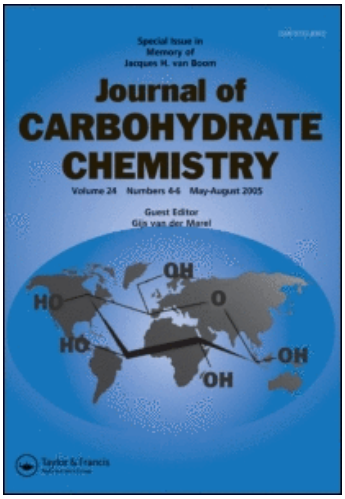

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Syntheses of (-)-8-*EPI*-Swainsonine and (-)-1,8-DI-*FPI*-Swainsonine, Stereoisomers of Indolizidine Alkaloid, Swainsonine

Youichi Iimura[a]; Yukinori Hotta[a]; Chiyoko Fukabori[a]; Kin-Ichi Tadano[a]; Tetsuo Suami[a]
[a] Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Yokohama, Japan

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Communication

SYNTHESES OF (-)-8-*EPI*-SWAINSONINE AND (-)-1,8-DI-*EPI*-SWAINSONINE, STEREOISOMERS OF INDOLIZIDINE ALKALOID, SWAINSONINE

Youichi Iimura, Yukinori Hotta, Chiyoko Fukabori, Kin-ichi Tadano, and Tetsuo Suami*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

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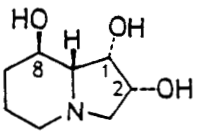
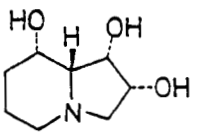
Recently, we have completed a total synthesis of swainsonine (1), (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyoctahydroindolizine, which exhibits remarkable physiological effects such as an α-mannosidase inhibitory activity, an immunoregulating activity and so on.[1] In order to elucidate a relationship between structures and physiological activities, a congener of swainsonine has been synthesized. In this communication, we wish to report a synthesis of (-)-8-*epi*-swainsonine (2) and (-)-1,8-di-*epi*-swainsonine (3) from methyl 3-acetamido-2-O-acetyl-4,6-O-benzylidene-3-deoxy-α-D-glucopyranoside[2] (4) and methyl 3-acetamido-2-O-acetyl-3-

 0732-8303/86/0501-0147$3.50/0



1



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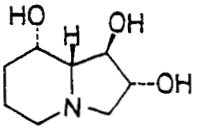
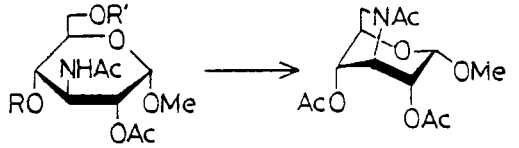


3

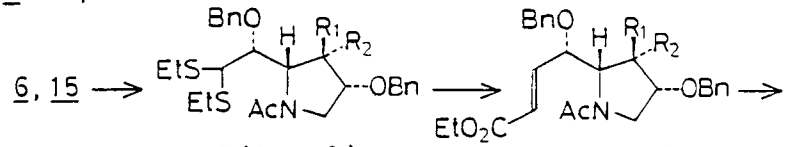
deoxy-4,6-di-O-mesyl-α-D-glucopyranoside[3] (14), respectively.

Acid hydrolysis of 4 in 50% aqueous acetic acid under reflux, followed by a regioselective tosylation of the primary hydroxyl group gave the 6-O-tosyl derivative (5) in 83% yield, $[\alpha]_D^{24}$+88.7° (*c* 1.10, $CHCl_3$). An intramolecular ring closure of 5 with sodium hydride (DMF, 100 °C) and successive acetylation afforded methyl 3,6-acetylimino-2,4-di-O-acetyl-3,6-dideoxy-α-D-glucopyranoside (6) in 68% yield, mp 166-168 °C; $[\alpha]_D^{22}$+89.0° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (3H, s, $NCOCH_3$), 2.00 (3H, s, $OCOCH_3$), 2.21 (3H, s, $OCOCH_3$), 3.56 (3H, s, OCH_3), 3.40-3.91 (2H, m, H-6,6'), 4.42-5.32 (5H, m, H-1,2,3,4,5). O-Deacetyaltion of 6 (CH_3ONa in CH_3OH), followed by dithioacetalation (ethanethiol, conc. HCl, 0 °C, 1 h), and O-benzylation (benzyl bromide, NaH, DMF) afforded the compound (7) in 59% yield, $[\alpha]_D^{22}$+8.5° (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.98 (3H, t, J=8 Hz, $SCH_2\underline{CH_3}$), 1.18 (3H, t, J=8 Hz, $SCH_2\underline{CH_3}$), 2.10 (3H, s, $NCOCH_3$), 2.38 (2H, q, J=8 Hz, $S\underline{CH_2}CH_3$), 2.70 (2H, q, J=8 Hz, $S\underline{CH_2}CH_3$), 3.40-4.75 (13H, m), 7.26, 7.33, 7.34 (total 15H). Removal of the thioacetal group in 7 with mercury (II) chloride and calcium carbonate in aqueous acetonitrile and treatment of the aldehyde with diethyl ethoxycarbonylmethylphosphonate (NaH, THF, room temperature, 90 min) gave an unsaturated ester (8)[4] in 82% yield, $[\alpha]_D^{23}$+71.5° (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 1.95, 2.10 (total 3H, each s, $NCOCH_3$),[5] 3.36 (1H, d, J=13 Hz), 3.72 (1H, d, J=7 Hz), 3.76-5.00 (12H, m), 6.10 (1H, dd, J=2 and 15 Hz, $CH=\underline{CH}COOEt$), 7.00-7.05 (16H, m, $\underline{CH}=CHCOOEt$, $3xOCH_2\underline{C_6H_5}$). Catalytic hydrogenation of 8 (Raney nickel, EtOH, 1 atom) afforded the saturated ester (9) in 86% yield, $[\alpha]_D^{22}$+0.9° (*c* 1.10, $CHCl_3$). Intramolecular cyclization of 9 (15 M KOH, EtOH, sealed tube,



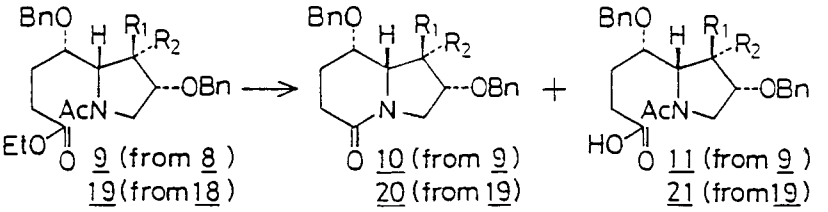
4: R=R'=CHPh
5: R=H, R'=Ts

6



7 (from 6)
17 (from 15)

8 (from 7)
18 (from 17)

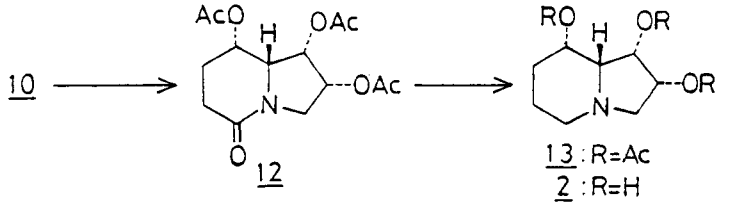


9 (from 8)
19 (from 18)

10 (from 9)
20 (from 19)

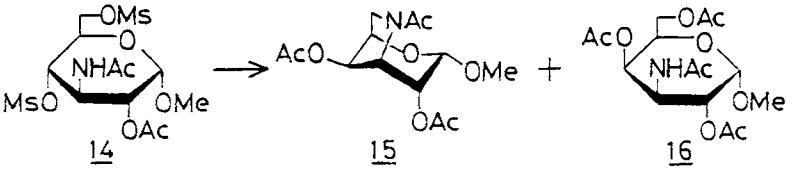
11 (from 9)
21 (from 19)

7, 8, 9, 10, 11 : R_1=H, R_2=OBn
17, 18, 19, 20, 21 : R_1=OBn, R_2=H



12

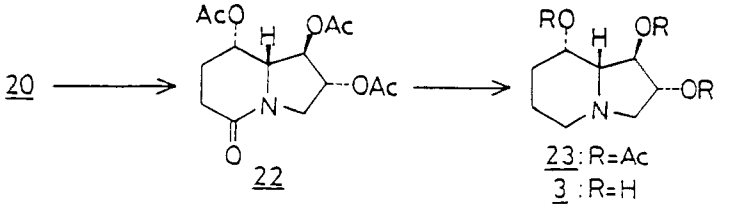
13 : R=Ac
2 : R=H



14

15

16



22

23 : R=Ac
3 : R=H

120 °C, 4 d) afforded compounds (10), mp 98-99 °C; $[\alpha]_D^{22}$-28.2° (*c* 1.00, $CHCl_3$), and (11), $[\alpha]_D^{22}$-4.0° (*c* 1.05, $CHCl_3$), in 40% and 51% yield, respectively. O-Debenzylation of 10 (cyclohexene, 20% $Pd(OH)_2$ on charcoal, EtOH, reflux)[6] and successive acetylation (acetic anhydride in pyridine) gave the compound (12) in 84% yield, mp 126-127 °C; $[\alpha]_D^{21}$-21.8° (*c* 0.90, $CHCl_3$). Reduction of 12 with borane-dimethylsulfide complex (THF, room temperature 2 h) gave 8-*epi*-swainsonine triacetate (13) in 64% yield, mp 79-80 °C; $[\alpha]_D^{19}$-17.1° (*c* 0.35, $CHCl_3$). Acid hydrolysis of 13 (1 M HCl, reflux, 3 h) followed by deionization with Amberlite IRA 400 (OH^-) resin afforded 8-*epi*-swainsonine [(1*S*,2*R*,8*S*,8a*R*)-1,2,8-trihydroxyoctahydroindolizine] 2, in 86% yield, mp 93-95 °C; $[\alpha]_D^{21}$ -24.8° (*c* 0.67, MeOH); [lit.[7] 2, syrup; $[\alpha]_D^{21}$-3.43° (*c* 0.9, MeOH)], ^{13}C NMR (CD_3OD, δ 49.03) δ 20.68, 32.08, 54.27, 62.98, 67.53, 69.40, 69.96, 74.29; calcd for $C_8H_{15}NO_3$: *m/z* 173.1051, found: M, 173.1056.

1,8-Di-*epi*-swainsonine, 3, was synthesized as follows. Compound 14 was converted into methyl 3,6-acetylamino-2,4-di-O-acetyl-3,6-dideoxy-α-D-galactopyranoside (15) by solvolysis in 90% aqueous 2-methoxyethanol with sodium acetate and subsequent acetylation in 68% yield,[8,9] and as a byproduct methyl 3-acetamido-2,4,6-tri-O-acetyl-3-deoxy-α-D-galactopyranoside (16)[10] was obtained in 27% yield, 15: $[\alpha]_D^{26}$+25.3° (*c* 1.36, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.03 (3H, s, $NCOCH_3$), 2.09, 2.12, 2.15, 2.19 (total 6H, each s, 2x$OCOCH_3$),[5] 3.45, 3.49 (total 3H, each s, OCH_3),[5] 4.71, 4.73 (total 1H, each d, J=2 Hz, H-1),[5] 16: mp 102-108 °C; $[\alpha]_D^{26}$+117.8° (*c* 1.48, $CHCl_3$). By the analogous reactions described above (from 6 to 13), 15 was converted into 1,8-di-*epi*-swainsonine triacetate (23) *via* compounds (17), (18), (19), (20), and (22). 17 (56% yield from 15): $[\alpha]_D^{27}$+9.6° (*c* 1.17, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.13 (3H, t, J=8 Hz, $SCH_2\underline{CH_3}$), 1.20 (3H, t, J=8 Hz, $SCH_2\underline{CH_3}$), 2.09 (3H, s, $NCOCH_3$), 2.50 (2H, q, J=8 Hz, $S\underline{CH_2}CH_3$), 2.66 (2H, q, J=8 Hz, $S\underline{CH_2}CH_3$), 3.20-4.70 (13H, m), 7.25, 7.30, 7.35 (total 15H). 18 (52% yield from 17)[4]: $[\alpha]_D^{27}$ +9.9° (*c* 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22, 1.31 (total 3H,

each t, J=7 Hz, $COOCH_2CH_3$), 2.00, 2.05 (total 3H, each s, $NCOCH_3$),[5] 5.91, 6.01 (total 1H, d and dd, J=15 Hz and J=2,15 Hz, CH=CHCOOEt),[5] 6.00-7.02 (1H, m, CH=CHCOOEt), 7.30, 7.34 (total 15H). 19 (86% yield from 18): $[\alpha]_D^{20}$-28.1° (*c* 1.34, $CHCl_3$). 20 (34% yield from 19, 120 °C, 10 d)[12]: mp 52-54 °C; $[\alpha]_D^{20}$+15.1° (*c* 1.18, $CHCl_3$). 21 (62% yield from 19): $[\alpha]_D^{20}$-21.5° (*c* 0.93, $CHCl_3$). 22 (83% yield from 20): mp 118-119 °C; $[\alpha]_D^{24}$-20.9° (*c* 1.04, $CHCl_3$). 23 (67% yield from 22): mp 124-125 °C; $[\alpha]_D^{20}$ -20.8° (*c* 1.00, $CHCl_3$). Hydrolysis of 23 (K_2CO_3, MeOH) gave 1,8-di-*epi*-swainsonine 3 [(1*R*,2*R*,8*S*,8a*R*)-1,2,8-trihydroxyoctahydroindolizine] in 98% yield, mp 138-140 °C; $[\alpha]_D^{21}$-35.6° (*c* 0.59, MeOH); ^{13}C NMR (CD_3OD, δ 48.97) δ 20.29, 32.19, 54.08, 62.74, 64.66, 75.05, 77.89, 80.23; calcd for $C_8H_{15}NO_3$: *m/z* 173.1051, found: M, 173.1052.

The first synthesis of 1,8-di-*epi*-swainsonine 3 has been achieved, and a facile synthesis of 8-*epi*-swainsonine 2 has been established.

ACKNOWLEDGEMENTS

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3. R. D. Guthrie and G. P. B. Mutter, J. Chem. Soc., 1614 (1964).

4. Only the *E* geometric isomer was formed under the Horner-Emmons olefination employed.

5. This spectral phenomenon is explained by the existence of both *endo* and *exo* stereoisomers on the tri-substituted nitrogen atom.

6. S. Hanessian, T. J. Liak, and B. Vanasse, Synthesis, 396 (1981).

7. Compound 2 has been synthesized recently by a different route, N. Yasuda, H. Tsutsumi, and T. Takaya, Chem. Lett., 31 (1985). However, the authors did not isolate crystalline 2.

8. Guthrie and Mutter[3] examined the solvolysis under the same condition employed by us. The authors isolated 3-amino-3-deoxy-D-galactose as a sole product (no yield was given). They did not mention the formation of 15.

9. The structure of 15 was confirmed by conversion of 16 into 15 as follows: 1) O-deacetylation of 16, 2) preferential tosylation of the primary hydroxyl group, 3) base (NaH) treatment of the 6-O-tosyl derivative, and 4) acetylation.

10. Compound 16 was converted into the known 3-acetamido-1,2,4,6-tetra-O-acetyl-3-deoxy-α-D-galactopyranose by acid hydrolysis followed by acetylation, mp 180-181 °C (lit.[11] mp 181-182 °C).

11. F. W. Lichtenthaler, G. Bambach, and U. Scheidegger, Chem. Ber., 102, 986 (1969).

12. Compound 21 was efficiently converted into 20 in 75% yield (15 M KOH, EtOH, sealed tube, 120 °C, 10 d).