Pergamon

Tetrahedron 58 (2002) 8921–8927

TETRAHEDRON

Synthesis of vinca alkaloids and related compounds. Part 101: A new convergent synthetic pathway to build up the aspidospermane skeleton. Simple synthesis of 3-oxovincadifformine and 3-oxominovincine. Attempts to produce 15β-hydroxyvincadifformine☆

János Éles,[a,b] György Kalaus,[a,*] István Greiner,[b] Mária Kajtár-Peredy,[c] Pál Szabó,[c] Lajos Szabó[a] and Csaba Szántay[a,c,*]

[a]*Department for Organic Chemistry, Budapest University of Technology and Economics, Gellért tér 4, H-1111 Budapest, Hungary*
[b]*Chemical Works of Gedeon Richter Ltd, Gyömrői út 19-21, H-1103 Budapest, Hungary*
[c]*Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences, Pusztaszeri út 59-67, H-1025 Budapest, Hungary*

Received 9 July 2002; revised 28 August 2002; accepted 19 September 2002

Abstract—A molecule with an indole skeleton, containing a latent acrylic ester function—acting as a diene—was produced from N_b-trityl-2-(hydroxy-methyl)-tryptamine and reacted with esters containing an aldehyde or aldehyde-equivalent structural unit, yielding 3-oxo-16,17-dihydro-Δ^{20}-secodin-17-ol type intermediates from which dehydration, followed by [4+2]cycloaddition, furnished 3-oxovincadifformine and 3-oxominovincine. We also wished to apply the method to produce 15β-hydroxyvincadifformine, however, the appearance of a dimeric product with indole skeleton was observed instead of the expected cycloaddition.

1. Introduction

Earlier, Kuhne et al. developed a simple entry[2] into alkaloids and related compounds with the aspidospermane skeleton. Their synthetic strategy was based on the reaction of appropriately formed aldehyde and indolazepine ester. In this reaction, reactive and occasionally easily dimerizing[3] secodine-type intermediates are generated, from which the aspidospermane skeleton can be easily formed. In our former publications[4–8] we also reported on an effective convergent synthetic pathway in which a reaction of appropriately arranged aldehyde or aldehyde-equivalent and N_b-benzyl-tryptamine derivative results in molecules with the D-*seco*-aspidospermane skeleton. Ring D was obtained by intramolecular acylation or alkylation. By means of this method, numerous alkaloids and alkaloid-like molecules with the aspidospermane and ψ-aspidospermane skeleton, such as 3-oxovincadifformine (**4**), vincadifformine (**6**), 3-oxominovincine (**5**) and minovincine (**7**), were successfully produced (Fig. 1). We note here that the subsequent formation of ring D caused problems in particular cases.[9] This work aims at developing a simple synthetic strategy in the biomimetic way to build up the aspidospermane skeleton through stable 3-oxo-16,17-dihydro-Δ^{20}-secodin-17-ol derivatives. In our publication,

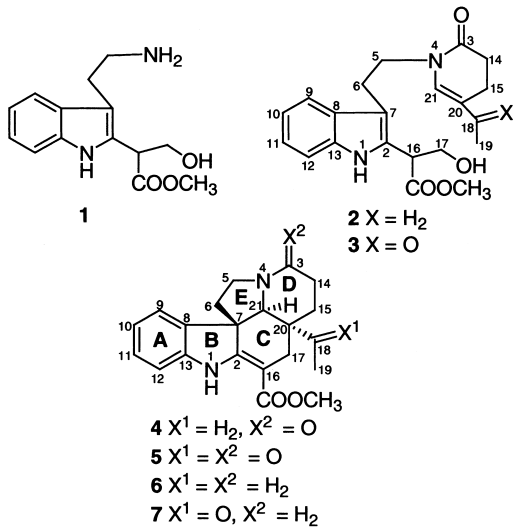


Figure 1.

☆ For Part 100, see Ref. 1.

Keywords: indoles; tryptamines; 3-oxovincadifformine; 3-oxominovincine; aspidospermane; alkaloids.

* Corresponding authors. Address: Department for Organic Chemistry, Budapest University of Technology and Economics, Gellért tér 4, H-1111 Budapest, Hungary. Fax: +361-4633297; e-mail: szantay@mail.bme.hu

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01179-1

we describe the formation of the key intermediate **1** as well as the synthesis of the alkaloid molecule **5** and alkaloid-like molecule **4** obtained from **1**. We also describe our attempts to produce 15β-hydroxyvincadifformine (**16**).

2. Results and discussion

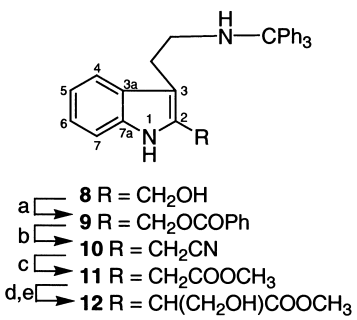
For the synthesis of **1** we chose N_b-trityl-2-(hydroxymethyl)-tryptamine[10] (**8**) as the starting material. The carbon chain of molecule **8** was elongated by the reaction sequence developed by Kutney et al.[11] (**8**→**9**→**10**→**11**, 80% overall yield).

Hydroxymethylation of ester **11** was realized by the method of Battersby[12] resulting in formation of **12** (73%) (Scheme 1).

The trityl protection group was removed by catalytic hydrogenolysis (Pd/C/H_2) in methanol. The resulting key intermediate (**1**) of the reaction tends to decompose, therefore, we allowed it to react with aldehyde and aldehyde-equivalent partners without isolation.

First, we boiled the tryptamine derivative **1** and 4-formylhexanoic acid methyl ester[13] (**13**) in benzene (Fig. 2). Having processed the reaction mixture, we obtained the expected 3-oxo-16,17-dihydro-Δ^{20}-secodin-17-ol (**2**, 79%) in crystalline form. We had already produced **2**[14] in another way from which after dehydration-in the biomimetic way-3-oxovincadifformine (**4**) can be yielded.

For the synthesis of 3-oxominovincine[8] (**5**), 4-(2-methyl-[1,3]dioxolan-2-yl)-5-oxo-pentanoic acid methyl ester[9] (**14**) was chosen as the reaction partner of **1**. The reaction was effected here again by refluxing in benzene using the crude evaporation residue from the conversion **12**→**1** as the



Scheme 1. *Reagents and conditions*: (a) PhCOCl, Et_3N, THF, rt, 95%; (b) KCN, DMSO, 60°C, 98%; (c) HCl (g), MeOH, rt, 86%; (d) NaH, $HCOOCH_3$, rt; (e) $NaBH_4$, MeOH, 0°C, 73% (d and e steps).

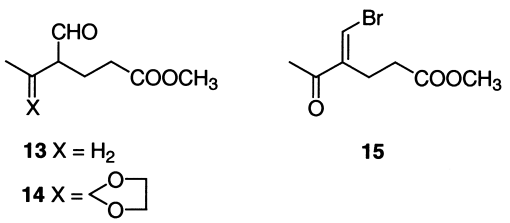
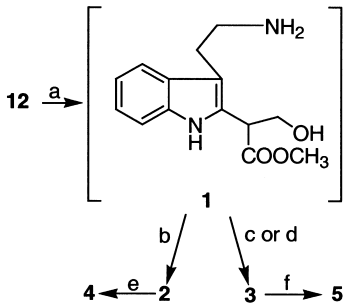


Figure 2.



Scheme 2. *Reagents and conditions*: (a) H_2, Pd/C, MeOH, rt; (b) **13**, benzene, Δ, 79% (a and b steps); (c) **14**, benzene, Δ, 76% (a and c steps); (d) **15**, Et_3N, MeOH, rt, 82% (a and d steps); (e) Ac_2O, toluene, Δ, 48%, Ref. 14; (f) TsOH, xylene, Δ, 42%.

substrate. Processing the reaction mixture offered a surprise as the dioxolanyl protection group dissociated and 3,19-dioxo-16,17-dihydro-Δ^{20}-secodin-17-ol (**3**, 76%) was obtained as the product.

The reaction was repeated also with an alternative to the aldehyde[14] mentioned above. We allowed 4-acetyl-5-bromo-4-pentenoic acid methyl ester[8] (**15**) to react with the tryptamine derivative **1** in methanol in the presence of triethylamine, then the reaction mixture was processed from which the secodine derivative **3** was isolated in a good yield (82%). Spontaneous cyclization in boiling xylene in the presence of TsOH after dehydration led to the alkaloid 3-oxominovincine (**5**, 42%) (Scheme 2).

In light of the successfully applied strategy, the synthesis of 15β-hydroxyvincadifformine (**16**) (Fig. 3) seemed to be a reasonable idea.

The activated vinylchloride derivative **19** was chosen as the reaction partner of **1**. The synthesis of **19** was realized by starting from 3-chloro-2-ethyl-acrolein[15] (**17**). Reformatsky reaction of aldehyde **17** and bromo-acetic-acid ethyl ester in the presence of zinc powder led to hydroxy ester **18** in an excellent yield (78%). Oxidation of alcohol **18** by Jones' reagent resulted in the expected molecule (**19**, 84%) (Scheme 3).

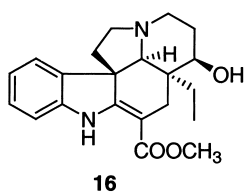
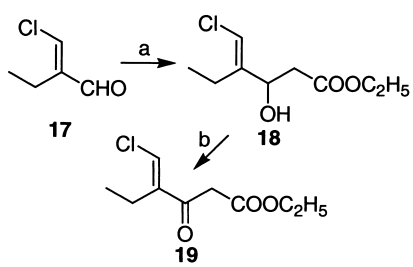
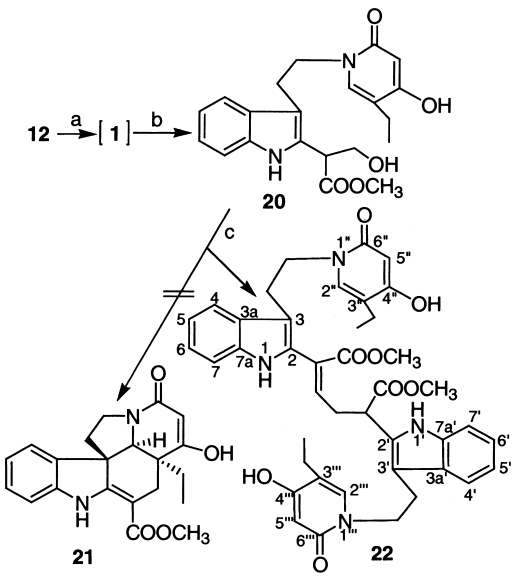


Figure 3.



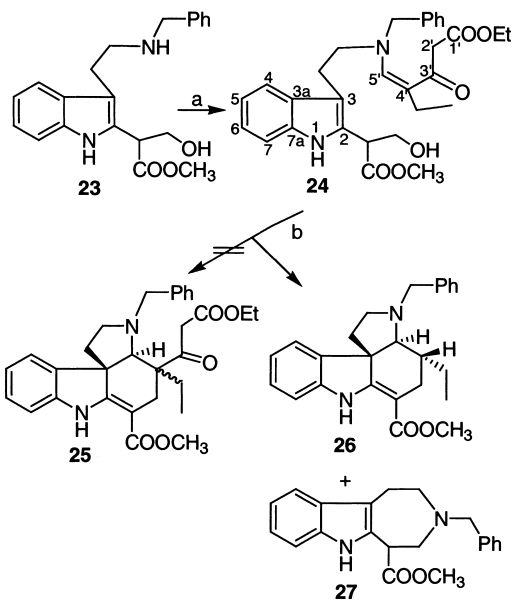
Scheme 3. *Reagents and conditions*: (a) $BrCH_2COOC_2H_5$, Zn, benzene, Δ, 78%; (b) CrO_3, H_2SO_4, acetone, rt, 84%.



Scheme 4. *Reagents and conditions*: (a) H_2, Pd/C, MeOH, rt; (b) **19**, Et_3N, MeOH, rt 58% (a and b steps); (c) TsOH, toluene, Δ, 42%.

Compounds **1** and **19** readily reacted in methanol in the presence of triethyl amine. Having processed the reaction mixture, we found that the carbonyl function in position 15 was present exclusively in the enol form (**20**, 58%). Compound **20** was then boiled in toluene in the presence of TsOH and surprisingly we found that after dehydration an anomalous dimerization (**22**, 42%) had occurred instead of the expected cyclization (**21**) (Scheme 4).

Afterwards, we tried to produce alkaloid **16** with the synthetic strategy published by us earlier.[8] In this case the formation of rings C,E precedes the build-up of ring D. We allowed the activated vinyl halide **19** to react in methanol with **23**[4] in the presence of triethyl amine. Processing the reaction mixture led to enamine **24** in a good yield (70%). The toluene solution of **24** was then boiled in order to form



Scheme 5. *Reagents and conditions*: (a) **19**, Et_3N, MeOH, rt, 70%; (b) toluene, Δ, 27% for **26**, 23% for **27**.

rings C and E. However, the reaction did not supply the expected result either. Having processed the reaction mixture which contained two components according to chromatography, we found that the expected compound **25** did not appear among the products. Structure elucidation studies revealed that the major product was molecule **26**[16] (27%) with the D-*seco*-aspidospermane skeleton as a consequence of carbon–carbon bond cleavage, while the by-product N_b-benzyl-indolazepinester (**27**)[2d] (23%) (Scheme 5) was also found.

3. Conclusion

A new biomimetic synthetic strategy has been developed to build up molecules with the aspidospermane skeleton. A simple synthesis of 3-oxovincadifformine and 3-oxominovincine has been realized. However, generation of 15β-hydroxyvincadifformine failed because of unexpected side reactions.

4. Experimental

4.1. General

Melting points (uncorrected): Hotstage microscope Boetius. IR spectra: Specord JR-75 Spectrophotometer. ^1H and ^{13}C NMR spectra: Varian Unity INOVA-400. Chemical shifts (in ppm) are relative to Me_4Si. Mutual $^1H-^1H$ couplings are given only once, at their first occurrence. Mass spectra: VG ZAB-SEQ double focussing high resolution mass spectrometer. Preparative thin-layer chromatography: Silica gel plates F254 (Merck).

4.1.1. N_b-Trityl-2-[(benzoyloxy)methyl]tryptamine (9). To an ice-cooled solution of **8** (20.0 g, 47.8 mmol) and Et_3N (9.0 g, 88.8 mmol) in anhydrous THF (380 mL) was added benzoyl chloride (10.4 g, 74.1 mmol) dropwise. The reaction mixture was allowed to stir for 4 h at rt then the solvent was evaporated. To the residue 10% NaOH solution (80 mL) was added and extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The brown oil was crystallized from methanol, and filtration yielded 23.7 g (95%) of **9** as white crystals. R_f=0.46 (acetone/hexane=1/2); mp 151–153°C; IR (KBr) ν_{max} 3390, 1710, 1450, 1265, 1100; δ_H ($CDCl_3$): 1.73 (1H, brs; NH), 2.49+3.03 (2×2H, 2×t, J=6.6 Hz; 3-CH_2CH_2NH), 5.48 (2H, s; 2-CH_2O), 7.03 (1H, m; 5-H), 7.11 (3H, m; 3×4′-H), 7.16 (1H, m; 6-H), 7.17 (3×2H, m; 3×3′-H+3×5′-H), 7.29 (1H, m; 7-H), 7.38 (3×2H, m; 3×2′-H+3×6′-H), 7.39 (2H, m; 3″-H+5″-H), 7.47 (1H, m; 4-H), 7.53 (1H, m; 4″-H), 7.94 (2H, m; 2″-H+6″-H), 8.57 (1H, brs; indole-NH); δ_C ($CDCl_3$): 25.45 (3-CH_2), 44.65 (CH_2–NH), 58.10 (2-CH_2O), 70.96 (*C*Ph_3), 111.00 (C7), 114.32 (C3), 119.37+119.51 (C4+C5), 122.86 (C6), 126.14 (3×C4′), 127.59 (C3a), 127.73 (3×C2′+3×C6′), 128.41 (C3″+C5″), 128.59 (3×C3′+3×C5′), 129.70 (C2+C1″), 129.78 (C2″+C6″), 133.26 (C4″), 135.79 (C7a), 146.17 (3×C1′), 167.76 (COO); MS *m*/*z* (rel inten) 536 (5.0, M^+), 243 (74.0), 165 (50.0), 143 (38.0), 122 (78.0), 105 (100.0), 91 (10.0), 77 (90.0). Anal. calcd for $C_{37}H_{32}N_2O_2$: C, 82.81; H, 6.01; N, 5.22; found: C, 82.90; H, 5.91; N, 5.68.

4.1.2. N_b-Trityl-2-(cyanomethyl)tryptamine (10). To a solution of **9** (20.0 g, 38.3 mmol) in anhydrous DMSO (400 mL) was added KCN (7.6 g, 116.9 mmol) and the reaction mixture was stirred for 3 h at 60–62°C. After the mixture cooled, it was poured into 5% $NaHCO_3$ solution (1.5 L) and extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with 10% aqueous NaCl (3×80 mL), dried ($MgSO_4$), and evaporated in vacuo. The brown oil was crystallized from methanol, and the filtration yielded 16.0 g (98%) of **10** as light brown crystals. R_f=0.39 (acetone/hexane=1/2); mp 127–130°C; IR (KBr) ν_{max} 3390, 2245, 1490, 1450, 750, 705; δ_H ($CDCl_3$): 1.75 (1H, brs; NH), 2.47+2.90 (2×2H, 2×t, J=6.6 Hz; 3-CH_2-CH_2NH), 3.87 (2H, s; 2-CH_2CN), 7.09 (1H, m; 5-H), 7.17 (3H, m; 3×4′-H), 7.23 (7H, m; 6-H+3×3′-H+3×5′-H), 7.32 (1H, m; 7-H), 7.38 (6H, m; 3×2′-H+3×6′-H), 7.44 (1H, m; 4-H), 8.12 (1H, brs; indole-NH); δ_C ($CDCl_3$): 15.69 (*C*H_2CN), 25.32 (3-CH_2), 43.88 (CH_2NH), 71.04 (*C*Ph_3), 110.91 (C7), 112.53 (C3), 116.50 (CN), 119.03+119.97 (C4+C5), 122.23 (C2), 122.77 (C6), 126.30 (3×C4′), 127.81 (3×C2′+3×C6′), 128.11 (C3a), 128.58 (3×C3′+3×C5′), 135.73 (C7a), 145.98 (3×C1′); MS *m/z* (rel inten) 441 (6.0, M^+), 243 (100.0), 194 (5.0), 170 (12.0), 165 (38.0), 142 (4.0), 115 (4.0), 91 (4.0), 77 (6.0). Anal. calcd for $C_{31}H_{27}N_3$: C, 84.32; H, 6.16; N, 9.52; found: C, 84.48; H, 6.23; N, 9.60.

4.1.3. N_b-Trityl-2-[(methoxycarbonyl)methyl]tryptamine (11). A solution of **10** (20.0 g, 38.3 mmol) in saturated methanolic HCl (300 mL) was allowed to stir at rt for 3 h. The reaction mixture was poured onto ice-cooled 25% aqueous NH_3 solution (300 mL). The mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The brown oil was crystallized from methanol, and the filtration yielded 19.2 g (86%) of **11** as light brown crystals. R_f=0.42 (acetone/hexane=1/2); mp 128–130°C; IR (KBr) ν_{max} 3390, 1730, 1490, 1450, 750, 705; δ_H ($CDCl_3$): 1.70 (1H, brs; NH), 2.42+2.90 (2×2H, 2×t, J=6.5 Hz; 3-CH_2CH_2-NH), 3.66 (3H, s; OMe), 3.80 (2H, s; 2-CH_2), 7.03 (1H, m; 5-H), 7.13 (4H, m; 6-H+3×4′-H), 7.19 (6H, m; 3×3′-H+3×5′-H), 7.28 (1H, m; 7-H), 7.37 (6H, m; 3×2′-H+3×6′-H), 7.40 (1H, m; 4-H), 8.50 (1H, brs; indole-NH); δ_C ($CDCl_3$): 25.41 (3-CH_2), 31.70 (2-CH_2), 44.17 (CH_2NH), 52.33 (OMe), 71.00 (*C*Ph_3), 110.66 (C7), 111.55 (C3), 118.79+119.30 (C4+C5), 121.82 (C6), 126.16 (3×C4′), 127.02 (C2), 127.73 (3×C2′+3×C6′), 128.25 (C3a), 128.66 (3×C3′+3×C5′), 135.69 (C7a), 146.23 (3×C1′), 171.11 (*C*OOMe); MS *m/z* (rel inten) 474 (3.0, M^+), 397 (0.1), 243 (100.0), 202 (40.0), 175 (44.0), 165 (30.0), 142 (13.0), 115 (7.0), 91 (6.0), 77 (6.0). Anal. calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.90; found: C, 80.95; H, 6.45; N, 6.05.

4.1.4. Hydroxymethylation of 11. To a solution of **11** (5.0 g, 10.5 mmol) in anhydrous methyl formate (90 mL) was added oil free NaH (1.5 g, 62.5 mmol) and the reaction mixture was allowed to stir for 0.5 h. The mixture was cooled to below −15°C. At this temperature anhydrous methanol (175 mL) and glacial acetic acid (5.9 mL) were added. With the temperature below −15°C sodium borohydride (6.1 g, 160.8 mmol) was added. The reaction mixture was allowed to warm to 0°C and was stirred for 1 h, poured onto water (300 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1/2, R_f=0.52) to afford 3.9 g (73%) of product **11** as amorf solid. IR (KBr) ν_{max} 3424, 1728, 1596, 1448, 1168; δ_H ($CDCl_3$): 1.67 (1H, br; OH+NH), 2.47 (2H, t, J=6.8 Hz; CH_2NH), 2.96 (2H, m; 3-CH_2), 3.60 (3H, s; OMe), 3.96+4.07 (2×1H, 2×dd, J_{gem}=11.2 Hz, J_{vic}=5.4, 4.7 Hz, respectively; 2-CHCH_2OH), 4.14 (1H, dd; 2-CHCH$_2$), 7.03 (1H, m; 5-H), 7.14 (4H, m; 6-H+3×4′-H), 7.20 (6H, m; 3×3′-H+3×5′-H), 7.29 (1H, m; 7-H), 7.36 (6H, m; 3×2′-H+3×6′-H), 7.42 (1H, m; 4-H), 8.80 (1H, brs; indole-NH); δ_C ($CDCl_3$): 25.35 (3-CH_2), 44.23 (CH_2NH), 44.53 (2-CH), 52.48 (OMe), 64.27 (CH_2OH), 71.08 (*C*Ph_3), 110.93 (C7), 111.84 (C3), 118.99+119.36 (C4+C5), 122.13 (C6), 126.21 (3×C4′), 127.75 (3×C2′+3×C6′), 127.88 (C3a), 128.67 (3×C3′+3×C5′), 129.49 (C2), 135.64 (C7a), 146.07 (3×C1′), 173.12 (*C*OOMe); HRMS (FAB) calcd for $C_{33}H_{33}N_2O_3$ 505.2491, found for [MH^+] 505.2491.

4.1.5. 4-Chloromethylene-3-hydroxy-hexanoic acid ethyl ester (18). A 100 mL, 3-necked flask fitted with a condenser, mechanical stirrer, and 20 mL dropping funnel was purged with nitrogen. Freshly activated zinc powder (1.2 g, 18 mmol), and anhydrous benzene (10 mL) were placed in the flask. Ethyl bromoacetate (2.5 g, 15 mmol), 2-chloromethylene-butyraldehyde (2.2 g, 18 mmol), and anhydrous benzene (10 mL) were placed in the dropping funnel. Nitrogen was introduced into the apparatus via a septum on the condenser with a septum on the dropping funnel as outlet. Without applied stirring, the bromide–aldehyde solution (~2 mL) was added to the zinc suspension and the mixture was cautiously brought to reflux. After ca. 10 min of gentle reflux the heating mantle was removed and the rest of the bromide–aldehyde solution was then added at such a rate as to maintain a gentle reflux. After the addition was complete the dark yellow reaction mixture was vigorously stirred and again brought to reflux with the heating mantle. Over the course of 1 h reflux, the reaction mixture became a cloudy pale green colour and most of the zinc reacted. The reaction mixture was cooled and 10% H_2SO_4 (15 mL), ethyl acetate (15 mL) were added. The mixture was shaken well, and the two-phase system was filtered to remove unchanged zinc. The aqueous layer was then further extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated brine (2×20 mL), dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1/2, R_f=0.53) to afford 3.0 g (78%) of product **18** as yellow oil. IR (neat) ν_{max} 2990, 1730, 1725, 1510, 1350, 1180; δ_H ($CDCl_3$): 1.09 (3H, t, J=7.6 Hz; 4-CH_2CH_3), 1.28 (3H, t, J=7.0 Hz; COOCH_2CH_3), 2.16+2.32 (2×1H, 2×dq, J_{gem}=13.5 Hz, J_{vic}=7.6 Hz; 4-CH_2CH$_3$), 2.54+2.60 (2×1H, 2×dd, J_{gem}=16.1 Hz, $J_{2,3}$=8.7, 3.8 Hz, respectively; 2-CH_2), 3.18 (1H, brd, J=3.8 Hz; 3-OH), 4.19 (2H, q, J=7.0 Hz; COOCH_2CH$_3$), 4.57 (1H, brdddd, $J_{3,5}$=1.3 Hz; 3-H), 6.20 (1H, d; 5-H). NOE: 6.20 (5-H)→4.57 (3-H), 3.18 (3-OH), 2.54+2.60 (2-H_2); δ_C ($CDCl_3$): 12.22 (4-CH_2*C*H_3), 14.14 (COOCH_2-*C*H_3), 21.21 (4-*C*H_2CH$_3$), 40.24 (C2), 61.01 (COO*C*H_2-CH$_3$), 70.12 (C3), 115.99 (C5), 144.18 (C4), 172.23 (*C*OOEt); MS *m/z* (rel inten) 188 (10.0, $M-H_2O^+$), 171

(18.0), 119 (45.0), 89 (23.0), 83 (100.0); HRMS (EI) calcd for $C_9H_{12}ClO_2$ 188.0604, found for [M−H_2O^+] 188.0602.

4.1.6. 4-Chloromethylene-3-oxo-hexanoic acid ethyl ester (19). Jones' reagent was prepared by the addition of concentrated H_2SO_4 (5 mL) to CrO_3 (5.6 g) followed by the careful dilution with water (to give 42 mL of total solution). Then the Jones' reagent (18 mL, 18 mmol) was added dropwise to a stirred solution of **18** (3.0 g, 14 mmol) in acetone (70 mL) at 0°C. After complete addition of the oxidizing agent, the mixture was allowed to warm up to rt and stirred for 12 h. Methanol (10 mL) was added to quench excess Jones' reagent. The reaction mixture was extracted with diethyl ether (3×70 mL). The organic extracts were washed with water (3×70 mL) and then 5% $NaHCO_3$ (50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with ether/hexane=1/3, R_f=0.71) to afford 2.5 g (84%) of product **19** as yellow oil. IR (neat) ν_{max} 2952, 1740, 1684, 1624, 1396, 1236; δ_H ($CDCl_3$): 1.01 (3H, t, J=7.5 Hz; 4-CH_2CH_3), 1.27 (3H, t, J=7.0 Hz; $COOCH_2CH_3$), 2.50 (2H, q, J=7.5 Hz; 4-CH_2CH_3), 3.66 (2H, s; 2-H_2) 4.20 (2H, q, J=7.0 Hz; $COOCH_2CH_3$), 7.24 (1H, s; 5-H); δ_C ($CDCl_3$): 12.02 (4-CH_2CH_3), 14.08 ($COOCH_2CH_3$), 20.01 (4-CH_2), 45.71 (C2), 61.62 ($COOCH_2CH_3$), 134.48 (C5), 145.37 (C4), 167.04 (C1), 190.06 (C3); MS m/z (rel inten) 204 (2.0, M^+) 169 (17.0), 141 (43.0), 117 (48.0), 88 (29.0), 69 (48.0), 53 (100.0); HRMS (EI) calcd for $C_9H_{12}ClO_3$ 204.0553, found for [M^+] 204.0551.

4.2. General method I for synthesis of secodin type intermediates (2, 3). Reaction of 1 with esters containing aldehyde structural unit

A mixture of **12** (5.0 g 18.2 mmol) and 3 g of 10% palladium/charcoal in methanol (50 mL) was hydrogenated for 12 h at rt and then filtered. The filtrate was evaporated in vacuo. To the solution of the residue in benzene (50 mL) **13** or **14** (27.0 mmol) was added. The reaction mixture was refluxed for 1 h. The solvent was evaporated. The residue was purified by column chromatography.

4.2.1. 3-Oxo-16,17-dihydro-Δ^{20}-secodin-17-ol (2). Yield: 3.0 g (79%). The authenticity of product was confirmed by comparison of R_f,[14] mp,[14] IR,[14] ^{1}H NMR,[14] ^{13}C NMR[14] and mass spectrum[14] with those of genuine sample.

4.2.2. 3,19-Dioxo-16,17-dihydro-Δ^{20}-secodin-17-ol (3). Yield: 3.1 g (76%). R_f=0.46 (CH_2Cl_2/methanol=15/1); mp 169–170°C; IR (KBr) ν_{max} 3392, 3232, 1728, 1668, 1616, 1440, 1384, 1300, 1180, 1088; δ_H (DMSO-d_6): 1.90 (3H, s; $COCH_3$), 2.28+2.39 (2×2H, 2×m; 4′-H_2+5′-H_2), 2.97 (2H, t, J=7.0 Hz; 3-CH_2), 3.63 (3H, s; OMe), 3.67–3.84 (3H, m; CH_2N+2′-CH), 4.13 (2H, m; CH_2OH), 5.13 (1H, t, J=4.7 Hz; OH), 6.69 (1H, m; 5-H), 7.03 (1H, m; 6-H), 7.12 (1H, s; 2′-H), 7.31 (1H, brd, J=8.0 Hz; 7-H), 7.49 (1H, brd, J=7.9 Hz; 4-H), 10.80 (1H, brs; indole-NH); δ_C (DMSO-d_6): 18.11 (C4′), 23.15 (3-CH_2), 24.34 ($COCH_3$), 30.21 (C5′), 46.07 (2-CH), 47.58 (CH_2N), 52.04 (OMe), 61.90 (CH_2OH), 108.87 (C3), 111.28 (C7), 116.72 (C3′), 118.01 (C4), 118.62 (C5), 121.15 (C6), 127.78 (C3a), 130.61 (C2), 135.86 (C7a), 142.71 (C2′), 169.43 (C6′), 171.74 (COOMe), 194.37 (COCH$_3$); MS m/z (rel inten) 385.3 (100.0), 367.3 (58.0), 316.3 (12.0). Anal. calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29; found: C, 65.44; H, 6.40; N, 7.12.

4.3. General method II for synthesis of secodin type intermediates (3, 20). Reaction of 1 with esters containing aldehyde-equivalent structural unit

A mixture of **12** (5.00 g 18.2 mmol) and 3 g of 10% palladium/charcoal in methanol (50 mL) was hydrogenated for 12 h at rt and then filtered. To the filtrate, Et_3N (3.8 mL. 27.3 mmol) and **15** or **19** (27.0 mmol) was added. After being stirred for 24 h at rt, the mixture was concentrated in vacuo. The residue was purified by column chromatography.

4.3.1. 3,19-Dioxo-16,17-dihydro-Δ^{20}-secodin-17-ol (3). Yield: 3.3 g (82%). The compound was identical to that prepared by method I.

4.3.2. 3-Oxo-16,17-dihydro-Δ^{14,20}-secodin-15,17-diol (20). Yield: 2.2 g (58%). R_f=0.32 (CH_2Cl_2/methanol=15/1); mp 106–109°C; IR (KBr) ν_{max} 3408, 1728, 1660, 1548, 1440, 1232; δ_H ($CDCl_3$): 0.72 (3H, t, J=7.4 Hz; 3′-CH_2CH_3), 2.12 (2H, m; 3′-CH_2), 3.07+3.17 (2×1H, 2×dt, J_{gem}=14.5, J_{vic}=6.8 Hz; 3-CH_2), 3.58 (3H, s; OMe), 3.66+3.99 (2×1H, 2×m; 2-CHCH_2OH), 3.98+4.14 (2×1H, 2×m; N1′–CH_2), 4.02 (1H, m; 2-CH), 5.2 (2H, br; CH_2OH+4′-OH), 6.07 (1H, s; 5′-H), 6.25 (1H, s; 2′-H), 7.09 (1H, m; 5-H), 7.14 (1H, m; 6-H), 7.29 (1H, d, $J_{6,7}$=7.9 Hz; 7-H), 7.50 (1H, d, $J_{4,5}$=7.7 Hz; 4-H), 9.10 (1H, brs; indole-NH); δ_C ($CDCl_3$): 13.10 (3′-CH_2CH_3), 19.76 (3′-CH_2), 23.75 (3-CH_2), 45.53 (2-CH), 49.70 (N1′–CH_2), 52.54 (OMe), 63.74 (CH_2OH), 99.19 (C5′), 109.04 (C3), 111.39 (C7), 117.85 (C3′), 117.97 (C4), 119.61 (C5), 122.16 (C6), 127.34 (C3a), 130.30 (C2), 135.59 (C2′), 135.86 (C7a), 164.26 (C6′), 169.93 (C4′), 173.45 (COOMe); MS m/z (rel inten) 385.3 (70.0), 367.3 (100.0), 316.3 (15.0). Anal. calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29; found: C, 65.51; H, 6.32; N, 7.24.

4.3.3. (±)-3-Oxominovincine (5). A solution of **3** (1.0 g, 2.5 mmol) and p-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in xylene (100 mL) was refluxed under argon for 24 h. The reaction mixture was extracted with brine (2×40 mL), and the combined brines were extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=1/2, R_f=0.28) to afford 0.4 g (42%) of product **3** as white crystals. The authenticity of product was confirmed by comparison of R_f,[8] mp,[8] IR,[8] ^{1}H NMR,[8] ^{13}C NMR[8] and mass spectrum[8] with those of a genuine sample.

4.3.4. Dimer (22). A solution of **20** (1.00 g, 2.5 mmol) and p-toluenesulfonic acid monohydrate (10 mg, 0.06 mmol) in toluene (100 mL) was refluxed under argon for 24 h. The reaction mixture was extracted with brine (2×40 mL), and the combined brines were extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with CH_2Cl_2/

methanol=15/1, R_f=0.53) to afford 0.4 g (42%) of product **22** as an amorphous solid. IR (KBr) ν_{max} 3416, 2960, 1724, 1660, 1552, 1440, 1224; δ_H ($CDCl_3$+DMSO-d_6): 0.81 (3H, t, J=7.4 Hz; 3″-CH_2CH_3), 0.87 (3H, t, J=7.4 Hz, 3‴-CH_2CH_3), 2.14 (2H, brq; 3″-CH_2), 2.18 (2H, brq; 3‴-CH_2), 2.89+3.37 (2×1H, 2×ddd, J_{gem}=15.4 Hz, J_{vic}=7.8+6.8 Hz; =CH−CH_2CH), 2.97 (2H, t, J=6.6 Hz; 3-CH_2), 3.11+3.19 (2×1H, 2×dt, J_{gem}=14.5 Hz, J_{vic}=7.5 Hz, 3′-CH_2), 3.62 (3H, s; CH−COO*Me*), 3.69 (3H, s; =C−COO*Me*), 3.98+4.11 (2×1H, 2×m; N1‴−CH_2), 4.00 (2H, m; N1″−CH_2), 4.18 (1H, t, J=7.5 Hz; 2′-CH), 5.93 (1H, s; 5″-H), 5.95 (1H, s; 5‴-H), 6.13 (1H, t, J=7.2 Hz; 2-C=C*H*), 6.43 (1H, s; 2″-H), 6.65 (1H, s; 2‴-H), 6.99 (1H, m; 5-H), 7.00 (1H, m; 5′-H), 7.07 (2H, m; 6-H+6′-H), 7.27 (1H, d, J=8.0 Hz; 7-H), 7.34 (1H, d, J=8.0 Hz; 7′-H), 7.55 (2H, d, J=7.6 Hz; 4-H+4′-H), 10.49 (2H, brs; 2×indole-NH); δ_C ($CDCl_3$+DMSO-d_6): 13.30 (3″-CH_2CH_3), 13.38 (3‴-CH_2CH_3), 19.75 (3″-CH_2), 19.86 (3‴-CH_2), 24.02 (3′-CH_2), 24.22 (3-CH_2), 32.38 (=CH−CH_2CH), 42.11 (2′-CH), 48.76 (N1″−CH_2), 49.31 (N1‴−CH_2), 51.81 (=C−COOCH_3), 52.10 (CH−COOCH_3), 98.61 (C5‴), 98.70 (C5″), 108.63 (C3′), 109.14 (C3), 111.19 (C7), 111.30 (C7′), 115.22 (C3″), 115.67 (C3‴), 118.05+118.39 (C4+C4′), 118.89 (C5′), 118.98 (C5), 121.37 (C6′), 121.92 (C6), 126.72 (C8), 127.56 (C3a′), 127.70 (C3a), 132.09 (C2′), 132.43 (C2), 135.21 (C2″), 135.30 (C2‴), 135.71+136.07 (C7a′+C7a), 140.12 (2-C=*C*H), 163.45 (C6″), 163.56 (C6‴), 166.94 (=C−*C*OOMe), 167.30 (C4″), 167.60 (C4‴), 172.44 (CH−*C*OOMe); HRMS (FAB) calcd for $C_{42}H_{45}N_4O_8$ 733.3237 found for $[MH]^+$ 733.3305.

4.3.5. Enamine (24). To a mixture of **23** (1.0 g, 2. 5 mmol), triethylamine (0.4 g, 4 mmol) and methanol (50 mL) were added **19** (0.7 g, 3.4 mmol). After being stirred for 24 h at rt, the mixture was concentrated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=2/3, R_f=0.48) to afford 1.0 g (70%) of product **24** as an amorphous solid. IR (KBr) ν_{max} 3390, 1730, 1570, 1450, 1340; δ_H ($CDCl_3$): 0.97 (3H, t, J=7.5 Hz; 4′-CH_2CH_3), 1.26 (3H, t, J=7.1 Hz; $COOCH_2CH_3$), 2.37 (2H, q; 4′-CH_2), 3.03+3.50 (2×2H, 2×m; 3-CH_2CH_2−N), 3.1 (1H, br; OH), 3.38+3.42 (2×1H, 2×d, J_{gem}=14.3 Hz; 2′-H_2), 3.69 (3H, s; OMe), 4.00–4.14 (3H, m; 2-C*H*CH_2OH), 4.17 (2H, q; $COOCH_2CH_3$), 4.42+4.46 (2×1H, 2×d; J_{gem}=16.0 Hz; NCH_2Ph), 7.08 (1H, m; 5-H), 7.14 (2H, m; 2″-H+6″-H), 7.17 (1H, m; 6-H), 7.29 (1H, m; 4″H), 7.30 (1H, s; 5′-H), 7.33(1H, m; 7-H), 7.34 (2H, m; 3″-H+5″-H), 7.40 (1H, m; 4-H), 8.95 (1H, brs; indole-NH); δ_C ($CDCl_3$): 14.16 ($COOCH_2CH_3$), 15.51 (4′-CH_2CH_3), 17.59 (4′-CH_2), 24.26 (3-CH_2), 44.77 (2-CH), 45.12 (C2′), 52.59 (OMe), 54.16 (CH_2CH_2N), 56.49 (NCH_2Ph), 61.16 ($COOCH_2CH_3$), 64.17 (2-CHCH_2OH), 109.89 (C4′), 111.31 (C7), 112.47 (C3), 118.18 (C4), 119.80 (C5), 122.46 (C6), 126.93 (C3″+C5″), 127.33 (C3a), 127.84 (C4″), 128.91 (C2″+C6″), 129.90 (C2), 135.72 (C7a), 137.25 (C1″), 150.99 (C5′), 169.68 (C1′), 172.65 (*C*OOMe), 190.24 (C3′); HRMS (FAB) calcd for $C_{30}H_{37}N_2O_6$ 521.2651 found for $[MH]^+$ 521.2630.

4.3.6. (±)-2,16-Didehydro-16-methoxycarbonyl-3-phenyl-14,15-dinoraspidospermidine (26) and methyl 3-benzyl-1,2,3,4,5,6 hexahydroazepino[4,5-*b*]indole-5-carboxylate (27). A solution of **24** (1.00 g, 2.5 mmol) in toluene (100 mL) was refluxed under argon for 24 h. The reaction mixture was extracted with brine (2×40 mL), and the combined brines were extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by column chromatography (eluting with acetone/hexane=2/3). The less polar compound (**26**, R_f=0.89) was obtained as white crystals (0.2 g, 27%) after crystallization from methanol. The authenticity of product was confirmed by comparison of R_f,[16b] mp,[16b] IR,[16b] ^{1}H NMR,[16b] ^{13}C NMR[16b] and mass spectrum[16b] with those of genuine sample.

The less polar compound (**27**, R_f=0.75) was obtained as white crystals (0.15 g, 23%) after crystallization from methanol. The authenticity of product was confirmed by comparison of R_f,[4] mp,[4] IR,[4] ^{1}H NMR,[4] ^{13}C NMR[4] and mass spectrum[4] with those of genuine sample.

Acknowledgements

The authors are grateful to István Vágó for helping with the preparative work and the National Scientific Research Foundation (OTKA T31920) for financial support of this work.

References

1. Éles, J.; Kalaus, Gy.; Greiner, I.; Kajtár-Peredy, M.; Szabó, P.; Keseru, Gy. M.; Szabó, L.; Szántay, Cs. *J. Org. Chem.* in press.
2. (a) Kuhne, M. E.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3702–3704. (b) Kuhne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705–3710. (c) Kuhne, M. E.; Matsko, C. L.; Bohnert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002–2009. (d) Kuhne, M. E.; Bohnert, J. C.; Bornmann, W. G.; Kirkemo, C. L.; Kuhne, S. E. *J. Org. Chem.* **1985**, *50*, 919–924.
3. Kuhne, M. E.; Bormann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913–2927.
4. Kalaus, Gy.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *J. Org. Chem.* **1993**, *581*, 1434–1442.
5. Kalaus, Gy.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *J. Org. Chem.* **1993**, *58*, 6076–6082.
6. Kalaus, Gy.; Juhász, I.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Liebigs Ann. Chem.* **1995**, 1245–1252.
7. Kalaus, Gy.; Vágó, I.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Nat. Prod. Lett.* **1995**, *7*, 197–204.
8. Kalaus, Gy.; Juhász, I.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *J. Org. Chem.* **1997**, *62*, 9188–9191.
9. Kalaus, Gy.; Juhász, I.; Steinhauser, K.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Heterocycles* **1998**, *47*, 205–220.
10. Vágó, I.; Kalaus, Gy.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Heterocycles* **2001**, *55*, 873–880.
11. Kutney, J. P.; Badger, R. A.; Beck, J. F.; Bosshardt, H.; Matough, F. S.; Ridura-Sanz, V. E.; So, Y. H.; Sood, R. S.; Wort, B. R. *Can. J. Chem.* **1979**, *57*, 289–299.

12. Battersby, A. R.; Bhatnagar, A. K. *J. Chem. Soc., Chem. Commun.* **1970**, *189*, 193–194.
13. Kalaus, Gy.; Győry, P.; Kajtár-Peredy, M.; Radics, L.; Szabó, L.; Szántay, Cs. *Chem. Ber.* **1981**, *114*, 1476–1483.
14. Kalaus, Gy.; Chau, P. D.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *Heterocycles* **1990**, *31*, 1183–1188.
15. Arnold, Z.; Zemlicka, J. *Coll. Czech. Chem. Commun.* **1959**, *24*, 2385–2390.
16. (a) Kuhne, M. E.; Kuhne, S. E. *J. Org. Chem.* **1993**, *58*, 4147–4148. (b) Kalaus, Gy.; Juhász, I.; Éles, J.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, Cs. *J. Heterocycl. Chem.* **2000**, *37*, 245–252.