Enantioselective Synthesis of Linear Polypropionate Arrays Using Anthracene-Tagged Organosilanes
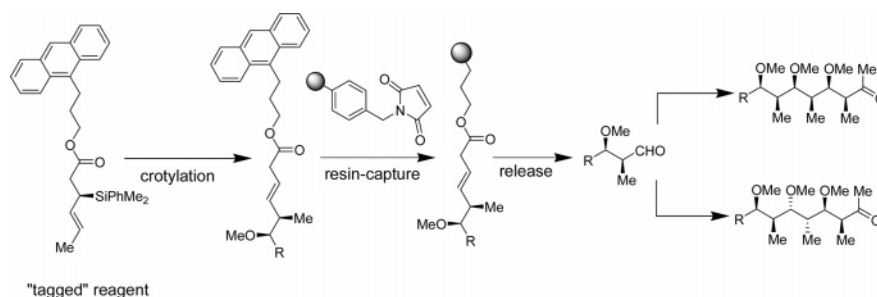
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ABSTRACT

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 erythrynolide (**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
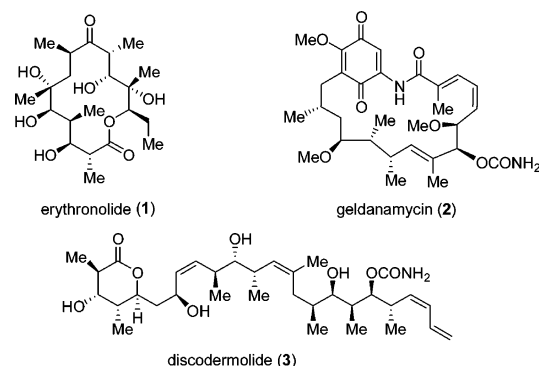

Figure 1. Representative polyketide natural products.

(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

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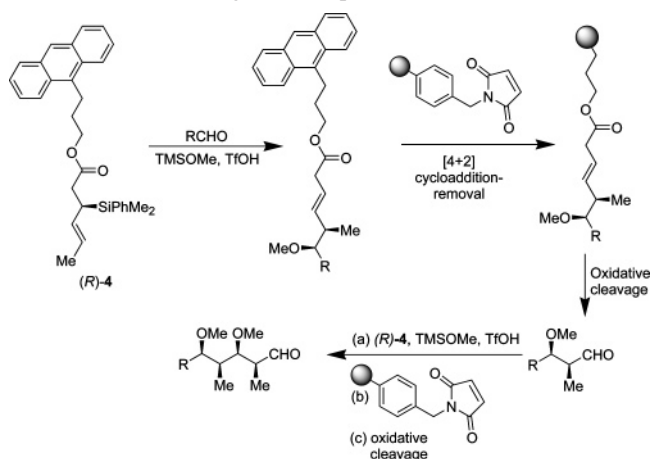
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(3) Gunasekera, S. P.; Cranick, S.; Longley, R. E. *J. Nat. Prod*. **1989**, *52*, 757.

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(5) Panek, J. S.; Zhu, B. *J. Am. Chem. Soc*. **1997**, *119*, 12022.

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

Figure 2. Anthracene-tagged organosilanes.

Scheme 2

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.

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**
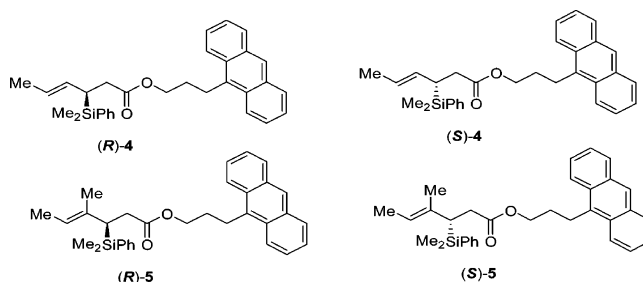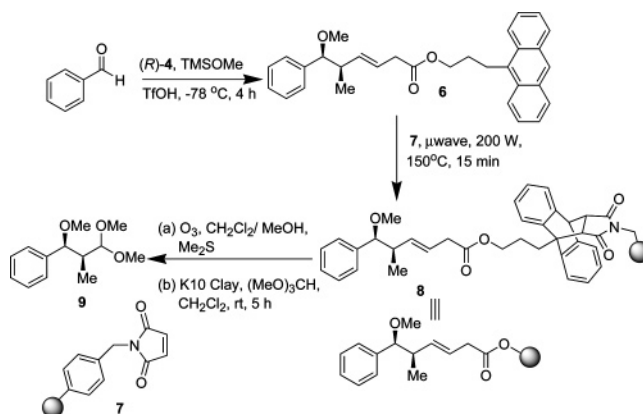
was sequestered to polystyrene maleimide resin **7**[11] (loading = 1.54 mmol/g) by microwave irradiation (150 °C, 200 W, 15 min) to afford resin **8**. Subsequent oxidative cleavage[12] of the olefin resulted in release of a mixture of dimethyl acetal and aldehyde, which was converted to dimethyl acetal **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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(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.
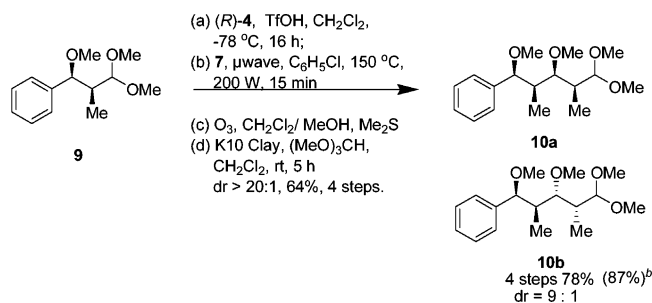
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(13) Diastereomeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz).

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Scheme 3[a]

10a

10b
4 steps 78% (87%)[b]
dr = 9 : 1

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

Scheme 4[a]

12
62% 4 steps
dr > 20:1 (> 95 %)[b]

13
69%, 3 steps
dr > 20:1

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

Scheme 5[a]

10a

14

15b
dr = 2:1

15c
dr = 10:1
60%

15a (> 95%)[b]
dr = 10:1

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

Scheme 6[a]

10a

16

17b
dr > 20:1, 59%

17a (92%)[b]
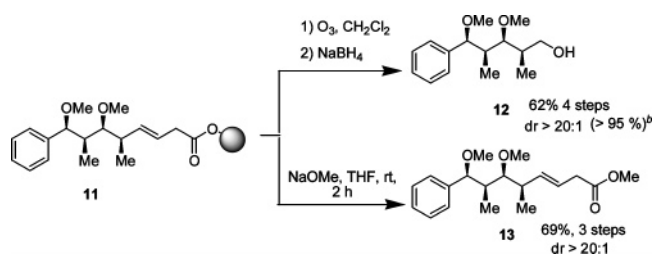
[a] Diasteromeric ratios (dr's) were determined by ^{1}H NMR analysis (400 MHz). [b] HPLC purity (ELSD).

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-stereo-differentiating 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
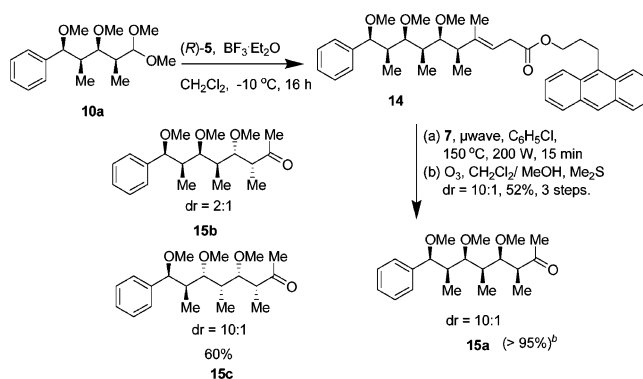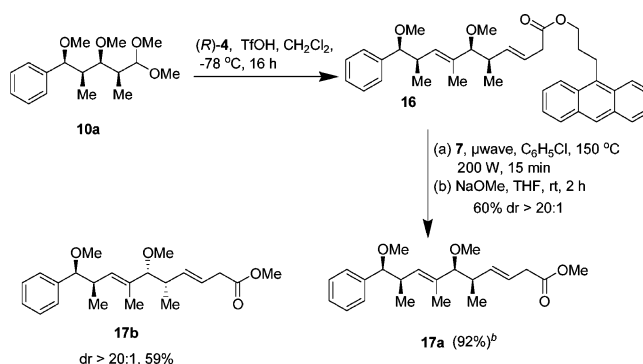
elimination-crotylation sequence (Scheme 6).[16] Diene **16** was sequestered using polystyrene maleimide resin **7** and was subsequently released as methyl ester **17a** (Scheme 6). The corresponding diastereoisomer **17b** was prepared using a similar procedure starting with silane (*S*)-**4**. Although 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]

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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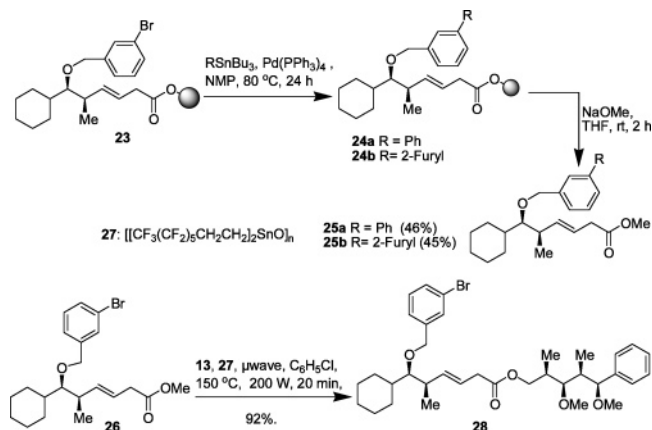
Scheme 7 [a]

(a) **18**, $C_6H_{11}CHO$, TfOH, CH_2Cl_2, -60 °C, 24 h
(b) **7**, μwave, C_6H_5Cl, 150 °C, 200 W, 15 min
(c) O_3, CH_2Cl_2/MeOH, Me_2S
(d) K10 Clay, $(MeO)_3CH$, CH_2Cl_2, rt, 5 h, dr > 20:1, 59%, 4 steps;

(a) (*R*)-**4**, TfOH, CH_2Cl_2, -60 °C, 24 h
(b) **7**, μwave, C_6H_5Cl, 150 °C, 200 W, 15 min
(c) O_3, CH_2Cl_2/MeOH, $NaBH_4$
dr > 20:1, 39%, 3 steps

(a) $C_6H_{11}CHO$, TMSOMe, TfOH, CH_2Cl_2, -60 °C, 16 h
(b) **7**, μwave, C_6H_5Cl, 150 °C, 200 W, 15 min
(c) O_3, CH_2Cl_2/MeOH, PMe_3
dr > 20:1, 61%, 3 steps

(a) **18**, (*S*)-**4**, TfOH, CH_2Cl_2, -60 °C, 48 h.
(b) **7**, μwave, C_6H_5Cl, 150 °C, 200 W, 15 min
(c) O_3, CH_2Cl_2/MeOH, $NaBH_4$
dr > 20:1, 47%, 3 steps

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

Scheme 8

27: $[[CF_3(CF_2)_5CH_2CH_2]_2SnO]_n$

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]

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.

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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