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Regioselective synthesis of fluoroaldols. Studies toward fluoroepothilones syntheses via antibody catalysis

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Abstract

A general method for the synthesis of fluoromethyl aldols has been developed. Tributylboron enolates of fluoroacetone react with thiazole aldehydes (**6**) to provide fluoromethylaldols (**4**) regioselectively in high yields. Regioisomeric fluoroaldols (**5**) are produced as a 1:1 isomeric mixture of the *erythro* and *threo* products via a two-step procedure: first, aldol reaction with Weinreb amide and then Grignard reaction.

Fluoro analogs of natural products are routinely synthesized to increase the potency of drugs and are also used as probes for conformational analysis studies in solution. In continuation of our program on the synthesis of epothilones by antibody catalysis, we became interested in synthesizing fluoro analogs of epothilones. Several fluoro analogs of epothilones (**1**)[1,2] have already been reported and some possess higher potency than the natural compounds. We anticipated that recently produced aldolase antibodies could be used to resolve enantiomerically pure thiazole aldols **4** and **5**, and the latter compounds would be converted to 13-fluoromethyl epothilones (**2**) and 13-methyl-14-fluoro epothilones (**3**).[3]

Regioselective aldol reaction of fluoroacetone with an aldehyde, in principle, could afford both fluoroaldol products **4** and **5** (Fig. 1). However, synthesis of fluoroaldols by aldol reaction using fluoroketones as donors poses a major challenge and to the best of our knowledge there are no chemical methods to achieve this goal in respectable yields. Based on our previous studies with aldolase antibodies, it was expected that compounds **5** could be obtained as a major product by aldol reaction of fluoroacetone with aldehydes **6**. In our initial studies, we found that the antibody 38C2[4] catalyzes the aldol reaction of fluoroacetone with aldehyde **6a**[5] providing **5** as a major product. Unfortunately, the stereo- and enantioselectivities of the reaction were low. To overcome this problem, we decided to produce **4** and **5** by resolution of their racemic

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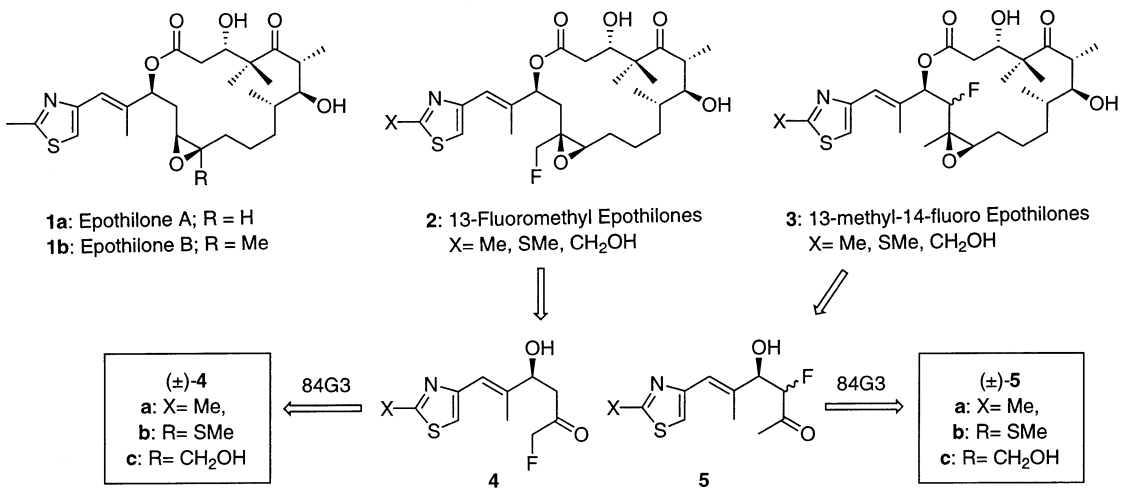
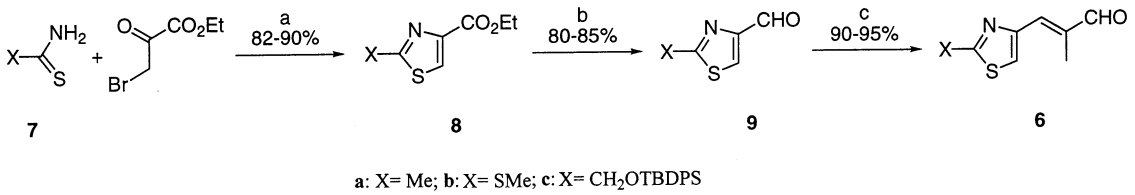


Figure 1.

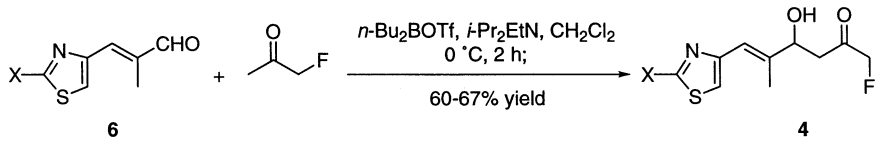
mixtures using aldolase antibody 84G3.[6] Since there is no straightforward method for the synthesis of racemic fluoroaldols, such as **4** and **5**, we decided to find suitable methods, which could be used to synthesize them in reasonable yields. Here, we report a general method for the aldol reaction of fluoroacetone with thiazole aldehydes (**6a–c**) to produce fluoromethyl thiazole aldols (**4a–c**), regioselectively. We also report a two-step process for the synthesis of the regioisomeric fluoroaldols **5a–c** and efficient methods for the large-scale production of thiazole aldehydes **6b** and **6c**.

Synthesis of thiazole aldehydes (6a–c): Syntheses of thiazole aldehydes **6b** and **6c** were similar to that of **6a**,[7] starting from **7a**, and required a slight modification in the condensation of **7b** and **7c** with ethyl bromopyruvate to produce the corresponding ester. Compound **7b**[8] was reacted with ethyl bromopyruvate in ethanol with a catalytic amount of concentrated HCl at reflux temperature for 2 h to produce the thiazole ester **8b**. The thiazole ester **8c**, on the other hand, was obtained by heating **7c**[9] with ethyl bromopyruvate in benzene at 80°C for 1 h. The produced thiazole esters **8b** and **8c** were first reduced with DIBAL-H affording **9b** and **9c**, respectively, and the latter compounds were then reacted with 2-(triphenylphosphoranylidene)-propionaldehyde to produce aldehydes **6b** and **6c** (Scheme 1).



Scheme 1. Synthesis of thiazole aldehydes **6a–c**. (TBDPS = *tert*-butyldiphenylsilyl). Key: (a) for **8a**: see reference 7; for **8b**: ethanol, HCl (cat.), reflux, 2 h; for **8c**: benzene, 80°C, 1 h; (b) DIBAL-H, CH_2Cl_2, –78°C, 2 h; (c) 2-(triphenylphosphoranylidene)-propionaldehyde, benzene, 100°C, 1 h

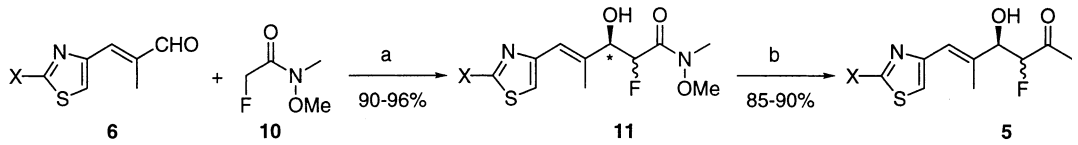
Synthesis of fluoromethylaldols (4):[10] Aldol reaction of fluoroacetone with an aldehyde using bases of alkali metals, including LDA, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$, is not trivial and usually no desired products are obtained from this reaction. Now, we found that aldolization of aldehydes **6a–c** with fluoroacetone could be achieved regioselectively using the boron enolate of the latter to provide **4a–c**. In a typical reaction, fluoroacetone (0.14 mL, 2 mmol) was added dropwise to a solution of dibutylboron triflate (1 M in CH_2Cl_2, 2 mL, 2 mmol) and *i*-Pr_2NEt (0.42 mL, 2.4 mmol) in dry CH_2Cl_2 (10 mL) at 0°C. After 2 h, a solution of aldehyde **6a** (167 mg, 1 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise and the reaction mixture was stirred at 0°C to room temperature overnight. Diethyl ether (10 mL) and ethanolamine (2 mL) were subsequently added, the mixture was stirred at room temperature for 6 h and then worked up with ether and water. The organic layer was washed with brine, concentrated and chromatographed over silica gel to afford **4a** (143 mg, 62%). Similarly, compounds **4b** and **4c** were obtained in 60–70% yield (Scheme 2). The regioisomers of compounds **4a–c**, if any formed, could not be isolated.



a: X= Me; **b**: X= SMe; **c**: X= $CH_2OTBDPS$

Scheme 2. Aldol reactions of aldehydes **6a–c** with fluoroacetone to (±)-**4**

Synthesis of fluoroaldols 5a–c: Reversal of regioselectivity of the addition of fluoroacetone to aldehyde **6** could afford the desired compound **5**. We briefly checked the effect of other amines, such as 2,6-lutidine and collidine, on the enolization of fluoroacetone with tributylborontriflate. With no favorable results, we decided to check a two-step process, in which Weinreb amide **10** was condensed with a thiazole aldehyde and then the resulting hydroxy amide **11** was reacted with an alkyl Grignard reagent (Scheme 3).[11] This method proved successful and provided an easy access to **5a–c** in 80–90% overall yield.



a: X= Me, **b**: X= SMe, **c**: X= $CH_2OTBDPS$

Scheme 3. Synthesis of fluoroaldols (±)-**5**. Key: (a) LDA, THF, −78°C, 2 h; (b) MeMgBr, THF, 0°C, 1 h

In a typical process, the Weinreb amide **10** (557 mg, 4.6 mmol) in dry THF (5 mL) was added dropwise to a solution of LDA (prepared from *n*-BuLi, 1.6 M in hexanes, 3.2 mL, 5.02 mmol and *i*-Pr_2NH, 0.89 mL, 6.34 mmol in 15 mL dry THF at 0°C) at −78°C. After stirring for 1 h at −78–0°C, a solution of **6a** (470 mg, 2.81 mmol) in dry THF (5 mL) was added dropwise at −78°C and then the mixture was stirred at −78°C for 2 h. Usual work-up and purification afforded the hydroxyamide **11a** (704 mg) in 93% yield. Compound **11a** was then reacted with methyl magnesium bromide as follows. To a solution of **11a** (200 mg, 0.72 mmol) in dry THF (3 mL), MeMgBr (1.4 M in THF, 1.4 mL, 1.96 mmol) was added at 0°C and the mixture was

stirred at the same temperature for 1 h. Usual work-up and purification afforded the hydroxyketone **5a** (141 mg) in 85% yield. Similarly compounds **5b** and **5c** were obtained in 88 and 81% overall yields, respectively.

After having compounds **4a**–**c** and **5a**–**c** in hand, we are now checking their resolutions using aldolase antibody 84G3. In our preliminary investigation, we have found that compound **4a** could be resolved in enantiomerically pure form using aldolase antibody 84G3 or its congeners, 85H6 and 93F3.[3c]

In conclusion, general methods for the synthesis of both regioisomers of fluoroaldols have been found and applied to prepare the starting materials for fluoroepothilones. Studies toward stereoselective addition of **10** with **6** to produce **11** (*threo* or *erythro*), antibody catalyzed resolutions of **4** and **5**, and total synthesis of fluoroepothilones using enantiomerically pure fluoroaldols are in progress and will be reported in due course.

Acknowledgements

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References

1. (a) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res*. **1995**, *55*, 2325. (b) Gerth, K.; Bedorf, N.; Hofle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot*. **1996**, *49*, 560. (c) Hofle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1567.
2. (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2014. (b) Nicolaou, K. C.; Hepworth, D.; King, N. Paul; Finlay, M.; Ray, V. *Pure Appl. Chem*. **1999**, *71*, 989. (c) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem*. **1999**, *64*, 8434, and references cited therein.
3. (a) For the total syntheses of epothilones A and C, see: Sinha, S. C.; Barbas III, C. F.; Lerner, R. A. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14603. (b) Total or formal syntheses of epothilones B, D and F, unpublished results. (c) Formal syntheses of epothilone E, see: Sinha, S. C.; Sun, J.; Miller, G.; Barbas III, C. F.; Lerner, R. A. *Org. Lett*. **1999**, *1*, 1623. (d) For synthesis of 13-alkyl epothilones: Sinha, S. C.; Sun, J.; Lerner, R. A., submitted for publication.
4. (a) Wagner, J.; Lerner, R. A.; Barbas, C. F. *Science* **1995**, *270*, 1797. (b) Zhong, G.; Shabat, D.; List, B.; Anderson, J.; Sinha, S. C.; Lerner, R. A.; Barbas, C. F. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2481. (c) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc*. **1999**, *121*, 7283, and references cited therein.
5. Sinha, S. C.; Miller, G.; Sun, J.; Barbas III, C. F.; Lerner, R. A. Book of Abstracts, 217th ACS National Meeting, Anaheim, CA, March 21–25, 1999.
6. Zhong, G.; Lerner, R. A.; Barbas, C. F. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 3738.
7. Taylor, R. E.; Haley, J. D. *Tetrahedron Lett*. **1997**, *38*, 2061.
8. Brandsma, L.; De Jong, R. P. L.; VerKruijsse, H. D. *Synthesis* **1985**, 948.
9. Compound **7c** was prepared in two steps from glycolamide: protection of alcohol as TBDPS ether using TBDPSCl and then conversion of amide to thioamide (for the latter step see: Schwarz, G. In *Organic Syntheses*; Horning, E. C., Ed.; John Wiley & Sons: New York, 1955; Coll. Vol. III, pp. 332–333).
10. The borontriflate-mediated aldol reaction of fluoroacetone was found to be general, which lead to the formation of aldol product not only with the thiazole aldehydes, but also with other aromatic and aliphatic aldehydes tested.
11. Synthesis of α-fluoroketones via Weinreb type fluoro amide are known, see: Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proc. Int*. **1999**, *31*, 125.

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