ORGANIC LETTERS

2005
Vol. 7, No. 20
4435−4438

Enantioselective Synthesis of Linear Polypropionate Arrays Using Anthracene-Tagged Organosilanes

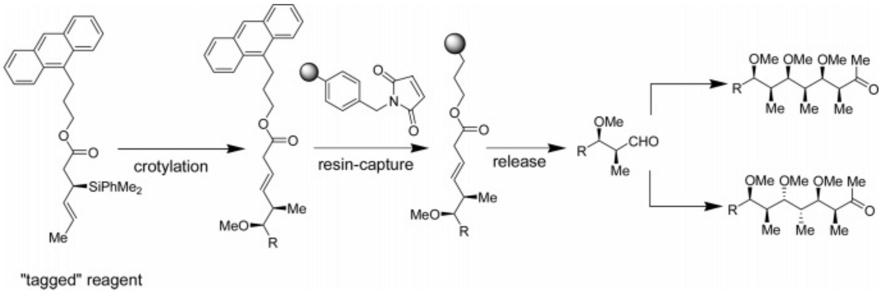
Sarathy Kesavan, Qibin Su, Jian Shao, John A. Porco Jr.,* and James S. Panek*

Department of Chemistry and Center for Chemical Methodology and Library Development, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

porco@bu.edu; panek@bu.edu

Received July 15, 2005

ABSTRACT



Preparation and use of anthracene-tagged organosilanes in an iterative, resin-capture-release protocol for the stereocontrolled synthesis of polypropionate arrays are described.

Polyketides represent a rich source of natural products possessing a broad spectrum of biological activity.[1] Representative examples of important polyketide-derived natural products and their derivatives include the antibiotic erythronolide (**1**),[2] the immunosuppressant discodermolide (**3**),[3] and the antitumor geldanamycin (**2**)[4] (Figure 1). As a potential source of molecular diversity, polyketides have also served as inspiration for the synthesis of complex chemical libraries. Recently we[5] and others[6] have developed solid-phase methods that may be applicable for generation of polyketide libraries. To expand the scope of these initial studies, we have considered an iterative, parallel solution-phase protocol employing anthracene-tagged[7] crotylsilanes featuring the use of our chiral silane-based bond construction methodology (Scheme 1). The sequence involves enantioselective crotylation, followed by [4 + 2] cycloaddition-removal[7a] of the tagged product, to afford a resin-bound adduct. Oxidative cleavage to afford an aldehyde may be followed by further

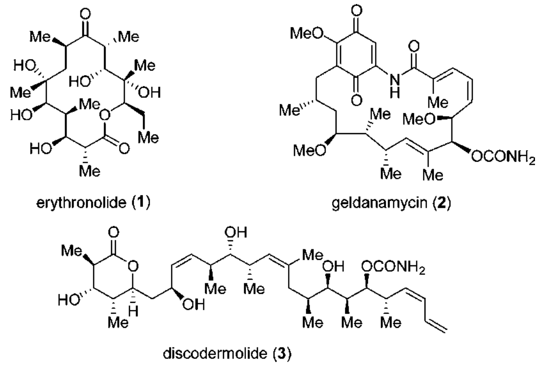


Figure 1. Representative polyketide natural products.

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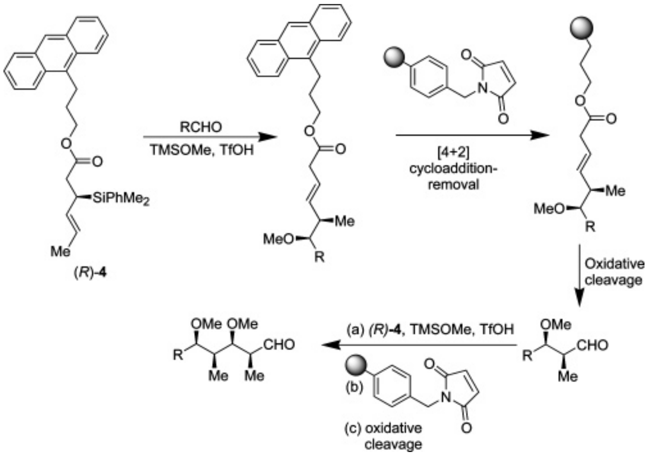
[1] (a) O'Hagan, D. *The Polyketide Metabolites*; Ellis Harwood: Chichester, 1991. (b) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1.
[2] Flynn, E. H.; Sigal, M. V., Jr.; Wiley: P. F.; Gerzon, K. *J. Am. Chem. Soc.* **1954**, *76*, 3121.
[3] Gunasekera, S. P.; Cranick, S.; Longley, R. E. *J. Nat. Prod.* **1989**, *52*, 757.
[4] Rinehart, K. L. *Acc. Chem. Res.* **1972**, *5*, 57.
[5] Panek, J. S.; Zhu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12022.

10.1021/ol0516723 CCC: $30.25

Scheme 1. Strategy for Synthesis of Polypropionate Arrays Using Resin Capture-Release



iterations of crotylation, cycloaddition-removal, and oxidative release. This overall strategy, combining synthesis and purification, represents a specific application of resin-capture-release involving asymmetric synthesis of complex stereochemical arrays.[8] Herein, we report our initial studies on the synthesis of stereochemically well-defined, polyproprionate-like molecules using anthracene-tagged, enantioenriched silane reagents.

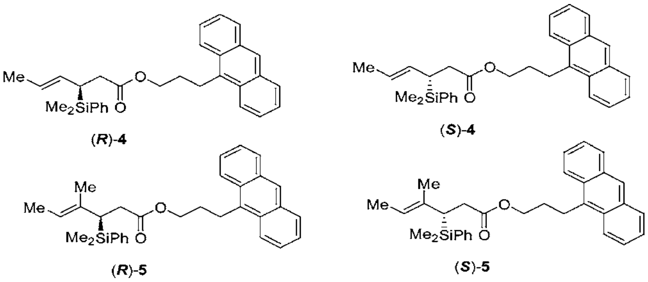
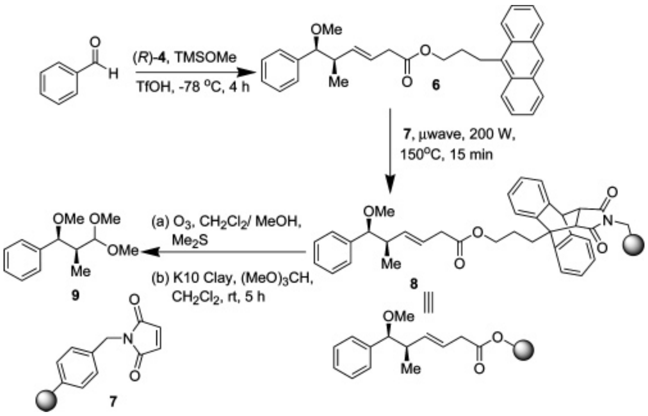


Figure 2. Anthracene-tagged organosilanes.

Scheme 2



We first established that enantioselective crotylations[9] may be performed using anthracene-tagged organosilanes (Figure 2).[10] Results of initial experiments involving enantioenriched organosilanes (*R*)-**4** are shown in Scheme 2. Reaction of silane (*R*)-**4** with benzaldehyde in the presence of triflic acid and methoxytrimethylsilane resulted in the formation of *syn*-homoallylic ether **6**. Without further purification, crude **6** was sequestered to polystyrene maleimide resin **7**[11] (loading = 1.54 mmol/g) by microwave irradiation (150 °C, 200 W, 15 min) to afford resin **8**. Subsequent oxidative cleavage[12] of the olefin resulted in release of a mixture of dimethyl acetal and aldehyde, which was converted to dimethyl acetal **9** (65% yield, four steps, dr > 30:1)[13] using montmorillonite K10 clay/CH(OMe)$_3$[14] in greater than 95% purity (determined using LC/evaporative light scattering detection (ELSD) analysis). The corresponding enantiomer *ent*-**9** was prepared using an identical procedure starting with silane (*S*)-**4**.

We next evaluated the second iteration of the crotylation sequence (Scheme 3). Crotylation of acetal **9** afforded an anthracene-tagged product, which was sequestered using PS-maleimide resin **7** as previously described. Subsequent oxidative cleavage and workup afforded dimethyl acetal **10a** (dr > 20:1). Stereoisomer **10b** was also prepared by an analogous procedure from (*S*)-**4**. We found that the diastereoselectivity of the all-*syn* product **10a** was greater than that of the *syn-anti-syn* product **10b**. The erosion in selectivity may arise from a set of mismatched reaction partners; addition of silane (*S*)-**4** to acetal **9** occurs with *syn*-bond

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(8) For resin-capture-release involving a resin-bound chiral auxiliary, see: Kerrigan, N, J.; Hutchinson, P. C.; Heightman, T, D.; Procter, D, J. *Chem. Commun.* **2003**, 1402.

(9) (a) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587. (b) Beresis, R. T. Ph.D. Thesis, Boston University, 1997; Chapter II. (c) Jain, N. F.; Takenake N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475. (d) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727.

(10) Prepared from the corresponding (*R*)- and (*S*)-crotylsilane methyl esters using microwave-mediated transesterification with 3-(anthracen-10-yl)propan-1-ol.[7e] See Supporting Information for experimental details. For preparation of the crotylsilanes, see: (a) Panek, J. S.; Yang. M. G.; Solomon, J. S. *J. Org. Chem.* **1993**, *58*, 1003. (b) Beresis, R. T.; Solomon, J. S.; Yang, M. J.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78. (c) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727.

(11) See Supporting Information for complete experimental details.

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(13) Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz).

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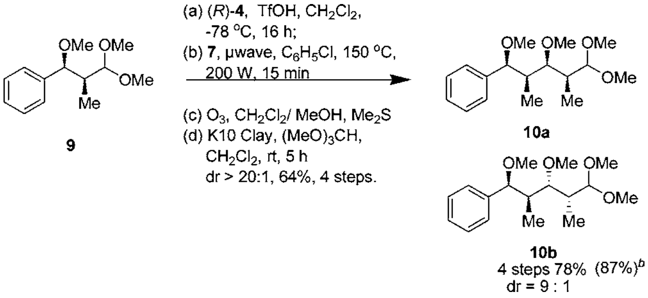
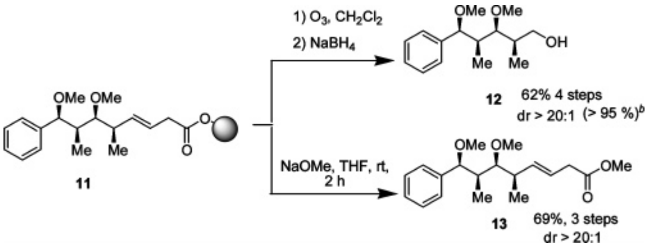
Scheme 3[a]



[a] Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz). [b] HPLC purity (ELSD).

Scheme 4[a]



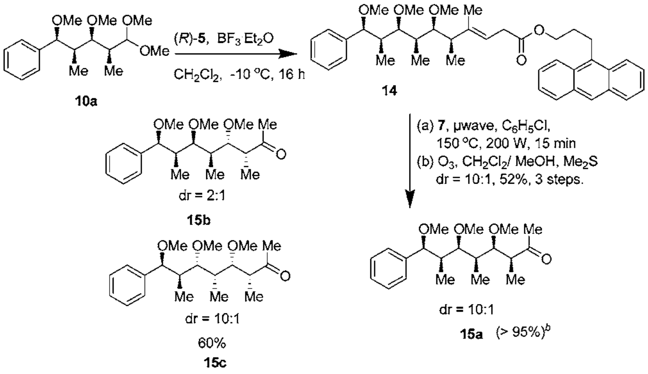
[a] Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz). [b] HPLC purity (ELSD).

construction but with an *anti*-Felkin stereochemical relationship between the existing methyl-bearing center and the emerging methoxy groups.[15] As anticipated, the chiral silane reagent was capable of overriding the chirality of acetal **9**, thus determining the stereochemistry in this double-stereodifferentiating reaction.

To further increase the utility of the resin-capture/release strategy as well as the diversity of end group functionality, resin-captured product **11** was cleaved from the resin using O$_3$/NaBH$_4$ to afford primary alcohol **12** (Scheme 4). Alternatively, treatment of **11** with NaOMe/MeOH resulted in the release of methyl ester **13**.

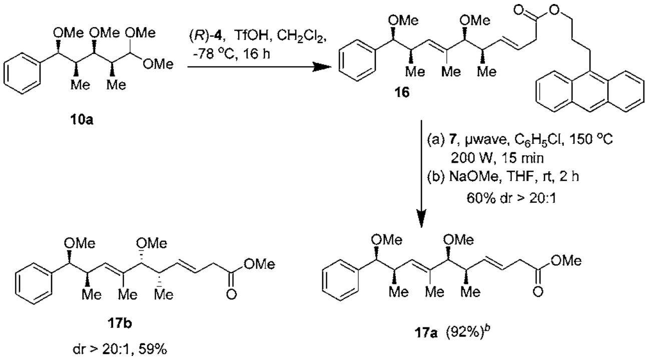
A third sequential crotylation of acetal **10a** with silane (*R*)-**5** afforded *syn*-homoallylic ether **14** bearing a *trans*-trisubstituted olefin (Scheme 5). This material, when subjected to the Diels−Alder capture/oxidative cleavage sequence, afforded methyl ketone **15a** (dr = 10:1, 52% yield from **10a**). However, reaction of **10a** with silane (*S*)-**5** (mismatched addition) led to the production of **15b** (Scheme 5) with severe erosion in diastereoselectivity (dr = 2:1). An additional diastereomer (**15c**) was also prepared using the methodology. In contrast, treatment of acetal **10a** with the less reactive silane (*R*)-**4** afforded the *syn*-homoallylic ether **16** bearing a *trans*-trisubstituted olefin through a tandem elimination-crotylation sequence (Scheme 6).[16] Diene **16** was sequestered using polystyrene maleimide resin **7** and was subsequently released as methyl ester **17a** (Scheme 6). The corresponding diastereoisomer **17b** was prepared using a similar procedure starting with silane (*S*)-**4**. Although unexpected, the elimination-crotylation sequence provides novel access to 1,5-diene-containing polyketide motifs found in complex natural products including geldanamycin (**2**, Figure 1).[4]

Scheme 5[a]



[a] Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz).[b] HPLC purity (ELSD).

Scheme 6[a]



[a] Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz). [b] HPLC purity (ELSD).

We next evaluated the synthesis of backbone-modified polypropionates using the iterative crotylation/resin-capture/release sequence (Scheme 7). Treatment of cyclohexanecarboxaldehyde with silane reagent (*R*)-**4** in the presence of triflic acid and silyl ether **18** resulted in production of a *syn*-homoallylic ether, which was taken through a resin-capture/release sequence to afford acetal **19** (59%, four steps). Acetal **19** was further advanced along the same lines to primary alcohol **20**. To establish additional diversity elements, we next evaluated installation of functionalized ethers at various

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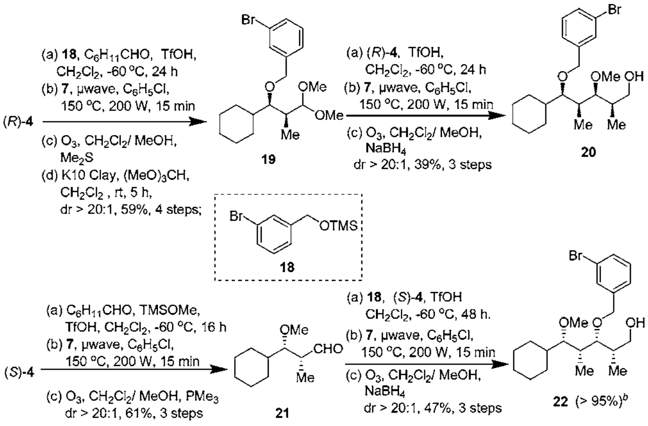
(15) For a review on matched and mismatched reaction partners, see: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(16) Further studies on this unexpected transformation are currently under investigation. For asymmetric crotylation of α,*β*-unsaturated aldehydes, see: Panek, J. S.; Xu, F.; Rondon, A. C. *J. Am. Chem. Soc.* **1998**, *120*, 4113.

Scheme 7[a]

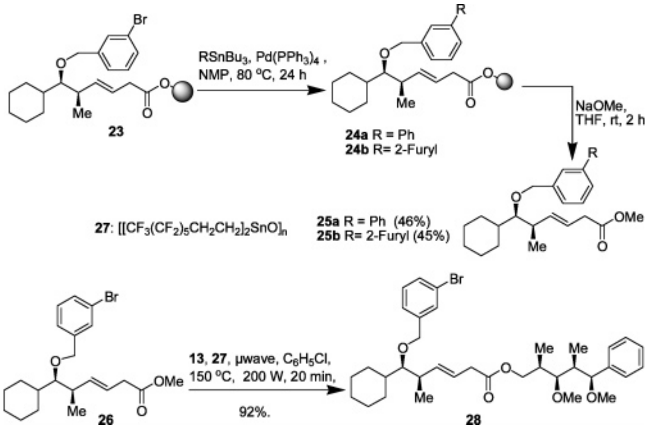


[a] Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz). [b]HPLC purity (ELSD).

positions along the polypropionate backbone. Treatment of cyclohexanecarboxaldehyde with (*S*)-**4** in the presence of triflic acid and methoxytrimethylsilane produced a *syn*-homoallylic ether. Sequestration of the product to resin **7**, followed by oxidative-cleavage using O_3/PMe_3, afforded aldehyde **21** (dr > 20:1). Use of PMe_3 as the reducing agent greatly simplified the workup procedure. Filtration of the crude reaction mixture through an Isolute cartridge led to the removal of trimethylphosphine oxide via supported-liquid extraction[17] to provide aldehyde **21**. Unlike Me_2S, use of PMe_3 as the reducing agent led to the isolation of aldehyde **21** without formation of the dimethyl acetal. Crotylation of aldehyde **21** with (*S*)-**4** in the presence of triflic acid and silyl ether **18** resulted in a *syn*-homoallylic ether, which was sequestered using maleimide resin **7** and subsequently cleaved from the resin using $O_3/NaBH_4$ to provide alcohol **22**.

Derivatives bearing modified backbones were further functionalized as shown in Scheme 8. Resin-captured homoallylic ether **23** was subjected to Stille coupling conditions using tributylphenyltin or tributylfuryltin to give functionalized polypropionates, which were subsequently released as methyl esters from the resin to yield **25a** and **25b**. Finally, we sought to expand the utility of our methodology through convergent fragment coupling[18] to produce highly complex, polypropionate-like molecules (Scheme 8). Coupling of alcohol **13** with ester **26** under microwave conditions using fluorous tin oxide **27**[19] led to the isolation of ester **28** (92% yield, > 95% ELSD purity) after removal of the tin catalyst using fluorous solid-phase extraction (SPE).[20]

Scheme 8



In summary, we have developed an iterative resin capture-release strategy for the synthesis of stereochemically well defined polypropionate arrays using anthracene-tagged organosilanes. Further applications of the methodology are currently in progress and will be reported in due course.

Acknowledgment. Financial support from the NIGMS CMLD initiative (P50 GM067041) is gratefully acknowledged. We thank Drs. Aaron Beeler and Sivaraman Dandapani (Boston University) for helpful discussions and Ms. Dawn Troast (Boston University) for initial experimental studies. We thank Synthematix, Inc. for assistance with chemical reaction planning software, and CEM Corp. (Matthews, NC) for assistance with microwave instruments.

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

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