SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS LXXXVIII.[1] HIGHLY ENANTIOSELECTIVE SYNTHESIS OF (+)-VINCAMINE

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Abstract - The interaction of the chiral malonic ester derivative (**5**) with formaldehyde and Wenkert enamine (**1**) yields the tetrahydropyranoindoloquinolizine (**6**), from which a highly enantioselective synthesis of the commercially important alkaloid (+)-vincamine (**12**) was achieved.

The interaction of diethyl malonic ester with formaldehyde and Wenkert enamine (**1**) gave the tetrahydropyranoindoloquinolizine (**2**). Resolution of **2** was also established.[2] Reduction of (1S)-**2** followed by basic treatment yielded compound (**3**).

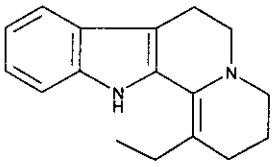
On the basis of the above results a similar reaction sequence was envisaged yielding directly the desired enantiomer thus avoiding the resolution step. To achieve this goal the isoborneol derivative (**4**), prepared by Oppolzer,[3] was acylated with ethyl malonyl chloride giving rise to compound (**5**). The components (**1**), (**5**) and paraformaldehyde were allowed to react in ethanol at ambient temperature. From the clear solution after 3 d derivative (**6**) crystallized in pure form in 82% yield.

Catalytic reduction of **6** afforded the hydroxymethyl derivative (**7**) together with small amount of **8** with high *cis*-selectivity. Removal of the hydroxymethyl group was easily and quantitatively achieved by treatment of **7** with silica gel in ethanol yielding the diastereomeric mixture of **8**. This diastereoisomerism was inconsequential, since difference was found only on C-2, which as a stereogenic center will be eliminated later on, anyway.

Hydrolysis of **8** at room temperature afforded the half ester (**9**). Decarboxylation of the latter occurred in boiling benzene. The obtained ester (**10**) was hydrolysed with boiling sodium hydroxide yielding the key intermediate (**11**) of vincamine synthesis in 98% enantiomeric purity. The combined chemical yield based on enamine (**1**) was the excellent 78%. The chiral auxiliary was recovered in 54% yield regarding

the whole chemical process.

Transformation of **11** into the natural, and commercially important alkaloid (+)-vincamine (**12**), used in the clinical praxis, can be carried out according to the method described by us earlier.[4] Very recently two papers have been published dealing with the enantioselective synthesis of vincamine.[5]



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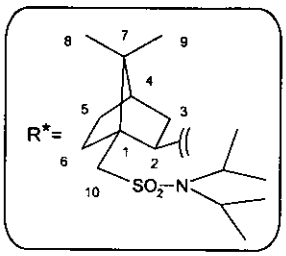
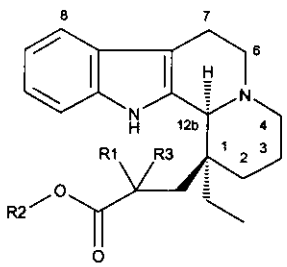
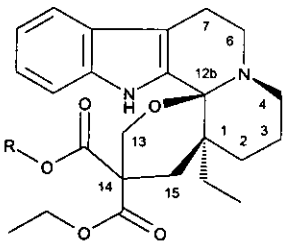


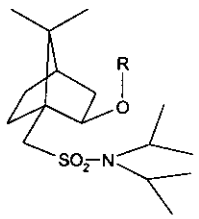


	R^1=	R^2=	R^3=
3	COOEt	Et	H
7	COOEt	R*	CH_2OH
8	COOEt	R*	H
9	COOH	R*	H
10	H	R*	H
11	H	H	H



2 R= Et

6 R= R*



4 R= H

5 R= -OC-CH_2-COOEt

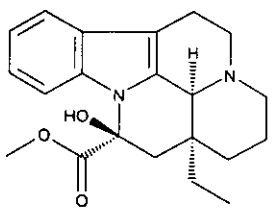


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Table ^{13}C-NMR spectra[a, b] of the new compounds

Carbon atom	5	6	8 with higher R_f	8 with lower R_f	9	10
C-1[c]		38.5	38.9	39.2	66.5	39.3*
C-2[c]		25.9*	e)	f)	g)	32.2
C-3[c]		21.6	e)	f)	g)	22.0#
C-4[c]		52.6	56.6	56.6	54.4	56.7
C-6[c]		49.8	52.9	52.3	53.2	53.0
C-7[c]		22.3	21.7	21.7	21.6	22.1#
C-7a[c]		125.9	111.7	112.0	111.7	111.8
C-7b[c]		125.9	126.7	126.8	126.2	126.9
C-8[c]		118.3	117.6	117.7	117.7	117.7
C-9[c]		119.1	119.0	119.1	119.6	119.2
C-10[c]		122.3	121.3	121.3	122.3	121.3
C-11[c]		111.9	111.0	110.8	110.4	110.7
C-11a[c]		136.2	136.2	136.1	136.8	136.0
C-12a[c]		136.2	132.7	132.6	129.3	133.2
C-12b[c]		89.9	65.8	65.8	66.5	66.2
1-$\underline{C}H_2$-CH_3		28.4*	e)	f)	g)	30.0
1-CH_2-$\underline{C}H_3$		6.9	7.9	7.9	7.7	8.0
C-13		66.0				
C-14		47.7				
C-15		37.2				
-CH_2-$\underline{C}H$-(COO-)$_2$			47.2	47.4	48.3	
-$\underline{C}H_2$-CH-(COO-)$_2$			e)	f)	g)	
-$\underline{C}H_2$-CH_2-COO-						29.0
-CH_2-$\underline{C}H_2$-COO-						27.0
-COO-$\underline{C}H_2$-CH_3	61.4	62.0	61.3	61.0		
-COO-CH_2-$\underline{C}H_3$	14.1	14.0	13.9	13.7		
-OC-$\underline{C}H_2$-CO-	42.0					
-$\underline{C}$OOEt	166.5*	171.7#	168.3	169.1		
-$\underline{C}$OOH					173.6	
-$\underline{C}$OO-CH=	164.8*	171.3#	170.7	170.0	170.4	172.6
C-1[d]	49.1°	49.2	49.0	48.8	49.3	49.0
C-2[d]	79.6	79.9	79.7	79.5	79.1	78.2
C-3[d]	39.2	39.2	39.3	40.0	39.4	39.5*
C-4[d]	44.5	44.4	44.3	44.3	44.5	44.4
C-5[d]	27.0	27.1	e)	f)	g)	28.2
C-6[d]	30.2	30.8	e)	f)	g)	30.9
C-7[d]	49.4°	49.2	49.2	49.3	49.3	49.3
C-8[d]	20.4	20.3	19.5	19.6	20.0	20.4
C-9[d]	19.8	19.8	20.3	20.3	20.4	19.8
C-10[d]	52.9	52.8	54.3	53.9	54.4	54.0
^{i}Pr-$\underline{C}$H=	48.3	48.4	48.2	48.0	48.3	48.1
^{i}Pr-$\underline{C}H_3$	22.3	21.6	22.1	21.7	22.2	22.3
^{i}Pr-$\underline{C}H_3$	22.5	23.4	22.6	22.5	22.6	22.3

a) All spectra were recorded in $CDCl_3$; b) The peaks marked with #,* or ° are interchangeable; c) refers to the indoloquinolizine skeleton; d) refers to the bornane skeleton; e) unidentifiable interchangeable peaks: 27.0; 30.3; 30.6; 31.0; 31.3; 31.5; f) unidentifiable interchangeable peaks: 26.8; 29.8; 30.5 (overlapped); 31.9; 32.5; g) unidentifiable interchangeable peaks: 27.2; 30.1; 30.2; 30.3; 30.4

EXPERIMENTAL

IR spectra were recorded on a ZEISS SPECORD 75 infrared spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were taken on JEOL FX-100 NMR (100 MHz) spectrometer. The chemical shifts (δ) given in ppm are referred to tetramethylsilane. MS spectra were determined on JEOL JMS-01SG-2 mass spectrometer. Melting points are uncorrected.

Ethyl [(1'*S*,2'*R*,4'*R*)-*N*,*N*-diisopropylbornan-10'-sulfonamid-2'-yl]malonate (5)

6.00 g (18.9 mmol) of (1*S*,2*R*,4*R*)-*N*,*N*-Diisopropyl-2-hydroxybornan-10-sulfonamide[3] (**4**) was dissolved in the mixture of 70 mL of isopropyl ether and 4.4 mL (31.7 mmol) of triethylamine. To the above mixture 4.5 g (29.9 mmol) of freshly distilled ethyl malonyl chloride[6] was added drop by drop at ambient temperature, and the resulting suspension was refluxed for 10 h with vigorous stirring. After cooling the solid phase was filtered off and washed twice with isopropyl ether successively. The combined filtrates were evaporated to dryness in vacuum and the crude product (10.2 g oil) was flash chromatographed on 250 g silica gel (Merck KG, 0.040-0.063 mm) by using n-hexane/acetone 10:1 as eluant. The fraction containing the product having an R_f value of 0.65 (silica gel; n-hexane/acetone 10:4) was collected and crystallized from n-hexane to yield 5.73 g (70.2 %) of compound (**5**) as white crystals, mp 127-128 °C; $[\alpha]^{23}_{546}$ = -47.9° (c 1.022, CH_2Cl_2); IR(KBr): 2980, 2890, 1760 (C=O), 1730 (C=O) cm^{-1}; MS m/z (%): 431 (2.5, M^+), 416 (100.0), 300 (10.4), 153 (45.2), 135 (53.3), 115 (50.0), 86 (47.5); ^{1}H-NMR ($CDCl_3$): 1.30 (3H, t, J= 7.1 Hz, -O-CH_2-C<u>H</u>$_3$), 1.34 (12H, d, J= 8.3 Hz, ^{i}Pr-CH_3), 1.5-2.1 (7H, m, bornane-skeleton, $J_{H\text{-}2\ endo,\ H\text{-}3\ endo}$= 6.8 Hz, $J_{H\text{-}2\ endo,\ H\text{-}3\ exo}$= 4.9 Hz), 2.70 (1H, d, J= 13.2 Hz, -S-CH_2-), 3.17 (2H, s, C<u>H</u>$_2$(COO-)$_2$), 3.28 (1H, d, J= 13.2 Hz, -S-CH_2-), 3.78 (2H, m, ^{i}Pr-C<u>H</u>), 4.22 (2H, q, J= 7.1 Hz, -O-C<u>H</u>$_2$-CH_3), 5.07 (1H, dd, J= 8.0 and 3.7 Hz, -COO-C<u>H</u>); ^{13}C-NMR ($CDCl_3$): see Table. Anal. Calcd for $C_{21}H_{37}NO_6S$: C, 58.43; H, 8.64; N, 3.24. Found: C, 58.20; H, 8.75; N, 3.22.

14-Ethoxycarbonyl-14-[(1'*S*,2'*R*,4'*R*)-*N*,*N*-diisopropylbornan-10'-sulfonamid-2'-oxycarbonyl]-1α-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]tetrahydropyranyl[2,3-*c*]quinolizine (6)

3.75 g (10.6 mmol) of 1-ethyl-1,2,3,4,6,7-hexahydro-12*H*-indolo[2,3-*a*]quinolizin-5-ium perchlorate (**1*HClO$_4$**) was portioned between 40 mL of CH_2Cl_2 and 30 mL of 2% aq. NaOH solution. After 10 min vigorous stirring the phases were separated, the organic phase was dried over $MgSO_4$ and evaporated in vacuum to dryness. The residual Wenkert enamine (**1**) was dissolved in 20 mL of ethanol, and to this mixture 5.50 g (12.7 mmol) of ethyl [(1'*S*,2'*R*,4'*R*)-*N*,*N*-diisopropylbornan-10'-sulfonamid-2'-yl]malonate (**5**) and 0.80 g (26.7 mmol) of paraformaldehyde were added. The reaction mixture was stirred at rt for 3 d. The precipitated crystals were separated by filtration, washed twice with small portions of cold ethanol and dried in dessicator over P_2O_5 yielding 6.36 g (82.4 %) pale yellow crystals. mp 170-172 °C; $[\alpha]^{23}_{546}$ =

76.0° (c 0.974, CH_2Cl_2); IR (KBr): 3400 (indole-NH), 2980, 1740 (C=O), 1710 (C=O) cm^{-1}; MS m/z (%): 725 (M^+, only in enhanced spectra), 427 (30.5), 252 (35.4), 237 (100.0), 134 (20.5), 126 (59.5); ^{1}H-NMR ($CDCl_3$): 0.74 (3H, t, J= 6.9 Hz, -O-CH_2-C<u>H</u>$_3$), 0.89 (3H, s, bornane-CH_3), 0.98 (3H, s, bornane-CH_3), 1.0-4.5 (other aliphatics), 1.34 and 1.36 (12H, d, J= 7.0 Hz, ^{i}Pr-CH_3), 2.80 (1H, d, J= 13.4 Hz, -S-CH_2-), 3.31 (1H, d, J= 13.4 Hz, -S-CH_2-), 3.89 (2H, m, ^{i}Pr-C<u>H</u>), 4.20 (1H, d, J= 13.1 Hz, ether O-CH_2-), 4.25 (2H, q, J= 6.9 Hz, -COO-C<u>H</u>$_2$-CH_3), 4.80 (1H, d, J= 13.1 Hz, ether O-CH_2-), 5.20 (1H, dd, J= 7.4 and 2.9 Hz, -COO-C<u>H</u>), 7.0-7.7 (4H, m, aromatics), 9.50 (1H, br, indole-NH); ^{13}C-NMR ($CDCl_3$): see Table. Anal. Calcd for $C_{40}H_{59}N_3O_7S$: C, 66.17; H, 8.19; N, 5.78. Found: C, 66.03; H, 7.94; N, 5.67.

C-2 Diastereomeres of ethyl {(1''*S*,2''*R*,4''*R*)-*N*,*N*-diisopropylbornan-10''-sulfonamid-2''-yl} 2-{(1'α-ethyl-1',2',3',4',6',7',12',12b'α-octahydroindolo[2',3'-*a*]quinolizin-1'β-yl)methyl}malonate (8)

5.63 g (7.75 mmol) of **6** "ether" was hydrogenated over 0.7 g of 10% Pd/C in a mixture of DMF (56 mL) and acetic acid (1.2 mL, 21.0 mmol) under atmospheric pressure. After the H_2 consumption had ceased, the catalyst was removed by filtration, washed with ethanol and the filtrate was evaporated in vacuum. The residue was treated with 10% aqueous $NaHCO_3$ solution, triturated, collected by filtration and washed successively with two portions of cold water, to give 5.56 g of beige crystals (mainly the hydroxymethyl-group containing **7** together with some **8**), which was dissolved in ethanol (65 mL), 2.5 g silica gel (Merck KG 60 PF 254) was added to it and the suspension was boiled under stirring for 1 h. Concentration under vacuum and filtration of a CH_2Cl_2 of the residual oil through celite and concentration again in vacuum gave 5.30 g (98%) of pale yellow oil. The product was a diastereomeric mixture at the C-2 carbon atom wearing the two carboxyl groups. $[\alpha]^{23}_{546}$ = -66.0° (c 0.053, CH_2Cl_2); IR (KBr): 3450 (indole-NH), 2780 (Bohlman-band), 1730 (C=O) cm^{-1}; MS m/z (%): 700 (1.0, M+3$^+$), 699 (3.5, M+2$^+$), 698 (10.9, M+1$^+$), 697 (23.4, M^+, $C_{39}H_{59}N_3O_6S$), 381 (5.1), 307 (4.1), 268 (20.9), 267 (100.0), 252 (6.8), 237 (7.2), 135 (8.3), 86 (28.2).

A small part of the above mentioned isomeric product was purified by preparative TLC (silica gel 60 PF 254, eluted with CH_2Cl_2-MeOH 20:1 and dissolved with CH_2Cl_2-MeOH 4:1) giving two fractions containing one of the isomers as main component in it, respectively. Being not perfectly pure isomers in the samples the spectral interpretation can contain some uncertainty, but regarding that none of the protonation shift of the methyl-groups of 1-ethyl could be found under 1 ppm in both spectra it can be concluded that in both isomers the 12b-H atom and the C-1-ethyl groups have the *cis* orientation.

Product with the higher R_f value: ^{1}H-NMR ($CDCl_3$): 0.83 (6H, s, bornane-CH_3), 1.0-3.5 (aliphatics), 1.28 (6H, d, J= 7.1 Hz, ^{i}Pr-CH_3), 1.35 (6H, d, J= 7.1 Hz, ^{i}Pr-CH_3), 3.73 (2H, m, ^{i}Pr-C<u>H</u>), 4.05 (2H, q, J= 6.9 Hz, -COO-C<u>H</u>$_2$-CH_3), 4.90 (1H, dd, J= 7.1 and 2.9 Hz, -COO-C<u>H</u>=), 7.0-7.5 (4H, m, aromatics), 7.96 (1H, br, indole-NH); ^{13}C-NMR ($CDCl_3$): see Table.

Product with the lower R_f value: ^{1}H-NMR ($CDCl_3$): 0.85 (6H, s, bornane-CH_3), 1.0-3.8 (m, aliphatics), 4.02 (2H, q, J= 6.9 Hz, -COO-C$\underline{H}_2$-CH_3), 4.96 (1H, dd, J= 7.1 and 2.9 Hz, -COO-C$\underline{H}$=), 7.0-7.6 (m, aromatics), 7.90 (1H, br, indole-NH); ^{13}C-NMR ($CDCl_3$): see Table.

C-2 Diastereomeres of {(1''*S*,2''*R*,4''*R*)-*N*,*N*-diisopropylbornan-10''-sulfonamid-2''-yl} 2-{(1'α-ethyl-1',2',3',4',6',7',12',12b'α-octahydroindolo[2',3'-*a*]quinolizin-1'β-yl)methyl}malonate (9)

5.16 g (7.30 mmol) of **8** diester was solved in the mixture of 70 mL of ethanol and 8.8 mL of (6.4 w%) of aqueous potassium hydroxide solution and the mixture was stirred for 2 d at ambient temperature. After adding 0.60 mL (10.4 mmol) of acetic acid it was evaporated in vacuum. The residue was portioned between water and CH_2Cl_2. After separation of the phases the aqueous phase was extracted twice more with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and evaporated in vacuum to dryness. The residue was triturated in n-hexane, filtered off and washed twice with n-hexane yielding 4.80 g of yellow solid, mp 127-130 °C; $[\alpha]^{24}_{546}$ = -108.9° (c 0.560, DMF); IR (KBr): 3450 (indole-NH), 2850-2780 (Bohlman-bands), 1720 (C=O), 1600 cm^{-1}; MS m/z (%): 624 (46.9), 623 (15.6), 325 (14.0), 308 (20.3), 267 (100.0). ^{1}H-NMR ($CDCl_3$): 0.9-4.0 (aliphatics), 0.98 and 1.04 (bornane-CH_3), 4.90 (br, -COO-C$\underline{H}$=), 6.8-7.6 (aromatics), 8.40 (br, indole-NH); ^{13}C-NMR ($CDCl_3$): see Table.

(-)-{(1''*S*,2''*R*,4''*R*)-*N*,*N*-Diisopropylbornan-10''-sulfonamid-2''-yl} 3-{1'α-ethyl-1',2',3',4',6',7', 12', 12b'α-octahydroindolo[2',3'-*a*]quinolizin-1'β-yl}propionate (10)

2.49 g (3.7 mmol) of the **9** monoester diastereomeres were decarboxylated by refluxing them in dry benzene (25 mL) for 4.5 h. Evaporation in vacuum yielded 2.5 g of crude **10** ester.

A small part of the above product was purified by preparative TLC (silica gel 60 PF 254, elution with benzene-methanol 14:3; dessolving with CH_2Cl_2-MeOH 4:1). mp 194 °C; $[\alpha]^{22}_{546}$ = -106,7° (c 0.516, CH_2Cl_2); IR (KBr): 3420 (indole-NH), 2800-2750 (Bohlman-bands), 1720 (C=O) cm^{-1}; MS m/z (%): 627 (3.9, M+2$^-$), 626 (13.0, M+1$^+$), 625 (32.2, M$^+$), 624 (11.4), 462 (5.6), 326 (14.3), 309 (21.0), 267 (100.0), 198 (10.6), 197 (20.1), 170 (17.4), 169 (12.5); ^{1}H-NMR ($CDCl_3$): 0.70, 0.75, 0.80 (s, bornane-C$\underline{H}_3$), 1.15 (t, J= 7.1 Hz, CH_2-C$\underline{H}_3$), 1.20, 1.26 (d, J= 7.1 Hz, ^{i}Pr-C$\underline{H}_3$), 1.30-3.25 (other aliphatics), 3.35 (s, 12b'-H), 3.62, 3.64 (m, ^{i}Pr-C$\underline{H}$=), 4.85 (m, -COO-C$\underline{H}$), 6.95-7.50 (m, aromatics), 7.80 (s, indole-NH); ^{13}C-NMR ($CDCl_3$): see Table. Anal. Calcd for $C_{36}H_{55}N_3O_4S$: C, 69.08; H, 8.85; N, 6.71. Found: C, 68.83; H, 8.63; N, 6.58.

(-)-(1'*S*,12b'*S*)-3-(1'α-Ethyl-1',2',3',4',6',7',12',12b'α-octahydroindolo[2',3'-*a*]quinolizin-1'β-yl)-propionic acid (11)

2.50 g (3.7 mmol) of crude **10** *cis*-adduct-ester was dissolved in ethanol (47 mL). 3.8 mL (7.2 mmol) of 7 w% aqueous sodium hydroxide solution was added and the mixture was refluxed for 12 h. Adding 7 mL of water to the evaporated residue it was extracted with ether (3x6 mL).

The combined ethereal phases were washed with brine, dried ($MgSO_4$) and evaporated. The rest was crystallized from n-hexane yielding 0.93 g (79 % for this single step, or 54 % based on the totally used amount of **5**) chiral alcohol (**4**).

The rest of the ether from the above prepared aqueous phase was eliminated by a short evaporation in vacuum at rt, then acidified to pH 6 by addition of acetic acid (*ca.* 0.43 mL) and was extracted four times with 8 mL portions of chloroform. The combined organic extracts were dried ($MgSO_4$), evaporated and triturated with n-hexane. The solid was filtered off and washed twice with cold hexane yielding 1.14 g (87 %) yellowish solid. The combined chemical yield based on the consumpted **1** was 78 %. mp 125 °C (lit.,[4] 136-140 °C); The IR, ms, ^{1}H- and ^{13}C-NMR spectral properties were identical to the authentic sample. $[\alpha]^{22}_{546}$ = -146.0° (c 0.678, DMF); $[\alpha]^{24}_{546}$ of the reference sample[4] = -151.7° (c 0.957, DMF); e.e.= 96%

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