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Silyl-enolization-asymmetric Claisen rearrangement of 2-allyloxyindolin-3-one: enantioselective total synthesis of 3a-hydroxypyrrolo[2,3-*b*]indoline alkaloid alline

Tomomi Kawasaki,* Wataru Takamiya, Naoki Okamoto, Miyuki Nagaoka and Tetsuya Hirayama

Meiji Pharmaceutical University, 2-522-1 Kiyose, Tokyo 204-8588, Japan

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Abstract—Asymmetric Claisen rearrangement triggered by silyl-enolization of 2-(1′-nonel-3′-yloxy)indolin-3-ones was performed in order to prepare 3-(2′-nonenyl)-3-hydroxyindolin-2-ones. Total synthesis of 3-hydroxypyrrolo[2,3-*b*]indoline alkaloid, (+)-alline was achieved by transformation of the allylic moiety of 3-(2′-nonenyl)-3-hydroxyindolin-2-one to amine followed by reductive cyclization.

3-Hydroxyindolin-2-ones have drawn much interest recently due to their importance as synthetic intermediates in the synthesis of biologically active compounds. Although a number of routes to racemic 3-hydroxyindolin-2-ones have already been known,[1,2] there are few synthetic methods for chiral 3-hydroxyindolin-2-ones. The known asymmetric examples are the enantioselective Me_2Zn[3] and $(allyl)_4Sn$ additions,[4] organocatalyzed aldol addition[5] and diastereoselective vinylogous aldol addition to isatin derivatives,[6] and the diastereoselective arylation of mandelic acid enolates[7] and dihydroxylations of 3-alkylidene-2-indolinones.[8] We have recently described a synthetic method for racemic 3-hydroxyindolin-2-one alkaloids through enolization-Claisen rearrangement of 2-allyloxyindolin-3-ones.[2] Herein, we disclose an asymmetric Claisen rearrangement triggered by silyl-enolization of 2-(1′-nonen-3′-yloxy)indolin-3-ones **3** to (*E*)-3-(2′-nonenyl)-3-silyloxyindolin-2-ones **5** for the first total enantioselective synthesis of the 3a-hydroxypyrrolo[2,3-*b*]indoline alkaloid, alline (**10**).[9]

The starting (3′*R*)-2-(1′-nonen-3′-yloxy)indolin-3-one **3a** was readily available by bromination of 1-acetylindolin-3-one **1** followed by substitution with (3*R*)-1-nonen-3-ol (**2a**, 99% ee)[10] according to our reported method.[11]

Initially, we examined the enolization of **3a** with DBU, DBN, and DMAP as a base under several reaction conditions and the results are summarized in Table 1. The enolization-Claisen rearrangement of **3a** with DBN at 0 °C in toluene followed by deacetylation with LiOH afforded (+)-3-(2′-nonenyl)-3-hydroxyindolin-2-one **4** in 98% yield, but its optical purity was low (Table 1, entry 2). When DMAP was used instead of DBN, the reaction, even at room temperature, was slow to result in a low yield of (+)-**4**, but the optical purity was fairly improved (entry 5). The low stereoselectivity may be caused by indistinguishable predominance between the boat-like **A** and chair-like transition states **B** in the Claisen rearrangement (Scheme 1).

Next, we attempted the O-silylation of **3a** to define the predominance among possible transition states in the Claisen rearrangement (Table 2).[12,13] When **3a** was treated with TMS chloride in the presence of DMAP in CH_2Cl_2 at −20 °C, the desired reaction did not proceed at all (Table 2, entry 1). On using DBU instead of DMAP, silyl-enolization-Claisen rearrangement **3a** took place smoothly via the more stable chair-like transition state **D** to give 3-(2′-nonenyl)-3-silyloxyindolin-2-one **5a** in 89% yield (entries 2 and 3). The optical purity (85–86% ee) was determined by chiral HPLC analysis of (+)-**4** obtained through deacetylation and desilylation of **5a** with LiOH. A similar reaction with TMS triflate in the place of TMS chloride worked out (entry 4), but the

* Corresponding author. Tel./fax: +81 424 95 8763; e-mail: kawasaki@my-pharm.ac.jp

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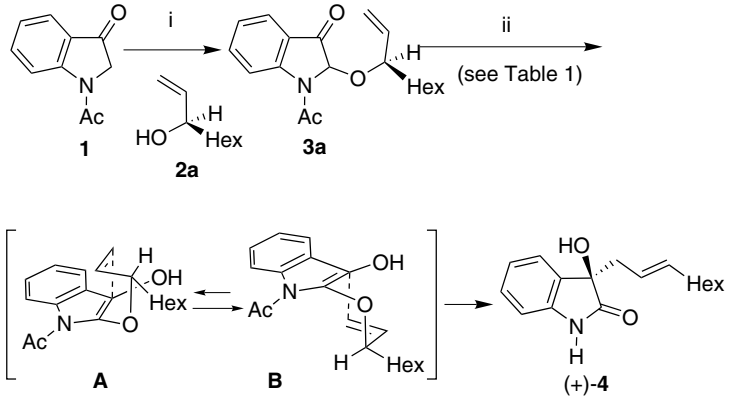
Table 1. Enolization-Claisen rearrangement

Entry	Base	Solv.	Temp (°C)	Time	(+)-**4** Yield (%)[a] [% ee][b]
1	DBN	Toluene	rt	2 h	93 [28]
2	DBN	Toluene	0	5 h	98 [32]
3	DBN	CH_2Cl_2	0	5 h	93 [32]
4	DBU	Toluene	0	0.2 h	83 [17]
5	DMAP	Toluene	rt	3 days	37[c] [61]

[a] Two-step yield from **3a**.
[b] The % ee was determined by chiral HPLC analysis of **4**.
[c] Starting material **3a** was recovered in 39% yield.



Scheme 1. Reagents and conditions: (i) Br_2, CH_2Cl_2, 0 °C, 0.5 h, then (3*R*)-1-nonen-3-ol (**2a**), MS-4 Å, MeCN–DMF (10:1), rt, 4 d, 56%; (ii) base, solv., temp, then 10% LiOH, MeOH, 0 °C.

Table 2. Silyl-enolization-Claisen rearrangement

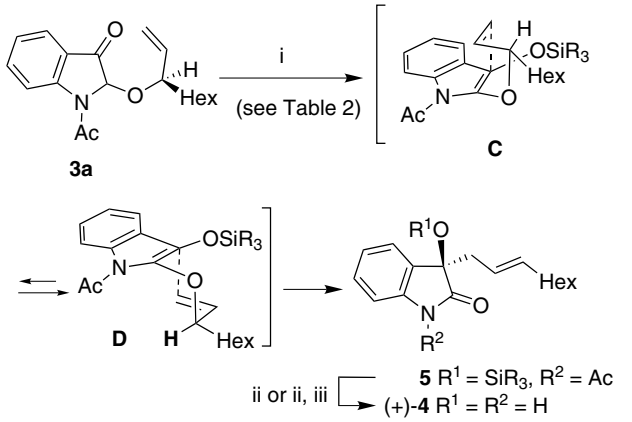
Entry	R_3Si–X	Base	Temp (°C)	Time (h)	**5** Yield (%)	(+)-**4** Yield (%) [% ee][a]
1	TMS–Cl	DMAP	−20	24	—	—
2	TMS–Cl	DBU	−20	10	89	91[d] [85]
3	TMS–Cl	DBU	−30	11	89	94[d] [86]
4	TMS–OTf	DBU	−20	16	89	81[d] [88]
5	TES–OTf	DBU	−20	36	65[b]	66[e] [63]
6	TBS–OTf	DBU	−20	36	13[c]	68[e] [81]

[a] The % ee was determined by chiral HPLC analysis of (+)-**4**.
[b] Starting material **3a** was recovered in 16% yield.
[c] Starting material **3a** was recovered in 86% yield.
[d] Deprotection with LiOH was performed.
[e] Deprotection with LiOH and TBAF was carried out.

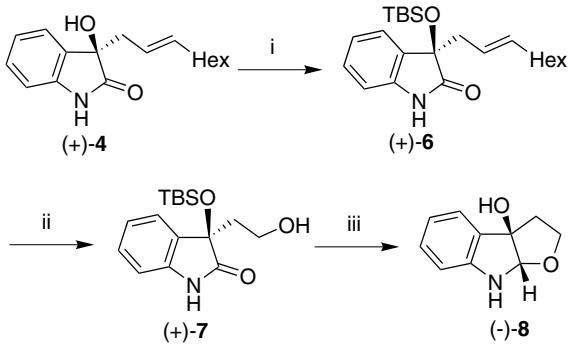
use of TES and TBS triflates as a bulky silylating agent resulted in reduced reaction rate, yield, and stereoselectivity (entries 5 and 6). To sum up, the suitable reaction protocol for preparation of (+)-**4** is shown in entry 3 (Scheme 2).

The (*R*)-configuration at the 3 position of (+)-**4** was confirmed by transformation to furo[2,3-*b*]indoline **8** as follows. The TBS protection of the hydroxyl group in (+)-**4**,[14] ozonolysis of (+)-**6** followed by $NaBH_4$-reduction, and reductive cyclization of (+)-**7** with $NaBH_4$ in THF afforded (−)-**8**, of which the spectral data and specific rotation were identical with those of the authentic (3a*R*)-(−)-3a-hydroxyfuro[2,3-*b*]indoline (Scheme 3).[15]

Next, we attempted to apply 3-hydroxyindolin-2-one **4** to a total synthesis of the pyrrolo[2,3-*b*]indoline alkaloid



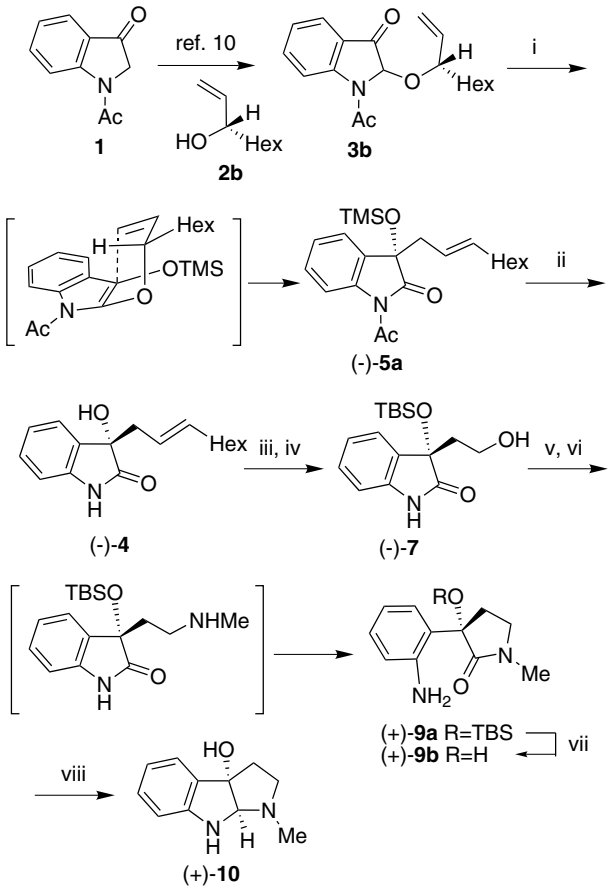
Scheme 2. Reagents and conditions: (i) R_3Si–X, base, CH_2Cl_2, temp, **5a**, R^1 = TMS, **5b**, R^1 = TES, **5c**, R^1 = TBS; (ii) 10% LiOH, MeOH, 0 °C; (iii) TBAF, MeCN, rt.



Scheme 3. Reagents and conditions: (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 4.5 h, then AcOH–MeOH, reflux, 8 h, 75%; (ii) O_3, CH_2Cl_2–MeOH (5:1), −78 °C, 1 h, then $NaBH_4$, rt, 0.5 h, 52%; (iii) $NaBH_4$, THF, rt, 2 d, 27%.

alline (**10**), which was isolated from *Allium odora*,[9a] *A. senescens*, and *A. anisoprodium*.[9b] The racemic compound **10** was synthesized by photosensitized oxidation of tryptamine prior to its isolation,[16] but its absolute configuration has not yet been determined. We presumed the absolute configuration of natural (+)-**10**[9a] to be 3a*S*,8a*R* by comparing with the specific rotation of (−)-physostigumine[17] and (−)-**8**, and tried the synthesis of (3a*S*,8a*R*)-**10** from (3′*S*)-2-(1′-nonen-3′-yloxy)indolin-3-one **3b**[10] as follows. Silyl-enolization-Claisen rearrangement of (3′*S*)-**3b** followed by hydrolysis with LiOH produced (3*S*)-(−)-**4** (86% ee) in 85% two-step yield.[18] *O*-TBS-silylation of (−)-**4**[14] followed by ozonolysis and $NaBH_4$-reduction afforded alcohol (−)-**7** in high yield. Substitution of *O*-tosylate of (−)-**7** with methylamine accompanying transamidation of methylamino intermediate[19] provided (+)-anilinopyrrolidinone **9a**.[20] Desilylation of (+)-**9a** with TBAF followed by reduction of **9b** with $AlH_3{\cdot}EtNMe_2$ in THF at 0 °C proceeded with cyclization to give alline (3a*S*,8a*R*)-(+)-**10**,[21] of which the spectral data were identical with those of the natural[9a] and synthetic products.[16] Since the optical rotation of both synthetic **10** and natural alline indicated dextrorotatary, it is shown that natural alline (**10**) also has 3a*S*,8a*R*-configuration (Scheme 4).

In summary, we have presented a useful method for enantioselective synthesis of optically active 3-(2′-nonenyl)-3-silyloxyindolin-2-ones **5** through Claisen rearrangement triggered by silylation of 2-(1′-nonen-3′-yloxy)indolin-3-ones **3**. We also transformed (+)-**4** to (−)-furo[2,3-*b*]indoline **8** for confirming its absolute configuration and achieved the first asymmetric total synthesis of alline (**10**) to disclose its absolute configuration.



Scheme 4. Reagents and conditions: (i) TMSCl, DBU, CH_2Cl_2, −30 °C, 16 h, 89%; (ii) 10% LiOH, MeOH, 0 °C, 0.5 h, 95%, 86% ee; (iii) TBSOTf, 2.6-lutidine, CH_2Cl_2, 0 °C, 4 h, then AcOH–MeOH, reflux, 7 h, 98%; (iv) O_3, CH_2Cl_2–MeOH (5:1), −78 °C, 1 h, then $NaBH_4$, rt, 1 h, 99%; (v) TsCl, pyridine, 0 °C, 3 h, 95%; (vi) $MeNH_2$, MeOH, 85 °C in sealed tube, 6 h, 54%; (vii) TBAF, THF, 0 °C, 1.5 h, 87%; (viii) $AlH_3{\cdot}EtNMe_2$, THF, 0 °C, 24 h, 39%.

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12. General procedure for preparation of silyl-enolization-Claisen rearrangement of **3a** (Table 2): To a solution of **3a** (1.0 mmol) and R_3Si–X (2.0 mmol) in CH_2Cl_2 (12 mL) at −20 to −30 °C was added a solution of DBU (2.5 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for the desired period and reaction was monitored by TLC analysis. After neutralizing with 10% HCl, the resulted mixture was concentrated and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (AcOEt–hexane = 1:15) to give **5** as a colorless oil.
13. The *E*-geometry of **5** was determined by NOE experiments between allyl and vinyl protons. The tentative assignment of the (*R*)-configuration of (+)-**5** was based on the stereochemistry of Claisen rearrangement reported until **5** is converted to **8**. Most recently, the absolute configuration of (−)-3-allyl-3-hydroxyindolin-2-one was confirmed to be *S* by comparing the CD spectra of the related compounds by Takayama's group.[4]
14. O,O′-Disilylated by-product in TBS-silylation of **4** was transformed to *O*-mono-silylate **6** by treatment with AcOH–MeOH.
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18. Compound (3*S*)-(−)-**4**: mp 83–85 °C, $[\alpha]_D^{25}$ −41.9 (*c* 0.92, $CHCl_3$). IR ($CHCl_3$): 3431, 3251, 1724, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.86 (t, 3H, $J = 6.9$ Hz), 1.18–1.27 (m, 8H), 1.90–1.97 (m, 2H), 2.54 (dd, 1H, $J = 13.5$, 8.1 Hz), 2.66 (ddd, 1H, $J = 13.5$, 6.4, 1.1 Hz), 2.88 (s, 1H), 5.28 (dddt, 1H, $J = 15.2$, 8.1, 6.4, 1.5 Hz), 5.53 (dt, 1H, $J = 15.2$, 6.7 Hz), 6.84 (d, 1H, $J = 7.8$ Hz), 7.06 (td, 1H, $J = 7.5$, 0.9 Hz), 7.25 (td, 1H, $J = 7.8$, 1.5 Hz), 7.34 (d, 1H, $J = 7.5$ Hz), 7.66 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 22.7, 28.7, 29.2, 31.7, 32.6, 41.8, 76.4, 110.1, 121.0, 122.7, 124.3, 129.3, 130.3, 137.1, 140.1, 180.1; MS (EI) *m*/*z* (%): 357 (M^+, 17), 315 (5), 297 (26), 255 (16), 233 (33), 191 (100), 187 (12), 162 (27), 148 (60), 146 (18), 145 (13), 133 (5), 43 (18); Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.73; H. 8.60; N, 5.08.
19. The structures of **9** were confirmed by the HMBC cross-peak between the carbonyl carbon and the proton of *N*-methyl group. This type of transamidation was utilized to the total synthesis of chimonamidine; Takayama, H.; Matsuda, Y.; Masubuchi, K.; Ishida, A.; Kitajima, M.; Aimi, N. *Tetrahedron* **2004**, *60*, 893–900.
20. This five-step process from (−)-**4** to (+)-**9b** improved the overall yield as compared to our initial two-step approach to (+)-**9b** (13% overall yield) through ozonolysis of (−)-**4** followed by reductive amination with $MeNH_2$ and $NaBH_3CN$.
21. Synthetic alline (3a*S*,8a*R*)-(+)-**10**: mp 151–152 °C, $[\alpha]_D^{25}$ +100.2 (*c* 0.56, $CHCl_3$). IR ($CHCl_3$): 3585, 3412, 1610, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.22 (ddd, 1H, $J = 12.6$, 6.6, 4.8 Hz), 2.32 (ddd, 1H, $J = 12.6$, 7.8, 6.6 Hz), 2.40–2.49 (br, 1H), 2.45 (s, 3H), 2.63 (ddd, 1H, $J = 9.3$, 7.8, 6.6 Hz), 2.81 (ddd, 1H, $J = 9.3$, 6.9, 4.8 Hz), 4.16 (br, 1H), 4.49 (s, 1H), 6.64 (d, 1H, $J = 8.1$ Hz), 6.80 (ddd, 1H, $J = 8.1$, 7.5, 0.6 Hz), 7.13 (ddd, 1H, $J = 7.8$, 7.5, 1.2 Hz), 7.29 (dd, 1H, $J = 7.8$, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 37.4, 40.6, 52.3, 89.3, 90.3, 110.2, 119.4, 123.6, 129.5, 132.3, 149.7; MS (EI) *m*/*z* (%): 190 (M^+, 100), 173 (18), 172 (13), 147 (29), 146 (41), 133 (16), 132 (24), 130 (23), 118 (13), 93 (12); HRMS (EI) *m*/*z* Calcd for $C_{11}H_{14}N_2O$: 190.1106. Found: 190.1102. Natural alline: $[\alpha]_D$ +136.3 (*c* 1.218, $CHCl_3$).[9a]