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Enantioselective total synthesis of (−)-pseudophrynaminol through tandem olefination, isomerization and asymmetric Claisen rearrangement

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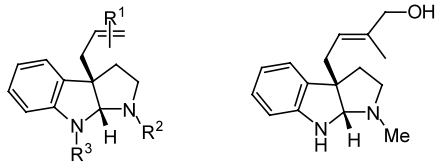
Abstract—A new and efficient total synthesis of (−)-pseudophrynaminol, the pyrrolo[2,3-*b*]indole alkaloid bearing the allylic moiety at the 3a-position, has been achieved by a sequence involving 3-allylindol-2-one **8** as a key intermediate. The enantioselective construction of the quaternary carbon in **8** was performed through a tandem cascade reaction of 2-allyloxyindolin-3-one **4**, olefination, isomerization, and asymmetric Claisen rearrangement.

The hexahydropyrrolo[2,3-*b*]indole alkaloids possessing the allylic moiety adjacent at the 3a-site, such as amauromine,[1] ardeemins,[2] aszonalenin,[3] flustramines,[4] roquefortine,[5] and pseudophrynamines[6] have been received considerable attention due to their potential biological activities. Recently, many diastereoselective approaches from tryptophan derivatives to the chiral hexahydropyrrolo[2,3-*b*]indole frameworks of these alkaloids have been reported.[7–12] However there are few enantioselective approaches to hexahydropyrrolo[2,3-*b*]indole alkaloids. The only known example is the enantioselective route to pseudophrynaminol through asymmetric nitroolefination of an indol-2-one.[13] Recently, we reported the efficient synthetic method for 3a-(1,1-dimethylallyl)dihydropyrrolo[2,3-*b*]indole via tandem reaction of 2-(1,1-dimethylallyloxy)indolin-3-ones, olefination, isomerization, Claisen rearrangement, and total synthesis of racemic flustramine C.[14] Herein, we report an enantioselective total synthesis of (−)-pseudophrynaminol (**1**) through the domino cascade reaction of 2-allyloxyindolin-3-one **4** involving asymmetric Claisen rearrangement of the intermediary 2-allyloxyindole **7** as a typical example of a novel and general method for synthesis of chiral pyrrolo[2,3-*b*]indole alkaloids.

Bromination of indolin-3-one **2**,[15] followed by substitution with (*S*)-1-nonen-3-ol (**3**, 99% ee)[16] in the presence of MS 4A, gave a diasteromeric mixture of 2-allyloxyindol-3-one (**4**) in 73% yield (Scheme 1). Horner–Wadsworth–Emmons reaction of **4** with diethyl cyanomethylphosphonate (**5**) in the presence of potassium *tert*-butoxide at −78°C to room temperature for 4 h proceeded smoothly with the tandem olefination, isomerization, Claisen rearrangement, and deacetylation to afford (*E*)-3-cyanomethyl-3-(2-nonenyl)indolin-2-one (**8**) with highly enantiomeric excess (97% ee) in 88% yield.[17] The chirality of alcohol **3** was perfectly transformed to the quaternary carbon center of the indolin-2-one **8**. The tentative assignment of the (*S*)-configuration of **8** was based on the stereochemistry of Claisen rearrangement reported[18] and the molecular orbital calculation of transition states in Claisen rearrangement of **A** as a model compound of **7** (Fig. 1). The difference ($\Delta\Delta G^{\ddagger}_{\mathbf{B}-\mathbf{C}}=4.88$ kcal/mol) between the free activation energy of two chair-like transition states **B** and **C**[19] suggests that Claisen rearrangement proceeded predominantly via the transition state **B** to (*S*)-indolin-2-one.



Hexahydropyrrolo[2,3-*b*]indole (-)-Pseudophrynaminol **1**

Alkaline hydrolysis of the nitrile **8** produced carboxylic acid **9** in high yields (Scheme 2). The acid **9** was condensed with methylamine using EDC and pentafluorophenol to give the amide **10** in 98% yield. For synthesis of pseudophrynaminol (**1**), we initially chose the reaction pathway through formation of the pyrrolo[2,3-*b*]indole moiety from **10** followed by con-

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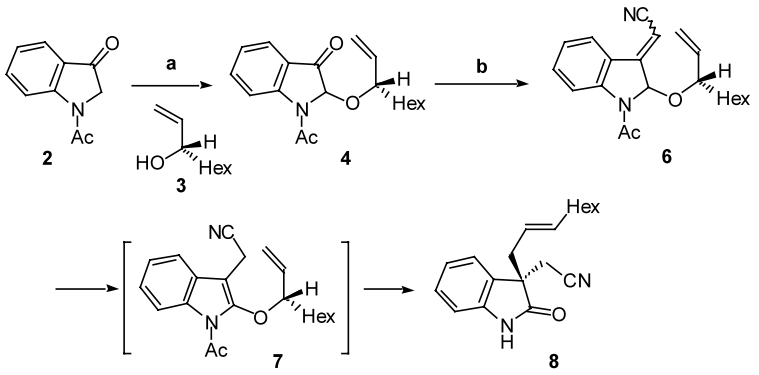

Scheme 1. *Reagents and conditions*: (a) Br_2, CH_2Cl_2, 0°C, then (*S*)-1-nonen-3-ol **3**, CH_3CN–DMF, MS 4A, rt, 4 days, 73%; (b) $(EtO)_2POCH_2CN$ **5**, KOBu-*t*, DMF, −78°C–rt, 88%.

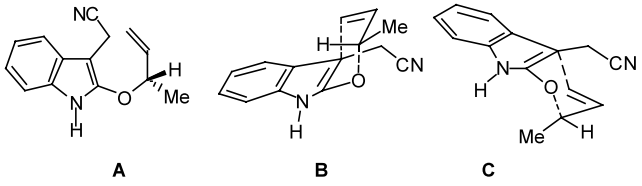

Figure 1. Transition states **B** and **C** in Claisen rearrangement of model compound **A**.

version of the allylic part. Treatment of **10** with excess $LiAlH_4$ in refluxing THF for 0.5 h took place smoothly with reductive cyclization to afford pyrrolo[2,3-*b*]indole **11** (92%), but several attempts to effect oxidative fission of the nonenyl group of **11** failed. Instead we tried another access to **1** via transformation of the allylic moiety prior to construction of the pyrrolo[2,3-*b*]indole framework. Oxidative cleavage of carbon–carbon double bond of **10** with OsO_4–$NaIO_4$ gave a mixture of two diastereomers (2.5:1) of aminal **12** in 82% yield. When Wittig olefination of **12** with the ylide **13** was carried out in refluxing toluene for 5 h, a mixture of *E*- and *Z*-isomers (2.4:1) of the olefin **14** was obtained in 87% yield. On the other hand, this olefination was performed in refluxing acetonitrile in the presence of pyridine to provide **14** (81%, *E*:*Z* = 11:1) stereoselectively. Finally, reductive cyclization of **14** with $LiAlH_4$ (10 equiv.) in refluxing THF for 6 h proceeded to give (−)-pseudophrynaminol **1**[20] in 44% yield, $[\alpha]_D = -87.5$ (*c* 0.24, $CHCl_3$), lit.:[12a] $[\alpha]_D = -82.8$ (*c* 0.98, $CHCl_3$), lit.:[13] $[\alpha]_D = -80.0$ (*c* 1.0, $CHCl_3$).[21] All spectral data are identical to those of the natural[6] and synthetic samples.[12,13]

In summary, we have demonstrated highly stereoselective synthesis of (−)-pseudophrynaminol (**1**) through the tandem cascade reaction of 2-allyloxyindolin-3-one **4**, olefination, isomerization, asymmetric Claisen rearrangement, and deacetylation to 3,3-disubstituted indolin-2-one **8** and the reductive cyclization of **14**. This asymmetric tandem reaction might be useful for construction of optically active pyrrolo[2,3-*b*]indole alkaloids possessing allylic moiety at the 3a-site.

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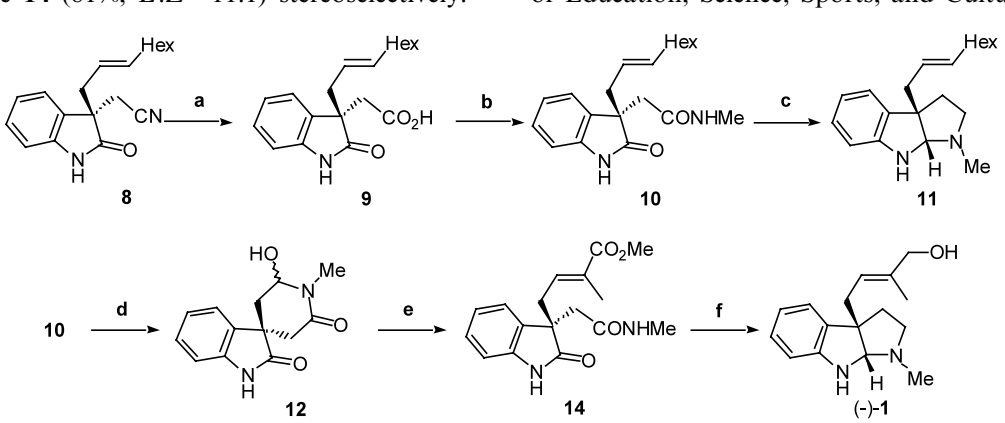

Scheme 2. *Reagents and conditions*: (a) 35% NaOH aq., MeOH, reflux, 99%; (b) HOC_6F_5, NEt_3, EDC THF, then $MeNH_2$, rt, 98%; (c) $LiAlH_4$, THF, reflux, 92%; (d) OsO_4, NMO, CH_3CN, rt, then $NaIO_4$, 1,4-dioxane–H_2O (2:1), 82%; (e) $Ph_3P{=}C(Me)CO_2Me$ **13**, pyridine, CH_3CN, reflux, 81%; (f) $LiAlH_4$, THF, reflux, 44%.

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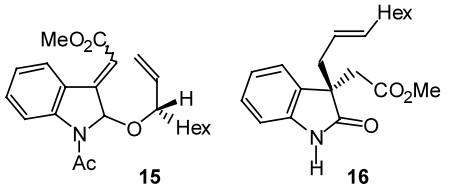
17. Wittig olefination of **4** with methyl triphenylphosphoranylideneacetate in refluxing toluene for 9 h gave indolylidene acetate **15** in 86% yield. Reaction of **15** with DBU in toluene at 40°C for 38 h took place with successive isomerization and Claisen rearrangement to produce indolin-2-one **16** (60%) and its *N*-acetyl derivative (22%), respectively. In this case, allylic alcohol **3** with 93% ee was used as the starting material to obtain **16** with 92% ee.



15 **16**

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19. The calculation was performed by using SPARTAN ver. 5.1.2 (pBP-DN**).
20. IR ($CHCl_3$): ν 3400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$-*d*): δ 1.63 (3H, s), 1.95 (1H, ddd, $J=12.1$, 6.0, 3.5 Hz), 2.14 (1H, ddd, $J=12.1$, 8.9, 6.6 Hz), 2.42 (3H, s), 2.45–2.60 (3H, m), 2.73 (1H, ddd, $J=9.5$, 6.6, 3.5 Hz), 3.94 (2H, s), 4.48 (1H, s), 5.37 (1H, t, $J=7.2$ Hz), 6.58 (1H, d, $J=7.6$ Hz), 6.73 (1H, t, $J=7.6$ Hz), 7.03 (1H, t, $J=7.6$ Hz), 7.04 (1H, d, $J=7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$-*d*): δ 36.7, 52.3, 38.6, 57.8, 123.1, 135.0, 118.8, 127.7, 109.0, 149.8, 86.2, 37.3, 121.0, 137.4, 14.3, 68.6; HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}ON_2$: 258.1732; found: 258.1733.
21. (+)-Enantiomer of **1**: $[\alpha]_D=+87.80$ (*c* 0.72, $CHCl_3$) (Ref. 12b).