Synthetic Methods

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Rapid Total Syntheses Utilizing "Supersilyl" Chemistry**

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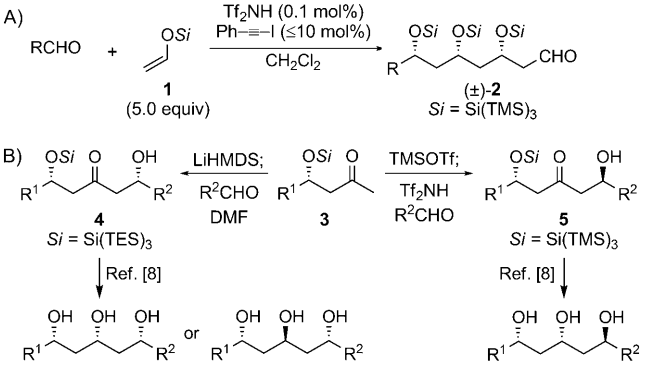
Although more than 100 years of study have demonstrated that the aldol reaction is one of the most fundamental and effective methods for the construction of complex molecules, in particular natural products, its full potential has not been realized.[1] Polyketides, a family of natural products, have 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 high-yielding 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 1,5-stereoselective 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 2 A) 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 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]



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

Our retrosynthetic analysis of EBC-23 relies on supersilyl-directed 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 (±)-**9** was prepared as shown in Scheme 2 B. Tetradecanal[10] was treated with **1** and Tf_2NAlMe_2[11] to give aldehyde (±)-**7** in 85% yield. This aldehyde was treated with silyl enol ether **8** in the presence of Tf_2NH and 1-iodo-2-phenylacetylene[6] to furnish (±)-**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 ≥ 84% (yield over two steps).

The endgame for the synthesis of EBC-23 commenced with the coupling of (±)-**9** and **11** under standard conditions,[8] which produced **12** in only 6% yield, presumably because of the low solubility of (±)-**9** in DMF (Table 1, entry 1). The addition of 10% (v/v) THF improved the yield slightly, but the solubility of (±)-**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] The optimal result was obtained by using toluene as the major

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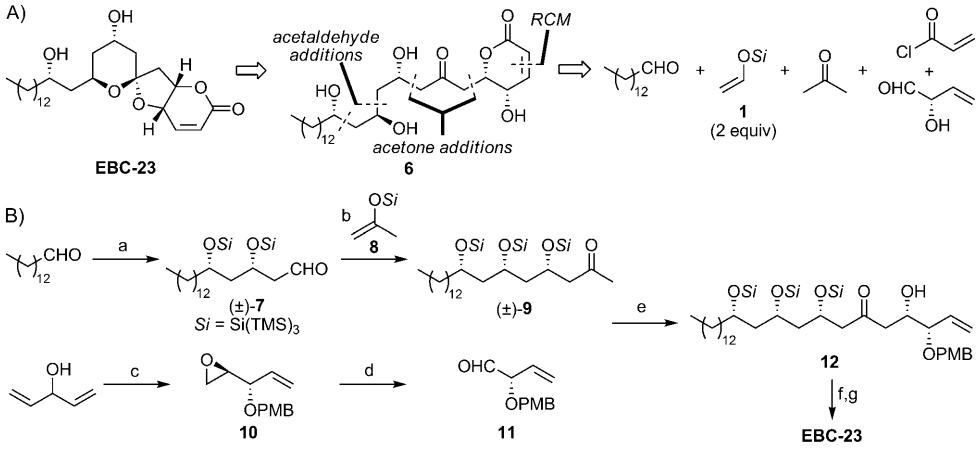


Scheme 2. Asymmetric retro- and forward syntheses of EBC-23: a) **1** (2.3 equiv), Tf_2NAlMe_2 (0.20 mol%), CH_2Cl_2, −40°C, 85%, 15:1 d.r.; b) **8** (1.8 equiv), Tf_2NH (0.30 mol%), 1-iodo-2-phenylacetylene (10 mol%), CH_2Cl_2, −40°C, 97%, 77:16:6:<1 d.r.; c) see Ref. [10]; then PMBBr (1.4 equiv), NaH (1.2 equiv), nBu_4NI (2 mol%), THF, 0→23°C, 90%; d) KOH (4.0 equiv), H_2O/DMSO (1:1), 75°C, 93%; then $NaIO_4$ (1.2 equiv), THF/H_2O (2:3), 0→23°C, 90→95%; e) LiHMDS (1.2 equiv), toluene, −40→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→23°C; then Zhan cat. 1B[15] (6 mol%), toluene, 95°C; then HF·py (excess), py, THF, 0→23°C, 33% (from **12**); g) DDQ (2.3 equiv), CH_2Cl_2, H_2O, 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 (±)-**9** and **11**.

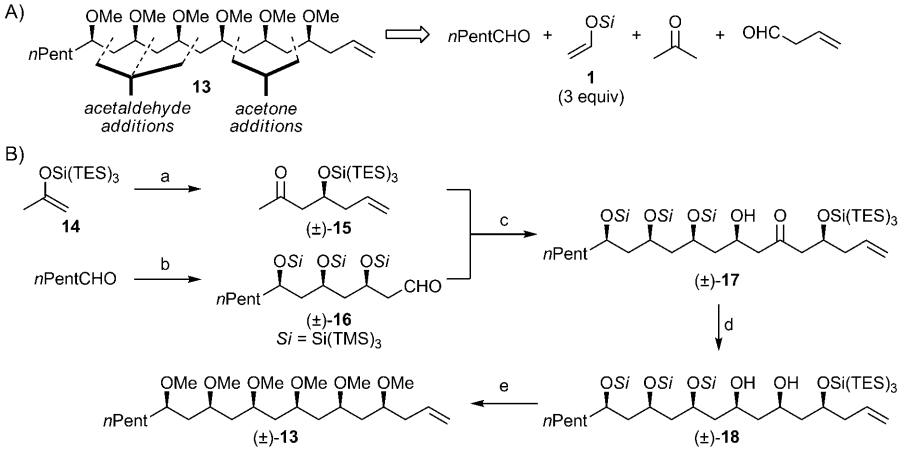
Entry	Solvent(s) (v/v)	*T* [°C]	**12** [%][a]	d.r.[b]
1	DMF	−65	6	48:44:6:2
2	DMF/THF (9:1)[a]	−65	10	48:44:6:2
3	THF	−78	56	47:38:12:3
4	Et_2O/DMF (19:1)[a]	−78	43	47:40:10:3
5	*t*BuOMe/DMF (19:1)[a]	−78	36	47:40:10:3
6	CH_2Cl_2/DMF (19:1)[a]	−78	29	48:43:7:2
7	toluene/DMF (19:1)[a]	−78	63	48:43:7:2
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 one-pot 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 polymethoxy-1-alkenes have generated significant 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 (±)-**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 (±)-**15** in 75% yield from 3-butenal[19] and silyl enol ether **14** in the presence of Tf_2NAlMe_2 (Scheme 3B). Hexanal was treated with silyl enol ether **1** in the presence of Tf_2NH and 1-iodo-2-phenylacetylene to afford (±)-**16** in 79% yield with high *syn* selectivity. The next key step was the union of (±)-**15** and (±)-**16** by a 1,5-*syn* aldol reaction. Initial attempts to assemble (±)-**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 (±)-**15** and aldehyde (±)-**16**. Fortunately, the addition of lithium tetrafluoroborate[20] allowed for the generation of (±)-**17** and other isomers in 64% yield.[21] Stereoselective reduction of the ketone with $NaBH_4$ gave (±)-**18** in 89% yield. Finally, removal of the silyl protecting groups by irradiation with UV light[8] and methylation gave natural product (±)-**13** in a total



Scheme 3. Retro- and forward syntheses of polymethoxy-1-alkene **13**: a) 3-butenal (1.2 equiv), Me_2AlNTf_2 (0.5 mol%), CH_2Cl_2, 0°C, 75%; b) **1** (5.0 equiv), Tf_2NH (0.05 mol%), 1-iodo-2-phenylacetylene (10 mol%), CH_2Cl_2, −40°C, 79%, 80:12:5:3 d.r.; c) LiHMDS (1.2 equiv), $LiBF_4$ (5.0 equiv), DMF, −60°C, 64%; d) $NaBH_4$ (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→23°C, 61% (yield over two steps).

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

In summary, the concise stereoselective total synthesis of EBC-23 and (±)-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 stereoisomers.

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[1] For aldol reactions using ester, thioester, and ketone enolates as nucleophiles with aldehydes, see a) T. Mukaiyama in *Organic Reactions*, *Vol. 28* (Eds.: W. G. Dauben, G. A. Boswell, Jr., S. Danishefsky, H. W. Gschwend, R. F. Heck, R. F. Hirshchmann, A. S. Kende, L. A. Paquette, G. H. Posner, B. M. Trost, R. Bittman, B. Weinstein), Wiley, New York, **1982**, pp. 203–331; b) C. H. Heathcock, B. M. Kim, S. F. Williams, S. Masamune, M. W. Rathke, P. Weipert, I. Paterson in *Comprehensive Organic Synthesis*, *Vol. 2* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 133–319; c) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357–389; d) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095–1120.

[2] a) J. Rohr, *Angew. Chem.* **2000**, *112*, 2967–2969; *Angew. Chem. Int. Ed.* **2000**, *39*, 2847–2849; b) S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040; c) A. M. P. Koskinen, K. Karisalmi, *Chem. Soc. Rev.* **2005**, *34*, 677–690.

[3] Or derivatives of the ester oxidation state.

[4] For the importance of redox economy, see N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896–2910; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854–2867.

[5] a) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 7585–7591; b) S.-S. Yun, I.-H. Suh, S.-S. Choi, S. Lee, *Chem. Lett.* **1998**, 985–986; c) A. Haeuseler, W. Henn, M. Schmittel, *Synthesis* **2003**, 2576–2589; d) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752–1755; e) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367–1369; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343–1345; f) X. Wang, Q. Meng, N. R. Perl, Y. Xu, J. L. Leighton, *J. Am. Chem. Soc.* **2005**, *127*, 12806–12807.

[6] B. J. Albert, H. Yamamoto, *Angew. Chem.* **2010**, *122*, 2807–2809; *Angew. Chem. Int. Ed.* **2010**, *49*, 2747–2749.

[7] M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48–49.

[8] Y. Yamaoka, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 5354–5356.

[9] a) P. W. Reddell, V. A. Gordon , WO 2007070984A1 20070628 PCT Int. Appl., **2007**; b) L. Dong, V. A. Gordon, R. L. Grange, J. Johns, P. G. Parsons, A. Porzelle, P. Reddell, H. Schill, C. M. Williams, *J. Am. Chem. Soc.* **2008**, *130*, 15262–15263; c) L. Dong, H. Schill, R. L. Grange, A. Porzelle, J. P. Johns, P. G. Parsons, V. A. Gordon, P. W. Reddell, C. M. Williams, *Chem. Eur. J.* **2009**, *15*, 11307–11318.

[10] Obtained by the oxidation of 1-tetradecanol with IBX: J. M. Wiseman, F. M. McDonald, D. C. Liotta, *Org. Lett.* **2005**, *7*, 3155–3157.

[11] A. Marx, H. Yamamoto, *Angew. Chem.* **2000**, *112*, 182–184; *Angew. Chem. Int. Ed.* **2000**, *39*, 178–181.

[12] Z. Li, W. Zhang, H. Yamamoto, *Angew. Chem.* **2008**, *120*, 7630–7632; *Angew. Chem. Int. Ed.* **2008**, *47*, 7520–7522.

[13] M. Nakatsuka, J. A. Ragan, T. Sammakia, D. B. Smith, D. E. Uehling, S. L. Schreiber, *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601.

[14] Noncoordinating solvents were found to be important. See the Supporting Information for full details.

[15] The catalyst was purchased from Strem Chemicals. Patents US 2007/0043180A1; PCT, WO 2007/003135A1.

[16] Williams and co-workers reported[9b] difficulties in acid-promoted spirocyclization, but success with a postulated cerium-templated preorganized spirocyclization. However, fortunately, greater than 50% spirocycliztion (additional cyclization during silica gel chromatography) occurred with DDQ under the acidic deprotection conditions.

[17] a) T. V. Desikachary, *Cyanophyta*, Indian Council of Agricultural Research, New Delhi, **1959**, 503; b) J. S. Mynderse, R. E. Moore, *Phytochemistry* **1979**, *18*, 1181–1183; c) S. Carmeli, R. E. Moore, G. M. Patterson, Y. Mori, M. Suzuki, *J. Org. Chem.* **1990**, *55*, 4431–4438; d) Y. Mori, Y. Kohchi, M. Suzuki, S. Carmeli, R. E. Moore, G. M. Patterson, *J. Org. Chem.* **1991**, *56*, 631–637.

[18] Previous syntheses of **13** and related compounds: a) T. Nakata, T. Suenaga, T. Oishi, *Tetrahedron Lett.* **1989**, *30*, 6525–6528; b) T. Nakata, T. Suenaga, K. Nakashima, T. Oishi, *Tetrahedron Lett.* **1989**, *30*, 6529–6532; c) H. Priepke, S. Weigand, R. Brückner, *Liebigs Ann.* **1997**, 1635–1644; d) H. Priepke, R. Brückner, *Liebigs Ann.* **1997**, 1645–1655; e) S. Weigand, R. Brückner, *Liebigs Ann.* **1997**, 1657–1666; f) S. Allerheiligen, R. Brückner, *Liebigs Ann.* **1997**, 1667–1676; g) K. Liu, J. W. Arico, R. E. Taylor, *J. Org. Chem.* **2010**, *75*, 3953–3957.

[19] Obtained from glyoxal: M. T. Crimmins, S. J. Kirincich, A. J. Wells, A. L. Choy, *Synth. Commun.* **1998**, *28*, 3675–3679.

[20] $LiBF_4$ was the best source of lithium screened. The use of LiCl, LiI, and $LiNTf_2$ as additives gave **17** in 45, 23, and 41% yields, respectively.

[21] See the Supporting Information for full details of this reaction.

