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Syntheses of Vinca Alkaloids and Related Compounds. 104. A Concise Synthesis of (−)-Vincapusine[1]

István Moldvai,*[,‖] Tamás Gáti,[§] Csaba Szántay Jr.,[§] and Csaba Szántay*[,‖,⊥]

Department of Natural Organic Compounds, Chemical Research Center of the Hungarian Academy of Sciences, Institute of Bimolecular Chemistry, H-1525 Budapest, POB 17, Hungary, Chemical Works of Gedeon Richter Ltd., Spectroscopic Research, H-1475 Budapest, POB 27, Hungary, and Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, H-1521 Budapest, Gellért tér 4, Hungary

imoldvai@chemres.hu; szantay@mail.bme.hu

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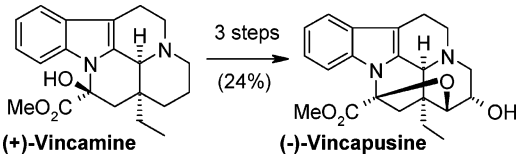

β-Iodo-enamines with an eburnane skeleton (**5a** and **5c**) were obtained with the aid of iodine from compounds **2a** and **2c** and were then transformed into hydroxyl lactams (**6a** and **6c**) with $CuSO_4 \cdot 5H_2O$ in a mixture of DMF and water. Lactams (**6a** and **6c**) were reduced selectively with $BH_3 \cdot SMe_2$ to result in the first synthesis of (−)-vincapusine (**4a**) as well as its natural 14-decarbomethoxy analogue (**4c**).

Introduction

In the eburnamine-vincamine group, there are six hexacyclic alkaloids with a common structural feature: all of them possess a tetrahydrofuranyl ring (Figure 1). The last discovered alkaloid (**1**),[2] isolated from the leaf of *Melodinus henry*, is a member of the eburnamine subgroup with an unusual additional ring (F) that forms, between rings D and E, an ether bridge connecting C15 and C18. The earlier discovered five alkaloids are members of the vincamine (**2a**) subgroup in which the oxygen bridge interconnects carbons C14 and C17. The latter alkaloids can be divided into two branches. Although the enamine-type alkaloids, (−)-criocerine (**3a**)[3,4] and (−)-craspidospermine (**3b**),[5,6] have been prepared by hemisynthesis by several research groups, the synthesis of the β-amino alcohol-type alkaloids, (−)-vincapusine (**4a**),[7] (−)-vincarodine (**4b**),[8] and a minor alkaloid isolated from *Voacanga africana* Stapf. regarded as 14-decarbomethoxy-vincapusine (**4c**),[9] has not yet been achieved synthetically.

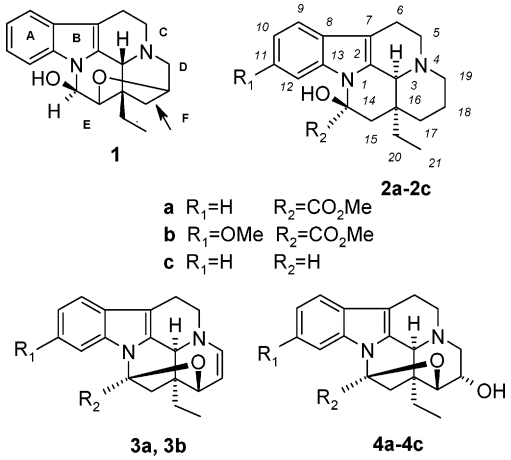

FIGURE 1. Structure of **1**−**4**.

* To whom correspondence should be addressed. Telephone: 00−36−1−438−1100/587. Fax: 00−36−1−325−7554.

‖ Chemical Research Center.

§ Chemical Works of Gedeon Richter Ltd.

⊥ Research Group for Alkaloid Chemistry.

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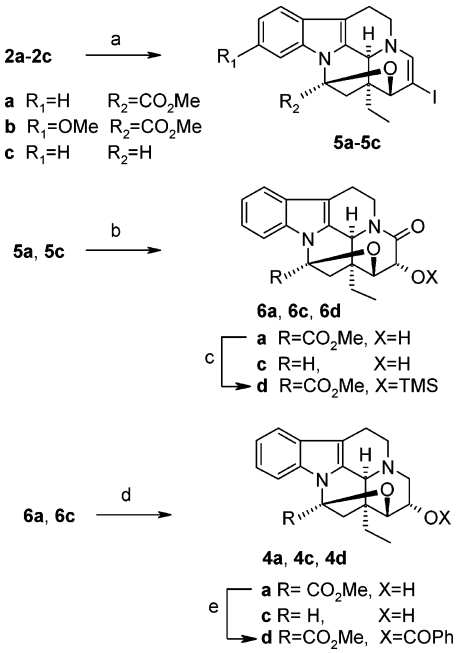
As for the biological effects of the above alkaloids, the literature contains only sparse information. The 18,19-dihydro derivatives of **3a** were found to possess vasodilating, spasmolytic, and antiischemic cardioregulatory activities as mentioned in a patent[10] but without further detailed data. Japanese researchers investigated **4b** to determine its combined effects with either vincristine or daunorubicin.[11] *Vinca pusilla*, native to the upper part of India, is known for its medicinal values;[7] the biological effects of the pure minor component (**4a**), however, are not clear.

As a part of our continued interest in the biological effect of vinca alkaloids, we intended to find a synthetic route to the β-amino alcohol-type alkaloids. The isolation technology resulted in a very small quantity of the pure alkaloids.[12] Lacking the exact information on the characteristic and valuable biological effects of **4a**−**c**, compounds having six rings and five stereogenic carbons, their total synthesis seemed to be a desirable goal.

Results and Discussion

The pathway presented in this publication has been built upon our earlier work.[4d,6d,13] The approach commenced with the preparation of β-iodo-enamines (**5a**−**c**) from **2a**−**c** with the aid of iodine in one step. Iodo-enamines **5a** and **5b** proved to be key compounds leading to alkaloids **3a**[4d] and **3b**[6d] by deiodination. Herein, another useful transformation of iodo-enamines, also leading to the amino alcohol-type alkaloids, will be shown. An iodine → OH exchange was described by Somei's group[14] in the field of indole derivatives; however, the yield of the obtained phenol derivatives was rather low (9−14%). An aromatic iodo compound, obviously, differs from our vinyl iodides **5**, so their procedure proved to be worth trying. In contrast to the above-cited poor yield, we were gratified to find that treatment of **5a** with $CuSO_4 \cdot 5H_2O$ (DMF + water, 100 °C, 2 h) resulted in a crude product. Purification of the product by chromatography on silica provided us with hydroxy compound **6a** as the main product (49%). This new compound is actually the 19-oxo derivative of the target molecule **4a** (Scheme 1). As side products, dimer **7** (21%) and keto-lactam **8** were isolated (5%) (Figure 2). It is worth mentioning that **5a**, without $CuSO_4 \cdot 5H_2O$, gave only dimer **7**; not a trace of **6a** or **8** could be detected. When **3a** was allowed to react by the above reaction conditions ($CuSO_4 \cdot 5H_2O$, DMF, H_2O), **7** was obtained as the sole product.

SCHEME 1. Synthesis of (−)-Vincapusine (4a) and Its Derivatives[a]



[a] Reagents and conditions: (a) I_2, $CHCl_3$, saturated $NaHCO_3$ solution, room temperature, 2−3 h (**5a**, 77%; **5b**, 92%; **5c**, 27%; see: ref 4d, 6d, and 13); (b) $CuSO_4 \cdot 5H_2O$, DMF, H_2O, 100 °C, 2 h (**6a**, 49%; **6c**, 41%); (c) TMSCl, imidazole, CH_2Cl_2, room temperature, 3 h (83%); (d) $BH_3 \cdot SMe_2$, THF, room temperature, 3 h (**4a**, 60%; **4c**, 48%); (e) PhCOCl, Py, room temperature, 4 h, (84%).

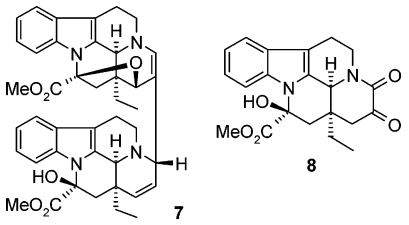


FIGURE 2. Structure of minor components (**7** and **8**).

A possible reaction sequence leading to the different types of products (**6a** and **7**) may be interpreted in the following way. In one line of two parallel reactions, **3a** can be formed from **5a** by deiodination under the mild acidic conditions,[4c] and then in an enamine D iminium equilibrium, the two reaction partners react with one another yielding dimer **7** as we presented earlier[15] in several cases. The route to **6a** seems to be more special and complicated. A plausible reaction sequence for the transformation of **5a** → **6a** has been depicted in Figure 3. Heteroatoms of **5a** (N, O, I) and the double bond may participate in the formation of an intramolecular copper(II)−chelate complex (**i**); however, an intermolecular donor−acceptor bond can be also

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(7) Isolation and structure determination: Mitra, A. K.; Patra, A.; Mukhopadhyay, A. K. *Phytochemistry* **1981**, *20*, 865−866.

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(11) Inaba, M.; Nakashima, K. *Jpn. J. Cancer Res*. **1986**, *77*, 197−204.

(12) For example, see: ref 7. The extracts of the leaves (5 kg) of *V. pusilla* Murr. afforded 15 mg of **4a**; the roots (7 kg) provided 10 mg.

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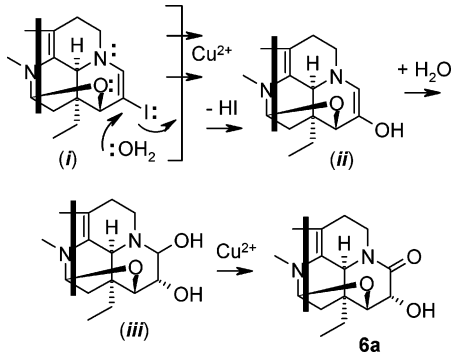

FIGURE 3. Plausible reaction sequence of **5a** → **6a**.

imagined. After a nucleophilic substitution of water at C18, an enol (**ii**) can be formed which is stabilized as a chelate again preventing an enol → ketone transformation. In the following step, a formal addition of water takes place on the double bond forming a diol (**iii**), and as the final step, the C19−OH is oxidized by the Cu(II) forming the lactam part of **6a**.

To achieve the natural product **4a** from **6a** or its O-protected derivative **6d**, prepared by a commonly used silylation procedure (TMSCl, imidazole, CH_2Cl_2, 83%), we needed a selective reduction of the lactam part in the presence of an ester group and an oxygen bridge strained and sensitive to acidic conditions. In the first series of experiments aimed to find a direct reductive method ($LiAlH_4$, $NaBH_4$ + *tert*-BuOH + MeOH, $NaBH_4$ + $BF_3{\cdot}OEt_2$, Me_3OBF_4, DBPy, then $NaBH_4$,[16] etc.), all runs afforded inseparable and unstable mixtures. The indirect method (lactam → thiolactam → *tert*-amine) was also tried without any success (P_4S_{10}, Lawesson's reagent, P_4S_{10} + hexamethyldisiloxane[17]). In the first trials, $BH_3{\cdot}SMe_2$ was neglected as it was known as a powerful reagent; furthermore, thus, a 6 N HCl solution seems to be a drastic workup.[18] Nevertheless, as a final hope, this reagent was also tried, applying, however, mild reaction conditions and workup.[19] To our pleasant surprise, we found that **6a** can be subjected to a selective reduction with $BH_3{\cdot}SMe_2$ providing us with **4a** in a straightforward way in 60% yield as white crystals. Applying this reagent in the third step, we achieved the first synthesis of (−)-vincapusine (**4a**).

The second natural product, (−)-14-decarbomethoxy-vincapusine (**4c**), was prepared on the basis of the above-described steps (**5c** → **6c** → **4c**). The summarized sequence leading to **6c** proved to be similar (41%) to that of **6a**, but in this case, no other side products could be isolated.

The third alkaloid, (−)-vincarodine (**4b**), in all probability should be achieved without any difficulty from **5b**, in the same way.

A few transformations of **4a** were also investigated. The C18−OH group was acylated smoothly with benzoyl chloride affording **4d**, but an expected Mitsunobu reaction (Ph_3P, DIAD, *p*-NO_2PhCO_2H) did not occur; only the starting material was isolated. Experiments toward opening the oxygen bridge (e.g., Et_3SiH, $BF_3{\cdot}OEt_2$)[20] only resulted in intractable tar.

Structure Elucidation. All of the molecular geometries were thoroughly verified by NMR spectroscopy, utilizing standard one- and two-dimensional pulse sequences (e.g., edited gs-HSQC, gs-HMBC, NOESY). Full ^1H and ^{13}C NMR assignments are given in the Experimental Section. All assignments are verified by 2D NMR data, examples of which are supplied as part of the Supporting Information. Although NMR assignments for **7** were published by us earlier,[15c] newly utilized $^1H-^{15}N$ HMBC measurements allowed the elimination of some previous assignment ambiguities and therefore full NMR data are given here for **7** as well. We also give much more detailed ^1H and ^{13}C NMR data for **4a** than that available from the literature.[7] All of these data prove the depicted structures unequivocally, and therefore, only some key aspects are mentioned here.

For **6a**, a three-bond correlation detected between H-17 and C-14 verifies the formation of the tetrahydrofuranyl ring (ring F). The ^{13}C signal at $\delta = 172.5$ ppm suggested that there is another carbonyl group in the molecule besides the methyl ester function. Its position (C-19) follows readily from the H-5/C-19 and H-18/C-19 cross correlations detected in the HMBC spectrum. NOE interactions between H-3 and H-20 as well as between H-3 and H-21 verified the D/E ring connection as being cis. The vicinal coupling between H-17 and H-18 is less than 1 Hz, which indicates that the two hydrogens are nearly orthogonal, thus 18-OH must be in the α position.

In compound **8**, the distinction of the carbonyl groups in the keto-lactam function was based on the long-range correlation of H_2-5/C-19 and H_2-17/C-18, respectively. Again, the NOE-confirmed steric proximity between H-3 and the ethyl group verifies the cis D/E ring connection. The configuration of C-14 follows from the relatively small difference between the diastereotopic H_2-15 ^1H chemical shifts as being diagnostic of the C-14 configuration in vincamine C-14 epimers.[21]

Conclusion

We have developed the first and practical reaction sequence to the *β*-amino alcohol-type subgroup of vinca alkaloids utilizing inexpensive, easy-to-handle, and nontoxic reagents. The starting materials are both easily and synthetically available alkaloids and alkaloid derivatives. The final structure, a tetrahydrofuranyl ring with a characteristic OH group occupying an α-position in ring D, has been built up in a short route applying only three steps in good yields. Our procedure proved to be suitable for a scaled-up preparation of a few hardly examined alkaloids.

Experimental Section

Reaction of 5a with $CuSO_4{\cdot}5H_2O$ in DMF and Water: (−)-19-Oxo-vincapusine (6a), (−)-19′α-(18,19-Dehydro-14α-carbomethoxy-14,17-epoxy-14,15-dihydroeburnamenine-(3α,14*β*,17*β*)-18-yl)-17′,18′-dehydro-14′*β*-hydroxy-14′,15′-dihydroeburnamenine-(3′α, 16′α)-14′α-carboxylic Acid Methyl Ester (7), and (−)-17,18-Dioxo-vincamine (8). To a suspension of **5a** (4.284 g, 9 mmol) in DMF and water (60 + 30 mL) was added copper(II) sulfate pentahydrate (6.75 g, 27 mmol), and the mixture was heated at 100 °C for 2 h while stirring. After being cooled to room temperature, the mixture was poured into a mixture of crushed ice (300 g), water (600 mL), and aqueous concentrated NH_4OH solution (15 mL), then extracted with EtOAc (4 × 500 mL). The

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(19) For examples of a lactam ring reduction with $BH_3{\cdot}SMe_2$ under mild reaction conditions, see: Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J.-R.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2004**, *69*, 130−141.

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(21) Bombardelli, E.; Bonati, A.; Gabetta, B.; Martinelli, E. M.; Mustich, G.; Danielli, B. *Fitoterapia* **1975**, *46*, 51−56.

organic phase was washed with water (2 × 600 mL) and brine (600 mL) and dried, and the solvent was evaporated. The residue (3.96 g) was fractionalized by chromatography (silica, Merck 9385, eluent/hexane + EtOAc 6:4; R_f of **7** > R_f of **8** > R_f of **6a**).

Compound **7**: 653 mg (21%), crystallized from MeOH, 435 mg (14%, white crystals). Physical data of **7** were identical with those reported in ref 15c. Mp: 218−220 °C.^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.97 (t, 3H, J = 7.5 Hz, H-21′), 1.06 (t, 3H, J = 7.5 Hz, H-21), 1.49 (m, 1H, H_x-20), 1.56 (m, 1H, H_x-20′), 1.71 (m, 1H, H_y-20), 1.89 (m, 1H, H_y-20′), 2.20 (m, 1H, H_x-6′), 2.23 (d, 1H, J = 14.3 Hz, H_β-15′), 2.27 (d, 1H, J = 14.3 Hz, H_α-15′), 2.39 (d, 1H, J = 11.9 Hz, H_β-15), 2.65 (m, 1H, H_α-5′), 2.68 (m, 1H, H_y-6′), 2.71 (m, 2H, H-6), 2.77 (d, 1H, J = 11.9 Hz, H_α-15), 2.80 (m, 1H, H_β-5′), 3.22 (m, 1H, H-19), 3.42 (m, 1H, H_α-5), 3.61 (s, 1H, 14′-OH), 3.63 (dd, 1H, J = 14.0, 6.6 Hz, H_β-5), 3.82 (s, 3H, H-23′), 4.01 (m, 1H, H-3′), 4.02 (s, 3H, H-23), 4.06 (m, 1H, H-17), 4.35 (m, 1H, H-3), 4.95 (dd, 1H, J = 10.1, 1.9 Hz, H-18′), 5.38 (dd, 1H, J = 10.1, 1.8 Hz, H-17′), 6.01 (s, 1H, H-19), 6.98 (m, 1H, H-12), 7.01 (m, 1H, H-12′), 7.08 (m, 2H, H-10′ and H-11′), 7.11 (m, 2H, H-10 and H-11), 7.38 (m, 2H, H-9 and H-9′). ^{13}C NMR: δ 172.6 (C-22′), 169.2 (C-22), 137.9 (C-13), 136.3 (C-2), 135.2 (C-19), 134.0 (C-13′), 132.0 (C-2′), 131.4 (C-18′), 131.2 (C-8), 129.1 (C-8′), 126.6 (C-17′), 122.3 (C-11), 121.4 (C-11′), 120.9 (C-10), 120.1 (C-10′), 118.1 (C-9′), 118.0 (C-9), 112.3 (C-18), 111.7 (C-12), 111.6 (C-7), 110.4 (C-12), 106.5 (C-7′), 91.3 (C-14), 82.1 (C-14′), 79.7 (C-17), 58.2 (C-3′), 55.6 (C-19′), 54.9 (C-3), 53.8 (C-23′), 53.1 (C-23), 49.6 (C-5), 46.1 (C-5′), 45.0 (C-15), 44.0 (C-15′), 44.0 (C-16), 36.4 (C-16′), 35.1 (C-20′), 24.8 (C-20), 21.2 (C-6), 16.6 (C-6′), 9.1 (C-21), 8.7 (C-21′).

Compound **8**: 168 mg (5%), crystallized from ether, 69 mg (2%, white crystals). Mp: 240−250 °C (decomp). $[\alpha]_D$ −224° (*c* 0.24, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.02 (t, 3H, J = 7.5 Hz, H-21), 1.62 (m, 1H, H_x-20), 1.94 (m, 1H, H_y-20), 2.26 (d, 1H, J = 14.6 Hz, H_β-15), 2.49 (d, 1H, J = 14.6 Hz, H_α-15), 2.78 (dd, 1H, J = 15.7, 1.3 Hz, H_α-17), 2.84 (ddd, 1H, J = 15.4, 4.6, 1.3 Hz, H_α-6), 3.15 (dd, 1H, J = 15.7, 1.3 Hz, H_β-17), 3.20 (m, 1H, H_β-6), 3.26 (m, 1H, H_α-5), 3.94 (s, 3H, H-23), 4.73 (m, 1H, H-3), 5.05 (dd, 1H, J = 12.5, 6.0 Hz, H_β-5), 7.08 (m, 1H, H-12), 7.20 (m, 2H, H-10, H-11), 7.51 (m, 1H, H-9). ^{13}C NMR: δ 191.3 (C-18), 173.2 (C-22), 157.6 (C-19), 134.8 (C-13), 130.5 (C-2), 128.9 (C-8), 123.1 (C-11), 121.3 (C-10), 119.1 (C-9), 110.5 (C-12), 109.9 (C-7), 81.7 (C-14), 59.9 (C-3), 54.7 (C-23), 43.6 (C-17), 43.4 (C-5), 42.3 (C-15), 36.0 (C-16), 30.9 (C-20), 20.9 (C-6), 7.2 (C-21). IR (KBr, cm^{-1}): 3349, 1748, 1733, 1660, 1455, 1432. MS (EI, *m*/*z*, %): 382 (M^+, 77), 335 (6), 323 (100), 294 (10), 276 (19), 265 (7), 252 (14), 224 (9). HRMS (EI): $C_{21}H_{22}N_2O_5$ *m*/*z* calcd 382.1529, found 382.1526.

Compound **6a**: 1.68 g (49%), recrystallized from MeOH, 1.379 g (40%, white crystals). Mp: 159−160 °C. $[\alpha]_D$ −204.3° (*c* 0.73, $CHCl_3$).^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.02 (t, 3H, J = 7.6 Hz, H-21), 1.75 (m, 1H, H_x-20), 1.91 (m, 1H, H_y-20), 2.62 (ddd, 1H, J = 16.3, 6.6, 1.5 Hz, H_α-6), 2.67 (d, 1H, J = 12.4 Hz, H_β-15), 2.83 (d, 1H, J = 12.4 Hz, H_α-15), 2.95 (m, 1H, H_β-6), 3.31 (m, 1H, H_α-5), 3.39 (dm, 1H, J = 5.5 Hz, H-18), 3.99 (s, 3H, H-23), 4.07 (m, 1H, H-17), 4.49 (dd, 1H, J = 13.4, 7.7 Hz, H_β-5), 4.88 (m, 1H, H-3), 6.04 (d, 1H, J = 5.5 Hz, 18-OH), 6.91 (m, 1H, H-12), 7.11 (m, 2H, H-10, H-11), 7.40 (m, 1H, H-9). ^{13}C NMR: δ 172.5 (C-19), 167.5 (C-22), 139.1 (C-2), 137.2 (C-13), 130.6 (C-8), 122.7 (C-11), 121.2 (C-10), 118.5 (C-9), 112.4 (C-7), 111.5 (C-12), 91.2 (C-14), 87.2 (C-17), 68.7 (C-18), 56.2 (C-3), 53.3 (C-23), 44.3 (C-15), 43.7 (C-5), 42.9 (C-16), 23.8 (C-20), 19.4 (C-6), 8.9 (C-21). IR (KBr, cm^{-1}): 3358, 1739, 1643, 1453, 1443, 1287, 1274. MS (EI, *m*/*z*, %): 382 (M^+, 78), 364 (5), 335 (5), 323 (56), 293 (4), 276 (17), 266 (11), 252 (8), 228 (49), 170 (100). HRMS (EI): $C_{21}H_{22}N_2O_5$ *m*/*z* calcd 382.1529, found 382.1533. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33. Found: C, 65.88; H, 5.73; N, 7.21.

18-Trimethylsilyloxy-19-oxo-vincapusine (6d). Hydroxy-lactam **6a** (1.054 g, 2.75 mmol) was silylated with TMSCl (0.99 g, 5.5 mmol) in the presence of imidazole (0.55 g, 8.6 mmol) in CH_2Cl_2 (50 mL) at room temperature for 2 h. After workup (extraction of 5% NH_4OH solution), **6d** (0.85 g, 83%) was obtained as white crystals by treatment with ether of the crude oil. Mp: 236−242 °C. $[\alpha]_D$ −167° (*c* 1.0, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.10 (s, 9H, 18-OSi$(CH_3)_3$), 1.07 (t, 3H, J = 7.6 Hz, H-21), 1.85 (m, 1H, H_x-20), 2.02 (m, 1H, H_y-20), 2.50 (d, 1H, J = 12.4 Hz, H_β-15), 2.58 (m, 1H, H_α-6), 2.86 (d, 1H, J = 12.4 Hz, H_α-15), 3.07 (m, 1H, H_α-5), 3.18 (m, 1H, H_β-6), 3.81 (m, 1H, H-18), 4.08 (s, 3H, H-23), 4.17 (m, 1H, H-17), 4.54 (m, 1H, H-3), 4.72 (dd, 1H, J = 12.5, 6.8 Hz, H_β-5), 6.97 (m, 1H, H-12), 7.14 (m, 2H, H-10 and H-11), 7.38 (m, 1H, H-9). ^{13}C NMR: δ 171.8 (C-19), 168.3 (C-22), 138.1 (C-2), 137.8 (C-13), 131.2 (C-8), 123.1 (C-11), 121.6 (C-10), 118.7 (C-9), 113.9 (C-7), 111.6 (C-12), 91.5 (C-14), 88.1 (C-17), 69.7 (C-18), 57.4 (C-3, 53.3 (C-23)), 45.4 (C-15), 44.6 (C-5), 43.4 (C-16), 24.5 (C-20), 19.8 (C-6), 9.0 (C-21), 0.0 (C−Si$(CH_3)_3$). IR (KBr, cm^{-1}): 1769, 1676, 1455, 1417, 1284, 1253, 1086. MS (EI, *m*/*z*, %): 454 (M^+, 78), 439 (35), 395 (14), 300 (100). HRMS (EI): $C_{24}H_{30}N_2O_5Si$ *m*/*z* calcd 454.1924, found 454.1926. Anal. Calcd for $C_{24}H_{30}N_2O_5Si$: C, 63.41; H, 6.65; N, 6.16. Found: C, 63.05; H, 6.34; N, 5.93.

(−)-19-Oxo-14-decarbomethoxy-vincapusine (6c). To a suspension of **5c** (1.68 g, 4 mmol) in DMF and water (28 + 12 mL) was added copper(II) sulfate pentahydrate (3.0 g, 12.1 mmol), and the mixture was heated at 100 °C for 45 min while stirring. After being cooled to room temperature, the mixture was poured into a mixture of cold water (350 mL) and aqueous concentrated NH_4OH solution (4 mL), then extracted with EtOAc (3 × 200 mL). The organic phase was washed with water (5 × 100 mL) and dried, and the solvent was evaporated. The residue (1.26 g) was purified by chromatography (silica, Merck 9385, eluent/hexane + EtOAc 1:1) to yield **5c** (503 mg, 41%) as pure pale oil. After treatment of the oil with ether, white crystals (342 mg, 26%) were obtained. Mp: 106−117 °C (crystal solvent/EtOAc). $[\alpha]_D$ −320° (*c* 0.25, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11 (t, 3H, J = 7.5 Hz, H-21), 1.75 (m, 1H, H_x-20), 1.97 (m, 1H, H_y-20), 2.43 (dd, 1H, J = 11.8, 4.6 Hz, H_β-15), 2.48 (d, 1H, J = 11.8 Hz, H_α-15), 2.71 (ddd, 1H, J = 16.1, 6.4, 2.0 Hz, H_α-6), 3.13 (m, 1H, H_β-6), 3.32 (m, 1H, H_α-5), 3.36 (brs, 1H, 18-OH), 3.45 (d, 1H, J = 1.3 Hz, H-18), 4.04 (m, 1H, H-17), 4.67 (m, 1H, H-3), 4.81 (dd, 1H, J = 13.3, 7.4 Hz, H_β-5), 6.10 (d, 1H, J = 4.6 Hz, H-14), 7.14 (m, 1H, H-10), 7.23 (m, 1H, H-11), 7.38 (m, 1H, H-12), 7.40 (m, 1H, H-9). ^{13}C NMR: δ 174.6 (C-19), 137.9 (C-13), 136.5 (C-2), 130.1 (C-8), 122.7 (C-11), 121.2 (C-10), 118.7 (C-9), 111.7 (C-7), 110.7 (C-12), 84.7 (C-17), 83.1 (C-14), 72.2 (C-18), 56.7 (C-3), 45.6 (C-5), 43.6 (C-16), 40.5 (C-15), 25.2 (C-20), 20.9 (C-6), 9.4 (C-21). IR (KBr, cm^{-1}): 3317, 1736 (EtOAc), 1638, 1456, 1431, 1239, 1047, 1022. MS (EI, *m*/*z*, %): 324 (M^+, 69), 228 (46), 208 (43), 171 (100). HRMS (EI): $C_{19}H_{20}N_2O_3$ *m*/*z* calcd 324.1474, found 324.1484.

(−)-Vincapusine (4a). To a cold solution (ice-bath) of **6a** (1.911 g, 5.0 mmol) in THF (100 mL) was added borane−dimethyl sulfide complex solution (2.8 mL, 2.0 M/L in THF; 5.6 mmol), and the mixture was stirred for 2 h while the temperature was allowed to warm to room temperature. The reaction mixture was decomposed with aqueous saturated $NaHCO_3$ solution (65 mL), and then the organic solvent was evaporated at reduced pressure. The precipitated white crude crystals were filtered off, washed with cold water (3 × 20 mL), and dried. The crude product (1.389 g) was purified by chromatography (eluent/$CHCl_3$ + 0.5% MeOH) to yield **4a** as pure white crystals (1.104 g, 60%), in close agreement with the reported data.[7] Mp: 265−267 °C (from ether). (Lit. mp: 263 °C). $[\alpha]_D$ −166° (*c* 0.26, $CHCl_3$). $[\alpha]_D$ −155° (*c* 0.25, MeOH). (Lit.: −122°, *c* 0.004, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.07 (t, 3H, J = 7.6 Hz), 1.79 (m, 1H, H_x-20), 2.12 (m, 2H, H_x-19 and H_y-20), 2.31 (dd, 1H, J = 12.9, 2.0 Hz, H_y-19), 2.39 (d, 1H, J = 7.2 Hz, 18-OH), 2.42 (d, 1H, J = 12.0 Hz, H_β-15), 2.67 (ddd, 1H, J = 16.6, 7.9, 1.8, H_α-6), 2.77 (d, 1H, J = 12.0 Hz, H_α-15), 2.90 (m, 1H, H_β-6), 3.16 (dd, 1H, J = 14.1, 8.0 Hz, H_β-5), 3.34 (ddd, 1H, J =

14.1, 10.1, 8.0 Hz, H_α-5), 3.75 (m, 1H, H-18), 3.96 (d, 1H, J = 2.9 Hz, H-17), 4.07 (s, 3H, H-23), 4.17 (brs, 1H, H-3), 6.97 (m, 1H, H-12), 7.14 (m, 2H, H-10 and H-11), 7.45 (m, 1H, H-9). ^{13}C NMR: δ 168.7 (C-22), 137.1 (C-13), 134.5 (C-2), 130.5 (C-8), 122.6 (C-11), 121.0 (C-10), 118.5 (C-9), 111.2 (C-12), 111.0 (C-7), 90.6 (C-14), 82.2 (C-17), 66.6 (C-18), 56.7 (C-3), 53.4 (C-23), 50.4 (C-5), 46.5 (C-19), 45.9 (C-15), 44.2 (C-16), 26.1 (C-20), 18.7 (C-6), 9.5 (C-21). IR (KBr, cm^{-1}): 3250, 1757, 1456, 1313, 1285, 1264, 1196, 1053. MS (EI, *m*/*z*, %): 368 (M^+, 57), 309 (7), 266 (100), 252 (9), 238 (15), 208 (18), 170 (31). HRMS (EI): $C_{21}H_{24}N_2O_4$ *m*/*z* calcd 368.1731, found 368.1731. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.52; H, 5.49; N, 7.52.

(−)-14-Decarbomethoxy-vincapusine (4c). To a cold solution (ice-bath) of **6a** (181 mg, 0.55 mmol) in THF (20 mL) was added borane−dimethyl sulfide complex solution (0.3 mL, 2.0 M/L in THF; 0.6 mmol), and the mixture was stirred for 2 h while the temperature was allowed to warm to room temperature. The reaction mixture was decomposed with aqueous saturated $NaHCO_3$ solution (5 mL), and then the organic solvent was evaporated at reduced pressure. The precipitated white crude crystals were filtered off, washed with cold water (3 × 5 mL), and dried. The crude product (136 mg) was purified by chromatography (eluent/CH_3Cl + 0.5% MeOH) to yield a pure clear oil (54 mg, 49%), which crystallized from ether to yield **4c** (32 mg, 29%), in close agreement with the reported data.[9] Mp: 238−242 °C. (Lit. mp: 241−243 °C). $[\alpha]_D$ −200° (*c* 0.36, $CHCl_3$). (Lit.: −250°, *c* 0.1, $CHCl_3$).^{1}H NMR: δ 1.11 (t, 3H, J = 7.5 Hz, H-21), 1.83 (m, 1H, H_x-20), 2.20 (m, 2H, H_y-20 and H_x-19), 2.37 (dd, 1H, J = 12.0, 5.3 Hz, H_β-15), 2.41 (m, 1H, H_y-19), 2.45 (d, 1H, J = 12.0 Hz, H_α-15), 2.75 (ddm, 1H, J = 16.4, 7.6 Hz, H_α-6), 2.94 (m, 1H, H_β-6), 3.25 (m, 1H, H_β-5), 3.40 (m, 1H, H_α-5), 3.70 (m, 1H, H-18), 3.75 (m, 1H, H-17), 4.27 (m, 1H, H-3), 6.01 (d, 1H, J = 5.2 Hz, H-14), 7.14 (m, 1H, H-10), 7.21 (m, 1H, H-11), 7.39 (dm, 1H, J = 8.1 Hz, H-12), 7.47 (dm, 1H, J = 7.9 Hz, H-9). ^{13}C NMR: δ 137.9 (C-13), 133.5 (C-2), 129.7 (C-8), 122.4 (C-11), 120.8 (C-10), 118.6 (C-9), 110.3 (C-12), 109.9 (C-7), 81.8 (C-14), 80.3 (C-17), 66.9 (C-18), 56.9 (C-3), 50.7 (C-5), 46.4 (C-19), 44.0 (C-15), 40.6 (C-15), 26.5 (C-20), 18.8 (C-6), 9.6 (C-21). IR (KBr, cm^{-1}): 3056, 2985, 2927, 2888, 2845, 1455, 1428, 1336, 1045. MS (EI, *m*/*z*, %): 310 (M^+, 38), 251 (7), 208 (100), 193 (4), 180 (12), 170 (6). HRMS (EI): $C_{19}H_{22}N_2O_2$ *m*/*z* calcd 310.1681, found 310.1675.

18-Benzoyloxy-vincapusine (4d). (−)-Vincapusine **4c** (147 mg, 0.4 mmol) was acylated with benzoyl chloride (0.06 mL, 0.5 mmol) in dry pyridine (4 mL) at room temperature for 4 h. After a workup, the crude product was purified by chromatography (eluent/hexane + EtOAc, 6:4) to yield **4d** (158 mg, 84%). Mp: 198−223 °C (decomp.). $[\alpha]_D$ −130° (*c* 0.75, $CHCl_3$).^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.10 (t, 3H, J = 7.6 Hz, H-21), 1.91 (m, 1H, H_x-20), 2.34 (m, 2H, H_y-20 and H_x-19), 2.47 (d, 1H, J = 12.2 Hz, H_β-15), 2.59 (dm, 1H, J = 13.1 Hz, H_y-19), 2.65 (ddd, 1H, J = 16.6, 7.5, 1.5, H_α-6), 2.86 (d, 1H, J = 12.2 Hz, H_α-15), 2.91 (m, 1H, H_β-6), 3.20 (dd, 1H, J = 14.1, 7.6 Hz, H_β-5), 3.34 (ddd, 1H, J = 14.1, 10.7, 7.5 Hz, H_α-6), 4.04 (d, 1H, J = 2.5 Hz, H-17), 4.08 (s, 3H, H-23), 4.28 (brs, 1H, H-3), 5.14 (m, 1H, H-18), 7.01 (m, 1H, H-12), 7.14 (m, 2H, H-10 and H-11), 7.45 (m, 3H, H-9 and H-27, H-27′), 7.57 (m, 1H, H-28), 8.04 (m, 2H, H-26, H-26′). ^{13}C NMR: δ 168.5 (C-22), 165.2 (C-24), 137.4 (C-13), 134.1 (C-2), 133.0 (C-28), 130.7 (C-8), 129.9 (C-25), 129.7 (C-26), 128.3 (C-27), 122.7 (C-11), 121.2 (C-10), 118.6 (C-9), 111.4 (C-7), 111.3 (C-12), 91.1 (C-14), 80.3 (C-17), 68.5 (C-18), 56.2 (C-3), 53.3 (C-23), 50.2 (C-5), 45.6 (C-15), 44.6 (C-16), 43.7 (C-19), 24.9 (C-20), 18.2 (C-6), 9.3 (C-21). IR (KBr, cm^{-1}): 2949, 2892, 2845, 1769, 1745, 1716, 1452, 1267. MS (EI, *m*/*z*, %): 472 (M^+, 100), 350 (7), 291 (13), 266 (76), 252 (19), 238 (29), 208 (36), 170 (92). HRMS (EI): $C_{28}H_{28}N_2O_5$ *m*/*z* calcd 472.1998, found 472.2001.

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Supporting Information Available: ^{1}H, ^{13}C, and 2D NMR spectra for **6a**, **6d**, **7**, **8**, **4a**, **4d**, **6c**, and **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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