HETEROCYCLES, Vol. 58, 2002, pp. 57-61, Received, 4th March, 2002

STEREOCONTROLLED SYNTHESIS OF A HIGHLY FUNCTIONALIZED 1,7-DIOXASPIRO[4.4]NONANE DERIVATIVE RELATED TO ANTIBIOTIC PSEUROTINS‡

Shin-ya Aoki, Takahiro Ohi, Kazuya Shimizu, Ryota Shiraki, Ken-ichi Takao, and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku Yokohama 223-8522, Japan
tadano@applc.keio.ac.jp

Abstract — For a total synthesis of pseurotins, unusual heterospirocyclic antibiotics, a key intermediate (**5**), having a highly functionalized 1,7-dioxaspiro-[4.4]nonane structure, has been synthesized from diacetone D-glucose.

Pseurotins A–E (A **1**, E **2**) are a class of secondary microbial metabolites, which were isolated from the cultures of *Pseudeurotium ovalis* STOLK by Tamm *et al.*[1] Pseurotins F_1/F_2 (**3**, **4**) were also found from *Aspergillus fumigatus* DSM 6598.[2] The structure of pseurotin A (**1**) including its absolute stereochemistry was determined by spectral analysis, chemical properties, and finally by X–Ray crystal analysis of its dibromo derivative.[1b] This antibiotic possesses a novel highly functionalized 1-oxa-7-azaspiro[4.4]nonane skeleton with five stereogenic centers, and exhibits a strong neurite formation activity to PC–12 pheochromocytoma cells.[3] Synthetic approaches toward the pseurotins have been reported by Tamm *et al.*[4] We have accomplished total synthesis of several γ-lactam natural products.[5] Herein, we report a synthetic approach toward this structurally as well as biologically intriguing pseurotin

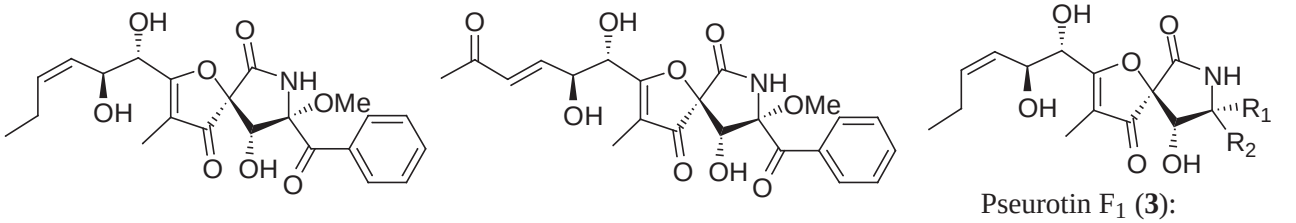
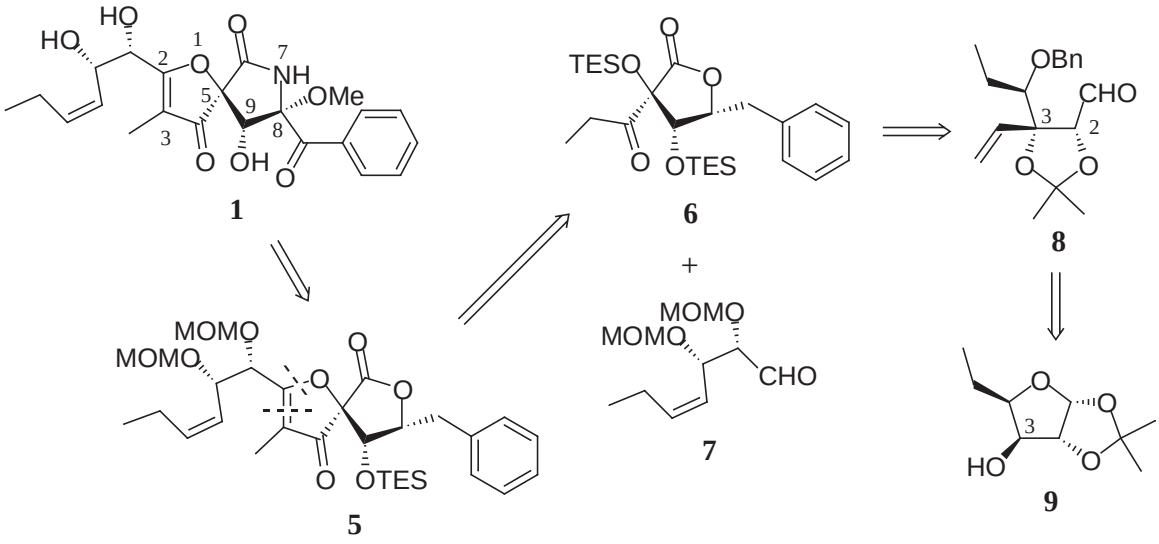


Figure 1. Structures of pseurotins A, E, and F

‡ This paper is dedicated to Professor Albert I. Meyers with respect and admiration on the occasion of his seventieth birthday.

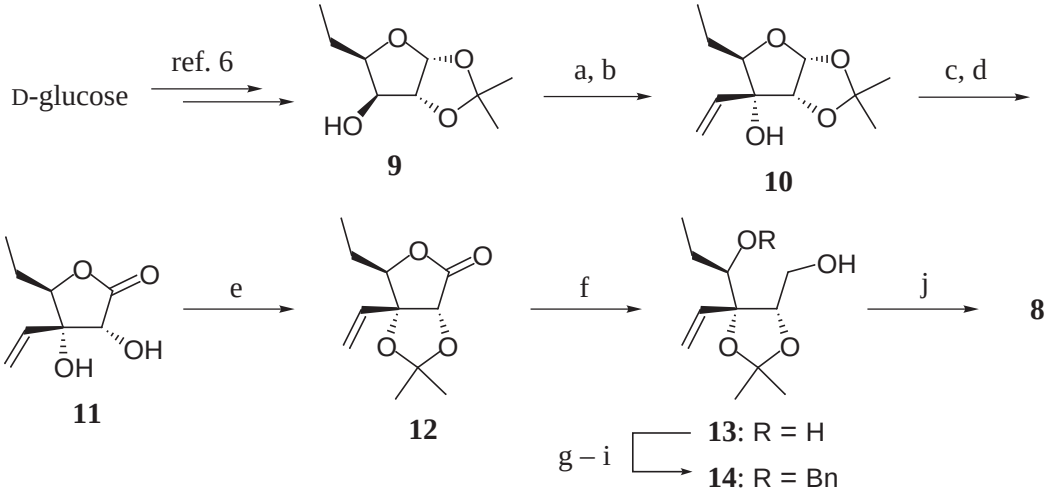
A (**1**). In this study, we synthesized a functionalized heterospirocyclic derivative (**5**), which possesses a 1,7-dioxaspiro[4.4]nonane core framework including four stereogenic centers required for pseurotins synthesis. Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that the target (**1**) would be obtained from the highly functionalized heterospirocycle (**5**) by oxidations of C-8 and the benzylic carbon and transformation of the γ-lactone to a γ-lactam. Construction of the 3(2*H*)-furanone structure in **5** would arise from the aldol reaction of a keto γ-lactone (**6**) with an aldehyde (**7**) followed by ring closure. The γ-lactone (**6**) could be obtained from an aldehyde (**8**), of which two stereogenic centers (C-2 and C-3) are corresponding to C-9 and C-5 in **1**, respectively. The intermediate (**8**) could be prepared from the known 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**9**)[6] *via* stereoselective vinyl Grignard addition to a carbonyl group at C-3 derived from **9**.



Scheme 1

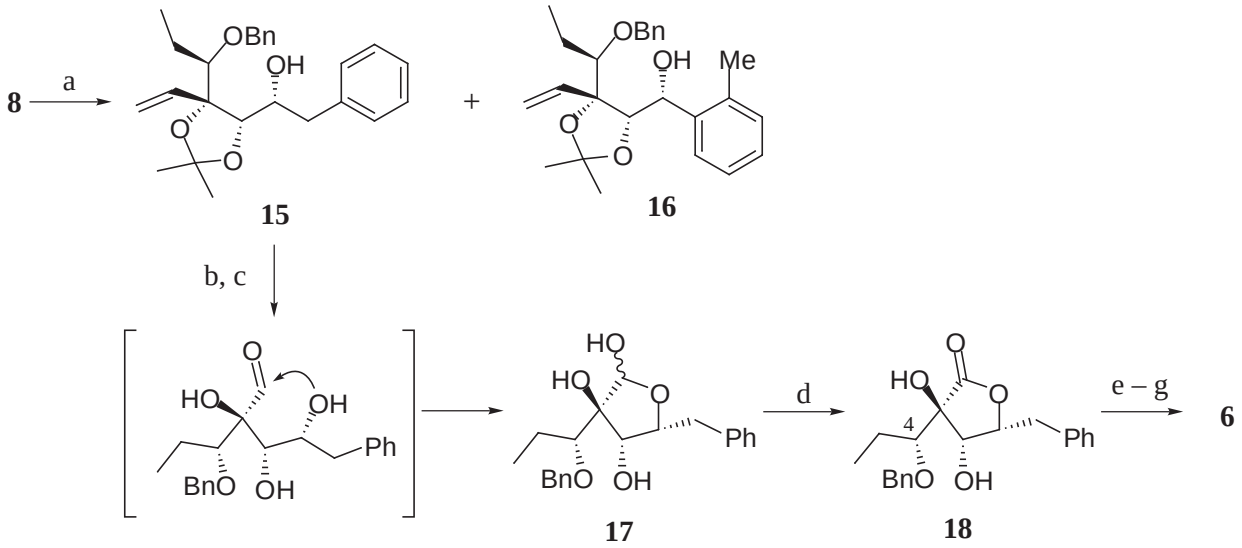
The synthesis of **8** began with **9**, which was prepared from diacetone D-glucose in the known five steps.[6] Oxidation of **9** with pyridinium chlorochromate (PCC) followed by the vinyl Grignard addition provided the adduct (**10**) in 83% yield as a single isomer (Scheme 2).[7] The nucleophile attacked exclusively from the convex face of the bicyclic structure of the C-3 keto derivative. Acidic hydrolysis of **10** and chemoselective oxidation of the resultant hemiacetal with *N*-iodosuccinimide (NIS) in the presence of *n*-Bu_4NI[8] gave γ-lactone (**11**). The *cis* diol in **11** was protected as an acetonide to provide bicyclic γ-lactone (**12**). Reduction of **12** with $LiAlH_4$ provided a ring-opened diol (**13**), which was converted into a primary alcohol derivative (**14**) by a protection–deprotection sequence. Dess–Martin oxidation[9] of **14** produced quantitatively the aldehyde (**8**). The introduction of a benzyl moiety into **8** was performed by a Cu(I)-mediated Grignard reaction to afford the adduct (**15**) in 89% yield as a single diastereomer along with a small amount of *ortho*-tolyl adduct (**16**) (Scheme 3). When the reaction was conducted in the absence of $CuBr{\cdot}Me_2S$, **16** was predominantly produced.[10,11] Ozonolysis of **15** and successive acidic hydrolysis of the acetonide group formed a five-membered hemiacetal, giving **17**. Chemoselective

oxidation of the γ-lactol (**17**) with NIS in the presence of *n*-Bu_4NI provided γ-lactone (**18**). The two hydroxy groups in **18** were protected as triethylsilyl (TES) ethers, and deprotection of the O-4 benzyl group by hydrogenolysis followed by Dess–Martin oxidation provided the keto lactone (**6**), the substrate for the aldol reaction.



Reagents and conditions: (a) PCC, MS4A, CH_2Cl_2; (b) vinylMgBr, THF, –18 °C (83% for 2 steps); (c) 80% aqueous AcOH, 80 °C; (d) NIS, *n*-Bu_4NI, CH_2Cl_2 (95% for 2 steps); (e) $Me_2C(OMe)_2$, CSA, acetone, reduced pressure (*ca.* 300 hPa), 40 °C (79%); (f) $LiAlH_4$, THF, 0 °C (91%); (g) TrCl, DMAP, pyr, reflux; (h) BnBr, NaH, DMF; (i) CSA, MeOH, EtOAc (78% for 3 steps); (j) Dess–Martin periodinane, CH_2Cl_2 (99%).

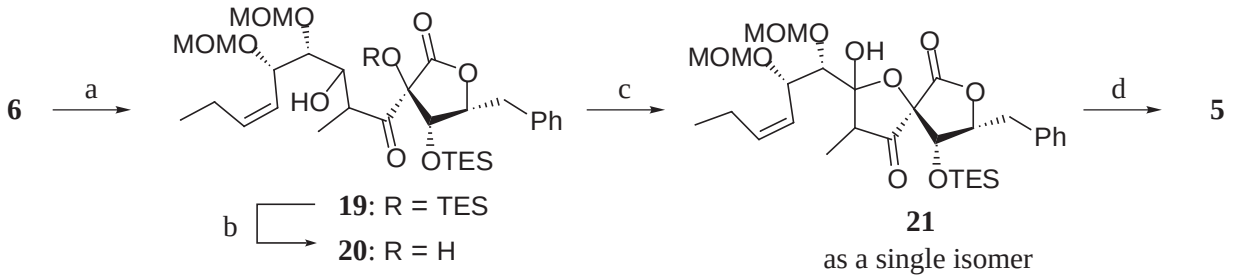
Scheme 2



Reagents and conditions: (a) BnMgCl, CuBr·Me_2S, THF, Me_2S, 0 °C (89% for **15** and 3% for **16**); (b) O_3, CH_2Cl_2, –78 °C; Me_2S; (c) 60% aqueous TFA; (d) NIS, *n*-Bu_4NI, CH_2Cl_2 (77% from **15**); (e) TESOTf, pyr, 50 °C (100%); (f) H_2, 10% Pd on C, EtOAc (93%); (g) Dess–Martin periodinane, CH_2Cl_2 (100%).

Scheme 3

We then performed the construction of the 3(2*H*)-furanone structure in **5** (Scheme 4). The aldol reaction of **6** with 4 molar equiv of **7**,[12] using 1 molar equiv of potassium bis(trimethylsilyl)amide (KHMDS) in THF at –78 °C, proceeded smoothly to produce the aldol (**19**) with a high level of diastereoselectivity. The newly introduced stereochemistries were not determined. Treatment of **19** with hydrogen fluoride–pyridine complex in pyridine[13] cleaved selectively the TES ether of the tertiary alcohol to afford **20**. Oxidation of **20** followed by dehydration of the resultant spiro-ketal (**21**) gave the desired heterospirocyclic compound (**5**),[14] which would be a key intermediate for the pseurotins synthesis.



Reagents and conditions: (a) KHMDS, THF, –78 °C; **7**; (b) HF·pyr, pyr, THF; (c) Dess–Martin periodinane, CH_2Cl_2 (49% from **6**); (d) $SOCl_2$, pyr, 0 °C (97%).

Scheme 4

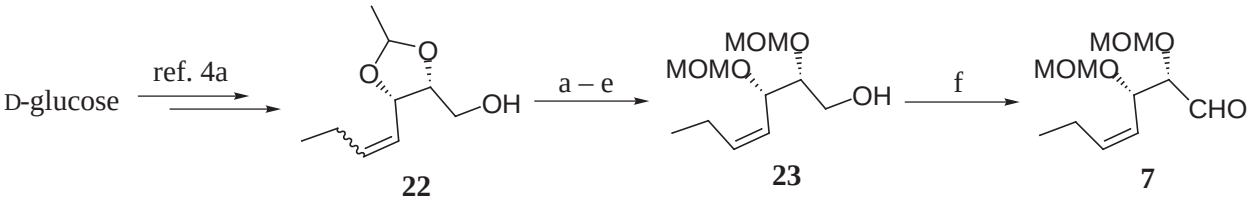
In conclusion, the stereoselective synthesis of the highly functionalized 1,7-dioxaspiro[4.4]nonane (**5**) from D-glucose has been accomplished. The total synthesis of pseurotins is in progress.

REFERENCES AND NOTES

1. (a) P. Bloch, C. Tamm, P. Bollinger, T. J. Petcher, and H. P. Weber, *Helv. Chim. Acta*, 1976, **59**, 133. (b) H. P. Weber, T. J. Petcher, P. Bloch, and C. Tamm, *Helv. Chim. Acta*, 1976, **59**, 137. (c) P. Bloch and C. Tamm, *Helv. Chim. Acta*, 1981, **64**, 304. (d) W. Breitenstein, K. K. Chexal, P. Mohr, and C. Tamm, *Helv. Chim. Acta*, 1981, **64**, 379.
2. W. Joachim, G. Susanne, G. Manfred, T. Ralf, and K. Reinhard, Eur. Pat. Appl. EP 546474, 16 Jun 1993, DE Appl. 4140382, 07 Dec 1991 (*Chem. Abstr.*, 1993, **119**, 137528y).
3. (a) J. Wenke, H. Anke, and O. Sterner, *Biosci. Biotech. Biochem.*, 1993, **57**, 961. (b) D. Komagata, S. Fujita, N. Yamashita, S. Saito, and T. Morino, *J. Antibiot.*, 1996, **49**, 958.
4. (a) M. Dolder, X. Shao, and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 63. (b) X. Shao, M. Dolder, and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 483. (c) Z. Su and C. Tamm, *Helv. Chim. Acta*, 1995, **78**, 1278. (d) Z. Su and C. Tamm, *Tetrahedron*, 1995, **51**, 11177.
5. (a) R. Shiraki, A. Sumino, K. Tadano, and S. Ogawa, *Tetrahedron Lett.*, 1995, **36**, 5551. (b) R. Shiraki, A. Sumino, K. Tadano, and S. Ogawa, *J. Org. Chem.*, 1996, **61**, 2845. (c) R. Shiraki and K. Tadano, *Rev. Heteroatom Chem.*, 1999, **20**, 283.
6. J. K. N. Jones and J. L. Thompson, *Can. J. Chem.*, 1957, **35**, 955.
7. All new compounds were fully characterized by spectroscopic means [^{1}H (300 MHz in $CDCl_3$) and

^{13}C (75 MHz in $CDCl_3$) NMR, IR] and gave satisfactory HRMS. Yields refer to homogeneous samples purified by chromatography on silica gel.

8. S. Hanessian, D. H. Wong, and M. Therien, *Synthesis*, **1981**, 394.
9. (a) D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155. (b) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277. (c) R. E. Ireland and L. Liu, *J. Org. Chem.*, 1993, **58**, 2899.
10. The reaction of benzylmagnesium chloride with aldehydes was reported to produce the *ortho*-tolyl adducts *via* Mg(II)-mediated six-membered transition states.[11] We considered that the addition of the Cu(I) salt suppressed the formation of the six-membered transition state and the expected 1,2-addition occurred.
11. (a) R. A. Benkeser, W. DeTalvo, and D. Darling, *J. Org. Chem.*, 1979, **44**, 225. (b) R. A. Benkeser and D. C. Snyder, *J. Org. Chem.*, 1982, **47**, 1243. (c) C. Bernardon and A. Deberly, *J. Chem. Soc., Perkin 1*, **1980**, 2631.
12. Compound (**7**) was prepared as follows.



Reagents and conditions: (a) MPMCl, NaH, DMF; (b) Amberlite IR-120 (H^+), MeOH (91% for 2 steps); (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (d) DDQ, CH_2Cl_2, H_2O; (e) separation of the geometrical isomers on silica gel (EtOAc/hexane, 1:4) (**23**: 88% for 2 steps, *E*-isomer: 7% for 2 steps); (f) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, –78 °C (89%).

13. J. Defaye and J. M. G. Fernández, *Carbohydr. Res.*, 1992, **273**, 223.
14. Compound (**5**) was obtained as white crystals: mp 56.0–56.3 °C; TLC R_f 0.20 (EtOAc/hexane, 1:5); $[\alpha]_D^{21}$ +23.0 ° (*c* 2.09, $CHCl_3$); IR (neat) 2960, 2880, 1790, 1715, 1640, 1150, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51–0.69 (m, 6H, $Si(CH_2CH_3)_3$), 0.94 (t, 9H, *J* = 8.1 Hz, $Si(CH_2CH_3)_3$), 1.01 (t, 3H, *J* = 7.6 Hz, CH_3 of the side chain at C-2), 1.79 (s, 3H, CH_3 at C-3), 2.09–2.27 (m, 2H, H-5, 5' of the side chain at C-2), 3.19 (dd, 1H, *J* = 2.7, 15.4 Hz, C*H*HPh), 3.31, 3.39 (2s, each 3H, $OCH_3 \times 2$), 3.65 (dd, 1H, *J* = 11.0, 15.4 Hz, CH*H*Ph), 4.57–4.68 (m, 5H, H-9, $OCH_2O \times 2$), 4.71–4.78 (m, 1H, H-2 of the side chain at C-2), 4.83 (ddd, 1H, *J* = 2.7, 7.3, 11.0 Hz, H-8), 5.00 (d, 1H, *J* = 7.3 Hz, H-1 of the side chain at C-2), 5.35 (dd, 1H, *J* = 9.5, 11.0 Hz, H-3 of the side chain at C-2), 5.78 (dt, 1H, *J* = 11.0, 7.3 Hz, H-4 of the side chain at C-2), 7.21–7.35 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.5 × 3, 5.7, 6.6 × 3, 14.0, 21.2, 36.3, 55.8, 56.0, 71.1, 72.7, 74.2, 82.7, 89.1, 94.5, 95.1, 114.9, 125.5, 126.6, 128.5 × 2, 129.3 × 2, 137.6, 138.6, 166.3, 183.4, 195.4; HRMS calcd for $C_{30}H_{43}O_8Si$ (M^+–OMe) *m/z* 559.2727, found 559.2722.