

Reaction of Chiral Titanium Z-Enolates with Chiral α -Silyloxy Aldehydes. Syntheses of NFX-2 and Antimycinone

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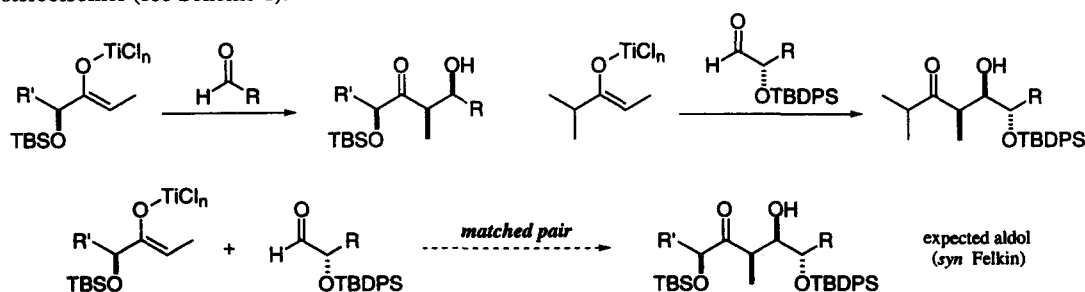
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Abstract

Titanium-mediated aldol reactions of **1** and (*S*)-2-*tert*-butyldiphenylsilyloxy aldehydes (*matched pair*) afford *syn* Felkin diastereomers in excellent yield and absolute stereochemical control. Having established that chain length does not affect the yield of the titanium aldol reactions, we have been able to achieve short, high yielding and enantioselective syntheses of NFX-2 and Antimycinone.

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Keywords: Aldol reactions; Diastereoselection; NFX-2; Antimycinone.

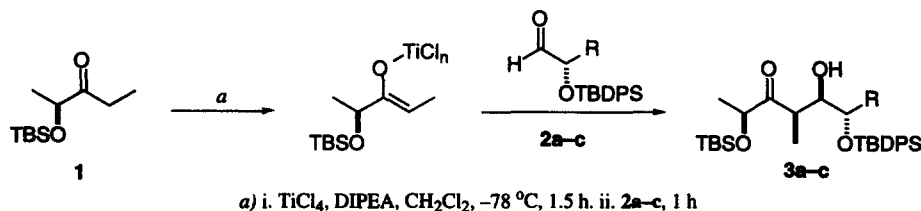
Double asymmetric synthesis represents one of the most useful strategies for gaining access to chiral compounds in excellent yield and with stereochemical control.¹ As we have recently disclosed highly stereoselective titanium-mediated aldol reactions of ethyl α -silyloxy ketones and achiral aldehydes,² as well as the Felkin induction caused by α -*tert*-butyldiphenylsilyloxy aldehydes in aldol reactions of titanium enolates derived from 2-methyl-3-pentanone,³ it was envisioned that the *matched pair* should lead to the *syn* Felkin stereoisomer (see Scheme 1).



Scheme 1

As anticipated, the aldol addition of the titanium enolate derived from (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone, **1**, to (*S*)-2-*tert*-butyldiphenylsilyloxy aldehydes **2a–c** (a: R = Me; b: R = Bn; c: R = Prⁱ) led, in

every case, to the *syn* Felkin stereoisomer (no other stereoisomers were detected in the crude mixtures) **3a–c** in excellent yields (see Scheme 2). The results are summarised in Table 1.⁴



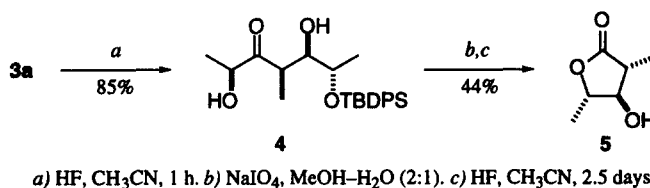
Scheme 2

Table 1. Diastereoselective aldol reactions of aldehydes **2**

entry	aldehyde, R	product	yield ^a , %
1	2a Me	3a	97 (90)
2	2b Bn	3b	97 (90)
3	2c Pr ⁱ	3c	83 (79)

^a. Isolated yields from 1.5 equiv. of **2**
(Figures in parentheses refer to the isolated yields from 1.1 equiv. of **2**)

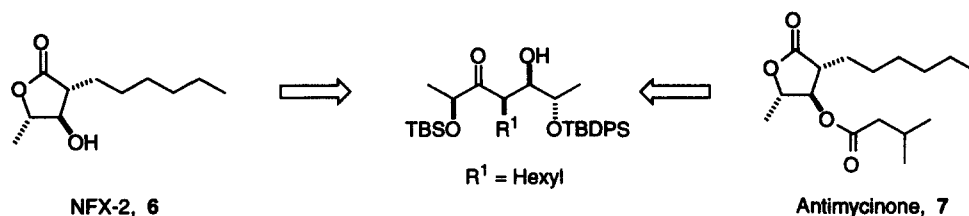
The stereochemistry of **3a** was confirmed by chemical correlation (see Scheme 3). Selective deprotection of the TBS group afforded hydroxy ketone **4** which was, in turn, oxidised with NaIO_4 and TBDPS-deprotected to give lactone **5**, whose ^1H and ^{13}C NMR spectra matched those reported in the literature.^{5a}



Scheme 3

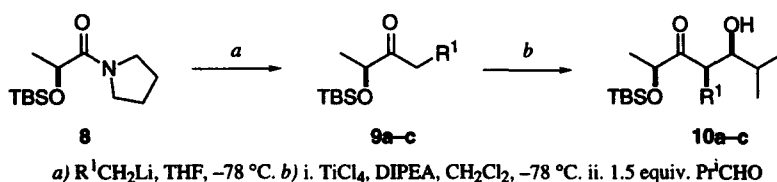
The configuration of stereocenters embodied in **5** suggested to us that NFX-2, **6**, and Antimycinone, **7**, might be amenable by this methodology. NFX-2 and Antimycinone are members of a family of polyketide metabolites which contain a 3-alkyl-4-hydroxy-5-methyl-2(3*H*)-dihydrofuranone substructure.⁶ We envisaged that both compounds could be synthesised from a common precursor similar to **3a** which, in turn, could be obtained by a double asymmetric aldol reaction (see Scheme 4).⁷

It is well known that the length of the lateral chain R^1 (see Scheme 4) may affect the yield and/or the diastereoselectivity of an aldol reaction.⁸ For example, it has been reported that yields of the aldol addition products of boron enolates derived from a chiral oxazolidinone dramatically drop when the chain length increases, because of the low extent of enolate formation; even using optimised conditions, only a 70% yield is attained for R^1 = hexyl (Hex).⁶



Scheme 4

Given that reaction of the titanium enolate derived from **1** ($R^1 = \text{Me}$ in Scheme 5) with isobutyraldehyde afforded the *syn* aldol product in excellent diastereoselectivity (30:1) and yield (90%),² we turned our attention to the analogous reaction of titanium enolates derived from other α -*tert*-butyldimethylsilyloxy ketones, **9a–c**. (a: $R^1 = \text{H}$; b: $R^1 = \text{Pr}$; c: $R^1 = \text{Hex}$). Ketones **9a–c** were easily prepared from amide **8**,⁹ then submitted to a standard enolisation protocol and allowed to react with isobutyraldehyde (see Scheme 5). Aldols **10a–c** were obtained in good yields (87–90%) irrespective of the length of R^1 ; diastereoselectivity was excellent in all cases ($\geq 30:1$) except for **10a** (2:1), corresponding to an acetate aldol reaction. The results are summarised in Table 2.



Scheme 5

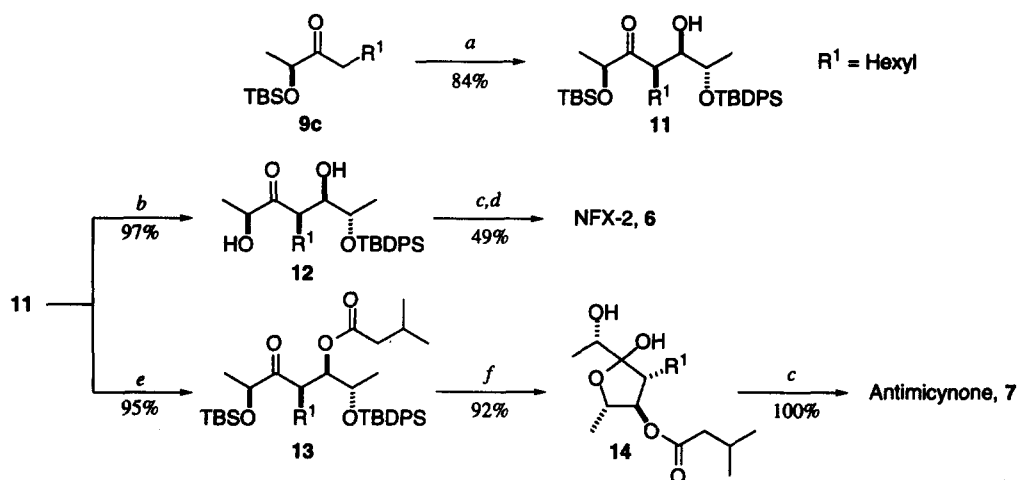
Table 2. Diastereoselective aldol reactions of ketones **9a–c**

entry	ketone, R^1	yield ^a , %	aldol	yield ^a , %
1	9a H	59	10a ^b	90
2	9b Pr	88	10b	87
3	9c Hex	77	10c	87

a. Isolated overall yield.

b. Stereochemistry of the major diastereomer not elucidated

Having established that the length of R^1 did not affect the yield nor the diastereoselectivity of the preceding aldol reactions, we focused our attention on the syntheses of NFX-2 and Antimycinone. Titanium-mediated aldol addition of ketone **9c** to aldehyde **2a** furnished, in 84% yield, a single stereoisomer **11**, a common precursor to NFX-2 and Antimycinone (see Scheme 6). Selective TBS-deprotection afforded α -hydroxy ketone **12** (97%), which was oxidised and TBDPS-deprotected (49%) to give NFX-2, **6**. Alternatively, acylation of **11** provided keto ester **13** in excellent yield (95%); simultaneous TBS and TBDPS-deprotection furnished a mixture (4:1) of two hemiacetals **14**, which were oxidised to Antimycinone, **7**, in quantitative yield (see Scheme 6). Spectroscopic and physical data of NFX-2 and Antimycinone are in agreement with those reported in the literature.⁶



a) i. TiCl_4 , DIPEA, CH_2Cl_2 , -78°C . ii. 1.25 equiv. of **2a**. b) HF, CH_3CN , 1 h. c) NaIO_4 , $\text{MeOH-H}_2\text{O}$ (2:1).
d) HF, CH_3CN , 3 days. e) Bu^tCOCl , py, CH_2Cl_2 . f) 5 equiv. of TBAF, 2 equiv. of AcOH, THF, 2 h.

Scheme 6

In summary, the titanium-mediated aldol reactions of **1** and (*S*)-2-*tert*-butyldiphenylsilyloxy aldehydes afford *syn* Felkin diastereomers in excellent yields and with absolute stereochemical control. Having established that the length of chain R^1 does not affect the yields of aldol reactions, we have been able to achieve short, high yielding and enantioselective syntheses of NFX-2 (4 steps, 40% from **9c**) and Antimycinone (4 steps, 73% from **9c**). Further studies in order to expand this methodology are underway in our laboratory.

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