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Yukihiro Kuge [a], Hideo Nakazawa [a], Toru Kometani [a], Toru Sugaya [a], Kenichi Mochida [a] & Shinji Tomioka [b]

[a] Sakai Research Laboraroties, Kyowa Hakko Kogyo Co. Ltd., 1-1-53, Takasu-cho, Sakai-shi, Osaka, 590, Japan

[b] Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., 3-3-6, Asahi-cho, Machida-shi, Tokyo, 194, Japan

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A FACILE ONE-POT SYNTHESIS OF VINPOCETINE

Yukihiro Kuge,*[a] Hideo Nakazawa,[a] Toru Kometani, [a]
Toru Sugaya, [a] Kenichi Mochida, [b] and Shinji Tomioka [a]

[a]Sakai Research Laboraroties, Kyowa Hakko Kogyo Co. Ltd.,
1-1-53, Takasu-cho, Sakai-shi, Osaka 590, Japan.
[b]Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd.,
3-3-6, Asahi-cho, Machida-shi, Tokyo 194, Japan.

ABSTRACT: A one-pot synthesis of vinpocetine from vincamine was established. Lewis acids caused transesterification and/or dehydration of vincamine in EtOH. $FeCl_3$ catalyzed both transesterification and dehydration while $Ti(OEt)_4$ selectively catalyzed transesterification.

Indole alkaloids play an important role in biological functions. Especially, 14,15-dihydro-14β-hydroxy-(3α,16α)-eburnamenine-14-carboxylic acid methyl ester (vincamine; **1**) from *Vinca Minor* L.[1] has a potent vasodilatory activity.[2-3] Therefore, synthetic[4-11] and pharmacological studies[2-3] have been carried out. Recently, the derivative of **1**, 3α,16α-eburnamenine-14-carboxylic acid ethyl ester (vinpocetine; **4**), has been found to be a potent improver of cerebral blood circulation and has been used clinically.[12-18] In the previous papers, **4** was synthesized from **1** in three steps including hydrolysis, dehydration and esterification.[19-27] We found that Lewis acids catalyzed transesterification and/or dehydration of **1** in ethanol to give ethyl vincaminate (**2**), apovincamine (**3**), or **4**

* To whom correspondence should be addressed

and aimed to achieve a one-pot synthesis of **4** from **1** using these catalysts. These results are summarized in Table I.

$AlCl_3$, $BF_3 \cdot Et_2O$, and $TiCl_4$ catalyzed the dehydration of vincamine (**1**) to afford **3**, while $FeCl_3$ and $SnCl_4$ catalyzed dehydration and transesterification simultaneously. Especially, $FeCl_3$ catalyzed the direct transformation of **1** to **4** in good yield. During the course of the reaction, both **2** and **3** were detected as intermediates concurrently. This means that there are two pathways to **4** from **1** (via **2** and via **3**, Scheme 1). From the standpoint of large-scale synthesis, several problems remained, *i.e.*, the reaction needed a higher temperature than the boiling point of ethanol (the reaction had to be performed in a sealed tube) and needed a long reaction time (more than 13 hours). This is because the reaction rate of the transesterification of **3** to **4** might be slower than that of **1** to **2**, probably due to the stabilization of **3** by conjugation of the ester group with an α,β-unsaturated bond. For these reasons, the first completion of selective transesterification followed by dehydration was considered to be more effective.

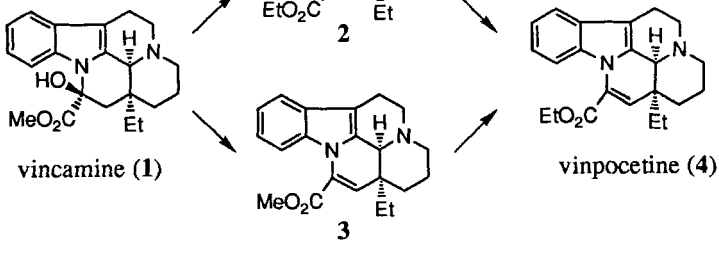
$ZnCl_2$ and $ZnBr_2$ catalyzed the transesterification of **1** in ethanol to afford **2**. Therefore, it was assumed that a one-pot synthesis of vinpocetine by the combination of these Lewis acids and dehydrating agents might be possible. Thus, the combination of $ZnCl_2$ and $AlCl_3$ afforded **4** starting from **1** (see Experimental section). Recently, Seebach reported very effective transesterification of esters catalyzed by $Ti(OR)_4$ in alcohol.[28] This alkoxide also catalyzed the transesterification of **1** in ethanol more effectively than $ZnCl_2$ to afford **2** in almost quantitative yield (Table I), which could be dehydrated without isolation by adding such Lewis acids as $TiCl_4$, $AlCl_3$ and $BF_3 \cdot Et_2O$ to afford **4**. After several attempts with these Lewis acids, a better result was obtained when methanesulfonic acid was added as the dehydrating agent to the transesterified reaction mixture catalyzed by $Ti(OEt)_4$, and the mixture was heated under refluxing to afford **4** in good yield. It was noticeable that methanesulfonic acid did not need azeotropic conditions (only refluxing in ethanol). So this method is quite applicable to the one-pot large-scale synthesis of **1.**

Table I Effects of Lewis acids on the transformation of vincamine in ethanol

Lewis acid	temp. (℃)	time (h)	**2** (%)	**3** (%)	**4** (%)
$ZnCl_2$	130*	20	57	0	0
$ZnCl_2$	80	18	31	0	0
$ZnBr_2$	80	34	48	0	0
$AlCl_3$	80	7	0	95	0
$BF_3 \cdot Et_2O$	80	18	0	85	7
$TiCl_4$	80	20	0	82	8
$SnCl_4$	80	7	22	53	7
$FeCl_3$	80	20	17	2	6
$FeCl_3$	130*	13	2	3	80
$Ti(OEt)_4$	80	10	97	0	0

Vincamine (1 g) was suspended in 10 mL of EtOH and each Lewis acid (1 g) was added and heated. Conversion rate was determined by HPLC.
* ; heated in a sealed tube.

Scheme 1



In summary, a facile and convenient method for the preparation of vinpocetine (**4**) was established. It is now quite possible to synthesize **4** by this method on a multi-kilogram scale.

EXPERIMENTAL

All the reagents including **1** and the solvents are commercially available. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Brucker AC-300 spectrometer, and signals are given in ppm using tetramethylsilane as an internal standard. Optical rotations were measured with a Horiba SEPA-200 polarimeter. Microanalyse were measured with a Yanaco MT-3 CHN corder. Melting points were determined with a Yanagimoto hot-stage microscope and are uncorrected. All the reactions were monitored with HPLC. (column, YMC Pack ODS 4×150mm; mobile phase, 0.01M KH_2PO_4 buffer : MeCN = 2 : 1 (adjusted to pH 3.0 with H_3PO_4); detection, UV 254 nm; flow rate, 1 mL/min; temp., 40 ℃)

Synthesis of vinpocetine (4) by the combination of two Lewis acids:

To a suspension of **1** (500 mg, 1.41 mmol) in EtOH (20 mL), $ZnCl_2$ (250 mg, 3.67 mmol) was added and the mixture was refluxed for 38 hr. The reaction mixture, after the addition of $AlCl_3$ (500 mg, 3.75 mmol), was heated under refluxing again for 8 hr. Then it was cooled and concentrated under reduced pressure to dryness. The residue was dissolved in AcOEt (20 mL) and washed with water at pH 7.0 (adjusted with 6N NaOH), sat. aqueous $NaHCO_3$, and brine. The organic layer was concentrated under reduced pressure to dryness and then recrystallized from EtOH to afford **4** as a white crystalline solid. (425 mg, 85%)

$C_{22}H_{26}N_2O_2$ calcd. C 75.40 H 7.48 N 7.99
(354.43) found 75.31 7.55 8.05

^{1}H NMR ($CDCl_3$, 300MHz) δ(ppm); 7.50 (d, 1H, J = 5.9Hz), 7.28 (d, 1H, J = 4.9Hz), 7.17 (m, 2H), 6.16 (s, 1H), 4.49 (m, 2H), 4.18 (s, 1H), 3.40-1.50 (12H), 1.44 (t, 3H, J = 7.1Hz), 1.03 (t, 3H, J = 7.5Hz). IR (KBr) ν max:

1720, 1630, 1605, 1455, 1080, 748 cm^{-1}. $[\alpha]_D^{20}$ = +130° (c=1, DMF). m.p.: 151°C.

Synthesis of vinpocetine (4) by $FeCl_3$:

A suspension of **1** (500 mg, 1.41 mmol) and $FeCl_3$ (500mg, 3.08mmol) in EtOH (20 mL) was heated at 130 °C in a sealed tube for 20 hr to afford 392 mg of **4** after the same purification method as described above. (yield, 78%)

Synthesis ethyl vincaminate (2):

$Ti(OEt)_4$ (4.82 g, 21.1 mmol) was added to a suspension of **1** (5.0 g, 14.1 mmol) in a mixture of EtOH (50 mL) and ethylene dichloride (50 mL) and refluxed for 8 hr. The mixture was concentrated under reduced pressure to dryness. 1N HCl (35mL) was added to the residue to afford the HCl salt of **2**. This solid, after filtration, was dissolved in a mixture of $CHCl_3$ (40mL) and then washed with sat. aqueous $NaHCO_3$ (40 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated, and recrystallized from ethanol to afford **2** as a white crystalline solid. (4.70 g, 90 %)

$C_{22}H_{28}N_2O_3$ calcd. C 71.71 H 7.66 N 7.60
(368.46) found 71.92 7.88 7.47.

^1H NMR (DMSO-*d6*, 300MHz) δ (ppm): 11.76(br, 1H), 7.54 (d, 1H, *J* = 7.2 Hz), 7.15 (m, 3H), 4.75(s, 1H), 4.23 (m, 2H), 3.70-1.50 (14H), 1.15 (t, 3H, *J* = 7.0 Hz), 0.90 (t, 3H, *J* = 7.2 Hz). IR (KBr) ν max: 1740, 1635, 1462, 1078, 748 cm^{-1}. $[\alpha]_D^{20}$ = +64° (c=1, pyridine). m.p.: 244 °C.

Synthesis of apovincamine (3):

Vincamine (**1**) (7.0g, 19.8mmol) was dissolved in a mixture of EtOH (70 mL) and $AlCl_3$ (3.96 g, 29.7 mmol), and heated under refluxing for 3 hr. The reaction mixture was concentrated and the residue was dissolved in $CHCl_3$ (70 mL), washed with water, sat. aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to dryness. The residue was recrystallized from AcOEt to afford **3** as colorless prisms. (5.2 g, 78%)

$C_{21}H_{24}N_2O_2$ calcd. C 74.95 H 7.19 N 8.32
(336.55) found 75.07 7.17 8.18.
^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 7.50 (d, 1H, J = 7.5Hz), 7.22 (m, 3H), 6.16 (s, 1H), 4.66(s, 1H), 3.98(s, 3H), 2.01-3.90 (10H), 1.66 (t, 2H, J = 15.8 Hz), 1.10 (t, 3H, J = 7.4 Hz). IR (KBr) ν max: 1730, 1638, 1458, 1085, 748 cm^{-1}. m.p.; 188.4 °C.

Synthesis of vinpocetine (4):

Apovincamine (**3**) (5.0 g, 14.9 mmol) was suspended in a mixture of dioxane (40 mL) and EtOH (30 mL) and $Ti(OEt)_4$ (3.6 g, 15.8 mmol) was added. The mixture was heated under refluxing for 40 hr, then concentrated under reduced pressure to dryness. The residue was dissolved in $CHCl_3$ (50 mL), washed with 1N HCl, and dried over anhydrous $MgSO_4$. The organic layer was concentrated under reduced pressure to dryness and recrystallized from EtOH to afford 4.79 g of **4** as a white crystalline solid. (4.79 g, 92 %)

Synthesis of vinpocetine (4) by the combination of $Ti(OEt)_4$ and methanesulfonic acid:

Ethyl vincaminate (**2**) was prepared using $Ti(OEt)_4$ from **1** (8 g, 22.6 mmol) as described above. The reaction mixture was treated with methanesulfonic acid (7.31 mL, 113 mmol) and heated under refluxing for 8 hr. The mixture was then concentrated under reduced pressure, and the residue was dissolved in a mixture of $CHCl_3$ (40 mL) and water (25 mL). The organic layer was washed with water, sat. aqueous $NaHCO_3$ and brine. After drying over anhydrous $MgSO_4$, the organic layer was concentrated under reduced pressure. The residue was recrystallized from EtOH to afford **4** as a white crystalline solid. (5.94 g, 79 %)

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