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

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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 F1/F2 (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

Pseurotin A (1)

Pseurotin E (2)

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(2H)-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) via stereoselective vinyl Grignard addition to a carbonyl group at C-3 derived from 9.

![Scheme 1](image)

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-Bu₄NI gave γ-lactone (11). The cis diol in 11 was protected as an acetonide to provide bicyclic γ-lactone (12). Reduction of 12 with LiAlH₄ provided a ring-opened diol (13), which was converted into a primary alcohol derivative (14) by a protection–deprotection sequence. Dess–Martin oxidation9 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 diastereomeric along with a small amount of ortho-tolyl adduct (16) (Scheme 3). When the reaction was conducted in the absence of CuBr·Me₂S, 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-Bu₄NI 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, CH₂Cl₂; (b) vinylMgBr, THF, −18 °C (83% for 2 steps); (c) 80% aqueous AcOH, 80 °C; (d) NIS, n-Bu₄NI, CH₂Cl₂ (95% for 2 steps); (e) Me₂C(OMe)₂, CSA, acetone, reduced pressure (ca. 300 hPa), 40 °C (79%); (f) LiAlH₄, 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, CH₂Cl₂ (99%).

Scheme 2

Reagents and conditions: (a) BnMgCl, CuBr·Me₂S, THF, Me₂S, 0 °C (89% for 15 and 3% for 16); (b) O₃, CH₂Cl₂, −78 °C; Me₂S; (c) 60% aqueous TFA; (d) NIS, n-Bu₄NI, CH₂Cl₂ (77% from 15); (e) TESOTf, pyr, 50 °C (100%); (f) H₂, 10% Pd on C, EtOAc (93%); (g) Dess–Martin periodinane, CH₂Cl₂ (100%).

Scheme 3
We then performed the construction of the 3(2H)-furanone structure in 5 (Scheme 4). The aldol reaction of 6 with 4 molar equiv of 7,\textsuperscript{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\textsuperscript{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),\textsuperscript{14} which would be a key intermediate for the pseurotins synthesis.

\[
\begin{align*}
\text{Reagents and conditions:} & \quad (a) \text{KHMDS, THF, } -78 \degree \text{C; } 7; (b) \text{HF-pyr, pyr, THF; (c) Dess–Martin periodinane, CH}_2\text{Cl}_2 (49\% \text{ from } 6); (d) \text{SOCl}_2, \text{pyr, } 0 \degree \text{C (97\%).}
\end{align*}
\]

\textbf{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


7. All new compounds were fully characterized by spectroscopic means $^1$H (300 MHz in CDCl$_3$) and
13C (75 MHz in CDCl₃) NMR, IR] and gave satisfactory HRMS. Yields refer to homogeneous samples purified by chromatography on silica gel.


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.


12. Compound (7) was prepared as follows.

\[
\text{D-glucose} \xrightarrow{\text{ref. 4a}} \text{22} \xrightarrow{a-e} \text{23} \xrightarrow{f} \text{7}
\]

*Reagents and conditions:* (a) MPMCl, NaH, DMF; (b) Amberlite IR-120 (H⁺), MeOH (91% for 2 steps); (c) MOMCl, i-Pr₂NEt, CH₂Cl₂; (d) DDQ, CH₂Cl₂, H₂O; (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, CH₂Cl₂; Et₃N, –78 °C (89%).


14. Compound (5) was obtained as white crystals: mp 56.0–56.3 °C; TLC Rf 0.20 (EtOAc/hexane, 1:5); [α]D²¹ +23.0 ° (c 2.09, CHCl₃); IR (neat) 2960, 2880, 1790, 1715, 1640, 1150, 1040 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.51–0.69 (m, 6H, Si(CH₂CH₃)₃), 0.94 (t, 9H, J = 8.1 Hz, Si(CH₂CH₃)₃), 1.01 (t, 3H, J = 7.6 Hz, CH₃ of the side chain at C-2), 1.79 (s, 3H, CH₃ 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, CH₂Ph), 3.31, 3.39 (2s, each 3H, OCH₃ × 2), 3.65 (dd, 1H, J = 11.0, 15.4 Hz, CH₂Ph), 4.57–4.68 (m, 5H, H-9, OCH₂O × 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, C₆H₅); ¹³C NMR (75 MHz, CDCl₃) 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 C₃₀H₄₃O₈Si (M⁺–OMe) m/z 559.2727, found 559.2722.