxy-2-methylenehexanoate 17d: yield 3.23 g (92%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 1H), 1.26−1.45 (m, 2H), 1.56−1.79 (m, 2H), 2.06 (s, 3H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.28−4.35 (m, 2H), 5.58−5.67 (m, 1H), 5.77 (t, J = 1.1 Hz, 1H), 6.29−6.32 (m, 1H).

MeOPEG-3-acetoxy-2-methylene-5-phenylpentanoate 17e: yield 3.32 g (95%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.60−2.71 (m, 2H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.24−4.36 (m, 2H), 5.62−5.68 (m, 1H), 5.79 (t, J = 1.1 Hz), 6.31−6.33 (m, 1H), 7.11−7.24 (m, 5H). The signal for the methylene group $PhCH_2CH_2$ could not be observed because it was hidden by the broad H_2O-signal ranging from 2.1 to 2.50 ppm.

MeOPEG-3-Acetoxy-2-methyleneoctanoate 17f: yield 3.55 g (101%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3H), 1.25−1.35 (m, 6H), 1.57−1.80 (m, 2H), 2.08 (s, 3H), 3.38 (s, 3H), 3.45−3.75 (m, PEG), 4.26−4.35 (m, 2H), 5.55−5.63 (m, 1H), 5.77 (t, J = 1.1 Hz, 1H), 6.28−6.30 (m, 1H).

General Procedure for the Substituion Reactions of MeOPEG-Bound Baylis−Hillman Allylic Acetates 17a−f with 2-Piperidinylmethanol (18a). To a solution of **17** (3.00 g, 0.577 mmol) in 12 mL of dichloromethane were added 2-piperidinyl methanol (0.66 g, 5.77 mmol) and potassium carbonate (0.40 g, 2.88 mmol). The mixture was stirred for 6 h at room temperature. It was filtered through a 2 cm pad of Celite which was subsequently rinsed with 15 mL of dichloromethane. The polymer was precipitated through addition of 300 mL of diethyl ether to the combined washings. The obtained suspension was kept at 0 °C for another 30 min and the polymer was filtered, rinsed with 200 mL of diethyl ether, and dried in vacuo to yield a colorless powder.

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-cinnamoate 19aa: yield 2.99 g (100%).

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-3-(4-nitrophenyl)acrylate 19ba: 3.00 g (100%).

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-pent-2-enoate 19ca: 2.81 g (94%).

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-hex-2-enoate 19da: yield 2.90 g (97%).

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-5-phenylpent-2-enoate 19ea: yield 3.19 g (106%).

MeOPEG-2-(2-hydroxymethylpiperidine-1-ylmethyl)-oct-2-enoate 19fa: yield 3.23 g (108%).

General Procedure for the Cleavage/Lactonization Leading to [1,4]Oxazepine-7-ones. A solution of a MeOPEG-bound amino alcohol **19aa−fa** (3.00 g, 0.577 mmol) and 4-toluenesulfonic acid monohydrate (219 mg, 1.15 mmol) in 30 mL of toluene was heated at reflux with stirring for 20 h. After that, the reaction mixture was cooled to room temperature, diluted with 60 mL of dichloromethane, and extracted

(41) Based on an estimated average molecular weight of 5200.

(42) To simplify matters the polymer's molecular weight change caused by the reaction was not taken into account.

with 3 × 20 mL of saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was dissolved in a small amount of dichloromethane, and the diastereomerically pure [1,4]oxazepine-7-ones were isolated through column chromatography on silica gel (eluent: ethyl acetate/hexanes (1:1)).

4-Oxo-3-phenylmethylen-1-aza-5-oxabicyclo[5.4.0]undecane (20aa): total yield 40 mg (27%).

(*E*)-Isomer: yield 30 mg; R_f = 0.73; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.90 (m, 6H), 2.20−2.40 (m, 2H), 2.87−2.96 (m, 1H), 3.02−3.40 (m, 1H), 3.52 (d, J = 14.5 Hz, 1H), 3.98−4.10 (m, 1H), 4.12−4.33 (m, 1H), 7.23 (s, 1H), 7.29−7.54 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.04, 25.64, 28.87, 55.22, 55.45, 63.69, 71.85, 128.54, 128.77, 129.72, 133.62, 134.69, 137.76, 173.17; HRMS (FAB) *m/e* calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1414. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H 7.44; N, 5.44. Found: C, 74.41; H, 7.41; N, 5.29.

(*Z*)-Isomer: yield 10 mg R_f = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.86 (m, 6H), 2.13−2.26 (m, 1H), 2.26−2.42 (m, 1H), 2.97 (d, J = 11.7 Hz, 1H), 3.12 (d, J = 13.0 Hz, 1H), 3.50 (d, J = 13.0 Hz, 1H), 4.05−4.22 (m, 1H), 4.22−4.38 (m, 1H), 6.83 (s, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.82, 25.19, 29.09, 53.40, 55.72, 63.31, 72.52, 128.47, 128.58, 128.86, 129.75, 134.20, 136.95, 171.83; HRMS (FAB) *m/e* calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1414.

4-Oxo-3-(4-nitrophenylmethylen)-1-aza-5-oxabicyclo-[5.4.0]undecane (20ba): total yield 24 mg (14%).

(*E*)-Isomer: yield 10 mg; R_f = 0.69; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05−1.98 (m, 6H), 2.18−2.48 (m, 2H), 2.91 (d, J = 11.2 Hz, 1H), 3.05−3.36 (m, 1H), 3.44 (d, J = 14.2 Hz, 1H), 4.00−4.34 (m, 2H), 7.25 (s, 1H), 7.66 (d, J = 8.6 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.99, 25.68, 28.83, 55.10, 55.51, 63.74, 72.40, 123.84, 130.41, 135.32, 137.59, 141.02, 147.58, 172.23; HRMS (FAB) *m/e* calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1264.

(*Z*)-Isomer: yield 14 mg; R_f = 0.08; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.15−1.98 (m, 6H), 2.20−2.52 (m, 2H), 2.89−3.11 (m, 1H), 3.21 (d, J = 13.3 Hz, 1H), 3.58 (d, J = 13.3 Hz, 1H), 4.03−4.46 (m, 2H), 6.88 (s, 1H), 7.53 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.74, 25.04, 28.95, 55.78, 59.95, 63.20, 72.21, 123.88, 129.31, 130.41, 140.59, 147.63, 170.50. the signal of the quaternary olefinic carbon atom was not detected; HRMS (FAB) *m/e* calcd for $C_{16}H_{18}N_2O_4$ 302.1267, found 302.1264.

4-Oxo-3-propyliden-1-aza-5-oxabicyclo[5.4.0]undecane (20ca): total yield 21 mg (17%); $R_f(E)$ = 0.16, $R_f(Z)$ = 0.08. The diastereomers could not be separated, and therefore, the following NMR and MS data refer to a mixture of diastereomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H), 1.16−1.89 (m, 6H), 2.05−2.41 (m, 4H), 2.75−2.98 (m, 1H), 3.09 (d, J = 15.2 Hz, 1H), 3.36 (d, J = 15.2 Hz, 1H), 3.80−4.34 (m, 2H), 6.07 (t, J = 7.3 Hz, 1H), 6.26 (t, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 12.92, 13.47, 21.47, 23.05, 23.80, 24.10, 25.23, 25.53, 29.17, 29.71, 53.77, 55.86, 55.96, 56.14, 63.37, 63.59, 70.65, 72.64, 133.01, 141.77, 172.82; HRMS (FAB) *m/e* calcd for $C_{12}H_{19}NO_2$ 209.1416, found 209.1411. The signals of the olefinic carbon atoms and the carbonyl carbon atom could not be detected for the (*Z*)-isomer. These signals were either too small for detection or they were hidden by the corresponding signals of the (*E*)-isomer.

4-Oxo-3-butyliden-1-aza-5-oxabicyclo[5.4.0]undecane (20da): total yield 41 mg (32%).

(*E*)-Isomer: yield 15 mg; R_f = 0.44; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz), 1.18−1.91 (m, 8H), 2.02−2.38 (m, 4H), 2.82−2.96 (m, 1H), 3.10 (d, J = 15.2 Hz, 1H), 3.37 (d, J = 15.2 Hz, 1H), 3.91 (dd, J = 12.9, 3.3 Hz, 1H), 4.19 (dd, J = 12.9, 3.3 Hz, 1H), 6.28 (t, J = 7.3 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.87, 21.69, 24.11, 25.53, 29.18, 30.11, 53.93, 55.97, 63.38, 70.61, 133.57, 140.24, 172.82; HRMS (FAB) *m/e* calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1572.

(*Z*)-Isomer: yield 26 mg; R_f = 0.26; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.12−1.94 (m, 8H), 2.03−2.40 (m, 4H), 2.84−2.95 (m, 1H), 2.96 (d, J = 13.2 Hz, 1H), 3.28 (d, J = 13.2 Hz, 1H), 3.93−4.16 (m, 2H), 6.06 (t, J = 7.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.83, 22.23, 23.86, 25.28, 29.04, 31.59, 55.82, 60.04, 63.52, 72.57, 131.08, 142.54, 171.18; HRMS (FAB) *m/e* calcd for $C_{13}H_{21}NO_2$ 223.1572, found 223.1570.

4-Oxo-3-(3-phenylpropyliden)-1-aza-5-oxabicyclo[5.4.0]-undecane (20ea): total yield 67 mg (41%).

(*E*)-Isomer: yield 28 mg; R_f = 0.50; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.13−1.88 (m, 6H), 1.98−2.11 (m, 1H), 2.11−2.30 (m, 1H), 2.31−2.51 (m, 2H), 2.62−2.86 (m, 3H), 2.90 (d, J = 16.0 Hz, 1H), 3.21 (d, J = 16.0 Hz, 1H), 3.79 (dd, J = 12.9, 3.2 Hz, 1H), 4.01 (dd, J = 12.9, 3.2 Hz, 1H), 6.26 (dddd, J = 7.5, 7.5, 1.7, 1.7 Hz, 1H), 7.11−7.40 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.10, 25.49, 29.15, 30.03, 34.52, 53.76, 55.87, 63.18, 70.39, 126.23, 128.49, 128.52, 134.59, 138.39, 140.93, 172.65; HRMS (FAB) *m/e* calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1725.

(*Z*)-Isomer: yield 39 mg; R_f = 0.24; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12−1.84 (m, 6H), 2.02−2.39 (m, 3H), 2.47−2.88 (m, 4H), 2.94 (d, J = 13.2 Hz, 1H), 3.24 (d, J = 13.2 Hz, 1H), 3.64−3.85 (m, 2H), 6.02 (t, J = 7.6 Hz, 1H), 7.08−7.31 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 23.74, 25.27, 29.01, 31.09, 34.94, 55.51, 59.69, 63.22, 72.14, 126.09, 128.45, 128.57, 131.97, 140.96 (2 overlapping signals), 171.12; HRMS (FAB) *m/e* calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1729.

4-Oxo-3-hexyliden-1-aza-5-oxabicyclo[5.4.0]undecane (20fa): total yield 39 mg (27%).

(*E*)-Isomer: yield 13 mg; R_f = 0.61; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 3H), 1.15−1.89 (m, 12H), 2.02−2.36 (m, 4H), 2.80−2.96 (m, 1H), 3.09 (d, J = 15.3 Hz, 1H), 3.36 (d, J = 15.3 Hz, 1H), 3.90 (dd, J = 12.9, 3.2 Hz, 1H), 4.18 (dd, J = 12.9, 3.2 Hz, 1H), 6.28 (t, J = 7.4 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.98, 22.44, 24.11, 25.53, 28.07, 29.17, 29.71, 31.50, 53.91, 55.98, 63.39, 70.68, 133.40, 140.56, 172.87; HRMS (FAB) *m/e* calcd for $C_{15}H_{25}NO_2$ 251.1885, found 251.1884.

(*Z*)-Isomer: yield 26 mg; R_f = 0.32; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3H), 1.15−1.89 (m, 12H), 1.95−2.39 (m, 4H), 2.81−2.95 (m, 1H), 2.96 (d, J = 13.1 Hz, 1H), 3.28 (d, J = 13.1 Hz, 1H), 3.94−4.15 (m, 2H), 6.06 (t, J = 7.6 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.96, 22.41, 23.85, 25.26, 28.63, 29.02, 29.56, 31.45, 55.81, 60.04, 63.53, 72.57, 130.79, 142.91, 171.20; HRMS (FAB) *m/e* calcd for $C_{15}H_{25}NO_2$ 251.1885, found 251.1885.

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Supporting Information Available: GC−MS data (mass spectra, retention times), listings of fully interpreted ^{1}H and ^{13}C NMR spectra of all compounds, ^{1}H and ^{13}C NMR of **20aa**−**20fa**, and NOESY spectra and ^{1}H NMR spectra for the polymers **12**, **14d**, **17d**, and **19da**. This material is available free of charge via the Internet at http://pubs.acs.org.

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