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Stereoselective total synthesis of (±)-7-deoxy-*trans*-dihydronarciclasine, a potent antineoplastic phenanthridone alkaloid

Gábor Szántó [a], László Hegedűs [b], Lenke Mattyasovszky [a], András Simon [c], Ákos Simon [c], István Kádas [a,*]

[a] Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8, H-1111 Budapest, Hungary
[b] Research Group for Organic Chemical Technology, Hungarian Academy of Sciences, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8, H-1111 Budapest, Hungary
[c] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Szt. Gellért tér 4, H-1111 Budapest, Hungary

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ABSTRACT

A short and efficient stereoselective total synthesis of (±)-7-deoxy-*trans*-dihydronarciclasine, a highly potent antineoplastic agent and constituent of the *Amaryllidaceae* alkaloids, is described. Starting from a known arylcyclohexylamine-type precursor **6**, the C-ring with the required stereochemistry is constructed using a chemo- and stereoselective enone reduction ($NaBH_4/CaCl_2$ system) and a Mitsunobu reaction. For the B-ring closure, the Banwell modification of the Bischler–Napieralski reaction was applied.

Amongst the family of *Amaryllidaceae* alkaloids, the highly potent cytostatic alkaloids possessing the phenanthridone skeleton and non-basic character form a small sub-group.[1] This alkaloid family has been reviewed extensively.[2–4] After isolation of the first derivatives, narciclasine (**1**)[5] and lycoricidine (**2**),[6] the most active[7,8] representative, pancratistatin (**3**), was isolated from the bulbs of *Hymenocallis littoralis* by Pettit and co-workers[9] in 1984. Due to its very strong anti-cancer activity,[7–12] a large number of total syntheses of pancratistatin have been reported.[13–24] Although the cytotoxic activity of two further alkaloids [*trans*-dihydronarciclasine (**4**)[9] and 7-deoxy-*trans*-dihydronarciclasine (**5**),[25] also isolated by Pettit and co-workers (Fig. 1)], is commensurate with that of pancratistatin, there are only a few total syntheses of these alkaloids, **4**[26] and **5**.[27–29] Surprisingly, the first total synthesis of compound **5** was realized before[27] its first isolation.[25] This synthesis,[27] and the two subsequent preparations[28,29] are lengthy, complicated and resulted in low overall yields. Thus, an efficient and short synthesis of alkaloid **5** is required to enable a thorough biological evaluation.

Herein, we report a new synthetic route to **5** (Scheme 1) which is significantly shorter and simpler than previous syntheses, even if the preparation of **6** is taken into account.

The first step involved the selective conversion of the known ketal **6**[30] to urethane **7** using a two-phase (THF/H_2O) reaction with methyl chloroformate, while keeping the hydroxy group intact. During the deketalization of **7** using stoichiometric *p*-TsOH, the elimination of water also takes place giving enone **8**. To convert enone **8** to allylic alcohol **9**, Utimoto's reduction method[31] ($NaBH_4$, in the presence of $CaCl_2$) was applied. This method gave allylic alcohol **9** stereoselectively in a good yield (82%).[32] Calcium chloride forms a chelate during the reduction ensuring the quasi cis–equatorial position of the new hydroxy group.[33,34] Since the orientation of the hydroxy group in the target molecule is quasi trans–axial, inversion of the hydroxy group in **9** is necessary. For this purpose the Mitsunobu reaction seemed to be the best method.[35] Thus, reaction of **9** under Mitsunobu conditions afforded the benzoate **10**, in good yield (73%), after column chromatography. The *cis*-dihydroxylation of **10** with OsO_4/NMO took place smoothly in THF/water, and the major product proved to be the required diol **11**. Protection of the hydroxy groups was carried out with acetyl chloride to afford compound **12**, quantitatively.

To form the B-ring the Banwell modification[36] of the Bischler–Napieralski reaction was applied. The cyclization proceeds via a lactim ether intermediate and hence the reaction mixture contains a proportion of lactim ether after the cyclization. This was converted to the corresponding lactam under acidic conditions, however, a reacetylation step with acetyl chloride was necessary due to partial hydrolysis of the acetoxy groups under the conditions used. Thus, phenanthridone **13** was obtained in a satisfactory yield (56%). Finally, the protecting groups were removed with 1% methanolic sodium hydroxide solution to form the title compound **5**.[37]

Compound **6** was first described by Weller and Seebach.[30] They synthesized it from the appropriate nitrostyrene under harsh

* Corresponding author. Tel.: +36 1 463 3695; fax: +36 1 463 3648.
E-mail address: ikadas@mail.bme.hu (I. Kádas).

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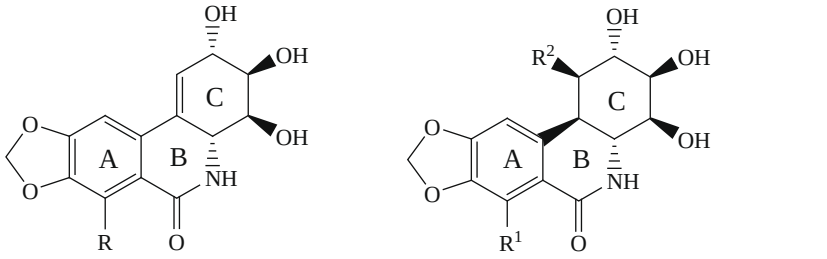


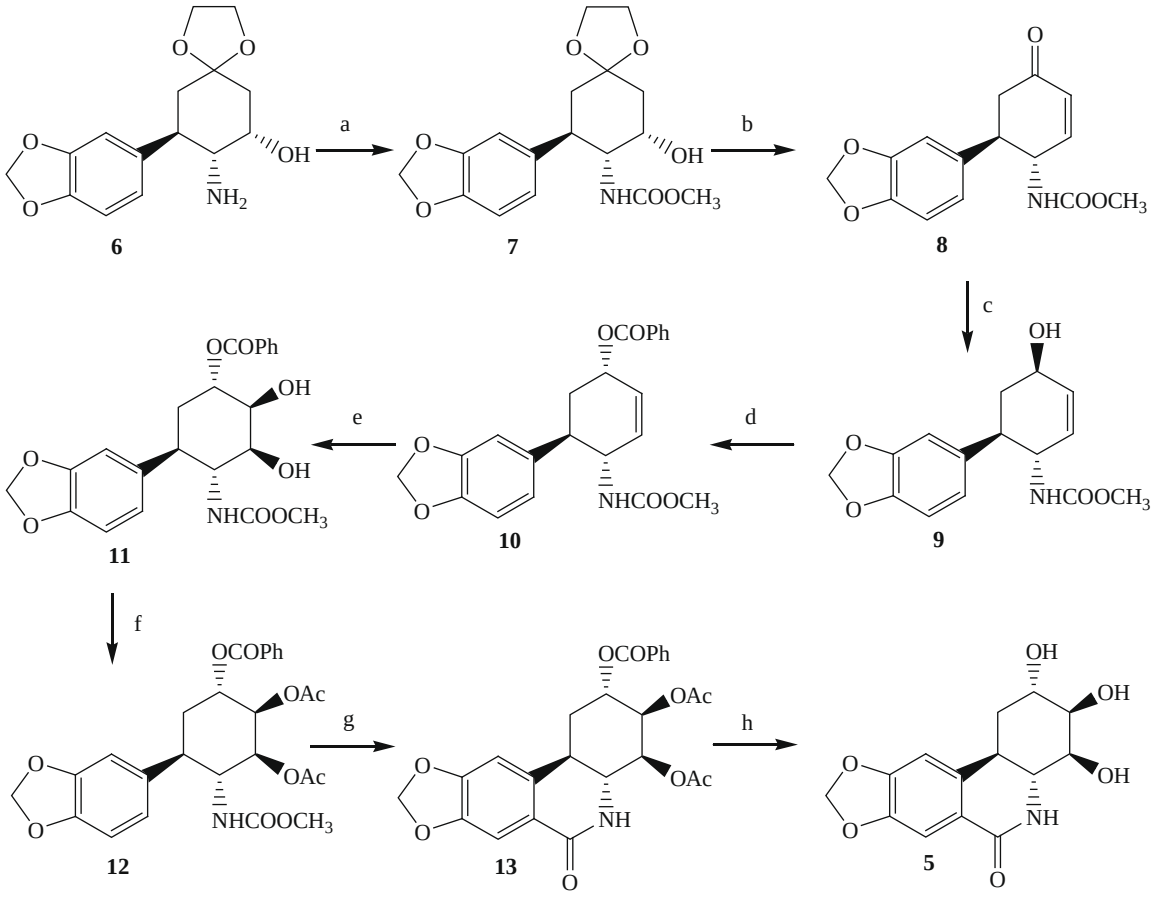
R = OH: narciclasine **1**
R = H : lycoricidine **2**

R^1 = OH; R^2 = OH: pancratistatin **3**
R^1= OH; R^2 = H: *trans*-dihydronarciclasine **4**
R^1 = H; R^2 = H: 7-deoxy-*trans*-dihydronarciclasine **5**

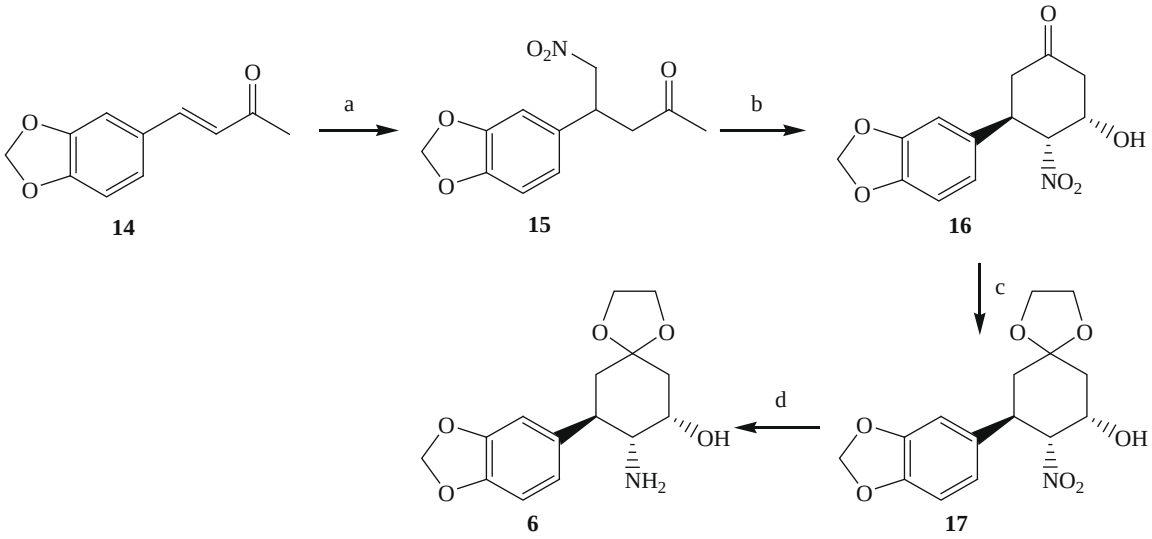
Figure 1. The structures of the most active representatives of the phenanthridone alkaloids.

conditions followed by two further steps, but yields were only partly reported.[30,38] According to our new and more practical method, amine **6** was obtained as follows (Scheme 2): after conjugate addition of nitromethane to 3,4-methylenedioxybenzylidene acetone (**14**), the nitro-ketone **15** was cyclized with ethyl formate via a Claisen aldol reaction.[39] Next, the oxo group of the cyclized product **16** was protected with ethylene glycol to afford ketal **17**. Finally, the nitro group was reduced catalytically to the amine **6** using 10% Pd/C catalyst, at 12 bar and 60 °C. The overall yield of **6** prepared from **14** was 39%.

In conclusion, (±)-7-deoxy-*trans*-dihydronarciclasine, a potent antineoplastic phenanthridone alkaloid, was synthesized efficiently in 24% overall yield using a newly developed method.



Scheme 1. Reagents and conditions: (a) $ClCOOCH_3$, THF/H_2O (70:30), NaOH, rt (87%); (b) TsOH, rt (88%); (c) $NaBH_4/CaCl_2$ (1:1), MeOH, 0 °C (82%); (d) DEAD, PPh_3, PhCOOH, THF, 0 °C→rt (73%); (e) OsO_4/NMO, THF/H_2O (85:15), rt (95%); (f) AcCl, rt (quant.); (g) (i) Tf_2O, DMAP, CH_2Cl_2, 0 °C→rt, (ii) H^+/H_2O, rt, (iii) AcCl, rt (56%); (h) 1% NaOH/MeOH, rt (quant).



Scheme 2. Preparation of the starting material **6**. Reagents and conditions: (a) $MeNO_2$, NaOMe/MeOH, reflux (53%); (b) HCOOEt, NaOMe/Et_2O, rt (85%); (c) oxalic acid, MeCN, ethylene glycol, rt (89%); (d) 10% Pd/C, MeOH, 12 bar, 60 °C, 7 h (92%).

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References and notes

1. Hoshino, O.. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: San Diego, 1998; Vol. 21, pp 181–236.
2. Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365.
3. Manpadi, M.; Kornienko, A. *Org. Prep. Proced. Int.* **2008**, *40*, 109.
4. Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982.
5. Ceriotti, G. *Nature* **1967**, *211*, 595.
6. Okamoto, T.; Torii, Y.; Isogai, Y. *Chem. Pharm. Bull.* **1968**, *16*, 1860.
7. Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Singh, S. B.; Gragg, G. M.; Schimdt, J. M.; Boettner, J. M.; William, F. E.; Sagawa, Y. *J. Nat. Prod.* **1986**, *49*, 995.
8. Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 1088.
9. Pettit, G. R.; Gaddamidi, V.; Herald, D. L.; Cragg, G. M.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.
10. Pettit, G. R.; Cragg, G. M.; Singh, S. B.; Duke, J. A.; Doubek, D. L. *J. Nat. Prod.* **1990**, *53*, 176.
11. Pettit, G. R.; Meng, Y.; Herald, D. L.; Knight, J. C.; Day, J. F. *J. Nat. Prod.* **2005**, *68*, 1256.
12. Pettit, G. R.; Eastham, S. A.; Melody, N.; Orr, B.; Herald, D. L.; McGregor, J.; Knight, J. C.; Doubek, D. L.; Pettit, G. R., III; Garner, L. C.; Bell, J. A. *J. Nat. Prod.* **2006**, *69*, 7.
13. Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.
14. Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 2643.
15. Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.
16. Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
17. Doyle, T. J.; Hendrix, M.; VanDerveer, D.; Javanmard, S.; Haseltine, J. *Tetrahedron* **1997**, *53*, 11153.
18. Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341.
19. Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509.
20. Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624.
21. Pettit, G. R.; Melody, N.; Herald, D. L. *J. Org. Chem.* **2001**, *66*, 2583.
22. Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *44*, 1343.
23. Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112.
24. Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707.
25. Pettit, G. R.; Pettit, G. R., III; Backhaus, R. A.; Boyd, M. R.; Meerow, A. W. *J. Nat. Prod.* **1993**, *56*, 1682.
26. Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303.
27. Isobe, K.; Taga, J.-I.; Tsuda, Y. *Heterocycles* **1978**, *9*, 625.
28. Chida, N.; Jitsuoka, M.; Yamamoto, Y.; Ohtsuka, M.; Ogawa, S. *Heterocycles* **1996**, *43*, 1385.
29. Fujimura, T.; Shibuya, M.; Ogasawara, K.; Iwabuchi, Y. *Heterocycles* **2005**, *66*, 167.
30. Weller, T.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 935.
31. Fujii, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1991**, 1847.
32. *Compound* **9**: mp: 142–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (td, J = 12.5, 10.0 Hz, 1H), 2.22–2.26 (m, 1H), 2.63 (t, J = 8.0 Hz, 1H), 3.54 (s, 3H), 4.31 (br s, 1H), 4.43–4.46 (m, 1H), 4.59 (br s, 1H), 5.75 (d, J = 10.0 Hz, 1H), 5.83 (dq, J = 10.0, 1.0 Hz, 1H), 5.94 (s, 2H), 6.66 (d, J = 9.3 Hz, 1H), 6.72–6.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.9, 46.5, 52.3, 67.9, 101.2, 107.7, 108.5, 120.8, 131.3, 132.8, 135.9, 146.7, 148.1. HRMS calcd for $C_{15}H_{17}NO_5$: 291.1107. Found: 291.1111.
33. Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1995**, *51*, 679.
34. Bream, R. N.; Ley, S. V.; McDermott, B.; Procopiou, P. A. *J. Chem. Soc., Perkin Trans. 1* **2003**, 2237.
35. Shull, B. K.; Sakai, T.; Nichols, J. B.; Koreeda, M. *J. Org. Chem.* **1997**, *62*, 8294.
36. Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551.
37. *Compound* **5**: mp: 296-299 °C, lit. mp.: 303–304 °C;[25] ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.65 (t, J = 13.5 Hz, 1H), 2.14 (dt, J = 13.5, 1.1 Hz, 1H), 2.89 (td, J = 13.2, 2.7 Hz, 1H), 3.68–3.80 (m, 2H), 3.89 (s, 1H), 4.80 (d, J = 2.4 Hz, 1H), 4.93 (d, J = 5.7 Hz, 1H), 4.99 (d, J = 2.8 Hz, 1H), 6.07 (s, 2H), 6.93 (s, 1H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.3, 34.3, 55.1, 68.6, 69.7, 71.7, 101.55, 104.3, 106.9, 123.3, 138.0, 145.9, 150.9, 164.3. HRMS calcd for $C_{14}H_{15}NO_6$: 293.0899. Found: 293.0896.
38. Ehrig, V.; Seebach, D. *Chem. Ber.* **1975**, *108*, 1961.
39. The overall yield of compound **16** from **14** was 1.3%: Walker, G. N. *J. Org. Chem.* **1965**, *30*, 1416.