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Toward the Combinatorial Synthesis of Polyketide Libraries: Asymmetric Aldol Reactions with α-Chiral Aldehydes on Solid Support

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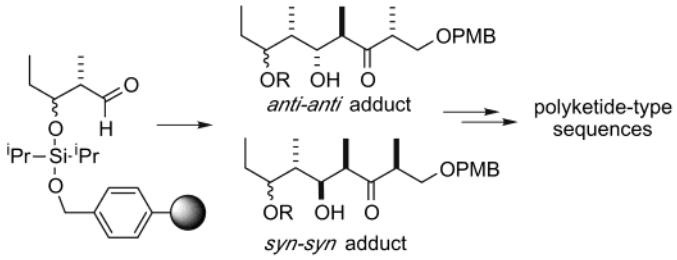
ABSTRACT

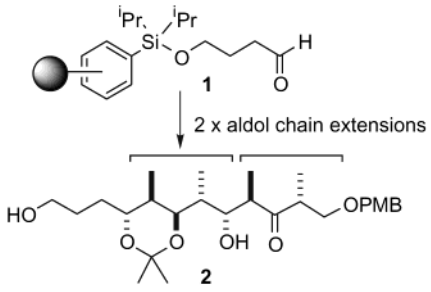


The viability of performing stereocontrolled aldol additions with α-chiral aldehydes attached by a silyl linker to a hydroxymethylpolystyrene resin is demonstrated for boron and titanium enolates. Subsequent ketone reduction and manipulation on the solid support leads to elaborate stereopentad sequences, as occur in 6-deoxyerythronolide B and discodermolide.

The polyketides represent an important reservoir of molecular diversity for drug discovery.[1] By applying the methods of combinatorial chemistry,[2] the synthesis of libraries of novel polyketide-type structures are possible.[3,4] For synthetic purposes, it is desirable to assemble such compounds by chain extension on solid support, enabling the permutation of the stereochemistry and substitution pattern in the nascent carbon skeleton. However, the controlled solid-phase synthesis of the characteristic sequences of contiguous stereocenters that occur in structurally complex polyketides is highly challenging. By starting from simple aldehydes on solid support, we have recently developed iterative aldol procedures[3,5] to generate libraries of polyketide-type sequences of increasing stereochemical complexity, as in **1** → **2** (Scheme 1).[3e]

As part of a general program to expand polyketide diversity,[6,7] we now demonstrate the use of more elaborate

Scheme 1



(1) (a) O'Hagan, D. *The Polyketide Metabolites*; Ellis Harwood: Chichester, 1991. (b) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1.

(2) (a) Balkenhohl, F.; Bussche-Hünnefeld, C. v. d.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. (b) MacLean, D.; Baldwin, J. J.; Ivanov, V. T.; Kato, Y.; Shaw, A.; Schneider, P.; Gordon, E. M. *J. Comb. Chem.* **2000**, *2*, 562. (c) An, H. Y.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311.

(3) (a) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7441. (b) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7445. (c) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999. (d) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003. (e) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315.

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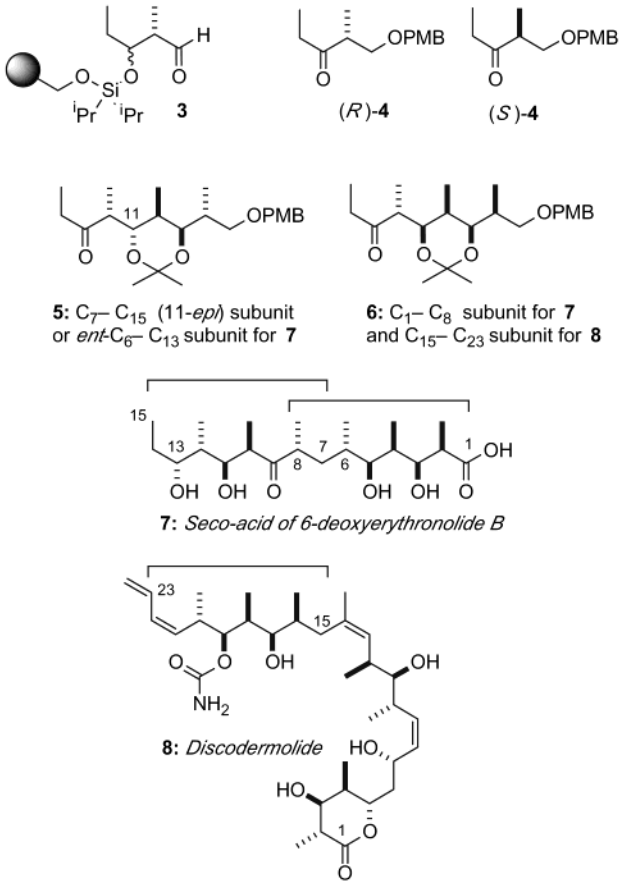
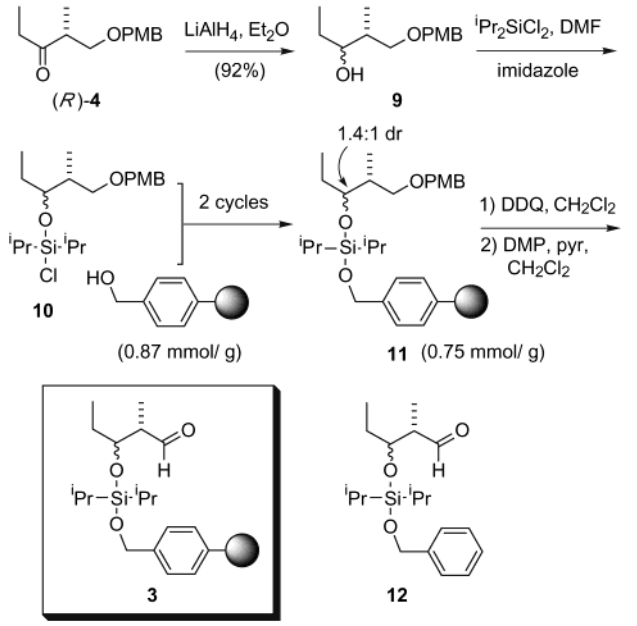
Scheme 2



resin-bound aldehydes **3** (Scheme 2), attached through a secondary alcohol by a novel silyl linker to a polystyrene support. Aldol chain extension with chiral ketone modules, such as (*R*)- and (*S*)-**4**, leads to the expedient construction of defined sequences of stereocenters. This is illustrated here by the solid-phase synthesis of tetrapropionates **5** and **6** that correspond configurationally to the indicated segments of the *seco*-acid of 6-deoxyerythronolide B (**7**) and the anticancer agent discodermolide (**8**).[8] By suitable structural permutation[3d,e] in **3** and **4**, this methodology should facilitate the parallel synthesis of diverse polyketide-type libraries.

By employing a diisopropylsilyl linker,[9,10] the required chiral aldehyde **3** was prepared on solid support (Scheme 3). Reduction of the ketone (*R*)-**4**,[3e] which is also used as a

Scheme 3



chain-extending module, with $LiAlH_4$ gave the alcohols **9** (92%, 1.4:1 diastereomeric mixture in favor of the *syn* isomer). As this hydroxyl center is later oxidized back to a ketone, both epimeric series were conveniently processed together; providing a check for any difference in reactivity and/or selectivity. A modification of Danishefsky's silyl linking protocol,[9] as introduced for glycopeptide synthesis, allowed attachment of the sterically hindered secondary alcohol **9** to the polystyrene support.[10] This involved silylation of the alcohol **9** with diisopropyldichlorosilane (1 equiv) in the presence of imidazole (6 equiv, 1 h) in DMF to generate a solution of intermediate **10**, followed by treatment of pre-swollen hydroxymethyl Merrifield resin[11] (0.87 mmol/g loading) with **10** (6 equiv) for 36 h (2 cycles). This two-step sequence gave the silyl ether **11** with a high loading value (0.75 mmol/g, as determined by cleavage with TBAF). Deprotection of the PMB ether in **11** with DDQ,[12] followed by Dess−Martin oxidation, then proceeded cleanly to provide

(4) For other approaches to solid-phase polyketide synthesis, see: (a) Reggelin, M.; Brenig, V. *Tetrahedron Lett.* **1996**, *37*, 6851. (b) Panek, J. S.; Zhu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12022. (c) Reggelin, M.; Brenig, V.; Welcker, R. *Tetrahedron Lett.* **1998**, *39*, 4801. (d) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4631.

(5) For the modular synthesis of polyketide building blocks by nitrile oxide cycloadditions, see: Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082.

(6) For reviews on polyketide synthesis, see: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) Bode, J. W.; Carreira, E. M. In *The Chemical Synthesis of Natural Products*; Hale, K. J., Ed.; Sheffield Academic Press: London, 2000; pp 40−62. (c) Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 249−297.

(7) For structural diversification by the reconstruction of polyketide biosynthetic pathways, see: (a) Cortes, J.; Wiesmann, K. E. H.; Roberts, G. A.; Brown, M. J. B.; Staunton, J.; Leadlay, P. F. *Science* **1995**, *268*, 1487. (b) Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 881. (c) Katz, L. *Chem. Rev.* **1997**, *97*, 2557. (d) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63.

(8) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. (b) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243. (c) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287. (d) Balachandran, R.; ter Haar, E.; Welsh, M. J.; Grant, S. G.; Day, B. W. *Anti-Cancer Drugs* **1998**, *9*, 67.

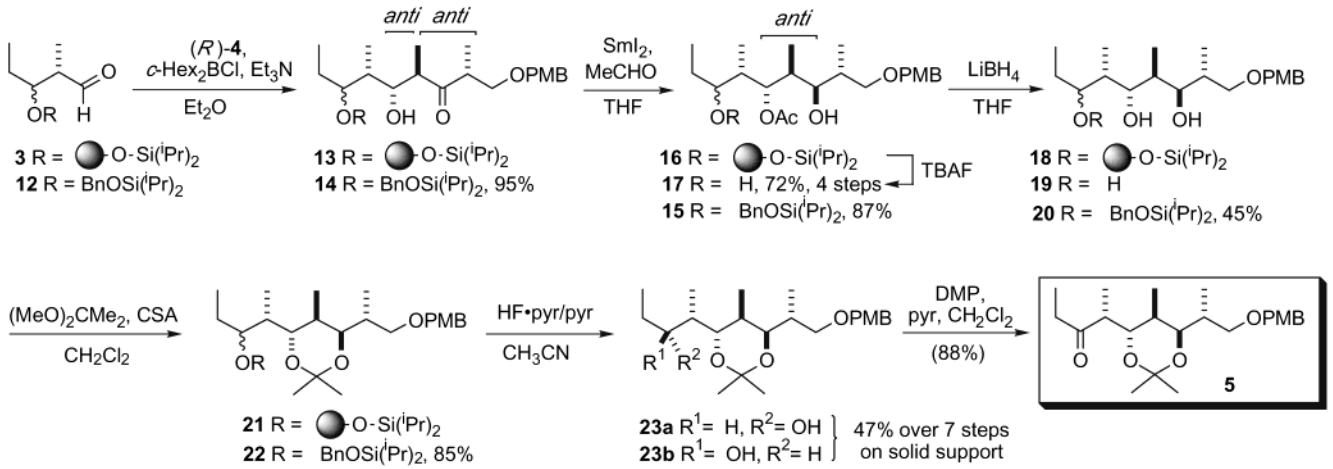
(9) Savin, K. A.; Woo, J. C. G.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 4183.

(10) It was not possible to attach alcohol **9** directly to the chlorodiisopropylsilylpolystyrene resin used in our earlier work (ref 3e), necessitating the introduction of this new silyl linker protocol.

(11) The hydroxy-modified Merrifield resin (1% DVB, 100−200 mesh) was purchased from Novabiochem and used without further manipulation.

(12) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

Scheme 4



the required aldehyde **3**. To develop the chemistry and assist characterization (gel-phase ^{13}C NMR, FT-IR) of the subsequent resin-bound intermediates, aldehyde **12** was prepared as a solution model from benzyl alcohol in an analogous manner, thus permitting a direct comparison of the reaction yields and diastereoselectivities.

Suitable conditions for the aldol chain extension of resin-bound aldehyde **3** with ketone (*R*)-**4** were first developed (Scheme 4). Reaction of aldehyde **3** (−78 to −27 °C, 17 h) with a preformed solution of the (*E*)-enol dicyclohexylborinate[13] derived from (*R*)-**4** (6 equiv, two cycles) in Et_2O gave the *anti-anti* adduct **13** after standard oxidative workup (H_2O_2, MeOH, DMF, pH 7 buffer). At this stage, gel-phase ^{13}C NMR and FT-IR analysis indicated essentially complete conversion,[14] with the resulting resin **13** displaying diagnostic carbonyl resonances (216.6 and 216.9 ppm). Additionally, comparison of the gel-phase ^{13}C NMR spectrum of adduct **13** with that obtained for the corresponding solution-phase model **14** suggested a high level of diastereoselectivity, as expected from a matched relationship of the aldol coupling partners.

To achieve an efficient *anti*-selective reduction of the *β*-hydroxy ketone **13**, a modified Evans−Tishchenko[15] protocol was developed for the solid-phase reaction. Initial experiments with the solution model **14** using a stoichiometric amount of SmI_2 and acetaldehyde at 0 °C gave acetate **15** in 87% yield (97:3 dr, where the two epimers at the linking center were separated by chromatography). Reaction of the resin-bound adduct **13** with this reagent system over two cycles (−20 to 0 °C, 16 h) gave resin **16** with complete conversion. At this stage, cleavage from the resin **16** gave alcohol **17** in 72% yield over four steps from **11**. Treatment of **16** with $LiBH_4$ led to reductive removal of the acetate, generating the corresponding resin-bound 1,3-*anti*-diol **18**.

Transformation of resin-bound alcohol **18** to the acetonide derivative **21** permitted confirmation of the 1,3-*anti* relationship from diagnostic ^{13}C NMR resonances (100.2, 23.5, 25.1 ppm).[16] Subsequent cleavage of the resin **21** (HF•pyr/pyr) provided the separable epimeric alcohols **23a** and **23b** (ca. 1.4:1) in 47% yield over seven steps, with high selectivity for the newly generated stereocenters (>95:5 dr). This represents an average yield of 90% for each step performed on the resin. In comparison, a 22% overall yield of **23a** and **23b** was obtained for the corresponding solution phase synthesis (**12** → **14** → **15** → **20** → **22** → **23a**,**b**), which required chromatographic purification of several intermediates. By regenerating the aldehyde functionality in resin **21**, further chain extension cycles can be potentially performed to access even more elaborate polyketide sequences. For our present purposes, Dess−Martin oxidation of the epimeric alcohols **23a** and **23b** led to isolation of the stereopentad **5** (88%) as a single isomer, which is configurationally related to two tetrapropionate fragments of 6-deoxyerythronolide B.

To expand polyketide diversity, other stereochemical permutations need to be developed as the chain is extended. For the solid-phase synthesis of tetraketide sequence **6**, relevant to discodermolide and 6-deoxyerythronolide B, a more challenging *syn*-selective addition of ketone (*S*)-**4** to the resin-bound aldehyde **3** was required. Previous studies in solution showed that such ethyl ketones provide *syn-syn* aldol adducts when enolized with $Sn(OTf)_2$ and Et_3N.[17] In the present case, these Lewis acidic conditions were found to partly cleave the silyl linker in the aldehyde component.[18]

(13) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185.

(14) Attempts to determine the yield and the diastereoselectivity at this stage by cleavage of the resin with HF•pyr/pyr gave only complex mixtures due to hemiacetal formation with the ketone group.

(15) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

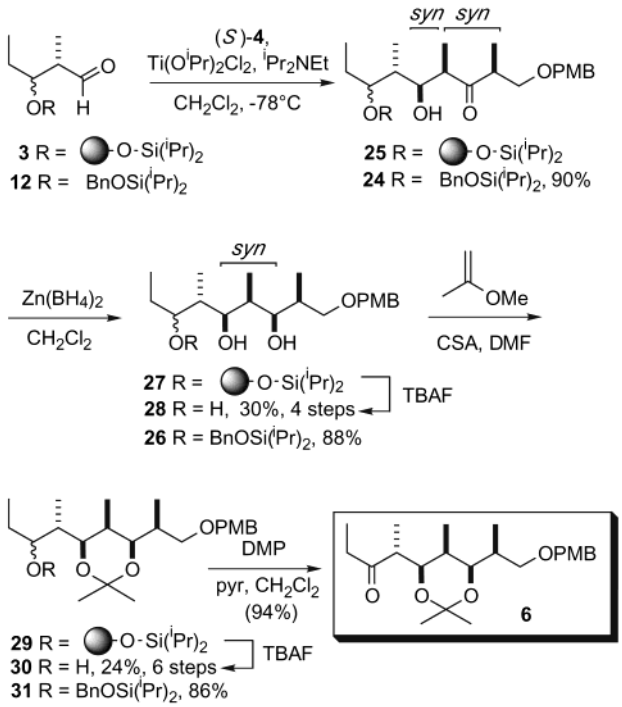
(16) (a) Rychnovsky, S. D.; Skalitzky, D. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(17) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.

(18) While boron-mediated *anti*-aldol reactions work well on solid support, the use of suitable boron reagents (9-BBNOTf, Bu_2BOTf, (+)-Ipc_2BOTf) to promote *Z*-enolization and *syn*-aldol additions of ketone (*S*)-**4** led only to poor yields and stereoselectivities with resin-bound aldehyde **3**.

However, mild $Ti(O^iPr)_2Cl_2$-mediated enolization[19] of ketone (*S*)-**4** proved to be compatible, leading to the isolation of the *syn*-*syn* aldol adducts **24** (Scheme 5) in high yields and

Scheme 5



diastereoselectivities (90%, 95:5 dr) from **12**. Gratifyingly, this protocol when applied to the resin-bound aldehyde **3** (5 h, −78 °C) enabled complete conversion into the adducts **25** with comparable selectivity in a single cycle.

In solution phase, the stereocontrolled reduction of **24** was best performed using $Zn(BH_4)_2$ in CH_2Cl_2 to afford the 1,3-*syn*-diol **26** (90:10 dr).[20] This reaction was then performed on the resin-bound ketone **25** to provide 1,3-diol **27**.[21] Acetonide protection of the resin-bound alcohol **27** proved demanding and required special conditions (2-methoxypropene, CSA, DMF) to prevent any cleavage of the silyl linker. The 1,3-*syn* relationship of the acetonide resin **29** was confirmed by gel-phase ^{13}C NMR spectroscopy (98.5, 29.8, 19.4 ppm)[16] and TBAF cleavage led to the isolation of the epimeric alcohols **30** in 24% overall yield over six steps (79% average yield). Dess−Martin oxidation of the released alcohols **30** then proceeded in 94% yield. At this stage, the overall diastereoselectivity of the solid-phase synthesis was determined as 90:10 dr in favor of isomer **6**, which is configurationally identical to major segments of discodermolide and 6-deoxyerythronolide B.

In conclusion, we have completed highly stereocontrolled solid-phase syntheses of tetraketides **5** and **6**, related to sizable fragments of 6-deoxyerythronolide B and discodermolide. This clearly demonstrates the efficiency of our methodology for solid-phase polyketide synthesis, along with the general suitability of the silyl linker[9] for attachment of hindered secondary alcohols to the resin. By mimicking the stereoregulated chain growth involved in the biosynthesis of polyketides,[3de,7] a variety of starting aldehydes may be combined with various ketone extension modules in an iterative fashion, enabling extensive diversification and library generation. Efforts are now directed toward extending this methodology and applying it to the synthesis of natural and unnatural polyketides.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(19) (a) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (b) Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123.

(20) Alternative reducing systems explored (c-$Hex_2BCl/LiBH_4$, $Et_3B/LiBH_4$, catecholborane, DIBAL) gave lower or overturned selectivities.

(21) After TBAF cleavage of resin **27**, triol **28** was isolated in 30% yield over four steps.