Tetrahedron Letters, Vol.31, No.21, pp 3007-3010, 1990
Printed in Great Britain

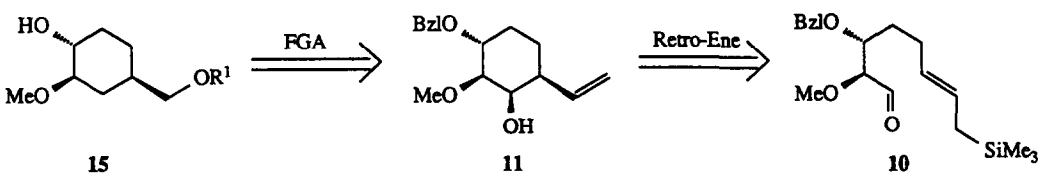
0040-4039/90 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF THE CYCLOHEXYL FRAGMENT OF FK-506 BY INTRAMOLECULAR ENE-REACTION

Martin E. Maier* and Bärbel Schöffling
Fakultät Chemie, Universität Konstanz
Postfach 5560, D-7750 Konstanz, Germany

Summary: An asymmetric synthesis of the cyclohexyl moiety of FK-506 **15a** is described.

The screening of the fermentation broth of *Streptomyces tsukubaensis* for immunosuppressive compounds has recently led to the discovery of the 23-membered macrolide[1] FK-506 and several related compounds.[2] Although the structure of FK-506 is completely different from the undecapeptide cyclosporin A, which is currently used in organ transplantations, it was found that both compounds show a similiar mode of action.[3] That is, they bind to cytosolic proteins with peptidylisomerase activity. Interestingly, FK-506 exhibits the same specific activity in much lower concentrations than cyclosporin A. These facts, as well as the challenging structure, initiated a series of synthetic studies, which include a total synthesis[4] and the synthesis of several fragments of this molecule.[5,6] In this Letter we report the synthesis of the cyclohexyl-moiety **15a** [C(28)-C(34) fragment] of FK-506. The key step of this approach is an intramolecular ene-type cyclization of an allylsilane aldehyde to generate a functionalized cyclohexane.[7,8]

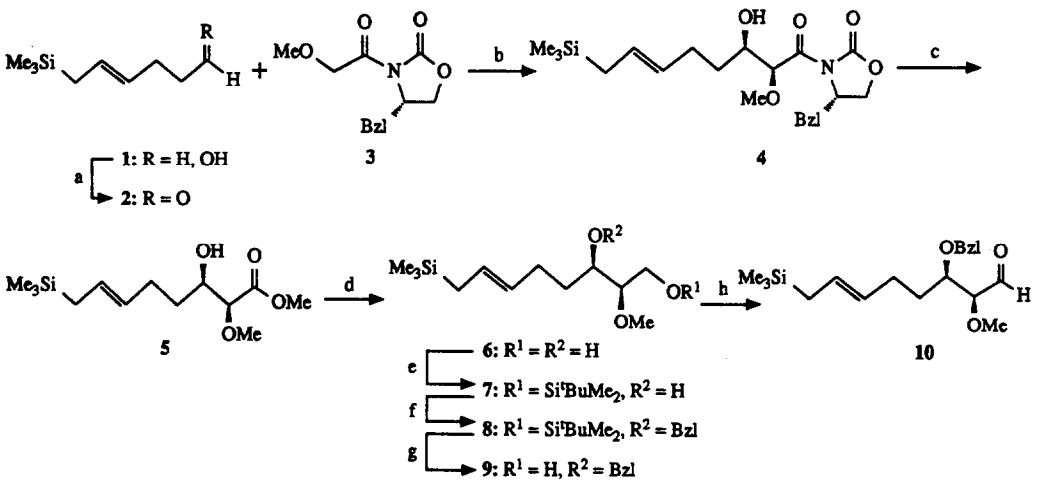


15 **11** **10**

The asymmetric synthesis of the required cyclization substrate **10** is shown in Scheme 1. Oxidation of the readily available (*E*)-6-(trimethylsilyl)-4-hexen-1-ol[9] (**1**) under Swern conditions[10] gave aldehyde[11] **2** in 90% yield. Aldol reaction between the boron enolate of (4S)-3-(methoxyacetyl)-4-(phenylmethyl)-2-oxazolidinone[12] (**3**) and aldehyde **2** afforded the adduct **4** in 89% yield ($[\alpha]_D^{20}$ +46.5° (*c* 1.0 acetone)) and greater than 96% diastereoselectivity. The oxazolidinone group was removed by transesterification of **4** with magnesium methoxide in methanol[13] to give the ester **5** (82% yield, $[\alpha]_D^{20}$ -18.7° (*c* 1.0 acetone)), which was reduced to the diol **6** in 84% yield. The primary hydroxy group of **6** was protected as its tert.-butyldimethylsilyl ether **7**. Benzylation of the secondary hydroxy group gave compound **8** in 73% yield. Selective removal of the primary t-butyldimethylsilyl ether, without affecting the allylsilane, was accomplished with pyridinium *p*-toluenesulfonate[14] in methanol to give the alcohol **9** (84% yield,

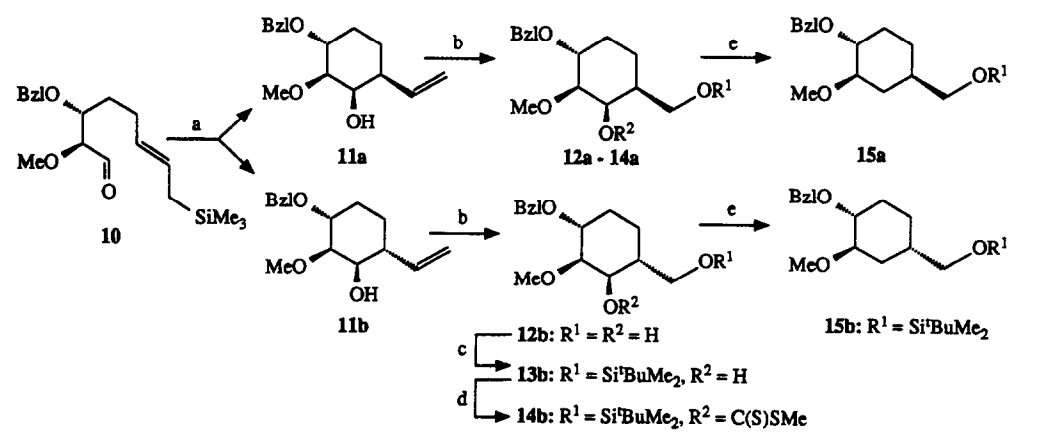
$[\alpha]_D^{20}$ +37.2° (*c* 1.0 acetone)). Alcohol **9** was then oxidized to the aldehyde **10** in quantitative yield. The aldehyde was used without further purification in the cyclization reaction.

Scheme 1



Reagents and conditions: (a) 2.2 equiv of DMSO, 1.1 equiv of $(COCl)_2$, 4.4 equiv of NEt_3, CH_2Cl_2, -70 °C, 1.5 h, 90%; (b) 1.3 equiv of **3**, 1.1 equiv of NEt_3, 1.2 equiv of Bu_2BOTf, CH_2Cl_2, -78 °C, 1 h, add **2**, -78 to -40 °C, 2h, 89%; (c) 1.1 equiv of MeMgBr, MeOH, 0 °C, 10 min, 82%; (d) 2.6 equiv of $LiAlH_4$, Et_2O, 0 to 20 °C, 3 h, 84%; (e) 2.5 equiv of imidazole, 1.0 equiv of *t*-$BuMe_2SiCl$, CH_2Cl_2, 20 °C, 18 h, 96%; (f) 1.5 equiv of BzlBr, 1.0 equiv of NaH, DMF, 0 to 20 °C, 18 h, 73%; (g) 0.3 equiv of PPTS, MeOH, 50 °C, 3.5 h, 84%; (h) 3.2 equiv of DMSO, 1.6 equiv of $(COCl)_2$, 6.8 equiv of NEt_3, CH_2Cl_2, -60 °C, 1 h, 100% (crude).

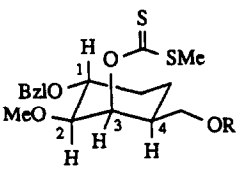
Scheme 2



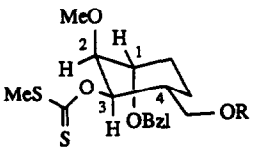
Reagents and conditions: (a) 1.0 equiv of BF_3-Et_2O, CH_2Cl_2, -78 °C, 45 min, 82%; (b) O_3, CH_2Cl_2/MeOH (4:1), -78 °C, then add 6.0 equiv of $NaBH_4$ (in H_2O/MeOH (1:1)), 0 to 40 °C, 3 h, 90% for **12a**, 79% for **12b**; (c) 2.5 equiv of imidazole, 1.0 equiv of *t*-$BuMe_2SiCl$, CH_2Cl_2, 20 °C, 18 h, 88% for **13a**, 78% for **13b**; (d) 1.5 equiv of NaH, 40 equiv of CS_2, 55 equiv of MeI, 70 °C, 3.5 h, 87% for **14a**, 80% for **14b**; (e) 10 equiv of Bu_3SnH, trace of AIBN, toluene, 110 °C, 2 h, 92% for **15a**, 77% for **15b**.

Treatment of a 0.05 M solution of aldehyde **10** in dichloromethane with boron trifluoride etherate at -78 °C gave a mixture of two cyclohexanols **11a** and **11b** in a ratio of 47:53 (82% total yield). Similar results were obtained with tin(IV) chloride as Lewis acid. The cyclization reaction failed with the corresponding substrate having no trimethylsilyl group[15]. After separation of the isomers **11a** ($[\alpha]_D^{20}$ -6.8° (*c* 1.0 acetone)) and **11b** ($[\alpha]_D^{20}$ +8.9° (*c* 1.0 acetone)) they were converted to the 3-deoxy compounds **15a** ($[\alpha]_D^{20}$ -27.2° (*c* 1.0 acetone)) and **15b** ($[\alpha]_D^{20}$ -19.2° (*c* 1.0 acetone)), respectively by (i) ozonolysis/sodium borohydride reduction[16], (ii) silylation [*t*-BuMe$_2$SiCl, imidazole], (iii) xanthate formation, and (iv) reaction of the latter with tributyltin hydride[17] (Scheme 2).

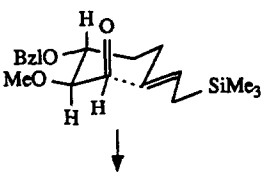
The configurations at the newly formed chiral centres were determined by analysis of the ^{1}H NMR spectra of the xanthates **14a** and **14b**. In compound **14b** 3-H appears as a doublet of doublet (δ = 6.00) with coupling constants $J_{2,3}$ = 2.3 Hz and $J_{3,4}$ = 10.6 Hz. This proves the assigned conformation and the configurations at C-3 and C-4. On the other hand, 3-H of **14a** is shifted downfield (δ = 6.49, equatorial H) and appears as a broad singlet. The coupling constants $J_{2,3}$ = 2.8 Hz and $J_{1,2}$ = 9.2 Hz of **14a** indicate the given conformation as well as the configuration at C-3. The configuration at C-4 follows from comparison of **15a** and **15b**. Thus, **15a** represents the cyclohexyl portion of FK-506. We note that **15b** also might be converted to **15a** by epimerization at C-4.



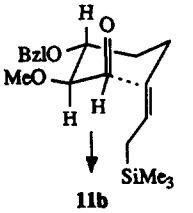
14a



14b



11a



11b

The stereochemical result of the cyclization reaction may be explained by assuming a transition structure with a chair-like conformation where the two alkoxy groups occupy equatorial positions. The carbonyl group must then point into axial direction. This corresponds to a Cram-Felkin type transition structure.[18] With regard to the orientation of the allylsilane and the carbonyl group this would mean that synclinal as well as antiperiplanar transition structures are operative.[19] Alternatively, one might also invoke product-like transition structures (cf. conformations of **14a** and **14b**).

Acknowledgement: Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and Notes

1. (a) T. Kino, H. Hatanaka, M. Hashimoto, M. Nishiyama, T. Goto, M. Okuhara, M. Kohsaka, H. Aoki, H. Imanaka, *J. Antibiotics* **40** (1987) 1249. (b) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto, T. Taga, *J. Am. Chem. Soc.* **109** (1987) 5031.
2. (a) H. Hatanaka, T. Kino, S. Miyata, N. Inamura, A. Kuroda, T. Goto, H. Tanaka, M. Okuhara, *J. Antibiotics* **41**, (1988) 1592. (b) H. Hatanaka, T. Kino, M. Asano, T. Goto, H. Tanaka, M. Okuhara, *J. Antibiotics* **42** (1989) 620. (c) R.E. Morris, B.M. Meiser, *Med. Sci. Res.* **17** (1989) 877.
3. J.J. Siekierka, S.H.Y. Hung, M. Poe, C.S. Lin, N.H. Sigal, *Nature* **341** (1989) 755.

4. T.K. Jones, S.G. Mills, R.A. Reamer, D. Askin, R. Desmond, R.P. Volante, I. Shinkai, *J. Am. Chem. Soc.* **111** (1989) 1157.

5. For synthetic studies which include the cyclohexyl moiety of FK-506, see: (a) S.G. Mills, R. Desmond, R. A. Reamer, R.P. Volante, I. Shinkai, *Tetrahedron Lett.* **29** (1988) 281. (c) S.L. Schreiber, D.B. Smith, *J. Org. Chem.* **54** (1989) 9. (c) E.J. Corey, H.C. Huang, *Tetrahedron Lett.* **30** (1989) 5235. (d) A.B. Smith, III, K.J. Hale, L.M. Laakso, K. Chen, A. Riera, *Tetrahedron Lett.* **30** (1989) 6963. (e) P. Kocienski, M. Stocks, D. Donald, M. Perry, *Synlett* **1990**, 38.

6. For syntheses of other fragments, see: Z. Wang, *Tetrahedron Lett.* **30** (1989) 6611 and references therein.

7. For a recent example of an intramolecular cyclization of an allylsilane aldehyde, see: K.A. Asao, H. Iio, T. Tokoroyama, *Tetrahedron Lett.* **30** (1989) 6397.

8. The chemistry of allylsilanes has been reviewed: (a) D. Schinzer, Synthesis **1988**, 263. (b) I. Fleming, J. Dunogues, R. Smithers, *Org. React.* **37** (1989) 57.

9. Prepared on a large scale by a modified Crombie synthesis (L. Crombie, S. Harper, *J. Chem. Soc.* **1950**, 1707) from 3,4-dihydro-2*H*-pyran through the following sequence: (i) Cl_2, Et_2O; (ii) Me_3SiCH_2MgCl, Et_2O, 82%; (iii) Na-sand, Et_2O, 53%, b.p. 96-99 °C/760 Torr.

10. A.J. Manusco, D. Swern, *Synthesis* **1981**, 165.

11. S.R. Wilson, C.E. Augelli-Szafran, *Tetrahedron* **44** (1988) 3983.

12. Prepared from (4S)-4-(phenylmethyl)-2-oxazolidinone [J.R. Gage, D.A. Evans, *Org. Synth.* **68** (1989) 77] and methoxyacetyl chloride. For a similiar reagent, see: T.W. Ku, K.H. Konrad, J. G. Gleason, *J. Org. Chem.* **54** (1989) 3487.

13. D.A. Evans, A.E. Weber, *J. Am. Chem. Soc.* **109** (1987) 7151.

14. C. Prakash, S. Saleh, I.A. Blair, *Tetrahedron Lett.* **30** (1989) 19.

15. B. Schöffling, unpublished results.

16. J.A. Sousa, A.L. Bluhm, *J. Org. Chem.* **25** (1960) 108.

17. (a) D.H.R. Barton, S.W. McCombie, *J. Chem. Soc., Perkin Trans.* I, **1975**, 1574. (b) review: W. Hartwig, *Tetrahedron* **39** (1983) 2609.

18. M.T. Reetz, *Angew. Chem.* **96** (1984) 542; *Angew. Chem. Int. Ed. Engl.* **23** (1984) 556 and references therein.

19. (a) S.E. Denmark, E.J. Weber, *Helv. Chim. Acta* **66** (1983) 1651. (b) S.E. Denmark, E.J. Weber, T.M. Wilson, T.M. Willson, *Tetrahedron* **45** (1989) 1053. (c) Y. Yamamoto, *Acc. Chem. Res.* **20** (1987) 243.

(Received in Germany 5 March 1990)