Tetrahedron xxx (2015) 1–5

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of rhazinilam through intramolecular arylcyanation of alkenes catalyzed cooperatively by nickel/aluminum

Yuuya Yamada [a], Shiro Ebata [a], Tamejiro Hiyama [a,b], Yoshiaki Nakao [a,*]

[a] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan
[b] Research and Development Initiative, Chuo University, Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

ARTICLE INFO

Article history:
Received 20 January 2015
Received in revised form 2 March 2015
Accepted 3 March 2015
Available online xxx

Keywords:
Rhazinilam
Nickel
Aluminum
Carbocyanation
C–C bond activation

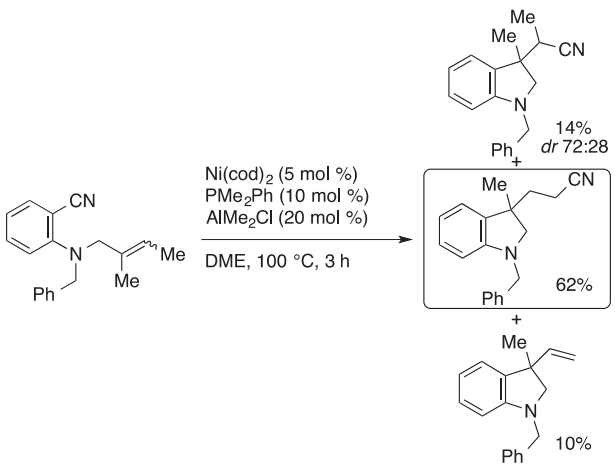
ABSTRACT

Intramolecular arylcyanation across a tri-substituted double bond proceeds to give a primary alkyl cyanide product through functionalization of C–CN and allylic C–H bonds and double C–C bond formation in a 1,3-manner by cooperative nickel/$AlMe_2Cl$ catalysis. The transformation is applied to the synthesis of rhazinilam, a tubulin-binding alkaloid containing unique structural motifs such as axially chiral biaryl and strained nine-membered lactam as well as quaternary carbon.

1. Introduction

Activation and functionalization of C–C bonds have gained increasing interest as a novel strategy to streamline organic synthesis.[1] Thanks to the development of transition metal catalysis, a variety of modes for C–C bond cleavage have been introduced to the synthetic community. Even applications of C–C bond activation to natural product syntheses have emerged recently.[2] Therefore, the strategies for C–C bond activation have started to show their potential to innovate retro-synthetic analysis of target molecules as has also been the case with the recent developments of metal-catalyzed C–H bond functionalization.[3]

Our group has engaged in the field of catalytic C–C bond activation, focusing our attention particularly on activation of C–CN bonds of nitriles.[4] We have developed C–C bond forming addition reactions through insertion of unsaturated bonds into C–CN bonds catalyzed cooperatively by nickel and Lewis acids, namely carbocyanation reaction.[5] The transformation allows simultaneous formation of two newly formed C–C bonds with no byproduct formation, and has been applied to the syntheses of several small natural products,[2a,6] which have particular biological activities. During our studies on the intramolecular arylcyanation of alkenes,[2a,7b] we observed an intriguing product in the reaction across a tri-substituted double bond in addition to an expected secondary alkyl cyanide product as a minor component (Eq. 1). The major product was likely derived from intramolecular arylnickelation across the double bond followed by β-hydride elimination, reinsertion of the resulting double bond into Ni–H, and reductive elimination (vide infra). This particular transformation represents formally simultaneous Ar–CN and allylic C–H bond functionalizations to result in double C–C bond formation in a 1,3-manner.

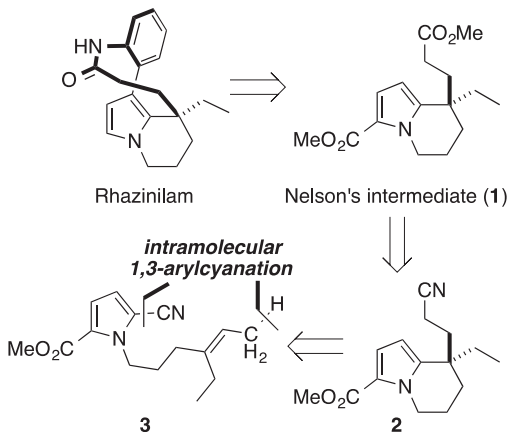


(1)

* Corresponding author. Tel.: +81 75 383 2443; fax: +81 75 383 2445; e-mail address: nakao.yoshiaki.8n@kyoto-u.ac.jp (Y. Nakao).

http://dx.doi.org/10.1016/j.tet.2015.03.012
0040-4020/

The unexpected observation prompted us to imagine its application to the synthesis of rhazinilam. Rhazinilam was isolated in 1965,[8] and its structure was characterized in 1972.[9] It has gained attention of synthetic organic chemists owing to its unique structure containing axially chiral biaryl, strained nine-membered lactam structures, and quaternary stereocenter as well as its taxol-like tubulin-binding activity.[10] Therefore, several research groups have already reported its concise synthesis[11] including asymmetric one, taking advantages of modern synthetic methodologies. Our own synthetic plan set highly substituted pyrrole **1** as a target, which was reported to be an intermediate of the total synthesis by Nelson and co-workers (Scheme 1).[11f] We imagined that **1** could be accessed by hydrolysis of the cyano group of **2**, for which the intramolecular 1,3-heteroarylcyanation using 2-cyanopyrrole **3** was envisaged. We report herein the successful application of the carbocyanation chemistry to the racemic synthesis of rhazinilam.

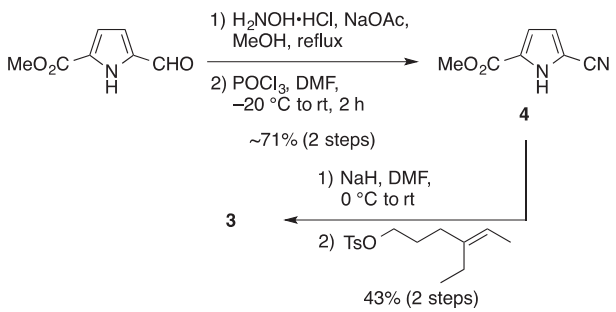


Scheme 1. Synthetic plan for the synthesis of rhazinilam through intramolecular arylcyanation.

2. Results and discussion

2.1. Intramolecular 1,3-arylcyanation

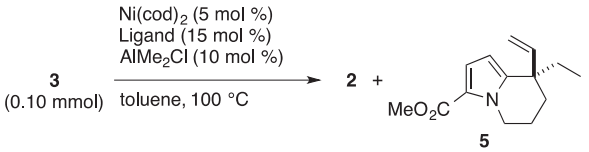
A substrate for the key 1,3-arylcyanation reaction was obtained in a straightforward manner (Scheme 2). Literature precedented methyl 5-formyl-1*H*-pyrrole-2-carboxylate[12] was treated with hydroxylamine and then with phosphorus oxychloride to give methyl 5-cyano-1*H*-pyrrole-2-carboxylate (**4**) through the formation of oxime and the subsequent dehydration. N-Alkylation of the 2,5-difunctionalized pyrrole with known alkyl tosylate[11l] containing a tri-substituted double bond gave the targeted substrate **3**.



Scheme 2. Synthesis of starting material **3**.

We then briefly investigated the conditions for the intramolecular arylcyanation reaction of **3** (Table 1). The reaction of **3** (0.10 mmol) in the presence of $Ni(cod)_2$ (5 mol %), P(4-MeO–C_6H_4)$_3$ (15 mol %), and $AlMe_2Cl$ (10 mol %) in toluene at 100 °C for 8 h proceeded with full conversion of **3** to give **2** in 80% yield as estimated by GC as well as a small amount of **5** (9%) as a byproduct (entry 1). The reaction was successfully scaled-up to give **2** in 81% yield after isolation (entry 2). The use of less electron-donating triarylphosphine (entry 3) and trialkylphosphine ligands (entries 4–6) was ineffective. Under these reaction conditions, we rarely observed the formation of secondary alkyl cyanide products.

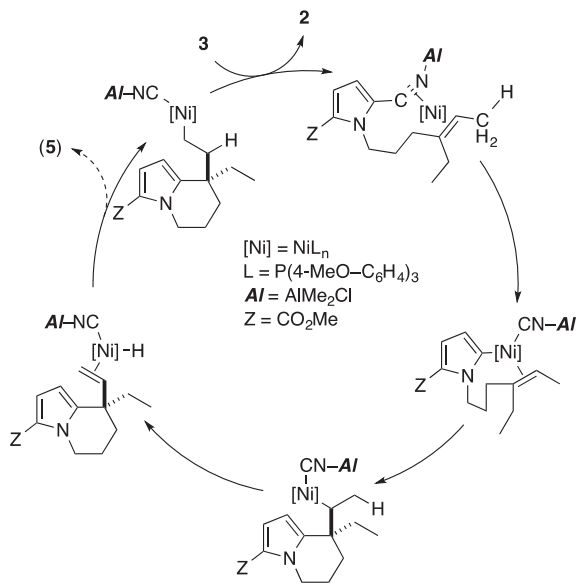
Table 1
Intramolecular 1,3-heteroarylcyanation of **3** catalyzed by nickel/$AlMe_2Cl$



Entry	Ligand	Time (h)	Yield of **2**[a] (%)	Yield of **5**[a] (%)
1	P(4-MeO–C_6H_4)$_3$	8	80	9
2[b]	P(4-MeO–C_6H_4)$_3$	5	81[c]	11[c]
3	P(4-F_3C–C_6H_4)$_3$	22	20	5
4	PMe_3	22	33	4
5	P(*c*-Hex)$_3$	22	6	5
6	P(*t*-Bu)$_3$	22	<1	<1

[a] Estimated by GC.
[b] Reaction run on a 1.0 mmol-scale.
[c] Isolated yield.

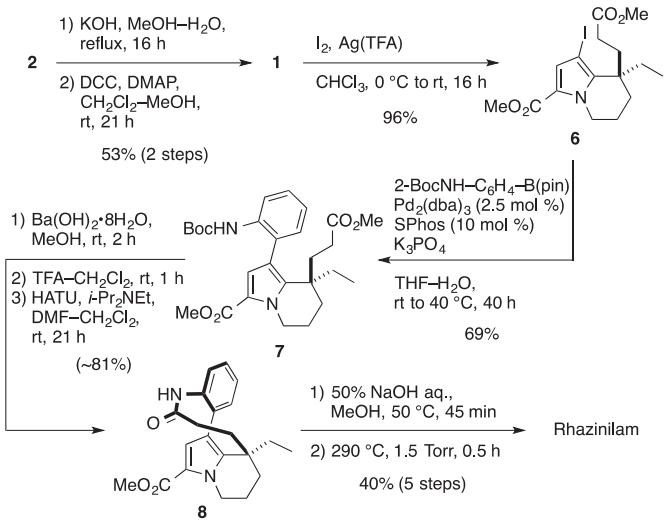
A plausible catalytic cycle of the present transformation is shown in Scheme 3. The reaction is initiated by the oxidative addition of the Ar–CN bond of **3** after η^2-coordination to nickel and η^1-coordination to aluminum of the cyano group.[2a] Coordination followed by migratory insertion of the tri-substituted double bond gives a secondary alkylnickel intermediate. This then undergoes β-hydride elimination to give an alkene–nickel complex, from which reinsertion of the double bond into the Ni–H bond takes place to give primary alkylnickel species. C–C bond forming reductive elimination affords **2** and regenerate catalytically active nickel(0) and the Lewis acid catalyst upon ligand exchange. Byproduct **5** is most likely derived from liberation of the alkene ligand before the reinsertion event.



Scheme 3. Plausible catalytic cycle.

2.2. Synthesis of rhazinilam

Having had key intermediate **2** through the formal simultaneous C–C and C–H functionalization, subsequent transformations to access rhazinilam were examined (Scheme 4). The cyano group of **2** was hydrolyzed under basic conditions, and the resulting carboxylic acid was subjected to esterification to give dimethyl ester **1**. Following the procedure reported by Nelson and co-workers with a slight modification in the final step,[11f] electrophilic iodination of **1** proceeded regioselectively at the position *ortho* to the fused alkyl chain to give **6** in high yield. The Suzuki–Miyaura cross-coupling of **6** with 2-aminophenylboronate ester was nicely catalyzed by a palladium complex ligated by the Buchwald's SPhos ligand to provide **7**. Intramolecular lactamization was effected by HATU after hydrolysis of the aliphatic methyl ester moiety and N-deprotection, giving **8**. Hydrolysis of another methyl ester of crude **8** followed by decarboxylation at high temperature under vacuum[11a] afforded racemic rhazinilam.[13]



Scheme 4. Synthesis of rhazinilam.

In conclusion, we have demonstrated the synthesis of rhazinilam, taking advantage of the intramolecular arylcyanation of alkenes across a tri-substituted double bond to give a primary alkyl cyanide product having quaternary carbon through formal C–C and C–H functionalizations and double 1,3-C–C bond formation by cooperative nickel/aluminum catalysis. Though racemic, this synthesis shows the power of metal-catalyzed C–C bond activation as an emerging tool for synthetic organic chemistry. Efforts toward further developments of C–C and C–H bond functionalizations by cooperative metal catalysis are currently under investigation.

3. Experimental section

3.1. General

All manipulations of oxygen- and moisture-sensitive materials were conducted with a standard Schlenk technique or in a dry box under an argon atmosphere. Medium pressure chromatography was performed using Kanto Chemical silica gel (spherical, 40–50 μm). Analytical thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F_{254} (0.25 mm) plates. Visualization was accomplished with UV light (254 nm) and/or an aq alkaline $KMnO_4$ solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sext=sextet, br=broad, m=multiplet), coupling constants (Hz), and integration. Melting points were determined using an OptiMelt MPA100. High-resolution mass spectra were obtained with a JEOL JMS-700 (EI). Medium pressure chromatography (MPLC) was performed with SHOKO Scientific Purif-espoir 2 chromatograph equipped with Purif-Pack (SHOKO Scientific, 20 mm×60 mm, spherical, 30 μm). Preparative recycling silica gel chromatography was performed with a JAI LC-908 chromatograph equipped with COSMOSIL 5SL-II (Nacalai Tesque, 20 mm×250 mm, spherical, 5 μm). GC analysis was performed on a Shimadzu GC 2014 equipped with an ENV-1 column (Kanto Chemical, 0.25 mm×30 m, pressure=31.7 kPa, detector=FID, 290 °C) with helium gas as a carrier. Unless otherwise noted, commercially available chemicals were used after distilled and degassed before use. $Ni(cod)_2$ was purchased from STREM and used without further purification. Anhydrous toluene was purchased from Kanto Chemical, degassed by purging vigorously with argon for 20 min, and further purified by passage through activated alumina under positive argon pressure as described by Grubbs and co-workers.[14]

3.2. Methyl 5-cyano-1*H*-pyrrole-2-carboxylate (4)

$NH_2OH\cdot HCl$ (0.58 g, 8.4 mmol) and NaOAc (0.63 g, 7.6 mmol) were added to a solution of methyl 5-formyl-1*H*-pyrrole-2-carboxylate[12] (1.14 g, 7.6 mmol) in anhydrous MeOH (8 mL), and the mixture was heated at the reflux temperature for 1 h. The resulting solution was quenched with $NaHCO_3$ aq, and the aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the corresponding aldoxime (1.11 g, <87%). The crude oxime (5.8 g, 34 mmol) thus obtained was dissolved in anhydrous *N*,*N*-dimethylformamide (DMF, 28 mL), and the solution was added dropwise $POCl_3$ (8.4 g, 55 mmol) at −20 °C. After being stirred for 30 min at −20 °C and then at rt for 2 h, the reaction was quenched with water. The aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were washed with water for five times, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the title compound (4.2 g, ~71%) as a colorless solid (mp=173.7–174.8 °C), R_f 0.23 (hexane/ethyl acetate=3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (br, 1H), 6.89 (dd, *J*=3.9, 2.5 Hz, 1H), 6.84 (dd, *J*=4.0, 2.6 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 126.7, 120.1, 115.2, 112.8, 105.7, 52.7; HRMS (EI) calcd for $C_7H_6N_2O_2$: M^+, 150.0429. Found: *m*/*z* 150.0430.

3.3. (*E*)-Methyl 5-cyano-1-(4-ethylhex-4-en-1-yl)-1*H*-pyrrole-2-carboxylate (3)

A solution of crude **4** (2.3 g, 15.0 mmol) in anhydrous DMF (15 mL) was added dropwise at 0 °C to a suspension of sodium hydride (0.38 g 15.0 mmol) in anhydrous DMF (35 mL), and the mixture was stirred for 1 h before addition of (*E*)-4-ethylhex-4-en-1-yl 4-methylbenzenesulfonate[11l] (3.2 g, 11.5 mmol) at 0 °C. After being stirred for 12 h at rt, the reaction was quenched with water. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with water for five times, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by MPLC to give the title compound (1.28 g, 43%) as a colorless oil, R_f 0.23 (hexane/ethyl acetate=20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J*=4.2 Hz, 1H), 6.73 (d, *J*=4.2 Hz, 1H), 5.20 (q, *J*=6.7 Hz, 1H), 4.46 (t, *J*=7.6 Hz, 2H), 3.86 (s, 3H), 2.05 (q, *J*=7.4 Hz, 4H), 1.94–1.82 (m, 2H), 1.58 (d, *J*=6.8 Hz, 3H), 0.95 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 140.0, 126.2, 118.8,

118.1, 117.2, 112.7, 110.1, 51.8, 48.2, 33.3, 29.8, 22.6, 13.0, 12.7; HRMS (EI) calcd for $C_{15}H_{20}N_2O_2$: M^+, 260.1525. Found: *m*/*z* 260.1516.

3.4. Intramolecular heteroarylcyanation of 3 catalyzed by nickel/$AlMe_2Cl$

To a solution of $Ni(cod)_2$ (13.8 mg, 50 μmol) and P(4-MeO−C_6H_4)$_3$ (53 mg, 0.15 mmol) dissolved in toluene (1.0 mL) prepared in a 3 mL vial in a dry box were added **3** (0.26 g, 1.0 mmol), a 1.04 M solution of $AlMe_2Cl$ in hexane (96 μL, 0.10 mmol), and undecane (internal standard, 57 mg, 0.33 mmol) sequentially. The vial was sealed with a screw-cap, taken outside the dry box, and heated at 100 °C for 5 h. The resulting mixture was filtered through a silica gel pad, and then concentrated in vacuo. The residue was purified by MPLC to give **2** (0.21 g, 81%) and **5** (26 mg, 11%).

*3.4.1. Methyl 8-(2-cyanoethyl)-8-ethyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (**2**).* A colorless oil, R_f 0.23 (hexane/ethyl acetate=3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J*=4.0 Hz, 1H), 5.90 (d, *J*=4.0 Hz, 1H), 4.37−4.23 (m, 2H), 3.78 (s, 3H), 2.26−2.17 (m, 2H), 2.06−2.00 (m, 4H), 1.81−1.68 (m, 4H), 0.83 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 140.8, 121.1, 120.0, 117.6, 105.7, 50.9, 45.1, 38.3, 35.7, 33.3, 28.7, 19.8, 12.8, 8.4; HRMS (EI) calcd for $C_{15}H_{20}N_2O_2$: M^+, 260.1525. Found: *m*/*z* 260.1524.

*3.4.2. Methyl 8-ethyl-8-vinyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (**5**).* A colorless oil, R_f 0.46 (hexane/ethyl acetate=10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J*=4.0 Hz, 1H), 5.97 (d, *J*=4.0 Hz, 1H), 5.83 (dd, *J*=17.3, 10.5 Hz, 1H), 5.04 (dd, *J*=10.4, 0.7 Hz, 1H), 4.72 (dd, *J*=17.3, 0.8 Hz, 1H), 4.58 (dt, *J*=13.7, 4.5 Hz, 1H), 4.05−3.94 (m, 1H), 3.78 (s, 3H), 2.13−1.84 (m, 2H), 1.79−1.67 (m, 4H), 0.85 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 145.2, 141.6, 120.5, 117.5, 113.9, 106.5, 50.8, 45.5, 43.1, 33.8, 28.8, 19.5, 8.5; HRMS (EI) calcd for $C_{14}H_{19}NO_2$: M^+, 233.1416. Found: *m*/*z* 233.1415.

3.5. Methyl 8-ethyl-8-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (1)[11f]

A solution of **2** (0.21 g, 0.81 mmol) and KOH (1.2 g, 21.4 mmol) in MeOH (1.8 mL) and water (2.4 mL) was heated at the reflux temperature for 16 h. After being cooled at 0 °C, the resulting solution was acidified with 1 M HCl aq, and the aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated until the volume became about 3 mL. The residue and *N*,*N*′-dicyclohexylcarbodiimide (0.67 g, 3.2 mmol) were sequentially added to a solution of *N*,*N*-dimethyl-4-aminopyridine (15 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (10.8 mL) and anhydrous MeOH (3.6 mL) at rt under an argon atmosphere. After being stirred at rt for 21 h, the resulting solution was diluted with water. The aqueous layer was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by MPLC to give the title compound (0.13 g, 53%) as a colorless oil, R_f 0.21 (hexane/ethyl acetate=5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J*=4.0 Hz, 1H), 5.92 (d, *J*=4.2 Hz, 1H), 4.29 (t, *J*=6.2 Hz, 2H), 3.77 (s, 3H), 3.63 (s, 3H), 2.32−2.10 (m, 2H), 2.05−1.85 (m, 4H), 1.76−1.49 (m, 4H), 0.82 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 161.7, 142.6, 120.5, 117.6, 105.8, 51.6, 50.8, 45.1, 38.0, 34.9, 33.5, 29.6, 29.0, 19.9, 8.5. ^{1}H NMR and ^{13}C NMR spectra of the title compound were identical to those reported in the literature.[11f]

3.6. Methyl 8-ethyl-1-iodo-8-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (6)[11f]

Silver trifluoroacetate (0.50 g, 2.3 mmol) and iodine (0.58 g, 2.3 mmol) were added sequentially to a solution of **1** (0.55 g, 1.9 mmol) in anhydrous $CHCl_3$ (55 mL) at 0 °C. After being stirred at rt for 16 h, the reaction was quenched with satd $Na_2S_2O_5$ aq The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with satd $NaHCO_3$ aq and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by MPLC to give the title compound (0.76 g, 96%) as a colorless oil, R_f 0.11 (hexane/ethyl acetate=10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 4.40 (dt, *J*=13.5, 5.8 Hz, 1H), 4.26 (dt, *J*=13.5, 7.0 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 2.68−2.53 (m, 1H), 2.27−2.00 (m, 3H), 1.98−1.49 (m, 6H), 0.80 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 160.6, 139.9, 126.9, 122.6, 57.8, 51.7, 51.1, 46.1, 39.4, 33.2, 31.4, 29.7, 28.5, 20.3, 8.6. ^{1}H NMR and ^{13}C NMR spectra were identical to those reported in the literature.[11f]

3.7. Methyl 1-{2-[(*tert*-butoxycarbonyl)amino]phenyl-8-ethyl-8-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydroindolizine-3-carboxylate (7)[11f]

$Pd_2(dba)_3$ (3.3 mg, 3.7 μmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 6.0 mg, 14.6 μmol), and *tert*-butyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (93 mg, 0.29 mmol) were placed in a 15 mL−vial. The vial was transferred into a dry box, and K_3PO_4 (0.12 g, 0.58 mmol) and a 0.90 M solution of **6** in THF (163 μL, 0.15 mmol) were added sequentially to the vial. The vial was sealed with a screw-cap, and taken outside the dry box. To the vial were added THF (5.8 mL) and degassed water (1.5 mL). After being stirred at rt for 1 h and then at 40 °C for 40 h, the reaction was quenched with satd NH_4Cl aq. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with satd $NaHCO_3$ aq, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by MPLC to give the title compound (49 mg, 69%) as a 3:2 mixture of rotamers as a brownish oil, R_f 0.18 (hexane/ethyl acetate=5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J*=9.0 Hz, 0.4H), 8.09 (d, *J*=8.2 Hz, 0.6H), 7.30 (t, *J*=7.4 Hz, 1H), 7.12 (d, *J*=7.3 Hz, 1H), 6.96 (t, *J*=7.4 Hz, 1H), 6.81 (s, 0.4H), 6.80 (s, 0.6H), 6.44 (s, 0.4H), 6.31 (s, 0.6H), 4.54−4.40 (m, 1H), 4.38−4.21 (m, 1H), 3.80 (s, 3H), 3.63 (s, 1.8H), 3.56 (s, 1.2H), 2.32−1.22 (m, 19H), 0.82−0.67 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 173.6, 161.5, 161.4, 152.44, 152.37, 139.9, 139.4, 137.2, 131.2, 131.1, 128.53, 128.49, 125.5, 125.3, 121.8, 121.6, 120.8, 120.1, 119.9, 118.2, 117.9, 116.2, 116.0, 80.3, 51.6, 51.0, 45.8, 45.7, 40.1, 35.7, 34.0, 33.6, 33.3, 30.2, 29.9, 29.7, 28.8, 28.30, 28.26, 28.21, 21.0, 20.4, 9.4, 9.1. ^{1}H NMR and ^{13}C NMR spectra were identical to those reported in the literature.[11f]

3.8. Rhazinilam[11f]

$Ba(OH)_2·8H_2O$ (1.5 g, 4.9 mmol) was added to a solution of **7** (94 mg, 0.19 mmol) in MeOH. After being stirred at rt for 2 h, the solution was acidified with 1 M HCl aq The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3.0 mL) and trifluoroacetic acid (6.1 mL), and the mixture was stirred at rt for 1 h before concentration in vacuo to give a brown oil. The crude product was dissolved in anhydrous CH_2Cl_2 (23 mL) and added dropwise over 17 h to a stirred solution of *O*-(7-azabenzotiazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU, 0.22 g, 0.58 mmol) and *N*,*N*′-diisopropylethylamine (0.13 g, 0.97 mmol) in anhydrous DMF (38 mL) and CH_2Cl_2 (15 mL). After being stirred at rt for additional 4 h, the resulting solution was diluted with water. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with 1 M HCl aq, 1 M NaOH aq, brine, and $NaHCO_3$ aq, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was passed through MPLC to give crude **8** (55 mg, ~81%). Crude **8**

Please cite this article in press as: Yamada, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.03.012

dissolved in MeOH (6.0 mL) and 50% NaOH aq (1.8 mL) was heated at 50 °C for 40 min. The solution was acidified with 1 M HCl aq, and the aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was heated at 290 °C for 30 min under 1.5 Torr, and the volatiles were collected. The collected solid was purified by MPLC to give rhazinilam (23 mg, 40%) as a white solid, R_f 0.18 (hexane/ethyl acetate=1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J=7.4, 1.7 Hz, 1H), 7.34 (td, J=7.5, 1.9 Hz, 1H), 7.30 (td, J=7.3, 1.6 Hz, 1H), 7.20 (dd, J=7.3, 1.0 Hz, 1H), 6.67 (br s, 1H), 6.51 (d, J=2.9 Hz, 1H), 5.75 (d, J=2.7 Hz, 1H), 4.01 (dd, J=12.1, 5.2 Hz, 1H), 3.79 (td, J=12.2, 4.8 Hz, 1H), 2.46 (t, J=12.8 Hz, 1H), 2.37 (t, J=12.9 Hz, 1H), 2.30–2.14 (m, 1H), 2.05–1.91 (m, 1H), 1.86 (dt, J=13.7, 2.3 Hz, 1H), 1.72 (td, J=13.4, 3.2 Hz, 1H), 1.58–1.38 (m, 3H), 1.36–1.17 (m, 1H), 0.72 (t, J=7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 140.4, 138.0, 131.4, 130.5, 128.0, 127.2, 126.8, 119.1, 117.3, 109.5, 46.0, 38.8, 36.6, 33.0, 30.1, 28.1, 19.4, 8.1. ^{1}H NMR and ^{13}C NMR spectra were identical to those reported in the literature.[11f]

Acknowledgements

This work has been supported financially by Grant-in-Aid for Scientific Research on Innovative Areas 'Molecular Activation Directed toward Straightforward Synthesis' (no. 22105003) from Ministry of Education, Culture, Sports, Science, and Technology and The Asahi Glass Foundation.

References and notes

1. (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610; (b) Kondo, T.; Mitsudo, T.-a. *Chem. Lett.* **2005**, *34*, 1462; (c) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, 1100; (d) C–C Bond Activation *Dong, G., Ed.. Topics in Current Chemistry*; Springer: Berlin, Germany, 2014; Vol. 346; (e) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613.
2. (a) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874; (b) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10733.
3. (a) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885; (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976; (c) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.
4. (a) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300; (b) Nakao, Y. *Top. Curr. Chem.* **2014**, *346*, 33.
5. Nakao, Y. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 731.
6. Hirata, Y.; Yukawa, T.; Kashihara, N.; Nakao, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 10964.
7. (a) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594; (b) Hsieh, J.-C.; Ebata, S.; Nakao, Y.; Hiyama, T. *Synlett* **2010**, 1709.
8. Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822.
9. Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909.
10. Baoudoin, O.; Guenard, D.; Gueritte, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 333.
11. (a) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179; (b) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321; (c) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647; (d) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900; (e) Bowie, A. L., Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207; (f) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352; (g) Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163; (h) Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224; (i) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288; (j) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168; For synthesis of rhazinal, see: (k) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296; (l) Bowie, A. L., Jr.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581; (m) Sui, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318; For synthesis of rhazinicine, see: Ref. 11j and (n) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.
12. Schmuck, C.; Bickert, V.; Merschky, M.; Geiger, L.; Rupprecht, D.; Dudaczek, J.; Wich, P.; Rehm, T.; Machon, U. *Eur. J. Org. Chem.* **2008**, 324.
13. Attempted decarboxylation under acidic conditions demonstrated by Nelson and co-workers (Ref. 11f) resulted in lower conversion in our hands.
14. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

Please cite this article in press as: Yamada, Y.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.03.012