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

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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 avermitilis, display complex structural features, including a 16-membered macro lactone, 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 (27) 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 3.7−10 The stereochecmy at C17 and C19 would be dictated by the configuration of 3 and stereochemical outcome of the methyl ketone aldol reaction.
Scheme 2. Synthesis of Diastereomeric Ketones 4a−4d\(^{7b}\)

![Diagram of synthesis](image)

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

![Diagram of aldol reaction](image)

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 spiroketal 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 = 96:4, 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

| entry\(^{b}\) | reactants | reagents\(^{b}\) | % yield (dr)\(^{c}\) | product (C19 configuration) | C19−C23 (1,5) | 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, Et₃N (ii) BF₃·OEt₂, DCM. B: LiHMDS, PhMe/DMF (10:1). C: (c-Hex)₂BCl/Et₃N, Et₂O. D: Bu₃BOTf, Et₃N, Et₂O. E: NaHMDS, CH₂Cl₂. \(^{c}\)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). 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 spiroketal 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). For this synthesis, methylketone 4a was prepared in one step on 0.3 mmol scale at −78 °C. Sixteen aldehydes (20−27) were subjected to Mukaiyama aldol reaction conditions (Table 1) and converted to the corresponding TMS-enolsilane and underwent a BF3-promoted Mukaiyama aldol reaction with aldehyde partner 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 spiroketal based on the avermectin framework, including the formal total synthesis of avermectin A1a (Scheme 5).
synthesis of avermectin A1a, was developed. The route relies on stereoselective propionaldehyde, acetone, and 1,5-dimethyl 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 stereochemically permutations of keto-tetral 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 spiroketalts 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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