ORGANIC LETTERS

2006
Vol. 8, No. 21
4763−4766

Efficient Approach to the Azaspirane Core of FR 901483

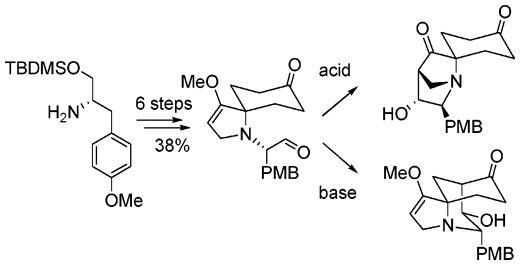
Silvia Kaden and Hans-Ulrich Reissig*

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustraβe 3, D-14195 Berlin, Germany

hans.reissig@chemie.fu-berlin.de

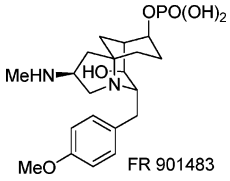
Received June 22, 2006

ABSTRACT



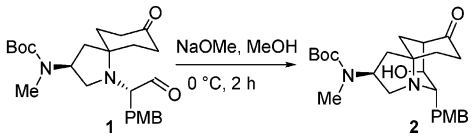
An efficient approach to the azaspirane core of FR 901483 is described employing lithiated methoxyallene as a crucial C3 building block and a suitably protected enantiopure ketimine as the second component. The resulting dihydropyrrole derivative was smoothly converted into a spiro keto aldehyde which under acidic conditions provided a novel azanorbornane derivative 15. Under basic reaction conditions, the desired 5-azatricyclo[6.3.1.0^{1,5}]dodecane skeleton 16 was generated. The ratio of diastereomers strongly depends on the reaction conditions employed with L-proline in DMSO providing the highest selectivity in favor of one azaspirane product.

The tricyclic natural product FR 901483 was isolated by scientists of the Fujisawa group from the fermentation broth of a *Cladobotryum* species.[1] The compound is a strong immunosuppressant which inhibits purine nucleotide biosynthesis by a mechanism different from that of cyclosporin A or FK-506. The unique ring junction of FR 901483 and its biological activity have motivated a number of research groups to prepare this intriguing natural product. Three total syntheses of the enantiopure compound[2] and two of the racemate[3] have been published so far. In addition, several attempts to approach the tricyclic core structure are reported.[4]



An intramolecular aldol reaction is the crucial C−C bond forming step in four of these syntheses. For example, in Sorensen's synthesis of FR 901483, treatment of spiro compound **1** with base provided the required tricyclic product **2** together with two other diastereomers (Scheme 1).[2b]

Scheme 1. Intramolecular Aldol Step in Sorensen's Synthesis



1 2

PMB = *para*-methoxybenzyl

Our approach to the FR 901483 skeleton regards tricyclic compound **3** as the crucial intermediate, which should be formed by the aldol reaction of keto aldehyde **4** (Scheme 2). Precursor **5** with suitable protective groups should be available by addition of lithiated alkoxyallene **6** to ketimine

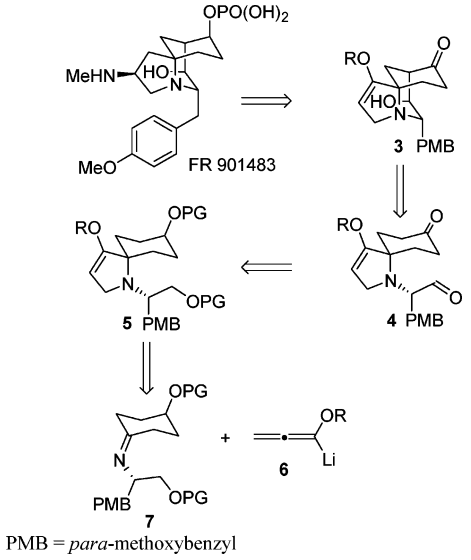
(1) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44.

(2) (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786. (b) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem.* **2000**, *112*, 4783−4785; *Angew. Chem., Int. Ed.* **2000**, *39*, 4593−4596. (c) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534−7538.

(3) (a) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125−1128. (b) Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. *Org. Lett.* **2004**, *6*, 2729−2731.

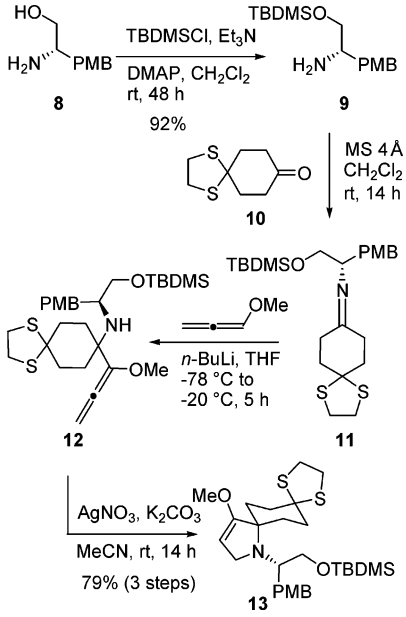
10.1021/ol061538y CCC: $33.50
Published on Web 09/21/2006

Scheme 2. Retrosynthetic Analysis of the FR 901483 Core



PMB = *para*-methoxybenzyl

Scheme 3. Synthesis of Dihydropyrrole **13**



7 which is generated by condensation of a L-tyrosine-derived amine and a cyclohexanone derivative. Lithiated alkoxyallenes **6** have already been successfully employed as functionalized C3 building blocks in stereocontrolled syntheses of natural products containing functionalized pyrrolidine rings[5] as well as for the preparation of other heterocycles.[6]

Amino alcohol **8** was smoothly prepared from L-tyrosine by four routine steps[2d] and protected as silyl ether to furnish primary amine **9** in excellent overall yield (Scheme 3). Ketone **10** containing a thioketal moiety[7] was also accessible according to a known method.[8] Under appropriate conditions, amine **9** and ketone **10** gave ketimine **11** (ca. 85% conversion). Because of its instability toward chromatography, crude **11** was directly combined with lithiated methoxyallene (generated in situ from methoxyallene with *n*-butyllithium), which provided allenylamine **12** in high efficiacy. Attempts to purify **12** failed, and therefore, the crude allenylamine was immediately cyclized in the presence of silver nitrate[9] and K_2CO_3 in MeCN to afford the desired dihydropyrrole derivative **13** in 79% overall yield (starting from **9**). Our approach to functionalized spiropyrrolidine derivatives such as **13** via lithiated alkoxyallenes is therefore very efficient, and it is potentially very flexible concerning the ketimine component.[10]

The thioketal moiety proved to be sufficiently stable during the formation of spiro compound **13**, and after trying a number of methods, we were able to selectively cleave this ketal with bis(trifluoroacetate) iodobenzene under optimized conditions according to a procedure by Stork et al. (Scheme 4).[11] Deprotection with TBAF provided a keto alcohol in good yield which upon oxidation with SO_3−pyridine and triethylamine in DMSO[12] furnished the required keto aldehyde **14**. Alternative methods such as Swern oxidation, DMP, TEMPO, or TPAP/NMO only resulted in decomposition of the starting material. With the sequences depicted in Schemes 3 and 4, the crucial aldol precursor **14** was obtained in six steps and 38% overall yield starting from amine **9** (starting from L-tyrosine: 10 steps and 24% overall yield).

(4) (a) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353−2356. (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013−3015. (c) Bonjoch, J.; Diaba, F.; Puigbo, G.; Peidro, E.; Sole, D. *Tetrahedron Lett.* **2003**, *46*, 8387−8390. (d) Brummond, K. M.; Hong, S.-p. *J. Org. Chem.* **2005**, *70*, 907−916. (e) Kropf, J. E.; Meigh, I. C.; Bebbington, W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046−2055. (f) Simila, S. T. M.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933−2936.

(5) (a) Pulz, R.; Al-Harrasi, A.; Reissig, H.-U. *Org. Lett.* **2002**, *4*, 2353−2355. (b) Flögel, O.; Okala Amombo, M. G.; Reissig, H.-U.; Zahn, G.; Brüdgam, I.; Hartl, H. *Chem.−Eur. J.* **2003**, *9*, 1405−1415. (c) Kaden, S.; Brockmann, M.; Reissig, H.-U. *Helv. Chim. Acta* **2005**, *88*, 1826−1838. (d) Hausherr, A. Dissertation; Freie Universität Berlin, 2001. (e) Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383−2386. (f) For a related approach to substituted pyrrolidines by addition of lithiated methoxyallene to hydrazones of aldehydes (including SAMP and RAMP hydrazones), see: Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1939−1950. Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1951−1960.

(6) Selected references: (a) Hormuth, S.; Reissig, H.-U. *J. Org. Chem.* **1994**, *59*, 67−73. (b) Okala Amombo, M. G.; Hausherr, A.; Reissig, H.-U. *Synlett* **1999**, 1871−1874. (c) Helms, M.; Schade, W.; Pulz, R.; Watanabe, T.; Al-Harrasi, A.; Fišera, L.; Hlobilová, I.; Zahn, G.; Reissig, H.-U. *Eur. J. Org. Chem.* **2005**, 1003−1019. (d) Al-Harrasi, A.; Reissig, H.-U. *Angew. Chem.* **2005**, *117*, 6383−6387; *Angew. Chem., Int. Ed.* **2005**, *44*, 6227−6231. For reviews, see: (e) Zimmer, R.; Reissig, H.-U. Donor-Substituted Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 425−492. (f) Zimmer, R. *Synthesis* **1993**, 165−178. (g) Zimmer, R.; Khan, F. A. *J. Prakt. Chem.* **1996**, *338*, 92−94.

(7) Other functional groups in this position such as simple ketals or trialkylsiloxy groups proved not to be easily compatible with the subsequent steps of our approach. Kaden, S. Dissertation; Freie Universität Berlin, 2006.

(8) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *Synlett* **2001**, 1641−1643.

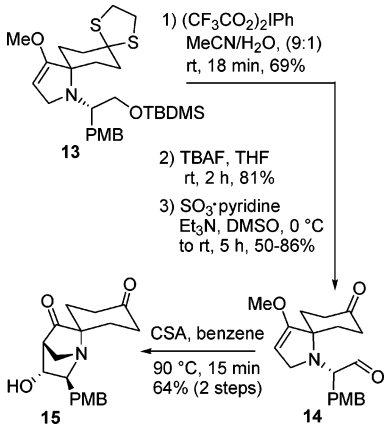
(9) (a) Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743−745. (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169−7171. (c) Flögel, O.; Reissig, H.-U. *Eur. J. Org. Chem.* **2004**, 2797−2804.

(10) For selected recently published methods to generate spiropyrrolidine derivatives, see: (a) El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Synthesis* **2004**, 2249−2262. (b) Planas, L.; Pérard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087−3092. (c) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337−4345.

(11) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290.

(12) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

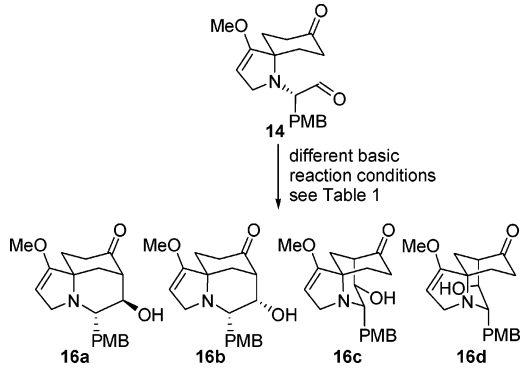
Scheme 4. Generation of Keto Aldehyde **14** Followed by Acid-Promoted Reaction to **15**



Treatment of keto aldehyde **14** with camphor sulfonic acid in analogy to conditions applied by Fukuyama et al.[3] resulted in an aldol-type reaction involving the enol ether moiety, which exclusively furnished tricyclic spiro compound **15** as a single diastereomer (64% yield based on the keto alcohol precursor of **14**). The configuration of the novel tricyclic skeleton **15** was established by analysis of the coupling constants and the NOESY spectrum.

In contrast, reactions of keto aldehyde **14** under basic conditions led to the desired aldol reaction of the cyclohexanone enolates, thus generating the tricyclic compound **16** with the FR 901483 skeleton. Using sodium methoxide in methanol, we isolated diastereomer **16a** as the major component, whereas with potassium *tert*-butoxide, diastereomer **16c** was the major product (Scheme 5, Table 1, entries

Scheme 5. Base-Promoted Aldol Reactions of Keto Aldehyde **14**



1−3). Only L-proline[13] in methanol afforded reasonable amounts of **16d** with the correct FR 901483 configuration, whereas in toluene or DMSO, diastereomer **16c** was obtained

(13) Reviews: (a) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591. (c) Moisan, L.; Dalko, P. I. *Angew. Chem.* **2004**, *116*, 5248−5286; *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175.

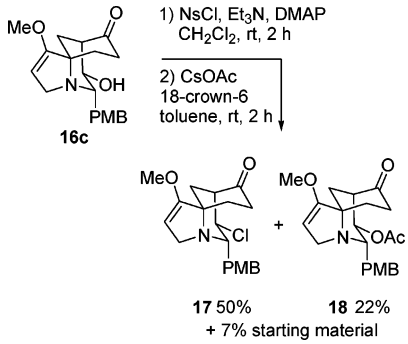
Table 1. Base-Promoted Intramolecular Aldol Reactions of Keto Aldehyde **14** Leading to Tricyclic Compounds **16a−d**

entry	reaction conditions	**16a** [%]	**16b** [%]	**16c** [%]	**16d** [%]
1	NaOMe, MeOH	**33**		16	9
2	KO^{t}Bu, ^{t}BuOH	16		**20**	
3	KO^{t}Bu, toluene	2		**34**	
4	L-proline, MeOH	20	4	18	17
5	L-proline, toluene	6	26	**36**	
6	L-proline, DMSO		13	**55**	
7	D-proline, MeOH	**28**	4	14	
8	D-proline, toluene	6	19	**44**	

as the major component (Table 1, entries 4−6). The configuration of the amino acid in these organo-catalyzed reactions seems to have a minor influence because D-proline induced rather similar product ratios (Table 1, entries 7 and 8). On the other hand, the nature of solvents is of great importance for these organo-catalyzed aldol reactions. L-Proline in DMSO provided the highest selectivity and yield for any of the four diastereomers (Table 1, entry 6) delivering compound **16c** in satisfying 55% yield. It is too early and speculative to interpret these results in detail; however, it should be noted that our precursor **14** behaves remarkably differently from the related compound **1** used by Sorensen et al. during their studies (see Scheme 1).

First attempts to invert the configuration of the secondary alcohol of major isomer **16c** were not successful. Under Mitsunobu conditions or by treatment of **16c** with nosyl chloride followed by cesium acetate[14] (Scheme 6), we almost

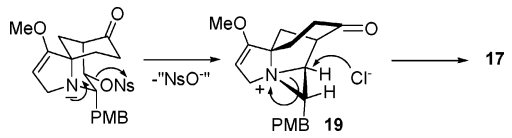
Scheme 6. Attempt to Invert the Configuration of Alcohol **16c**



exclusively obtained substitution products with retained configuration such as chloro compound **17** or acetate **18**. This may be due to the neighboring group participation of the nucleophilic dihydropyrrole nitrogen which probably leads to an aziridinium ion **19** as an intermediate (Scheme 7). The nucleophiles open this species and provide substitution products with overall retention of configuration.[15] The

(14) For an example, see: Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443.

Scheme 7. Neighboring Group Participation Leading to Retention of Configuration



constitutions and configurations of compounds **16**−**18** were unequivocally determined by NOESY spectra.

In summary, we have demonstrated that the alkoxyallene approach to functionalized pyrrolidine derivatives allows for a very fast and efficient generation of compound **16c** with the FR 901483 skeleton in enantiopure form (seven synthetic steps, five purifications, 21% overall yield). However, the crucial aldol reaction needs to be modified to obtain the correct diastereomer **16d** in excess. Attempts to achieve this objective as well as experiments to convert the enol ether moiety of type **3** compounds into the methylamino-substituted pyrrolidine function as required for the natural product will be reported in due course.

Acknowledgment. Generous support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Schering AG is most gratefully acknowledged. We thank Dr. Oliver Flögel for preliminary experiments in this field and Dr. Shahla Yekta for help during the preparation of this manuscript.

Supporting Information Available: Experimental procedures and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061538Y

(15) (a) Audia, J. E.; Colocci, N. *Tetrahedron Lett.* **1991**, *32*, 3779−3782. (b) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670−672. (c) Pfister, J. R. *Synthesis* **1984**, 969−970.