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Stereoselective Synthesis of *syn*- and *anti*-3a-Hydroxyl-1, 2, 3, 3a, 8, 8a-hexahydropyrrolo[2,3-*b*] indole-2-carboxylic Acid

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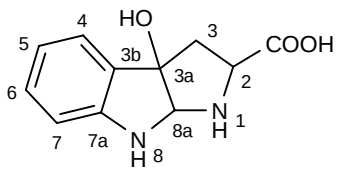
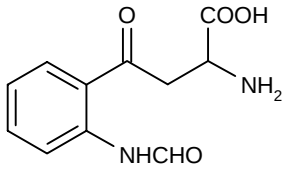
Abstract: The structure of *syn*- and *anti*-N^b-(*p*-toluenesulfonyl)-3a-hydroxyl-1, 2, 3, 3a, 8, 8a-hexahydro pyrrolo[2,3-*b*] indole-2-carboxylic *t*-butyl ester was stereoselectively synthesized by oxidative ring formation of N^b-(*p*-toluenesulfonyl)-L-tryptophan *t*-butyl ester in methylene chloride containing dimethyldioxirane (DMDO), the *p*-toluenesulfonyl group and *t*-butyl group can be easily removed by sodium naphthalenide and trifluoroacetic acid, respectively.

Keywords: Oxidative ring formation, stereoselective synthesis, sodium naphthalenide.

Alkaloids with 3a-hydroxyl-1, 2, 3, 3a, 8, 8a-hexahydropyrrolo[2,3-b] indole-2-carboxylic acid (HPI, **A**) substructure have been isolated from bacteria, fungi, plant and marine organism. These natural products show diverse biological activities, *e.g.* in antitumor, acyl-CoA (cholesterol acyltransferase) inhibition, neuropeptide and cholecystokinin receptor antagonistic inhibition. HPI is regarded as their toxophoric unit[1]. Thus the synthesis of this key substructure has been attracting the interest of organic chemists, some procedures towards the synthesis of HPI have been developed[2]. However these procedures are relatively complicated and a by-product, N-formylkynurenine **B**[3], was usually produced in these procedures. Recently the first diastereoselective approach to the *syn*- and *anti*-HPI scaffolds using the different configurations of D- and L-tryptophane as the starting material was reported[4]. Herein, we report a newly elaborated steroselective route for the synthesis of *syn*- and *anti*-HPI by using L-tryptophane as sole starting material.



A



B

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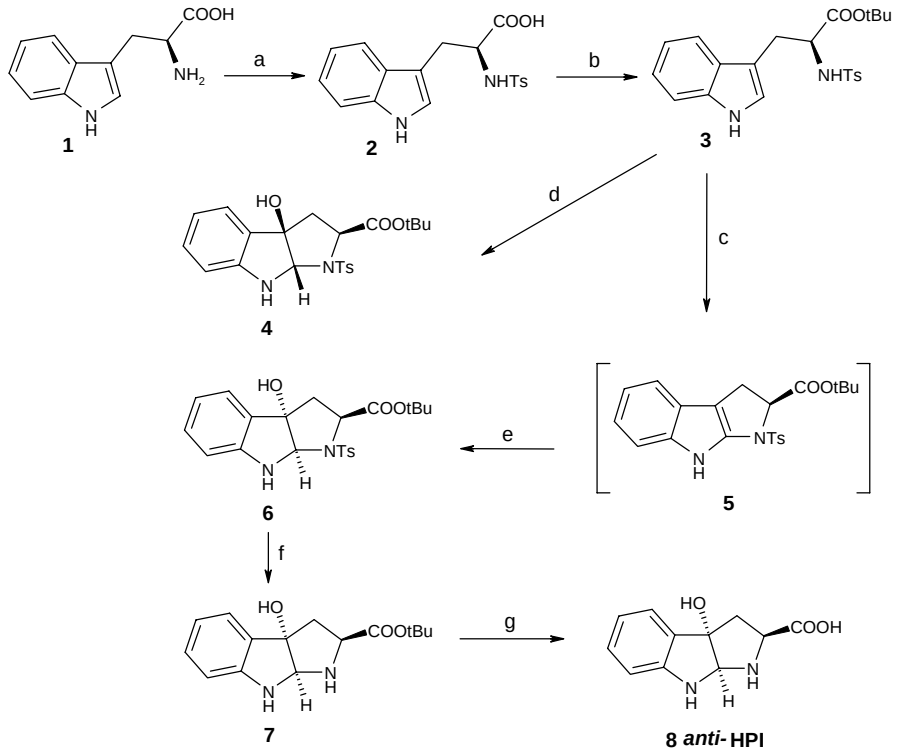
Our research started from the naturally abundant L-tryptophane **1**. *p*-Toluenesulfonyl-L-tryptophane **2** was synthesized smoothly from L-tryptophane **1** referring to the former literature[5]. Compound **3** was obtained by treating *p*-toluenesulfonyl-L-tryptophane **2** with N, N′-diisopropyl-O-*tert*-butylisourea without racemization under inert gas. Treatment of **3** with N-bromosuccinimide (NBS) and triethylamine generated the unstable dihydropyrroindole **5**, which could be quickly purified by chromatography on silica gel. Subsequent treatment of this compound with 3,3-dimethyl-dioxirane (DMDO) at -78°C followed by reduction with sodium borohydride led to the key intermediate **6** substantially as a single diastereomer (3a*S*, 8a*R*). According to the ^{1}H-NMR spectra data the ratio of diastereomers is 41.2 : 2.7 (*d.e*. = 88%). This diastereomeric excess can be enhanced by a purification over silica gel to *d.e.* > 95%. The relative configuration was determined by X-ray analysis and ^{1}H-NMR, ^{13}C-NMR. The *syn*-compound **4** can also be easily obtained by direct oxidation of **3** with DMDO at –78°C in 92% yield and *d.e.* of 72%. The configuration of **4** was determined by comparing of nmr data with compound **6**(**see Scheme 1**).

It is well known that the *p*-toluenesulfonyl protecting group attached to unaromatic amino group is quite difficult to be removed. In our approach, sodium naphthalenide was

Scheme 1



Reagents and conditions: (a) Ts-Cl, $NaHCO_3$ 95%; (b) N, N′-diisopropyl-O-*tert*- butylisourea, dry CH_2Cl_2, 85%; (c) NBS, Et_3N, 91%; (d) DMDO, -78°C; (e) (ⅰ) DMDO, -78°C, (ⅱ)$NaBH_4$, 97%; (f) $NaC_{10}H_8$, DME, 65%; (g) TFA, CH_2Cl_2, 98%.

employed to cleave this group to yield compound **7** in 65% with dimethoxyethane (DME) as solvent [6]. As to the *t*-butyl protecting group, it is quite easy to remove quantitatively in the presence of trifluoroacetic acid to afford the target molecular **8** (see **Scheme 1**).

The structures of compound **2**, **3**, **4**, **6**, **7** and *anti*-HPI **8** were confirmed by ^{1}H-NMR, ^{13}C-NMR, ESIMS[7].

Acknowledgments

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References and Notes

1. S. W. Pelletier, "*Alkaloid: Chemical and Biological Perspective*", Pergamon Verlag Oxford, **1999**, p. 163.
2. a) H. B. Arzeno, D. S. Kemp, *Synthesis*, **1988**, 32.
   b) M. Nakagawa, S. Kato, S. Kodato, H. Watanabe, H. Okajima, T. Hino, B. Witkop, *Chem. Pharm. Bull.*, **1981**, *29*, 1013.
3. M. Nakagawa, Y. Yokoyama, S. Kato, T. Hino, *Tetrahedron*, **1985**, *40*, 2125.
4. T. M. Kamanecka, S. J. Danishefsky, *Chem. Eur. J.*, **2001**, *7*, 41.
5. V. D. Vigneaud, M. F. Bartlett, U. D. Johl, *Am. Soc.*, **1957**, *79*, 5572.
6. C. H. Heathcock, T. A. Blumenkopf, K. M. Smith, *J. Org. Chem*., **!989**, *54*, 1548.
7. Selected data of compound **6**: Colorless needle, ^{1}H-NMR ($CDCl_3$, 600 MHz, δ_{ppm}): 1.10(s, 9H, *t*-Bu), 2.40(s, 3H, Ts-CH_3), 2.47(dd, 1H, J=9.7Hz, J=13.0Hz, H-3), 2.69(dd,1H, J=1.3Hz, J=13.0 Hz, H-3), 4.33(dd, 1H, J=1.3 Hz, J=9.7 Hz, H-2), 5.00 (s, 1H,H-8a), 6.62(d, 1H, J=7.8Hz, H-7), 6.80(t, 1H, J=7.8Hz, H-5), 7.18(m, 2H, H-4, 6), 7.36(d, 2H, J=7.3Hz, Ts), 7.80 (d, 2H, J=7.3Hz, Ts); ^{13}C-NMR ($CDCl_3$, 100 MHz, δ_{ppm}): 21.5(q,Ts-CH_3), 27.3(q×3, *t*-Bu), 40.6(t, C-3), 61.6 (d, C-2), 81.8(s, C-3a), 83.5 (d, C-8a), 87.6(s, *t*-Bu), 110.8(d, C-7), 119.8(d, C-5), 123.8(d, C-3b), 127.1(d×2, Ts), 128.5(s, Ts), 129.9(d×2, Ts), 131.1(d, C-6), 135.7(s, C-3b), 144.0(C-7a), 149.8(d, Ts), 169.4(d, COO-*t*-Bu). ESIMS (*m/z*): 431.0(25%) $[M+H]^+$, 453.1(100%) $[M+Na]^+$.

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