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Stereodivergent Approach to the Avermectins Based on "Super Silyl" Directed Aldol Reactions

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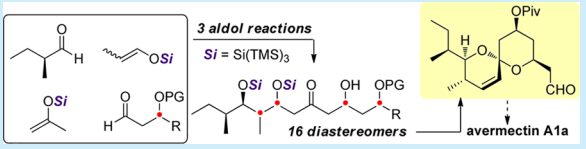
Supporting Information

ABSTRACT: A stereodivergent approach to the spiroketal fragment of the avermectins is described. The strategy utilizes a sequence of three aldol reactions directed by the *tris*(trimethylsilyl)silyl "super silyl" group. Central to this strategy is that each aldol reaction can be controlled to allow access to either diastereomer in high stereoselectivity, thereby affording 16 stereoisomers along the same linear skeleton. The aldol products can be transformed into spiroketals, including an advanced intermediate in the total synthesis of avermectin A1a.

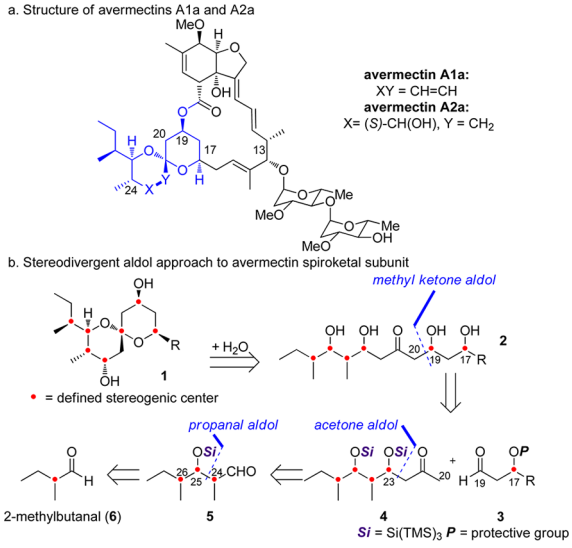


Since their discovery in 1978, the avermectins have held a prominent place in natural products chemistry, as they have become some of the most widely used polyketide-derived therapeutics to date.[1−3] Over the past 20 years, avermectin-based anthelmintics donated by Merck have been used to treat over 80 million cases of onchocerciasis in the developing world.[4] In addition, the avermectins have found widespread use in veterinary medicine and as anti-insecticides in crop protection.[5] The 10 structurally related members of the avermectin family, originating from soil bacterium *Streptomyces avermilitis*, display complex structural features, including a 16-membered macrolactone, a thermodynamic 6,6-spiroketal, an oxahydrindene ring system, an *E*,*E*-diene, and glycosylation (dioleandrose) at C13. These structural complexities make the avermectins challenging synthetic targets, with landmark synthetic studies by Hannessian, Danishefsky, Ley, and White.[6]

Recently, our group has been interested in the utilization of the *tris*(trimethylsilyl)silyl "super silyl" group in stereoselective aldol cascade reactions and in the rapid synthesis of polyketide natural products.[7] Given the increasing use of non-natural polyketides in diversity oriented synthesis (DOS),[8] and the increasing attention to stereochemical diversity in library design and drug development,[9] we became interested in further developing super silyl aldol methods to enable DOS strategies toward polyketides. In this context, we were attracted to the bioactivity and stereochemical complexity of the avermectins. With seven stereogenic centers, spiroketal subunit **1** represents just 1 of 128 (2^7) possible stereoisomeric forms (Scheme 1). We envisioned that a stereodivergent trialdol approach to the skeleton of subunit **1** would allow access to its non-natural stereoisomers. This strategy relies on three super silyl-directed aldol reactions, each of which would be manipulated to select for multiple stereochemical outcomes based on reaction conditions.

Analysis of **1** reveals that hydrolysis product **2** can be disconnected at C19−C20 by 1,5-directed aldol reaction of methyl ketone **4** and aldehyde **3**.[7h,10] The stereochemistry at C17 and C19 would be dictated by the configuration of **3** and stereochemical outcome of the methyl ketone aldol reaction.

Scheme 1. Avermectins: Structure and Approach



Ketone **4** is traced back to **5** by an acetone aldol addition, which also sets the stereocenter at C23. Aldehyde **5** is traced back to simple 2-methyl butanal by propanal aldol addition, which sets the configuration at C25 and C26.

We began our stereodivergent synthesis by utilizing our recently developed stereoselective propanal-aldol acetone-aldol reaction sequences to prepare ketones **4a**−**4d** (Scheme 2). With these stereoisomeric ketones in hand, we evaluated the feasibility of their use in the synthesis of spiroketals based on the avermectins by examining the critical 1,5-directed aldol reaction with achiral model substrate **8** (Scheme 3). In accordance with our previous studies,[7h] we found that the Li-enolate of **4c** provides 1,5-*syn* product **9a**, while the enolborinate and

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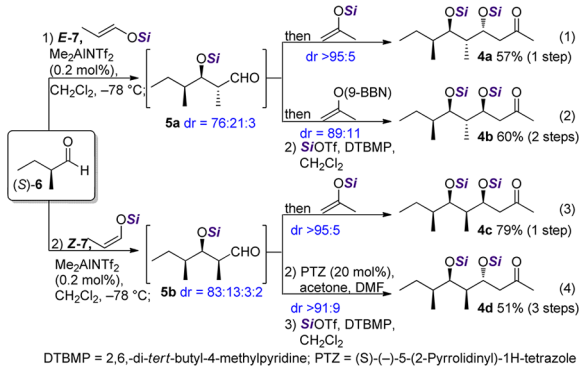
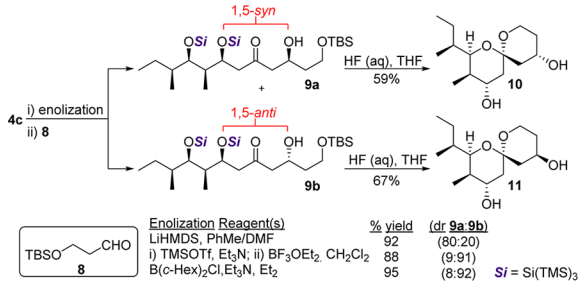
Scheme 2. Synthesis of Diastereomeric Ketones 4a−4d[7b]



Scheme 3. 1,5-Directed Aldol Reaction of 4c

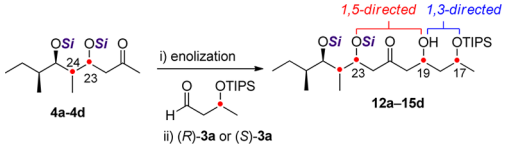


Mukaiyama aldol conditions provided the complementary 1,5-*anti* aldol adduct **9b** with good to excellent levels of diastereoselectivity. Simple treatment of **9a** and **9b** with 48% aq HF in THF affected the desired deprotection and cyclization to give respective spiroketals **10** and **11** in good yields.[11]

Upon validation of the key 1,5-directed *syn*- and *anti*-aldol reactions and spiroketal formation with model substrates, we turned our attention to the aldol reaction of ketones **4a−4d** with (*R*)- and (*S*)-*β*-siloxy butanal **3a** (Table 1). From the outset, we anticipated that matched/mismatched situations may arise due to the competing 1,3-asymmetric induction of the aldehyde aldol partner **3a**, especially under Mukaiyama aldol conditions.[12,13] However, reaction of ketone **4a** with (*R*)-**3a** showed excellent selectivity under both Mukaiyama conditions (entry 1, dr = 96:4, 1,5-*anti* selective) and Li-mediated conditions (entry 2, dr = 92:8, 1,5-*syn* selective). When enantiomeric aldehyde (*S*)-**3a** was used, high selectivity was obtained under Mukaiyama conditions (entry 3, dr = 86:14, 1,5-*anti*) indicating only a slight mismatched effect (10% ds, compare entries 1 and 3). Li-mediated aldol with (*S*)-**3a** gave the same result as with (*R*)-**3a**, indicating no matched/mismatched effects under these conditions (entries 2 and 4). We then examined ketone **4b** in the analogous aldol reactions with **3a**. Although **4a** and **4b** are epimers, differing only in the configuration of stereocenter C23, they differed greatly in their reactivity with **3a**. In the 1,5-*anti* selective reaction, enolborinate aldol gave higher selectivity than Mukaiyama conditions (see Supporting Information (SI)) with minor (12% ds) matched/mismatched effects. Ketone **4c** gave good selectivity (>87% ds) in all four scenarios (entries 9−12). **4d** (entries 13−16) showed curious reactivity,with the sodium enolate showing higher 1,5-*syn* selectivity than the lithium enolate (see SI). However, very high 1,5-*syn* selectivity was obtained with both enantiomers of **3** (entry 13, dr = 94:6; entry 15, dr = 91:9).

The data in Table 1 demonstrate the remarkable 1,5-asymmetric inductive effects of ketones **4** in double stereodifferentiating aldol reactions with aldehyde partners **3**. In all 16 cases, the 1,5-asymmetric induction of the ketone dictates the stereochemical outcome of the reaction, and the 1,3-asymmetric

Table 1. 1,5-1,3 Double Stereodifferentiating Methyl Ketone Aldol Reactions



entry[a]	reactants	reagents[b]	% yield (dr)[c]	product (C19 configuration)	relative configuration C19−C23 (1,5)	relative configuration C19−C17 (1,3)
1	**4a**; (*R*)-**3a**	**A**	87 (96:4)	**12a** (*S*)	*anti*	*anti*
2	**4a**; (*R*)-**3a**	**B**	70 (92:8)	**12b** (*R*)	*syn*	*syn*
3	**4a**; (*S*)-**3a**	**A**	81 (84:16)	**12c** (*S*)	*anti*	*syn*
4	**4a**; (*S*)-**3a**	**B**	85 (92:8)	**12d** (*R*)	*syn*	*anti*
5	**4b**; (*R*)-**3a**	**C**	57 (76:24)	**13a** (*R*)	*anti*	*syn*
6	**4b**; (*R*)-**3a**	**B**	62 (73:27)	**13b** (*S*)	*syn*	*anti*
7	**4b**; (*S*)-**3a**	**C**	80 (88:12)	**13c** (*R*)	*anti*	*anti*
8	**4b**; (*S*)-**3a**	**B**	60 (82:18)	**13d** (*S*)	*syn*	*syn*
9	**4c**; (*R*)-**3a**	**A**	78 (92:8)	**14a** (*R*)	*anti*	*syn*
10	**4c**; (*R*)-**3a**	**B**	69 (91:9)	**14b** (*S*)	*syn*	*anti*
11	**4c**; (*S*)-**3a**	**A**	80 (89:11)	**14c** (*R*)	*anti*	*anti*
12	**4c**; (*S*)-**3a**	**B**	70 (87:13)	**14d** (*S*)	*syn*	*syn*
13	**4d**; (*R*)-**3a**	**D**	53 (94:6)	**15a** (*S*)	*anti*	*anti*
14	**4d**; (*R*)-**3a**	**E**	90 (83:17)	**15b** (*R*)	*syn*	*syn*
15	**4d**; (*S*)-**3a**	**D**	76 (91:9)	**15c** (*S*)	*anti*	*syn*
16	**4d**; (*S*)-**3a**	**E**	59 (73:27)	**15d** (*R*)	*syn*	*anti*

[a]Experiments conducted on 0.3 mmol scale at −78 °C. [b]Reagent index: **A**: (i) TMSOTf, Et_3N (ii) $BF_3{\cdot}OEt_2$, DCM. **B**: LiHMDS, PhMe/DMF (10:1). **C**: $(c\text{-Hex})_2BCl/Et_3N$, Et_2O. **D**: Bu_2BOTf, Et_3N, Et_2O. **E**: NaHMDS, CH_2Cl_2. [c]Analysis by ^1H NMR.

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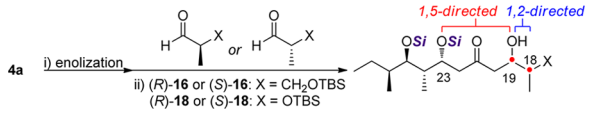
Table 2. 1,5-1,2 Double Stereodifferentiating Methyl Ketone Aldol Reactions



entry[a]	substrate	reagents[b]	% yield (dr)[c]	product (C19 configuration)	relative configuration C19–C23 (1,5)	relative configuration C19–C18 (1,2)
1	(*R*)-**16**	**A**	86 (85:15)	**17a** (*R*)	*anti*	*syn*
2	(*R*)-**16**	**B**	58 (96:4)	**17b** (*S*)	*syn*	*anti*
3	(*S*)-**16**	**A**	62 (58:42)	**17c** (*R*)	*anti*	*anti*
4	(*S*)-**16**	**B**	45 (90:10)	**17d** (*S*)	*syn*	*syn*
5	(*R*)-**18**	**A**	65(56:44)	**19a**/**19b**	—	—
6	(*R*)-**18**	**B**	76 (87:13)	**19b** (*S*)	*syn*	*syn*
7	(*S*)-**18**	**A**	60 (92:8)	**19c** (*R*)	*anti*	*anti*
8	(*S*)-**18**	**B**	87 (90:10)	**19d** (*S*)	*syn*	*anti*

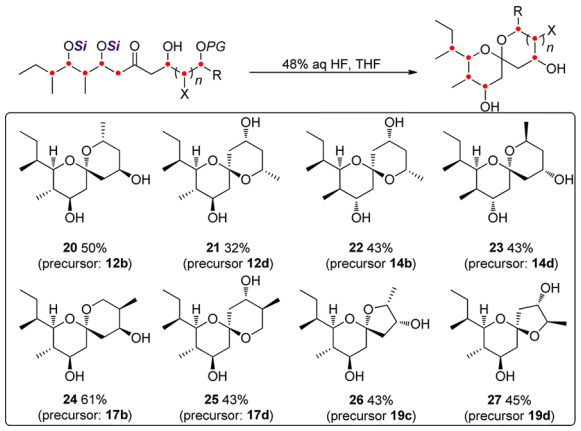
[a]Experiments conducted on 0.3 mmol scale at −78 °C. [b]Reagent index: **A**: (i) TMSOTf, Et_3N (ii) $BF_3{\cdot}OEt_2$, DCM. **B**: LiHMDS, PhMe/DMF (10:1). [c]Analysis by ^1H NMR.

inductive effects of the aldehyde **3** are subordinated. Importantly, good to excellent selectivity is obtained for 1,5-*anti* and *syn* products with all four diastereomeric ketones **4a**–**4d**, making this approach to polyketide construction very general. A curious observation is that the subtle variation in stereochemistry of **4a**–**4d** influences which aldol conditions give the highest selectivity (more data provided in SI). For instance, ketones **4a** and **4c** are C23–C24 *syn*-configured and give the highest 1,5-*anti* selectivity under Mukaiyama conditions, while ketones **4b** and **4d**, which are C23–C24 *anti*-configured, give the highest 1,5-*anti* selectivity under enol borinate conditions.

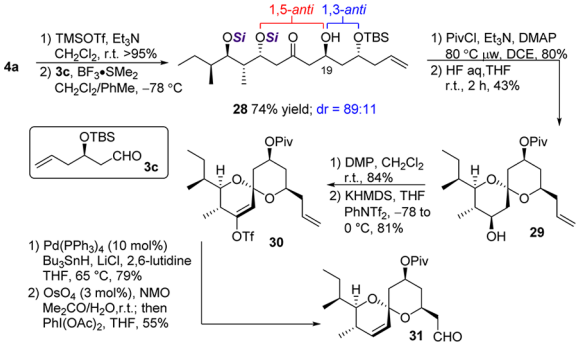
Curious to investigate other double stereodifferentiating situations, we considered aldehydes with an α-stereocenter, capable of strong 1,2-asymmetric induction (Table 2).[14] Reaction of ketone enolate **4a** with Roche aldehyde **16** under Mukaiyama aldol conditions showed good 1,5-*syn* selectivity for the *R* enantiomer, yet poor selectivity for the *S*-enantiomer, likely due to the 1,2-*syn* (Felkin) asymmetric induction of the aldehyde under Lewis acidic conditions (entries 1 and 3, dr = 85:15, 58:42, respectively). However, Li-mediated conditions gave excellent diastereoselectivity for both (*R*)- and (*S*)-enantiomers (entries 2 and 4). Lactate-derived aldehydes (*R*)-**18** and (*S*)-**18** gave high selectivity for the 1,5-*syn* products under Li-mediated conditions (entries 6 and 8) yet showed unexpected results under Mukaiyama conditions. We anticipated that the (*S*)-aldehyde would be matched under Mukaiyama conditions, given the reinforcing 1,5-*anti* and 1,2-*syn* (Felkin) effects. However, the aldol reaction with (*R*)-**18** was poorly selective (entry 5), while the presumed mismatched substrate (*S*)-**18** gave excellent selectivity (entry 7, dr = 92:8). The molecular underpinnings of these surprising results are unknown. Selected products of Tables 1 and 2 were transformed into the corresponding spiroketals products **20**–**27**, and their stereochemical configurations were determined by 1D and 2D NMR experiments (Scheme 4).

Finally, with this strategy we targeted spiroketal **31**, an advanced, functionalized intermediate in Danishefsky's salient total synthesis of avermectin A1a (Scheme 5).[6g] For this synthesis, methylketone **4a** was prepared in one step on preparative scale in reasonable yield (57%, 31.4 mmol; Scheme 2, eq 1). Importantly, isolation of **4a** as a pure single diastereomer required only simple crystallization. Methyl ketone **4a** was converted to the corresponding TMS-enolsilane and underwent a BF_3-promoted Mukaiyama aldol reaction with aldehyde partner

Scheme 4. HF(aq) Induced Spiroketalization



Scheme 5. Formal Total Synthesis of Avermectin A1a



3c, providing **28** with high 1,5-*anti* stereocontrol. The C19 hydroxyl was protected as its pivalate ester, and the product was subsequently treated with aqueous HF, which affected both cleavage of the silyl groups and spiroketalization to give **29**. Installation of the alkene was accomplished by oxidation and conversion to enol triflate **30**. Pd-catalyzed reduction and selective oxidative cleavage of the terminal olefin yielded **31**, prepared in nine steps from (*S*)-2-methylbutanal (*S*)-**6**, thus completing the formal total synthesis to Danishefsky's important intermediate of avermectin A1a.

In summary, a stereodivergent approach to spiroketals based on the avermectin framework, including the formal total

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synthesis of avermectin A1a, was developed. The route relies on stereoselective propanal, acetone, and 1,5-directed methyl ketone aldol reactions. In each step, the stereodirecting ability of the super silyl group is manipulated to selectively give multiple diastereomeric products. This route provides access to 32 stereochemical permutations of keto-tetraol scaffold **2**. The route is concise, requiring just nine linear steps for the synthesis of intermediate **31** from **6**, and 5−8 total steps for spiroketals **20**−**27**. The compounds prepared in this study will be deposited in the Chicago Tri-Institutional Center for Chemical Methods Library Development (CTCMLD) library for high-throughput screening for biological activities.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental data, characterization of new compounds, stereochemical assignments, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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