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SYNTHETIC STUDY TOWARD PANCRACINE

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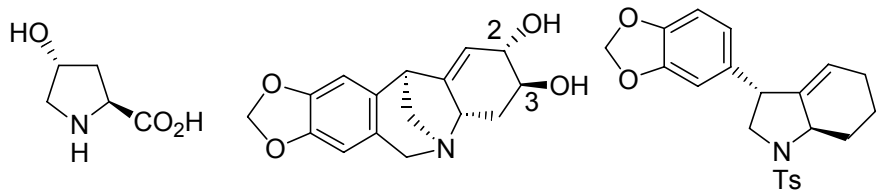
Abstract—A synthetic study toward pancracine (**2**) has been established starting from *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**).

1. INTRODUCTION

In view of structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**), it possesses three functional groups that can be easily modified, including 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents out the significant feature for producing a series of different carbon framework, such as monocycles (pyrrole,[2a] pyrrolidine,[2b-2c,2l] piperidine[2d] and azanucleoside[2e]), fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g-2h,2m]) and polycycles[2i-2k] etc., using an efficient modification. Here we report that a synthetic study toward pancracine (**2**) has been established by synthesizing Banwell's intermediate (**3**) from compound (**1**) (Figure 1). Pancracine, brunsvigine, montanine, coccinine and manthine with pentacyclic ring system are the members of the subclass of *Amaryllidaceae* alkaloids and differ only in the configurations of two stereocenters at C-2 and C-3.[3a] Because of the interesting carbon framework and pharmacological potential, pancracine (**2**) has induced many attempts to synthesize.[3b-3f]

Figure 1.

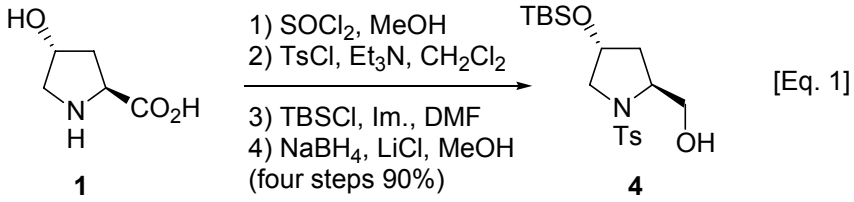


trans-4-hydroxyproline (**1**) (-)-pancracine (**2**) Banwell's intermediate (**3**)

2. RESULTS AND DISCUSSION

Synthesis of prolinol (**4**) contains the following four-step reactions from *trans*-4-hydroxyproline (**1**): (i) esterification with thionyl chloride and methanol in -78 ^{o}C, (ii) *N*-tosylation with *p*-toluenesulfonyl

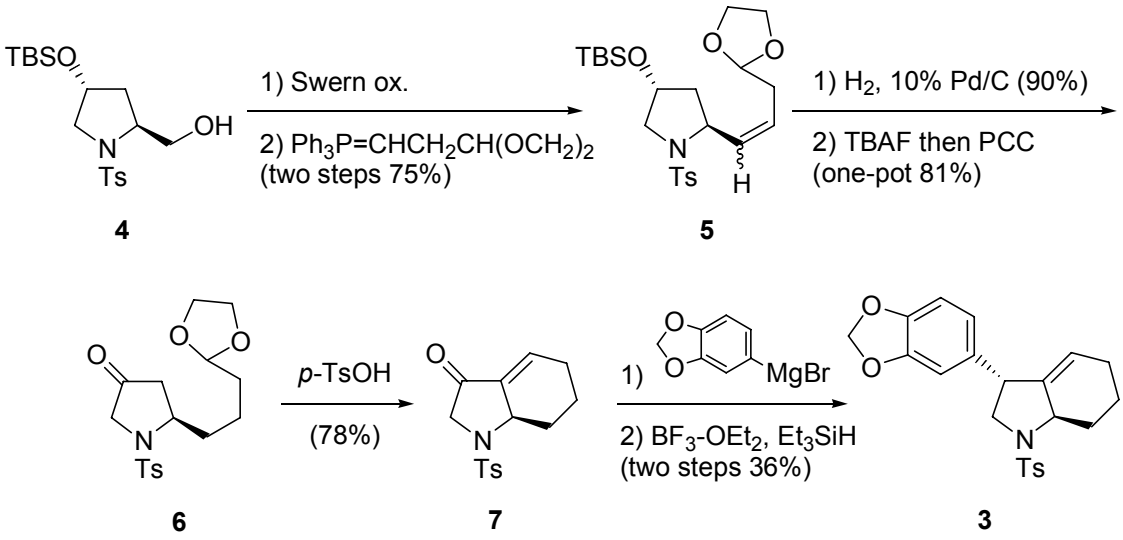
chloride and triethylamine, (iii) *O*-silylation with *t*-butyldimethylsilyl chloride and imidazole, and (iv) reduction of the ester with sodium borohydride in the presence of lithium chloride[4] (Equation 1). Thus, prolinol (**4**) was obtained in 90% overall yield with only once purification.[2m]



[Eq. 1]

We first studied the approach to pancracine (**2**) from alcohol (**4**) as shown in Scheme 1. Alcohol (**4**) was transformed into olefin (**5**) by Swern oxidation[5] and Wittig olefination under standard conditions. Hydrogenation of unsaturated compound (**5**) with a catalytic amount of 10% palladium on activated carbon was achieved to saturated compound. The corresponding compound was transformed to ketone (**6**) by desilyation with tetra-*n*-butylammonium fluoride in tetrahydrofuran followed by oxidation of the resulting alcohol with pyridinium chlorochromate in dichloromethane using one-pot synthesis.

Scheme 1.



Intramolecular aldol condensation of ketone (**6**) with a catalytic amount of *p*-toluenesulfonic acid under acid-mediated Dean-Stark distillation[6] gave compound (**7**), which was then further converted to Banwell's intermediate (**3**)[3c] as the major product using Grignard addition and acidic dehydroxylation.[2j,2l] The ^{1}H-NMR spectral data of compound (**3**) were in accordance with those reported in the literature.[3c] Sha and coworkers reported a facile anionic cyclization approach toward the hexahydro-1*H*-indol-3-one skeleton, and also utilized the building block (**7**) to the synthesis of brunsvigine,[3b] steine[3d] and lentiginosine.[7]

3. CONCLUSION

In summary, we have developed a straightforward approach to the hexahydro-1*H*-indol-3-one skeleton ring system (**7**) based on intramolecular aldol condensation of ketone (**6**) under acidic condition and applied this route to synthesize Banwell's intermediate (**3**) in the synthetic study toward pancracine (**2**).

4. EXPERIMENTAL

General. Tetrahydrofuran was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude product was purified using column chromatography on silica gel.

(2*S*,4*R*)-4-*t*-Butyldimethylsilyloxy-2-[3-(1,3-dioxolan-2-yl)prop-1-en-1-yl]-1-(4-methylphenylsulfonyl)-pyrrolidine (5).

A solution of oxalyl chloride (400 mg, 3.15 mmol) in dichloromethane (20 mL) was mixed with dimethyl sulfoxide (400 mg, 5.13 mmol) at –78 °C. The solution was warmed to –40 °C for 15 min and recooled to –78 °C, and then a solution of prolinol (**4**)[2m] (1.0 g, 2.60 mmol) in dichloromethane (10 mL) was added followed by excess triethylamine (4 mL, 28.46 mmol) for 30 min. The reaction mixture was warmed to rt and poured into 15% ammonium chloride solution (2 mL). The residue was diluted with water (15 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude aldehyde (950 mg). To a solution of [2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide (1.77 g, 4.0 mmol) in dry tetrahydrofuran (40 mL) was added *n*-butyllithium (2.0 mL, 1.6 M in hexane, 3.2 mmol) at –78 °C. The orange red colored mixture was stirred for 1 h. The crude aldehyde (950 mg) in dry tetrahydrofuran (5 mL) was added to the reaction mixture at –78 °C *via* a syringe and the mixture was further stirred for 8 h. The reaction was quenched with 15% ammonium chloride solution (10 mL) and the mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate = 10/1) afforded product (**5**) (910 mg, two steps 75% from **4**) as a viscous oil. $[\alpha]^{26}_{D}$ -21.79° (*c* 0.48, $CHCl_3$); IR ($CHCl_3$) 2955, 1670 cm^{-1}; FAB-MS: $C_{23}H_{38}NO_5SSi$ m/z (%) = 73 (100), 91 (29), 133 (21), 354 (6), 468 (M^++1, 2); HRMS (ESI, M^++1) calcd for $C_{23}H_{38}NO_5SSi$ 468.2240, found 468.2240; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.70-5.51 (m, 2H), 4.94-4.88 (m, 1H), 4.33 (dd, *J* = 8.5, 15.5 Hz, 1H), 4.24 (br s, 1H), 4.01-3.95 (m, 2H), 3.90-3.84 (m, 2H), 3.64 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.20 (d, *J* = 11.0 Hz, 1H), 2.56-2.43 (m, 2H), 2.41 (s, 3H), 1.90-1.71 (m, 2H), 0.71 (s, 9H), -0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.16, 134.05, 129.48 (2x), 127.79 (2x), 125.95, 123.15, 103.51, 69.66, 65.00 (2x), 57.84, 55.90, 42.88, 32.50, 25.54 (3x), 21.47, 17.79, -4.94, -5.06.

(2*R*)-2-[3-(1,3-Dioxolan-2-yl)prop-1-yl]-1-(4-methylphenylsulfonyl)pyrrolidin-3-one (6).

Compound (**5**) (1.0 g, 2.14 mmol) was dissolved in ethyl acetate (30 mL) and 10% palladium on activated carbon as catalyst was added. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 10 h. Filtration through a short plug of Celite and washing with ethyl acetate (3 x 10 mL) resulted in crude saturated product (900 mg, 90%) as a viscous oil. Without further purification, a solution of tetra-*n*-butylammonium fluoride (1.2 mL, 1.0 M in tetrahydrofuran, 1.2 mmol) in tetrahydrofuran (1 mL) was added to a solution of the corresponding saturated compound (700 mg) in tetrahydrofuran (5 mL) at rt for 1 h. A mixture of pyridinium chlorochromate (1.08 g, 5.01 mmol), Celite (3.0 g) and dichloromethane (20 mL) was added to the stirring reaction. After being stirred at rt for 10 h, the mixture was filtered through a short silica gel column. The filtrate was dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate = 5/1) yielded product (**6**) (430 mg, 81%) as a viscous oil. $[\alpha]^{22}_{D}$ -2.55^{o} (*c* 0.075, $CHCl_3$); FAB-MS: $C_{17}H_{24}NO_5S$ m/z (%) = 91 (29), 155 (8), 354 (M^++1, 15); HRMS (ESI, M^++1) calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1377; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.83 (t, *J* = 4.5 Hz, 1H), 4.21 (ddd, *J* = 2.5, 6.5, 15.5 Hz, 1H), 3.96-3.92 (m, 2H), 3.87-3.82 (m, 2H), 3.78 (d, *J* = 19.0 Hz, 1H), 3.64 (d, *J* = 19.0 Hz, 1H), 2.43 (s, 3H), 2.20 (dd, *J* = 9.0, 19.0 Hz, 1H), 2.11 (dd, *J* = 2.5, 19.0 Hz, 1H), 1.74-1.64 (m, 2H), 1.60-1.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.05, 144.21, 134.78, 130.09 (2x), 127.24 (2x), 104.09, 64.84, 64.82, 57.63, 52.90, 42.31, 35.47, 33.18, 21.51, 19.96; Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96. Found: C, 58.00; H, 6.38; N, 4.13.

(7a*R*)-1-(4-Methylphenylsulfonyl)-1,2,5,6,7,7a-hexahydro-1*H*-indol-3-one (7).[3b]

Compound (**6**) (350 mg, 0.99 mmol) was dissolved in toluene (20 mL), and a catalytic amount of *p*-toluenesulfonic acid (20 mg) was added. The mixture was reflux for 5 h under Dean-Stark condition. Saturated sodium bicarbonate solution (5 mL) was added to the resulting mixture and the solution was concentrated under reduced pressure. The residue was diluted with water (1 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/ethyl acetate = 4/1) yielded product (**7**) (225 mg, 78%) as a colorless solid. mp = 167-168 ^{o}C (dichloromethane/methanol); IR ($CHCl_3$) 2980, 2887, 1733, 1660 cm^{-1}; FAB-MS: $C_{15}H_{18}NO_3S$ m/z (%) = 77 (52), 91 (58), 107 (36), 136 (100), 154 (71), 292 (M^++1, 14); HRMS (ESI, M^++1) calcd for $C_{15}H_{18}NO_3S$ 292.1007, found 292.1005; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.83 (dd, *J* = 3.0, 6.5 Hz, 1H), 3.87 (d, *J* = 17.0 Hz, 1H), 3.72-3.68 (m, 1H), 3.40 (d, *J* = 17.0 Hz, 1H), 2.81-2.78 (m, 1H), 2.46 (s, 3H), 2.37-2.20 (m, 2H), 2.00-1.90 (m, 1H), 1.58-1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.31, 144.47, 137.45,

135.47, 131.46, 129.97 (2x), 128.15 (2x), 58.26, 55.50, 29.35, 25.07, 21.58, 19.62; Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.95; H, 5.80; N, 4.93.

(3*S*,7a*R*)-2,3,5,6,7,7a-Hexahydro-3-(3,4-methylenedioxyphenyl)-1-(4-methylphenylsulfonyl)-1*H*-indole (3).[3c]

A solution of 3,4-methylenedioxyphenylmagnesium bromide (0.5 mL, 1.0 M in tetrahydrofuran, 0.5 mmol) was added to a solution of compound (**7**) (88 mg, 0.3 mmol) in tetrahydrofuran (10 mL) –78 ^{o}C. After stirring at the same temperature for 5 h, the mixture was concentrated *in vacuo*. Ethyl acetate (20 mL) was added to the residue, and the solution was washed with saturated sodium bicarbonate solution (10 mL) and brine, dried, filtered, then concentrated *in vacuo* to yield crude product (82 mg). Without further purification, a mixture of the resulting tertiary alcohol (82 mg), boron trifluoride etherate (0.01 mL), and triethylsilane (2 mL) was stirred at rt for 10 h, and then the mixture was concentrated *in vacuo*. Ethyl acetate (20 mL) was added to the residue, and the solution was washed with saturated sodium bicarbonate solution (10 mL) and brine, dried, filtered, then concentrated *in vacuo* to give crude product. The crude product was purified by column chromatography (hexane/ethyl acetate = 3/1) to yield compound (**3**) (43 mg, two steps 36% from **7**) as a viscous oil. The ^{1}H NMR spectral data of compound (**3**) were in accordance with those reported in reference 3c.

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REFERENCES

1. For a review, see P. Remuzon, *Tetrahedron*, 1996, **52**, 13803.
2. For related references, see (a) J. Azizian, A. R. Karimi, Z. Kazemizadeh, A. A. Mohammadi, and M. R. Mohammadizadeh, *J. Org. Chem.*, 2005, **70**, 1471. (b) J. R. Del Valle and M. Goodman, *Angew. Chem., Int. Ed.*, 2002, **41**, 1600. (c) T. Gonzalez, O. Abad, M. C. Santano, and C. Minguillon, *Synthesis*, 2004, 1171. (d) T. Honda, R. Takahashi, and H. Namiki, *J. Org. Chem.*, 2005, **70**, 499. (e) X.-L. Qiu and F.-L. Qing, *Bioorg. Med. Chem.*, 2005, **13**, 277. (f) G. Pandey and G. Lakshmaiah, *Synlett*, 1994, 277. (g) G. Han, M. G. LaPorte, J. J. Folmer, K. M. Werner, and S. M. Weinreb, *J. Org. Chem.*, 2000, **65**, 6293. (h) P. G. Houghton, G. R. Humphrey, D. J. Kennedy, D. C. Roberts, and S. H. B. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1421. (i) O. Tamura, T. Yanagimachi, and H. Ishibashi, *Tetrahedron Asymm.*, 2003, **14**, 3033. (j) H. Hu and H. Zhai, *Synlett*, 2003, 2129. (k) H. J. Breslin, M. J. Kukla, D. W. Ludovici, R. Mohrbaeher, W. Ho, M. Miranda, J. D. Rodgers, T. K. Hitchens, G. Leo, D. A. Gauthier, Y. H. Chih, M. K. Scott, E. De Clercq, R. Pauwels, K. Andries, M.

A. C. Janssen, and P. A. Janssen, J. *J. Med. Chem.*, 1995, **38**, 771. (l) M. Y. Chang, S. T. Chen, and N. C. Chang, *Heterocycles*, 2003, **60**, 1203. (m) M. Y. Chang and H. P. Chen, *Heterocycles*, 2005, **65**, 1705.

3. For isolation of pancracine, see (a) W. C. Wildman and C. L. Brown, *J. Am. Chem. Soc.*, 1968, **90**, 6439. For recent synthetic studies on pancracine and the related analogs, see (b) C.-K. Sha, A.-W. Hong, and C.-M. Huang, *Org. Lett.*, 2001, **3**, 2177. (c) M. G. Banwell, A. J. Edwards, K. A. Jolliffe, and M. Kemmler, *J. Chem. Soc.*, *Perkin Trans 1*, 2001, 1345. (d) C.-K. Sha, S.-J. Huang, C.-M. Huang, A.-W. Hong, and T.-H. Jeng, *Pure Appl. Chem.*, 2000, **72**, 1773. (e) M. Ikeda, M. Hamada, T. Yamashida, K. Matsui, T. Sato, and H. Ishibashi, *J. Chem. Soc.*, *Perkin Trans 1*, 1999, 1949. (f) W. H. Pearson and B. W. Lian, *Angew. Chem.*, *Int. Ed.*, 1998, **37**, 1724.
4. Y. Hamada, M. Shibata, F. Sugiura, S. Kato, and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252.
5. A. J. Mancuso, S. L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
6. D. L. Commins, A. H. Libby, R. S. Al-awar, and C. J. Foti, *J. Org. Chem.*, 1999, **64**, 2184.
7. C.-K. Sha and C.-M. Chau, *Tetrahedron Lett.*, 2003, **44**, 499.