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Asymmetric Aldol Reactions on a Soluble Polymeric Support

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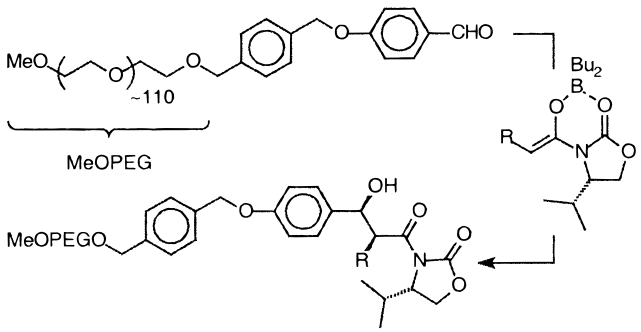
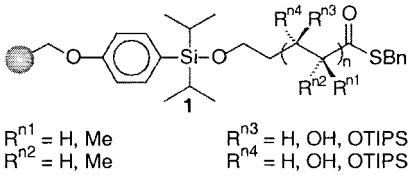
ABSTRACT



The combinatorial synthesis of small, nonpeptidic compounds is of increasing interest in current medicinal chemistry. To meet this demand, efficient entries, preferentially on polymeric supports, to pharmacologically interesting classes of compounds such as polyketides are necessary. Therefore, we have developed a synthetic protocol allowing for the asymmetric synthesis of diketides on the soluble support MeOPEG-5000. The strategy employed mainly allows for repeated aldolizations, thus providing access to functionalized polyketides of varying degree of oligomerization.

In 1996, as part of an endeavor to prepare polyketide libraries, we described the first asymmetric aldol reaction on a solid support using a resin-bound aldehyde as a starter unit.[1] Our approach was based on Evans' chiral enol borinates[2] and on the reduction of Weinreb amides[3] as the key transformation to regenerate the aldehyde functionality. Although feasable in principle, we encountered some difficulties originating from the absence of a suitable linker and the incomplete and sometimes sluggish reduction of the polymer-bound Weinreb amide. In 1998 we introduced a new silicon-based linker and a much more reliable, albeit longer, protocol to regenerate the aldehyde involving thioester **1** as key intermediate.[4] Using this methodology, we were able to synthesize chiral, nonracemic δ-lactones and a number of *O*-silylated di- and triketides.



Despite this success, some severe drawbacks related to the insoluble polymeric matrix became more and more obvious:[5](1) The heterogeneous reaction conditions entail reduced reaction rates. (2) Both the necessity for swelling and the chemical structure of the polymer are often incompatible with reaction temperature and reagents.[6](3) The insoluble polymer hampers routine reaction monitoring.

(1) Reggelin, M; Brenig, V. *Tetrahedron Lett.* **1996**, *37*, 6851.
(2) Evans, D. A.; Bartroli, J. A.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(3) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(4) Reggelin, M; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801.

(5) Reggelin, M. *Nachr. Chem. Tech. Lab.* **1997**, *45*, 1002.

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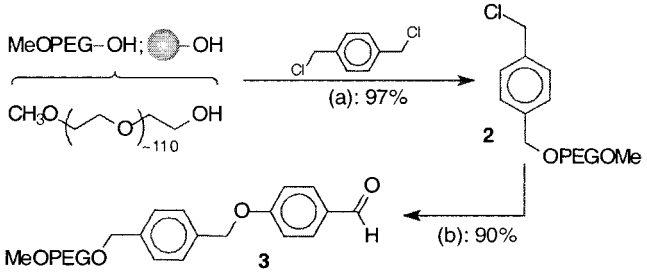
Because of these disadvantages, we often had to use tremendous excesses of reagents (50 equiv of TIPSOTf is needed to drive a silyl protection of the β-hydroxy group of the diketide product to completion!) and unacceptably long reaction times. Reactions involving heterogeneous catalysis (e.g., hydrogenations) or reactions producing insoluble byproducts during workup (e.g., DIBAH reductions) proceeded, if at all, only very unsatisfactorily. Thus, the polymer imposes restrictions on the choice of reagents and reaction conditions and renders development times high. Therefore, we decided to use a soluble polymer that can be precipitated in a solvent different from the one used in the reaction, which combines the best of two worlds.[5,7] The favorable properties of solution phase chemistry, particularly the higher reaction rates,[8] and the ease of reaction monitoring are combined with the operative advantages (easy separation of excess reagents by simple filtration of the reaction mixture) of an insoluble support.

For our purposes we found it advantageous to use the popular monomethylated poly(ethylene glycol), MeOPEG, as the polymer of choice, although there are other alternatives such as non-cross-linked polystyrenes evolving, leading to interesting alternatives.[9] Poly(ethylene glycol) and its monomethylated derivative, introduced by Bayer and Mutter in the early 1970s[10] as a polymeric support for peptide synthesis, is commercially available at different degrees of polymerization (up to 20 000 g/mol), are soluble in THF and dichloromethane and can be precipitated by addition of diethyl ether or *tert*-butyl methyl ether.

To attach the starter aldehyde onto the soluble support, we reacted MeOPEG-5000 (MW = 5000 g/mol) with 1,4-bis(chloromethyl)benzene following literature procedures (Scheme 1).[11] After precipitation of the polymeric aldehyde

Scheme 1. Preparation of the MeOPEG-Bound Aldehyde[a]



[a] Reagents and conditions: (a) 6 equiv of NaH, 2 equiv of NaI, 12 equiv of 1,4-bis(dichloromethyl)benzene, THF, rt, 5 d; (b) 6 equiv of *p*-hydroxybenzaldehyde, sodium salt, DMF, 50 °C, 24 h.

in diethyl ether (300 mL/mmol) and recrystallization from cold ethanol, we obtained a polymer loaded with 90% of the theoretical maximum load of 0.2 mmol/g.

(6) These problems have also been observed by others. See, for example: Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407.

(7) For recent reviews on the use of soluble polymers in other applications of organic synthesis, see: (a) Wentworth, P., Jr.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (c) Geckeler, K. E. *Adv. Polym. Sci.* **1995**, *121*, 31.

In the ^{1}H NMR, even without presaturation of the polymer-related intense resonances around 3.65 ppm, the signal of the terminal methoxy group appears as a baseline-separated singlet (Figure 1). Its integral serves as an internal standard to calculate the polymer loading.

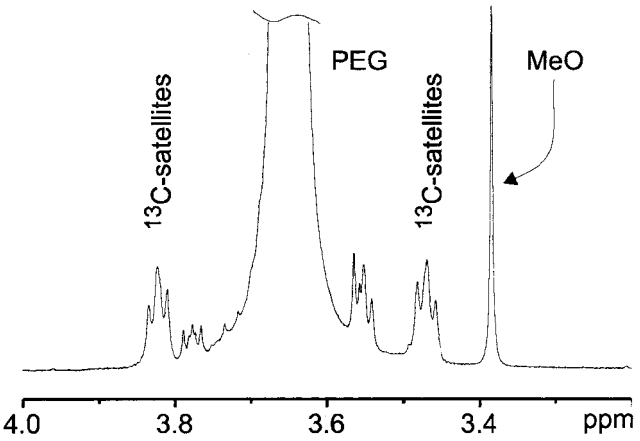
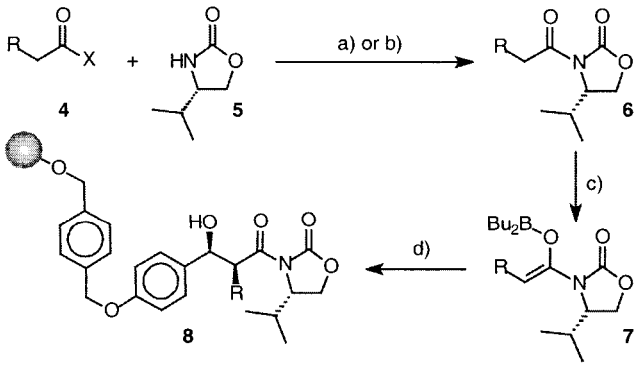


Figure 1. Part of the ^{1}H NMR of aldehyde **3** (400 MHz, 2.5 mg in 0.4 mL of $CDCl_3$). The terminal methoxy group of the polymer serves as an internal standard.

Polymeric aldehyde **3** was now dried by azeotropic distillation with toluene (100 mL/mmol),[12] dissolved in dichloromethane (80 mL/mmol), and cooled to −60 °C. To this solution were added three different enol borinates and their respective enantiomers from a separate flask at −78 °C using PTFE tubing (Scheme 2, Table 1). The enol

Scheme 2. Asymmetric Aldol Reactions on MeOPEG[a]



[a] Reagents and conditions: (a) X = Cl; 1.01 equiv of *n*-BuLi, THF, −78 °C to rt, 1 h; (b) X = OH; 1.03 equiv of **4**, 2.5 equiv of Et_3N, 1.03 equiv of Piv-Cl, 25 °C, 2 h, 1.0 equiv of **5**, 1.13 equiv of LiCl, rt, 7h; (c) 1.15 equiv of *n*-Bu_2BOTf (2.3 equiv, R = CH_2-ind), 3.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 30 min; (d) 0.16 equiv of **3**, CH_2Cl_2, −78 to −20 °C, 16 h. For R decoding, see Table 1.

borinates were prepared from the corresponding acylated oxazolidinones using standard procedures.[2] Only in the case of the novel 3-(3-indolyl)propyl imides **6c** and *ent*-**6c** was it

Table 1. Asymmetric Aldol Reactions on MeOPEG 5000

educt	aldol adducts	R	yield [%]
6a	8a	CH_3	56
ent-**6a**	*ent*-**8a**	CH_3	83
6b	**8b**	CH_2Ph	76
ent-**6b**	*ent*-**8b**	CH_2Ph	88
6c[a]	8c	CH_2-(3-ind)	57
ent-**6c**[a]	*ent*-**8c**	CH_2-(3-ind)	71

[a] Two equivalents of Bu_2BOTf were used.

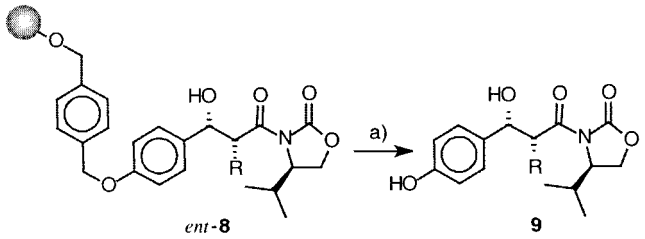
necessary to use an additional equivalent of Bu_2BOTf to temporarily protect the indole NH.

After precipitation of the polymeric aldol adducts as described above, their diastereomeric purity (≥97% ds) was confirmed by ^1H NMR spectroscopy. Following this protocol we were able to synthesize three pairs of enantiomeric polymer-bound diketides as pure isomers in unoptimized yields between 57% and 88%.

To validate the assumption that the soluble polymeric support should permit the removal of the benzyl linker by heterogeneous hydrogenation, we treated *ent*-**8a** with hydrogen (1 atm) over Pd black for 48 h in methanol at room temperature (Scheme 3).

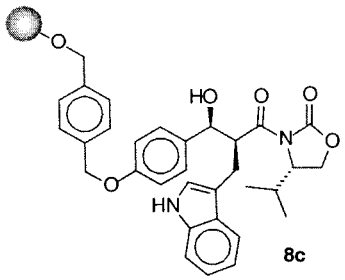
To our delight and in contrast to the results of a similar experiment using an unsoluble support,[13] cleavage of the desired aldol product **9** occurred smoothly. After filtration and precipitation of the unloaded polymer, evaporation of the supernatant liquid delivered the product as a pure isomer in 85% yield.

Scheme 3. Cleavage by Heterogeneous Hydrogenation[a]



[a] Reagents and conditions: (a) H_2 (1 atm), Pd black, MeOH, rt, 48 h.

In summary we have shown that asymmetric aldol reactions employing chiral enol borinates are feasable on the soluble polymeric support MeOPEG-5000 without deterioration of stereoselectivity. 3-Indolylmethyl-substituted diketides **8c** and *ent*-**8c** have been prepared for the first time, and their potential as open chain scaffolds in combinatorial di- and triketide libraries is of current interest in our laboratories.



Furthermore, it has been shown that catalytic hydrogenation using insoluble catalysts is compatible with the polymeric nature of the substrate, thus considerably widening the scope of applicable reagents in polymer-supported organic synthesis. Encouraged by these results we are currently exploring the possibility of returning to our initial concept for the synthesis of combinatorial libraries of decorated polyketides employing reactions which proved to be difficult to perform on an insoluble support.[1,3,4]

Acknowledgment. We gratefully acknowledge the Solvay Pharmaceuticals (Hannover, Germany) for their generous support of this work. Furthermore, we thank Prof. Dr. C. Griesinger for continuous support.

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(8) Kinetic studies on the aminolysis of glycine *p*-nitrophenyl esters with polymeric or monomeric glycine esters have shown that the reaction rate is not significantly affected by the presence of the polymer. Bayer, E.; Mutter, M.; Uhmann, R.; Polster, J.; Mauser, H. *J. Am. Chem. Soc.* **1974**, *96*, 7333.

(9) First application of non-cross-linked polystyrene in organic synthesis: (a) Shemyakin, M. M.; Ovchinnikov, Y. A.; Kinyushkin, A. A. *Tetrahedron Lett.* **1965**, *6*, 2323. (b) Peptide synthesis: Narita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477. (c) Recent application in prostanoid chemistry: Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859.

(10) (a) Mutter, M.; Hagenmaier, H.; Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 811. (b) Bayer, E.; Mutter, M. *Nature* **1972**, *237*, 512. (c) Small molecule library synthesis on MeOPEG: Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419.

(11) Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1995**, *117*, 2116.

(12) This treatment of the polymer prior to the aldol reactions proved to be an unavoidable necessity. As expected the polyether structure retains a considerable amount of water which has to be removed thoroughly.

(13) Even the application of a $Pd(OAc)_2$ solution prior to hydrogenation (Schlattner, J. M.; Mazur, R. H.; Goodmonson, O. *Tetrahedron Lett.* **1977**, *33*, 2851) was not very successful. Reggelin, M.; Brenig,V., unpublished results.