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Synthetic Methods

Rapid Total Syntheses Utilizing "Supersily!" Chemistry**

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Although more than 100 years of study have demonstrated that the aldol reaction is one of the most fundamental and effective methods for the construction of complex molecules, in particular natural products, its full potential has not been realized.^[1] Polyketides, a family of natural products, have provided chemists with a rich source of molecular architectures and biologically significant compounds.^[2] Polyketides often contain the 1,3-polyol motif, and unsurprisingly the aldol reaction has been the preferred method to access these structures.^[1,2] Unfortunately, however, the most selective aldol products afford ketones or esters^[3] and not aldehydes. Thus, the reported biomimetic routes require additional protection and redox steps for each iteration, thus making the preparation of long-chain polyketides excessively lengthy (poor redox economy).^[4] Therefore, interest in one-pot polyaldol cascade reactions has increased.^[5] Although, several elegant stereoselective approaches have been reported, all the methods inevitably stop after the second aldol reaction because of the cyclization of the hydroxyaldehydes or -ketones. This cyclization could be blocked if the pendant hydroxy groups were rendered non-nucleophilic by an in situ generated blocking variant, which, importantly, would afford aldehydes 2 as products. We recently reported the first highvielding triple aldol reaction (Scheme 1 A).^[6] This cascade results in high 1,3-stereoinduction, generated from the extreme bulk of the tris(trimethylsilyl)silyl (supersilyl) group, which also retards undesired polymerization.^[7]

The use of the bulky β -silyloxy methyl ketones **3** in 1,5stereoselective aldol reactions with aldehydes produces **4** or **5** with high diastereoselectivity (Scheme 1 B).^[8] Importantly, all three 1,3,5-triol stereoisomers can easily be prepared from **4** and **5**.^[8] The utilization of both of these strategies would allow for the facile synthesis of complex 1,3-polyols and spiroketals. Herein we report the rapid total syntheses of EBC-23 and polymethoxy-1-alkene **13** by these approaches.

As part of a screening program to identify new anticancer agents, spiroketal EBC-23 (Scheme 2A) was isolated from the fruit of *Cinnamomum laubatii*.^[9a] This natural product was active in vitro against several human cancer cell lines, and more importantly, inhibited the growth of a human prostate

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Scheme 1. Supersilyl-directed aldol reactions. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

cancer xenograft in mice with no observable side effects.^[9c] The structure and absolute stereochemistry of EBC-23 was determined by the Williams research group (in their 15-step total synthesis, 11 steps for the longest linear sequence).^[9b]

Our retrosynthetic analysis of EBC-23 relies on supersilyldirected aldol methods (Scheme 2 A). Hydrolytic opening of the spiroketal reveals polyhydroxy ketone **6**, which could be rapidly generated from tetradecanal, two equivalents of acetaldehyde silyl enol ether **1**, acetone, an α -hydroxyaldehyde, and acryloyl chloride.

With this strategy in mind, ketone (\pm) -9 was prepared as shown in Scheme 2B. Tetradecanal^[10] was treated with 1 and Tf₂NAlMe₂^[11] to give aldehyde (\pm) -7 in 85% yield. This aldehyde was treated with silyl enol ether 8 in the presence of Tf₂NH and 1-iodo-2-phenylacetylene^[6] to furnish (\pm) -9 in 75% yield and a diastereomerically pure form after column chromatography. The preparation of alkoxyaldehyde 11 commenced with our asymmetric epoxidation of 3-hydroxy-1,4-pentadiene.^[12] This epoxy alcohol was converted into 10 in 90% yield according to a literature procedure.^[13] Aldehyde 11 was prepared from 10 by a hydrolysis/oxidative cleavage sequence in $\geq 84\%$ (yield over two steps).

The endgame for the synthesis of EBC-23 commenced with the coupling of (\pm) -9 and 11 under standard conditions,^[8] which produced 12 in only 6% yield, presumably because of the low solubility of (\pm) -9 in DMF (Table 1, entry 1). The addition of 10% (v/v) THF improved the yield slightly, but the solubility of (\pm) -9 and its putative lithium enolate was still insufficient (entry 2). When the reaction was performed with THF as the lone solvent, 12 was obtained in good yield but poor diastereoselectivity (entry 3). Therefore, the use of DMF as a cosolvent in the aldol reaction was explored (entries 4–8), since we postulate that two molecules coordinate to the lithium atom in the closed transition state.^[8]

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Scheme 2. Asymmetric retro- and forward syntheses of EBC-23: a) **1** (2.3 equiv), $T_{2}NAIMe_{2}$ (0.20 mol%), $CH_{2}Cl_{2}$, -40 °C, 85%, 15:1 d.r.; b) **8** (1.8 equiv), $T_{2}NH$ (0.30 mol%), 1-iodo-2-phenylacetylene (10 mol%), $CH_{2}Cl_{2}$, -40 °C, 97%, 77:16:6: <1 d.r.; c) see Ref. [10]; then PMBBr (1.4 equiv), NaH (1.2 equiv), nBu₄NI (2 mol%), THF, $0 \rightarrow 23$ °C, 90%; d) KOH (4.0 equiv), $H_{2}O/DMSO$ (1:1), 75 °C, 93%; then NaIO₄ (1.2 equiv), THF/H₂O (2:3), $0 \rightarrow 23$ °C, 90 $\rightarrow 95$ %; e) LiHMDS (1.2 equiv), toluene, $-40 \rightarrow 0$ °C; DMF, -78 °C; **11**, -78 °C, 63% (95% based on recovered **9**); f) LiHMDS (1.1 equiv), -78 °C; acryloyl chloride (1.5 equiv), $-78 \rightarrow 23$ °C; then Zhan cat. 1B^[15] (6 mol%), toluene, 95 °C; then HF·py (excess), py, THF, $0 \rightarrow 23$ °C, 33% (from **12**); g) DDQ (2.3 equiv), $CH_{2}Cl_{2}$, $H_{2}O$, 23 °C, 72%. DDQ = 2,3-dichloro-5,6-dicyano-*para*-benzoquinone, PMB = *para*-methoxybenzyl, py = pyridine, RCM = ring-closing metathesis.

Table 1: Optimization of the coupling of (\pm) -9 and 11.

Entry	Solvent(s) (v/v)	T [°C]	12 [%] ^[a]	d.r. ^[b]
1	DMF	-65	6	48:44:6:2
2	DMF/THF (9:1) ^[a]	-65	10	48:44:6:2
3	THF	-78	56	47:38:12:3
4	Et ₂ O/DMF (19:1) ^[a]	-78	43	47:40:10:3
5	tBuOMe/DMF (19:1) ^[a]	-78	36	47:40:10:3
6	CH ₂ Cl ₂ /DMF (19:1) ^[a]	-78	29	48:43:7:2
7	toluene/DMF (19:1) ^[a]	-78	63	48:43:7:2
8	CyMe/DMF (19:1) ^[a]	-78	50	48:44:6:2

[a] Yield of the combined isolated diastereomers. [b] The diastereomeric ratios were determined by ¹H NMR spectroscopic analysis of the crude product. Cy = cyclohexyl.

solvent (entry 7), which allowed for the preparation of **12** in high diastereoselectivity and 63 % yield.^[14] This alcohol was then subjected to a onepot acylation/ring-closing metathesis^[15]/HF·py deprotection sequence to afford a mixture of anomers in 33 % yield (Scheme 2). This mixture was treated with DDQ, which resulted in spiroketalization occurring spontaneously^[16] to give EBC-23 in high enantiopurity in a total of ten steps, seven in the longest linear sequence.

Polymethoxy-1-alkene **13** was isolated from tolytoxin-producing blue-green algae *Tolypothrix conglutinate* var.^[17] This natural product and several closely related polyme-thoxy-1-alkenes have generated sigA) OMe OMe OMe OMe OMe OMe nPentCHO *n*Pent 1 (3 equiv) 13 acetone additions acetaldehvde additions OSi(TES)3 OSi(TES)3 QSi(TES)3 (±)-**15** QSi osi OSi nPentCHC (±)-17 (±)-**16** Si = Si(TMS)₃ d Me OMe OMe OMe OMe OMe OSi OSi ОH ОН OSi(TES)3 OSi *n*Pent *n*Pen⁻ (±)-13 (±)-**18**

Scheme 3. Retro- and forward syntheses of polymethoxy-1-alkene **13**: a) 3-butenal (1.2 equiv), Me_2AINTf_2 (0.5 mol%), CH_2Cl_2 , 0°C, 75%; b) **1** (5.0 equiv), Tf_2NH (0.05 mol%), 1-iodo-2-phenyl-acetylene (10 mol%), CH_2Cl_2 , -40°C, 79%, 80:12:5:3 d.r.; c) LiHMDS (1.2 equiv), LiBF₄ (5.0 equiv), DMF, -60°C, 64%; d) NaBH₄ (10 equiv), MeOH, -20°C, 89%, >10:1 d.r.; e) UV light, MeOH/ CH_2Cl_2 (4:1), 23°C; then MeI (40 equiv), NaH (20 equiv), THF, 0 \rightarrow 23°C, 61% (yield over two steps).

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nificant interest in the synthetic community.^[17d,18] The structure of **13** was proved by the Mori research group in their 21-step total synthesis,^[17d] and recently, it was prepared by Taylor and coworkers in 16 steps.^[18g]

We anticipated that (\pm) -13 could be prepared rapidly, by using our methods, from acetone, 3-butenal, three equivalents of acetaldehyde silyl enol ether 1, and n-hexanal (Scheme 3A). The forward synthesis commenced with the preparation of β siloxy methyl ketone (\pm) -15 in 75% yield from 3-butenal^[19] and silvl enol ether 14 in the presence of Tf₂NAlMe₂ (Scheme 3B). Hexanal was treated with silyl enol ether **1** in the presence of Tf_2NH and 1-iodo-2-phenylacetylene

to afford (\pm) -16 in 79% yield with high *syn* selectivity. The next key step was the union of (\pm) -15 and (\pm) -16 by a 1,5-*syn* aldol reaction. Initial attempts to assemble (\pm) -17 under standard conditions gave the desired adduct in 21% yield, which left room for improvement. Presumably, the somewhat low yield was due to the extreme steric bulk of ketone (\pm) -15 and aldehyde (\pm) -16. Fortunately, the addition of lithium tetrafluoroborate^[20] allowed for the generation of (\pm) -17 and other isomers in 64% yield.^[21] Stereoselective reduction of the ketone with NaBH₄ gave (\pm) -18 in 89% yield. Finally, removal of the silyl protecting groups by irradiation with UV light^[8] and methylation gave natural product (\pm) -13 in a total

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of ten steps, seven in the longest linear sequence, from commercially available chemicals.

In summary, the concise stereoselective total synthesis of EBC-23 and (\pm) -polymethoxy-1-alkene **13** have been achieved by using supersilyl-directed aldol reactions. Some of the salient points of this report are: 1) the syntheses of EBC-23 and **13** are the shortest routes to date, made possible by supersilyl chemistry, 2) the syntheses are redox-economical, requiring few redox manipulations, and 3) the supersilyl methods should allow the ready synthesis of various stereo-isomers.

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