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TOWARDS POLYKETIDE LIBRARIES - II: SYNTHESIS OF CHIRAL ARACEMIC DI- AND TRIKETIDES ON A SOLID SUPPORT

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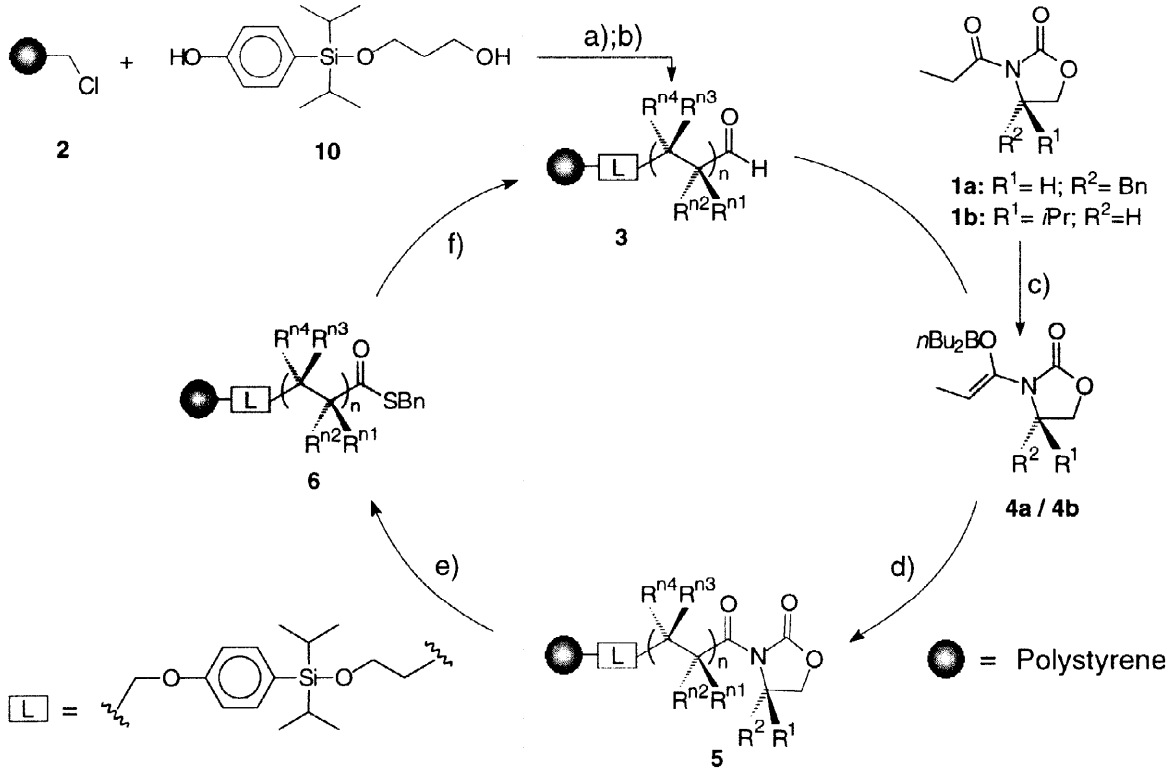
Abstract: A new fluoride ion cleavable linker serves as starter unit for iterative asymmetric aldol reactions on a solid support. The synthetic protocol relies on the boron enolate chemistry of D. A. Evans and a cyclic reestablishment of key functionalities. It entails the opportunity for the generation of di- and triketide libraries. © 1998 Elsevier Science Ltd. All rights reserved.

Polyketides [1,2] are an extremely rich source of bioactive substances with advantageous pharmacokinetic profiles. It has been estimated that the number of lead structures related to the total amount of known polyketides reaches 0.1%, which exceeds any lead/diversity ratio known of other classes of compounds. For that reason it seems highly promising to develop a flexible methodology, which allows to access as much as possible of the constitutional and configurational space available for polyketides in a combinatorial environment (Scheme 1, Table 1).



Scheme 1: Iterative asymmetric aldol additions on a solid support. a) NaOMe, DMF, 50°C, 24h; b) SO_3/Py, DMSO, NEt_3, rt, 3h; c) $(nBu)_2BOTf$, NEt_3; d) 4h, -78°C, 12h, -78°C → 0°C; e) (1) LiOH, H_2O_2, THF, H_2O, 0°C, 4h; (2) BnSH, DMAP, DCC; THF, rt, 18h; f) (1) TIPSOTf, 2.6-lutidine, 0°C, 48h; (2) $LiBH_4$, THF, rt, 12h; (3) DMP, CH_2Cl_2, rt, 18h. To identify individual substances use Table 1.

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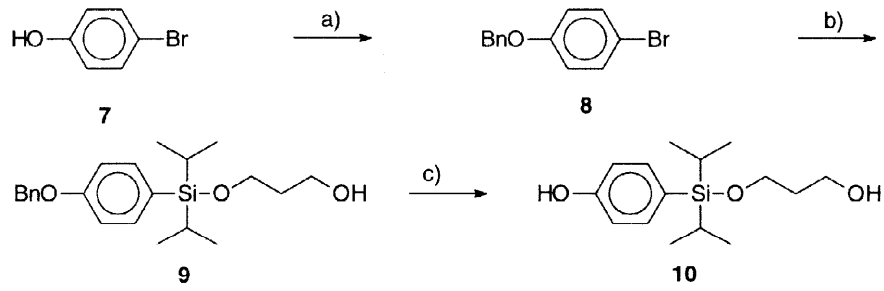
Following these lines, in 1996 [3] we introduced a resin bound protocol relying on iterative asymmetric aldol-reactions [4-9], based on the chiral boron enolates developed by D. A. Evans [10] and on the hydroxyl amine derived amides introduced by Weinreb et al. [11].

Table 1: Residue encoding for the compounds in Scheme 1.

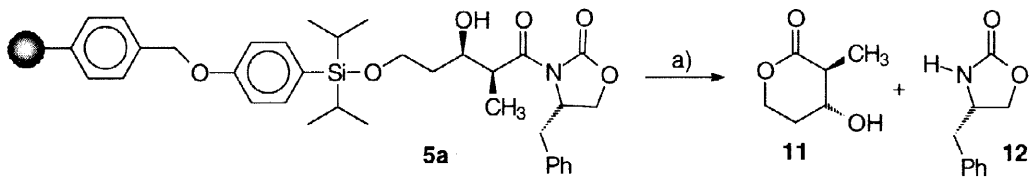
#	R^1	R^2	R^{11}	R^{12}	R^{13}	R^{14}	R^{21}	R^{22}	R^{23}	R^{24}
3a	-	-	-	-	-	-	-	-	-	-
3b	-	-	H	Me	H	OTIPS	-	-	-	-
5a	H	Bn	Me	H	OH	H	-	-	-	-
5b	iPr	H	H	Me	H	OH	-	-	-	-
5c	iPr	H	H	**Me**	H	**OTIPS**	H	Me	H	OH
5d	iPr	H	**Me**	H	**OTIPS**	H	H	Me	H	H
6b	-	-	H	Me	H	OH	-	-	-	-

Despite the principal feasibility of the approach we encountered a number of problems related to the absence of a suitable linker and the difficulty to reestablish the aldehyde functionality from the Weinreb amide in a quantitative fashion. Therefore we decided to introduce two major changes to the published protocol. First we replaced the Weinreb amide by thioester **6** as the aldehyde precursor and as a second modification we developed the new fluoride ion cleavable linker **10**, whose synthesis is illustrated in Scheme 2.



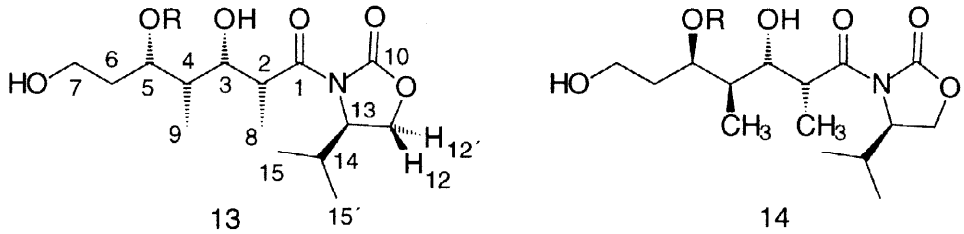
Scheme 2: Synthesis of fluoride ion cleavable linker **10**: a) BnCl, NaOMe, DMF (85%); b) (1) *n*BuLi, (2) dichlorodiisopropyl silane, (3) 1,3-propanediol, DMAP, NEt_3 (45%); c) H_2/Pd, MeOH (95%).

As a key transformation we silylated the aromatic bromide **8** leading to the benzylated precursor of the desired diol **10**, which then was attached to Merrifield resin **2** [12] using NaOMe as a base (Scheme 1). The resulting resin bound alcohol can be oxidised with SO_3-pyridine [13] yielding the aldehyde **3a** (n = 0, Scheme 1, Table 1, IR: 1724 cm^{-1}). In order to validate the suitability of the new linker in the context of the proposed reaction cycle we first prepared the diketide **5a** (IR: 1774 cm^{-1} and 1696 cm^{-1}) using the enol borinate **4a** derived from oxazolidinone **1a** (Scheme 1). Its fluoride ion induced desilylation uncovers an oxygen nucleophile, which attacks the exocyclic carbonyl group of the chiral imide producing the expected δ-lactone **11** [14] (14% yield; *ds*≥ 99% by capillary GC) as well as the deacylated oxazolidinone **12** (41% yield; Scheme 3) [15].



Scheme 3: Synthesis of chiral aracemic δ - lactones on Merrifield resin. Reaction conditions: a) TBAF, HOAc, THF, 40°C, 14h.

This successful completion of the resin bound oxidation, hydroxyalkylation and cleavage sequence encouraged us to tackle the challenge to obtain enantiopure di- and triketide products following the synthetic cycle outlined in Scheme 1. Starting with the already mentioned aldehyde **3a** we added the (*R*)-valine derived enol borinate **1b** yielding the diketide **5b**. The oxidative hydrolysis (LiOH, H_2O_2) of this intermediate [IR (carboxylic acid): 1715 cm^{-1}] followed by its DCC mediated coupling with benzyl mercaptane (30 eq) yields the thioester **6b** (IR: 1683 cm^{-1}). After protection of the hydroxyl function as TIPS-ether (30 eq TIPSOTf, 0°C, 48h, 2.6-lutidine as solvent), we reduced the protected ester using lithium borohydride in THF and reoxidised the reaction product with Dess-Martin periodinan [16] (DMP; 10 eq) thus obtaining the elongated aldehyde **3b** (IR: 1724 cm^{-1}). Thereby the successful reestablishment of the aldehyde functionality sets the stage for the next cycle. We repeated the already described sequence again using the (*R*)-valine derived oxazolidinone **1b**, which leads to the resin bound all-*syn*-configurated triketide **5c**. After TBAF induced cleavage the free triketide **13** [17] was isolated in 12% yield [18] (based on the amount of isolated oxazolidinone obtained after hydrolysis of **5b**, Scheme 4). According to ^1H- and ^{13}C-NMR-spectroscopic analysis the compound was pure and in all respects identical to a reference compound prepared in solution [19]. As a second example we changed the nucleophile used in the first aldoladdition from **4b** to *ent*-**4b**, thus inverting the induced absolute configuration at the C-atoms 4 and 5. This way we obtained the diastereomeric triketide **5d**, which can be cleaved from the resin ending up with the monoprotected triol **14** (7% yield). Again, the NMR-data of this compound is prooved to be in accordance with the expectation [20].



Scheme 4: Triketides obtained by iterative asymmetric aldoladditions on a solid phase. R = TIPS.

In summary we have shown that iterative aldol reactions based on chiral boron enolates can be employed to synthesise di- and triketides in diastereomerically pure form on a solid phase. Additionally the synthetic protocol introduced here offers the opportunity to prepare combinatorial libraries of di- and triketides, β-hydroxycarboxylic acids, β-hydroxythioesters, *1,2n+1*-polyols and δ-lactones. Beside the obvious possibility to "decorate" the hydroxyl groups a fascinating application of these libraries may be their use as starter units in polyketide synthesis with genetically manipulated polyketide synthases (PKS) [21]. This could be a means to translate molecular diversity at the di- and triketide level to diversity at much higher levels of molecular complexity. Due to the relatively low substrate specificity of the PKS's even glycosylated and ring expanded products should be accessible starting with the above mentioned libraries.

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References and Notes:

[1] O'Hagan D., Nat. Prod. Rep. 1995; 12: 1 - 32.

[2] Katz L., Donadio S. Annu. Rev. Microbiol. 1993; 47: 875 - 912.

[3] Reggelin M., Brenig V. Tetrahedron Lett. 1996; 37: 6851 - 6852.

[4] Review of solid phase synthesis of small organic molecules: Balkenhohl F., v. d. Bussche-Hünnefeld C., Lansky AL., Zechel C. Angew. Chem. 1996; 108: 2436 - 2488.

[5] Kurth MJ., Ahlberg Randall LA., Chen C., Melander C., Miller RB. J. Org. Chem. 1994; 59: 5862 -5864.

[6] Kobayashi S., Hachiya I., Yasuda M. Tetrahedron Lett. 1996; 37: 5569 - 5572.

[7] Polymer supported "Evans"-oxazolidinone: Allin SM., Shuttleworth SJ. Tetrahedron Lett. 1996; 37: 8023 - 8026.

[8] Purandare SV., Natarajan S. Tetrahedron Lett. 1997; 38: 8777 - 8780.

[9] Epothilone synthesis: Nicolaou KC., Winssinger N., Pastor J., Ninkovic S., Sarabia F., He Y., Vourloumis D., Yang Z., Li T., Giannakakou P., Hamel E. Nature 1997; 387: 268 - 272.

[10] Evans DA., Bartroli JA., Shih TL. J. Am. Chem. Soc. 1981; 103: 2127.

[11] Nahm S., Weinreb SM. Tetrahedron Lett. 1981; 22: 3815.

[12] Merrifield RB. J. Am. Chem. Soc. 1963; 85: 2149; Merrifield resin (1.1 mmol of CH_2Cl/g : Polystyrene 1 % divinylbenzene copolymer) was purchased from Novabiochem.

[13] Parikh JR., v. Doering WE. J. Am. Chem. Soc. 1967; 89: 5505 - 5507.

[14] ^1H- and ^{13}C NMR spectroscopic data were identical to published data: Guindon Y., Faucher AM., Bourque E., Caron V., Jung G., Landry SR. J. Org. Chem. 1997; 62: 9276 - 9283.

[15] For this deprotection to be successful it is mandatory to neutralise the tetrabutylammonium fluoride with acetic acid. Otherwise complete dehydration of **11** to the corresponding unsaturated δ-lactone occurs.

[16] Dess DB., Martin JC. J. Org. Chem. 1983; 48: 4156 - 4158.

[17] The crude product (25 mg) contains at least 60% (15 mg) of the isolated triketide **13**.

[18] Each synthetic step of the reaction cycle proceeded with an average yield of ≥ 70% (related to the maximum load of the resin).

[19] **13**: ^1H NMR (270 MHz, $CDCl_3$, 300 K, TMS): δ = 0.858 /0.891 (2×d, 15-H_3, 15´-H_3); 0.95 (d, 9-H_3); 1.058 (TIPS-H_{21}); 1.307 (d, 8-H_3); 1.677 (ddq, 4-H); 1.832 - 1.927 (m, 6-H_2); 2.292 (dqq, 14-H); 2.262 (brs, 2×OH); 3.640 (dt, 7-H_2); 3.942 (dq, 2-H); 4.081 (dd, 3-H); 4.135 (ddd, 5-H); 4.180 (dd, 12-H); 4.241 (dd, 12´-H), 4.424 (ddd,13-H)
$J_{2,3}$ = 6.5Hz; $J_{3,4}$ = 3.6Hz; $J_{4,5}$ = 3.3 Hz; $J_{5,6}$ = 5.5/7.7 Hz; $J_{6,7}$ = 6.5Hz; $J_{7,7'}$ = 2.0Hz; $J_{2,8}$ = 6.9 Hz; $J_{4,9}$ = 7.0Hz; $J_{12,12'}$ = 9.1Hz; $J_{12,13}$ = 3.5Hz; $J_{12',13}$ = 7.9Hz; $J_{14,15}$ / $J_{14,15'}$ = 6.9/7.1 Hz
^{13}C NMR (67.9 MHz, $CDCl_3$, 300 K): δ = 7.48 (C-9); 13.19 (CH-TIPS), 13.85 (C-8), 14.69/17.90 (C-15, C-15´); 18.16/18.20 (2×CH_3TIPS); 28.37 (C-14); 37.04 (C-6); 39.06 (C-4); 41.34 (C-2); 58.19 (C-13); 59.70 (C-7); 63.26 (C-12); 73.81 (C-3); 74.36 (C-5); 153.21 (C-10); 177.15 (C-1).
HRMS (CI^+): Calculated for ($C_{24}H_{47}NO_6Si+H^+$): 474.3251. Found: 474.3227.

[20] **14**: ^1H NMR (270 MHz, $CDCl_3$, 300 K, TMS): δ = 0.85 (d, 9-H_3); 0.857/0.891 (2×d, 15-H_3/15´-H_3); 1.066 (TIPS-H_{21}); 1.193 (d, 8-H_3); 1.528 - 2.192 (brs, 2×OH;m, 6-H_2/4-H); 2.395 (dqq, 14-H); 3.700 (dt, 7-H_2); 3.878 (dq, 2-H); 3.996 (dd, 3-H); 4.186 (dd, 12-H); 4.272 (dd, 12´-H); 4.308 (dt, 5-H); 4.449 (ddd, 13-H);
$J_{2,3}$ = 2.4Hz; $J_{3,4}$ = 9.7Hz; $J_{4,5}$ = 2.0Hz; $J_{5,6}$ = 6.5Hz; $J_{6,7}$ = 6.5Hz; $J_{7,7'}$ = 2.3Hz; $J_{2,8}$ = 7.0Hz; $J_{4,9}$ = 7.1Hz; $J_{12,12'}$ = 9.0Hz; $J_{12,13}$ = 3.0Hz; $J_{12',13}$ = 8.1Hz; $J_{13,14}$ = 3.8Hz; $J_{14,15}$ / $J_{14,15'}$ = 6.9/7.1Hz
^{13}C NMR (62.9 MHz, $CDCl_3$, 300 K): δ = 9.21 (C-8); 11.07 (C-9); 12.67 (CH-TIPS);14.43/17.82 (C-15,C-15´); 17.97/18.02(2×CH_3TIPS); 28.10 (C-14); 36.23 (C-6); 39.36 (C-4); 40.11 (C-2); 58.53 (C-13); 59.67 (C-7) 63.12 (C-12); 72.13 (C-5); 72.48 (C-3); 153.55 (C-10);176.52 (C-1).
HRMS (CI^+): Calculated for ($C_{24}H_{47}NO_6Si+H^+$): 474.3251. Found: 474.3222.

[21] Jacobsen JR., Hutchinson CR., Cane DE., Khosla C. Science 1997; 277: 367 - 369.