

TOWARDS POLYKETIDE LIBRARIES: ITERATIVE, ASYMMETRIC ALDOL REACTIONS ON A SOLID SUPPORT

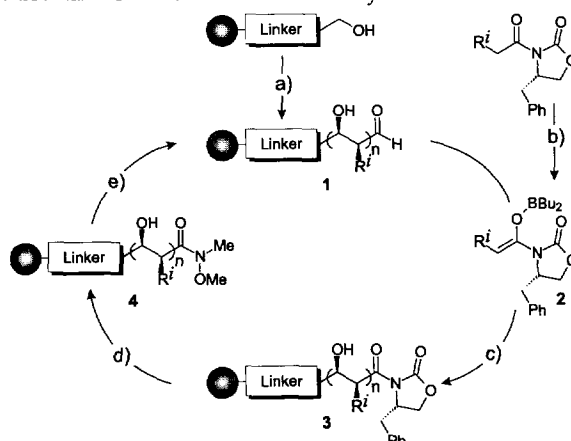
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Abstract: A polymer bound aldehyde obtained from the oxidation of Wang's resin can be used as starter unit for iterative, asymmetric aldol reactions. The synthetic protocol relies on the boron enolate chemistry of D. A. Evans, the *N*-methoxy substituted amides of S. M. Weinreb and entails the opportunity for the generation of polyketide libraries. Copyright © 1996 Elsevier Science Ltd

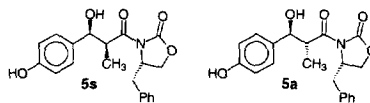
With the advent of combinatorial medicinal chemistry an aggressive, worldwide effort to exploit the enormous potential of the method to find and develop pharmaceutical leads has begun¹. For that reason there is an ongoing interest in the synthesis of biopolymer based libraries using a well established set of reactions being optimized for more than thirty years². But there are severe drawbacks associated with these oligonucleotide or oligopeptide libraries. Their low bioavailability caused by rapid physiological clearing times excludes them from being therapeutically useful. Therefore extensive modifications of the discovered leads is usually necessary. Furthermore diversification is hampered by restrictions on both the available building blocks and on the bond forming reaction.

In this report we would like to introduce a new approach involving polyketides as a group of biopolymers that has been completely excluded till now from the chemical synthesis of molecular diversity. Polyketides are an extremely rich source of bioactive molecules with advantageous pharmacokinetic profiles, including antibiotics, anticancer agents, immunosuppressants and veterinary products. Outside living systems the synthesis of reduced polyketides bearing multiple stereogenic centers demands for a sequence of stereocontrolled aldol reactions in combination with a repetitive reestablishment of a key functionality. According to Scheme 1 this aim should be achievable by a reaction sequence based on the well known procedures developed by D. A. Evans³ and S. M. Weinreb⁴. To put this concept into practice we chose Wang resin⁵ (0.84 mmol/g) and oxidized it with sulfur trioxide pyridine complex. A strong



Scheme 1: Iterative, asymmetric aldol reactions on a solid support based on the Evans and Weinreb procedures. a) $\text{SO}_3 \cdot \text{Py}$, DMSO, NEt_3 ; b) $(n\text{Bu})_2\text{BOTf}$, NEt_3 ; c) 6h, -78°C , 12h, 0°C , $\text{MeOH}/\text{H}_2\text{O}_2$; d) Me_3Al , $\text{MeNH}(\text{OMe}) \cdot \text{HCl}$; e) TIPSOTf , 2,6-lutidine; DIBAL , -40°C ; 5% HCl/EtOH .

absorption at 1696 cm^{-1} in the FT-IR spectrum of the resin bound product **1** ($n = 1$) proves the successful oxidation to an aromatic aldehyde. After the residual free hydroxy groups have been capped (TIPS-triflate), the resin was treated with the boron enolate **2** ($R^i = \text{CH}_3$). Two new carbonyl resonances were observed: The first at 1780 cm^{-1} is characteristic for an urethane carbonyl group in a five-membered ring and the second at 1700 cm^{-1} is related to the amide moiety. Finally the intense, broad absorption at 3530 cm^{-1} is indicative for the expected H-bonded hydroxy group of the aldol adduct. We analyzed yield and stereochemistry of this product, by cleaving the benzyl ether linkage with boron trichloride in CH_2Cl_2 at -78°C . The expected *syn*-aldol adduct **5s** together



with the *anti*-diastereomer **5a** was isolated in a 87:13 ratio. To answer the question what the reason for that diminished degree of stereocontrol might be, we synthesized the benzylated *syn* aldol in solution as a pure isomer and treated it with boron trichloride the same way we did to remove the adduct from the resin. As we had suspected, slight epimerization took place (*syn* : *anti* = 90 : 10) thus providing strong evidence that the observed reduction in stereocontrol is not a property of the polymer bound protocol but rather a workup problem. We next converted the imide **3** ($R^i = \text{CH}_3$) to the corresponding Weinreb-amide⁴ **4** ($R^i = \text{CH}_3$). This reaction was run with a tenfold excess of both $\text{Al}(\text{CH}_3)_3$ and *N,O*-dimethylhydroxylamine. After acidic workup 65% (related to the maximum load of 0.84 mmol/g) of the free oxazolidinone could be isolated. Therefore the oxidation step, the aldol addition and the transamidation reactions worked with a total yield exceeding 65% (74% in solution). The FT-IR of the resin at this point exhibits a C=O stretching vibration at 1640 cm^{-1} , which is in good agreement with the 1650 cm^{-1} observed in solution. To complete the reaction cycle we reduced the resin bound Weinreb amide, after protection of the free hydroxy group as TIPS-ether, with DIBAH in hexanes. IR spectroscopic analysis shows a new C=O vibration at 1723 cm^{-1} which is indicative for an aliphatic aldehyde. Unfortunately till now we were not able to suppress the formation of a by product which is characterized by an IR stretching at 1676 cm^{-1} . This frequency is in accordance with an α,β -unsaturated aldehyde and so we conclude that the acidic workup is accompanied by some desilylation and elimination.

In summary we have shown that iterative aldol reactions based on chiral boron enolates and Weinreb type amides on a solid support are possible. After some necessary improvements especially in the final step of the reaction cycle it will be possible to generate polyketide libraries. Unlike polypeptide or polynucleotide libraries diversification is not only achievable by the exploitation of a given pool of monomeric units, but by free choice of sidechains R^i and the absolute configuration at the newly created stereogenic centers. Furthermore every alternative procedure which regenerates a functionality occurring in the proposed cycle will further enhance the potential for diversification.

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REFERENCES AND NOTES

- (a) M. Gallop, R. W. Barrett, W. J. Dower, S. P. A. Fodor, E. M. Gordon, *J. Med. Chem.* **1994**, *37*, 1233-1251. (b) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994**, *37*, 1385-1401.
- R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149.
- D. A. Evans, J. A. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127.
- S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815.
- (a) S. S. Wang, *J. Am. Chem. Soc.* **1973**, *95*, 1328-1333. (b) Gui-shen Lu, S. Mojsov, J. P. Tam, R. B. Merrifield, *J. Org. Chem.* **1981**, *46*, 3433-3436.