Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1439-1442, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00042-7

Total Synthesis of Progesterone Receptor Ligands, (-)-PF1092A, B and C†

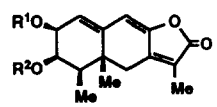
Kuniaki Tatsuta*, Shohei Yasuda, Ken-ichi Kurihara,[a] Kiyoshi Tanabe,[a] Rie Shinei,[a] and Tsuneo Okonogi[a]

Graduate School of Science and Engineering, Advanced Research Institute for Science and Engineering, Waseda University
Ohkubo, Shinjuku-ku, Tokyo 169, Japan

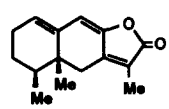
[a]Drug Discovery, Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., Morooka, Kohoku-ku, Yokohama 222, Japan

Abstract: Microbial metabolites (-)-PF1092A, B and C belonging to an eremophilane sesquiterpene group are synthesized from (*R*)-5-hydroxymethyl-2(5*H*)-furanone through the $SnCl_4$ promoted cyclization of an α-keto methyl sulfone and dimethyl acetal followed by a Stork annulation which gives the octalone core.

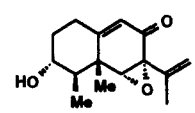
The microbial metabolites (-)-PF1092A, B and C (**1**, **2** and **3**) were isolated as new nonsteroidal progesterone receptor ligands by the Meiji Seika group from the culture broth of *Penicillium oblatum*[1,2], and the absolute structures were finally determined by X-ray crystallographic analysis[3]. Structurally, they are belonging to the complex eremophilane-type sesquiterpenes[4], with four contiguous *cis*-substituents on an octalone skeleton fused with a butenolide ring. The related natural products having an octalone core such as ligularenolide[4] (**4**), sporogen-AO 1[5] (**5**) and petasin[6] (**6**) have been known and synthesized by elegant methodologies.



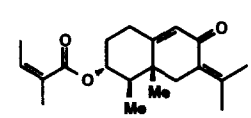
(-)-PF1092A (1): R^1=H, R^2=Ac
(-)-PF1092B (2): R^1=Ac, R^2=H
(-)-PF1092C (3): R^1= R^2=H



4: Ligularenolide



5: Sporogen-AO 1

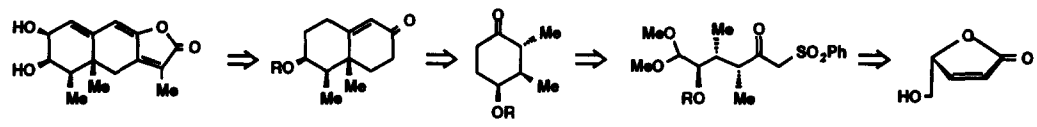


6: (+)-Petasin

Herein we described the first enantiospecific total synthesis of (-)-PF1092A, B and C (**1**, **2** and **3**).

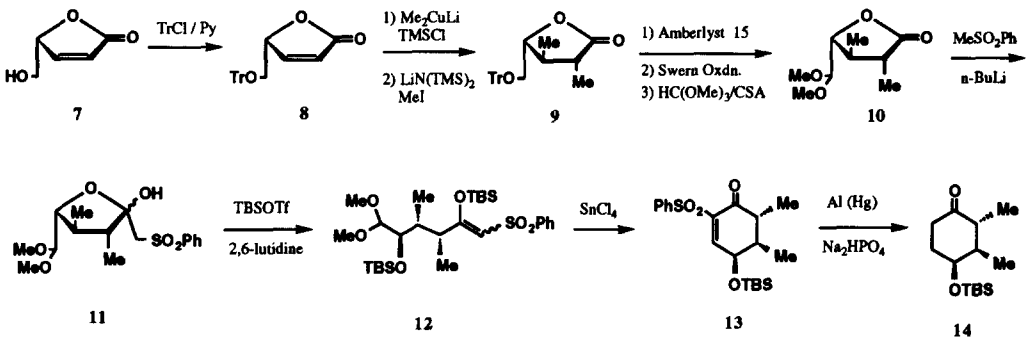
From the retrosynthetic perspective, we envisioned that the octalone core **I** (R = protecting group) would be accessible from the cyclohexanone **II** by a Stork annulation. In another critical step, we planned an efficient construction of **II** through the $SnCl_4$ promoted cyclization of an α-keto methyl sulfone having a dimethyl acetal **III**, which would be stereospecifically derived from commercially available (*R*)-(+)-5-hydroxymethyl-2(5*H*)-furanone (**7**).

† This paper is dedicated to Prof. Dr. Hans Paulsen in honor of his 75th birthday.



3 I II III 7

The synthesis was initiated with the stereoselective introduction of two methyl groups onto the butenolide **8** [needles (hexane-EtOAc), mp 120°C], which was prepared by tritylation of **7**. Conjugate addition[7] of Me_2CuLi ($TMSCl/Et_2O$), -78°C) to **8** followed by treatment with LiHMDS and MeI (THF, -78°C) provided the dimethylated lactone **9**[8] [67%; needles (hexane-ether), mp 108°C, $[\alpha]_D$ -32° ($CHCl_3$)] along with the C-2 epimer (13%). As this stereocenter will be lost in the formation of silyl enol ether **15** (*vide post*), both epimers could be used in the total synthesis of **3**. Their structures were confirmed by ^{1}H-NMR studies[7,8]. The NOE enhancement in **9** was observed between signals due to H-4 and Me-3 (3.4 %), but was not between two methyl signals. After detritylation (Amberlyst 15/90% MeOH, 80°C), the resulting alcohol was submitted to Swern oxidation [$(COCl)_2$/DMSO/TEA/CH_2Cl_2] to give the aldehyde, which was treated with $HC(OMe)_3$ (CSA/MeOH) to provide the dimethyl acetal **10** [85% from **9**; oil, $[\alpha]_D$ -4° ($CHCl_3$)]. Reaction of **10** with the lithiated $MeSO_2Ph$ (*n*-BuLi/THF, -78°C, 0.5 h) gave the lactol **11** (85%; oil), which was silylated (TBSOTf/2,6-lutidine/THF, r.t.) to the open chain having the silyl enol ether **12** (91%; oil). After investigating various derivatives and Lewis acids[9], the desired aldol-type cyclization of **12** was realized by treatment with $SnCl_4$ (CH_2Cl_2, -78°C, 3 h) to give, through β-elimination, the cyclohexenone **13** [84%; plates (hexane-EtOAc), mp 114°C, $[\alpha]_D$ +162° ($CHCl_3$)].

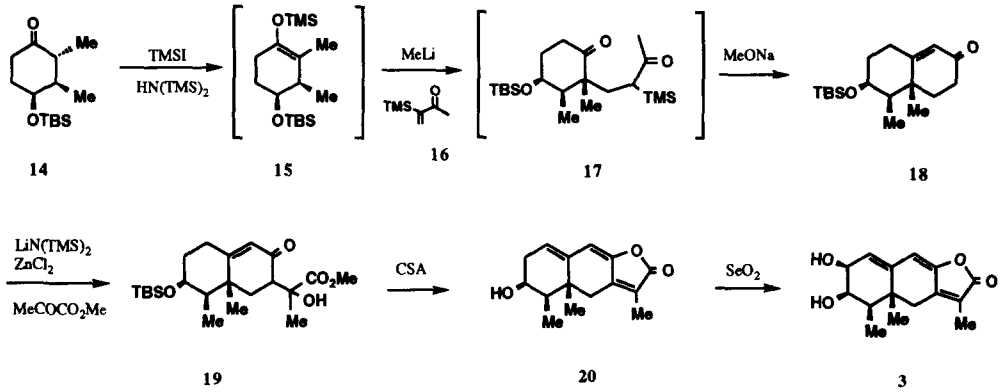


7 8 9 10 11 12 13 14

Desulfurization of **13** with Al(Hg) (Na_2HPO_4/EtOH, r.t., 4 h) with concomitant reduction of the olefin gave the cyclohexanone **14** [69%; oil, $[\alpha]_D$ +24° ($CHCl_3$)]. The annulation of **14** was carried out according to Stork's procedure[10] by silylation [TMSI/HN(TMS)$_2$/CH_2Cl_2, r.t., 0.5 h] to give **15**, followed by treatment with a silylated methyl vinyl ketone **16** (MeLi/THF, 0°C, 1 h) to give the key intermediate **17**. When this was cyclized with MeONa (MeOH, 70°C, 2 h), cleavage of the trimethylsilyl moiety occurred and the desired hexahydronaphthalenone **18** [needles (ether), mp 56°C, $[\alpha]_D$ +142° ($CHCl_3$)] was obtained in 60% overall yield from **14**. The introduction of the ethyl methyl ketone moiety to C-2 in **14** was expected to occur with addition *trans* to the C-3 methyl group to afford the natural configurations at C-2 and C-3 in **17**[5]. On irradiating at CH_3-5 (δ 1.30ppm) in **18**, the NOE enhancement of CH_3-4 signal (δ 1.01: 1.5%) was clearly detected to

support the *cis*-dimethyl structure. Compound **18** was converted into the Zn enolate[11] by lithiation (LiHMDS/THF, -78°C, 0.5 h) followed by treatment with 1M ethereal $ZnCl_2$ solution and reacted with methyl pyruvate (-78°C, 0.5 h) to give **19** quantitatively as a diastereomeric mixture. Closure to the desired lactone **20** [60%; needles (ether), mp 185°C, $[\alpha]_D$ -224° ($CHCl_3$)] was effected upon heating **19** with CSA[4] (aq. dioxane, 105°C). Finally, SeO_2 oxidation of **20** (aq. dioxane, 110°C, 14 h) with the aid of the hydroxy group[12] afforded stereospecifically the *cis* diol **3** [66%; needles (PhMe), mp (decomp.) 174°C, $[\alpha]_D$ -97° ($CHCl_3$)], identical with the natural product (-)-PF1092C in all respects.

Since (-)-PF1092C (**3**) has already been transformed into (-)-PF1092A and B (**1** and **2**) by selective acetylation[1,13], the synthesis of **3** constitutes the completion of the toal synthesis of **1** and **2**.



14 15 16 17 18 19 20 3

Acknowledgment : We are grateful to Meiji Seika Kaisha Ltd., Shikoku Chemicals Co., and Yamanouchi Pharmaceutical Co., Ltd for the generous support of our program.

REFERENCES AND NOTES

1. Tabata, Y.; Hatsu, M.; Miike, N.; Yaguchi, T.; Someya, A.; Kurata, Y. *Jpn. Kokai Tokkyo Koho* **JP 08 253,467** (1996).
2. Tabata, Y.; Miike, N.; Hatsu, M.; Kurata, Y.; Yaguchi, T.; Someya, A.; Miyadoh, S.; Hosho, S.; Tsuruoka, T.; Omoto, S. *J. Antibiot.*, in press.
3. Tabata, Y.; Hatsu, M.; Kurata, Y.; Miyajima, K.; Tani, M.; Sasaki, T.; Kodama, Y.; Tsuruoka T.; Omoto, S. *J. Antibiot.*, in press.
4. Yamakawa, K.; Kobayashi, M.; Hinata, S.; Sato, T. *Chem. Pharm. Bull.*, **28**, 3265 - 3274 (1980).
5. a) Mori, K.; Tamura, H. *Liebigs Ann. Chem.*, **1988**, 97 - 105 (1988).
   b) Kitahara, T.; Kurata, H.; Mori, K. *Tetrahedoron* ,**44**, 4339 - 4349 (1988).
6. Witschel, M. C.; Bestmann, H. J. *Tetrahedoron Lett.*,**36**, 3325 - 3328 (1995).
7. Hanessian, S.; Murrsy, P. J. *J. Org. Chem.*, **52**, 1170 - 1172 (1987).
8. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Optical rotations were measured using a 0.5 dm tube at 22°C. Significant ^{1}H-NMR spectral data (270, 400 and 500 MHz, δ; TMS=0, unless otherwise noted) are the following.

3($CDCl_3$): δ 1.21(3H,s), 1.26(3H,d ,*J*=7.0Hz), 1.80(1H,dq,*J*=1.5 &7.0Hz), 1.92(3H,br s), 2.19(1H,br d,*J*=16.0Hz), 2.27(1H,d,*J*=3.0Hz), 2.29(1H,d,*J*=8.0Hz), 2.85(1H,d,*J*=16.0Hz), 3.94(1H,ddd,*J*= 1.5,3.0 &5.0Hz), 4.39(1H,ddd,*J*=2.0,5.0 &8.0Hz), 5.66(1H,br s), 5.99(1H,s).

8($CDCl_3$): δ 3.39(1H,dd,*J*=5.0 &10.0Hz), 3.41(3H,dd,*J*=5.0 &10.0Hz), 5.08(1H,dddd,*J*=1.5,1.5,5.0 & 5.0Hz), 6.19(1H,dd,*J*=2.0 &6.0Hz), 7.2-7.5(16H,m).

9($CDCl_3$): δ 0.95(3H,d,*J*=7.5Hz), 1.16(3H,d,*J*=7.5Hz), 2.47(1H,ddq,*J*=5.0,7.5 &7.5Hz), 2.87(1H,dq,*J*=7.5 &7.5Hz), 3.20(3H,dd,*J*=5.0 &7.5Hz), 3.40(1H,dd,*J*=5.0 &10.5Hz), 4.14(1H,q-like,*J*=5.0Hz), 7.2-7.5(15H,m).

10($CDCl_3$): δ 1.02(3H,d,*J*=7.0Hz), 1.11(3H,d,*J*=7.5Hz), 2.65(1H,ddq,*J*=3.5,7.5 & 9.0Hz), 2.85(1H, dq,*J*=7.5 &9.0Hz), 3.44(3H,s), 3.45(3H,s), 4.01(1H,dd,*J*=3.0 &3.5Hz), 4.36(1H,d,*J*=3.0Hz).

12($CDCl_3$): δ 0.06(3H,s), 0.09(3H,s), 0.23(6H,s), 0.8-0.9(3H), 0.89(18H,s), 1.15(3H,d,*J*=7.0Hz), 1.5-1.6(1H,m), 2.37(1H,dq,*J*=7.5 &11.5Hz), 3.33(3H,s), 3.44(3H,s), 3.73(1H,dd,*J*=2.5 &7.0Hz), 4.12(1H,d,*J*=7.0Hz), 5.60(1H,s), 7.4-7.6(3H,m), 7.8-7.9(2H,m).

13($CDCl_3$): δ 0.15(3H,s), 0.19(3H,s), 0.74(3H,d,*J*=7.0Hz), 0.95(9H,s), 1.05(3H,d,*J*=7.0Hz), 2.32(1H,dddq,*J*=1.5,3.5,5.0 &7.0Hz), 2.59(1H,dq,*J*=3.5 &7.0Hz), 4.89(1H,dd,*J*=1.5 &5.0Hz), 7.4-7.6(3H,m), 7.78(1H,t-like,*J*=1.5Hz), 7.8-7.9(2H,m).

14(benzene-d_6): δ 0.05(3H,s), 0.06(3H,s), 0.82(3H,d,*J*=7.0Hz), 0.99(9H,s), 1.03(3H,d,*J*=7.0Hz), 1.5-1.6(1H,m), 1.75(1H,dddd,*J*=5.0,10.5, 12.5 &12.5Hz), 1.86(1H,ddd,*J*=7.0,12.5 &13.5Hz), 1.9-2.2(2H,m), 2.21(1H,ddd,*J*=3.5,5.0 &13.5Hz), 3.88(1H,ddd,*J*=4.5,4.5 &10.0Hz).

18($CDCl_3$): δ 0.07(3H,s), 0.08(3H,s), 0.93(9H,s), 1.01(3H,d,*J*=7.0Hz), 1.30(3H,s), 1.42(3H,dq,*J*= 3.0 &7.0Hz), 1.6-1.7(1H,m), 1.65(1H,ddd,*J*=5.0,14.5 &14.5Hz), 1.90(1H,dddd,*J*=3.0,5.0,6.0 & 14.0Hz), 2.00(1H,ddd,*J*=3.0,5.5 &14.5Hz), 2.08(1H,ddd,*J*=3.0,3.0 &14.0Hz), 2.31(1H,dddd,*J*=1.0 ,3.0,5.0 &18.0Hz), 2.47(1H,ddd,*J*=5.5,14.5 &18.0Hz), 2.82(1H,dddd,*J*=2.0,5.0,14.0 &14.0Hz), 3.86(1H,br q,*J*=3.0Hz) 5.76(1H,br s).

20($CDCl_3$): δ 1.18(3H,s), 1.21(3H,d,*J*=7.0Hz), 1.76(1H,dq,*J*=2.0 &7.0Hz), 1.91(3H,br s), 2.20(1H, br d,*J*=16.0Hz), 2.42(1H,dd,*J*=4.0 &20.0Hz), 2.59(1H,ddd,*J*=3.0,4.0 &20.0Hz), 2.83(1H,d, *J*=16.0Hz), 4.04(1H,br s), 5.76(1H,br t,*J*=4.0Hz), 5.99(1H,s).

9. Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.*, **111**, 8277 - 8279 (1989).
10. Stork, G.; Singh, J. *J. Am. Chem. Soc.*, **96**, 6181 - 6182 (1974).
11. House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.*, **95**, 3310 - 3324 (1973).
12. Arigoni, D.; Vasella, A.; Sharpless, K. B.; Jensen, H. P. *J. Am. Chem. Soc.*, **95**, 7917 - 7919 (1973).
13. Kurihara, K.; Tanabe, K.; Shinei, R.; Okonogi, T.; Yasuda, S.; Tatsuta, K. *J. Antibiot.*, in press.

(*Received in Japan* 9 *December* 1996; *revised* 26 *December* 1996; *accepted* 6 *January* 1997)