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Synthesis of the Oxindole Alkaloid (–)-Horsfiline

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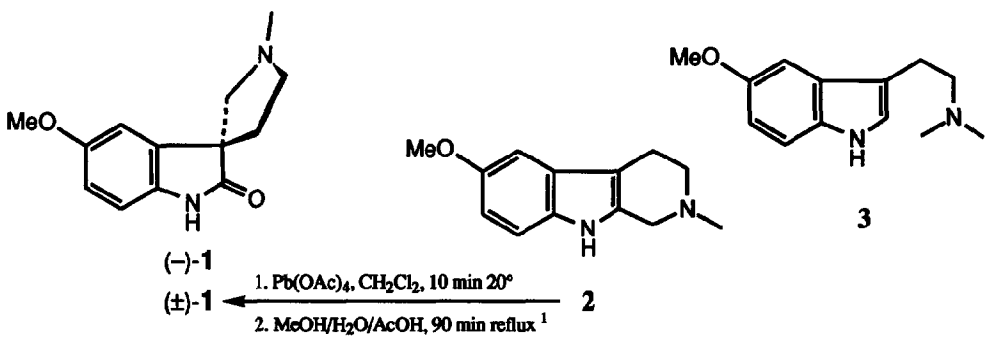
Abstract: A synthesis of (–)-horsfiline ((–)-**1**), a metabolite isolated recently from *Horsfieldia superba*, is described. The diastereoface selectivity of the crucial oxidative rearrangement of chiral tetrahydro-β-carboline precursors into the corresponding oxindoles was investigated in some detail and found to depend critically on the substitution pattern of the aliphatic amino group. These findings were exploited for the preparation of (–)-**1**, as well as of the unnatural optical antipode (+)-**1**, starting from 5-hydroxy-L-tryptophan as the single source from the chiral pool.

INTRODUCTION

In 1991 *Bodo* and co-workers isolated three indole alkaloids from the medicinal plant *Horsfieldia superba*, which grows in South East Asia [1]. Apart from the known achiral metabolites **2** and **3** *(Scheme 1)*, they isolated a novel oxindole alkaloid that was named horsfiline. The Malayan-French team deduced structure **1** for this compound on the basis of spectroscopic evidence and they corroborated their proposal through a two-step conversion of **2** into racemic **1** in 19 % yield. A second synthesis of (±)-**1** was reported in 1992 by *Jones* and *Wilkinson* who relied on a radical cyclization as the key step in their approach [2]. Very recently two alternative routes to (±)-**1** have been disclosed by a French team, one involving an oxidative rearrangement of a tetrahydro-γ-carboline derivative and the other a spirocyclization between 2-oxo-5-methoxytryptamine and formaldehyde [3].

Scheme 1

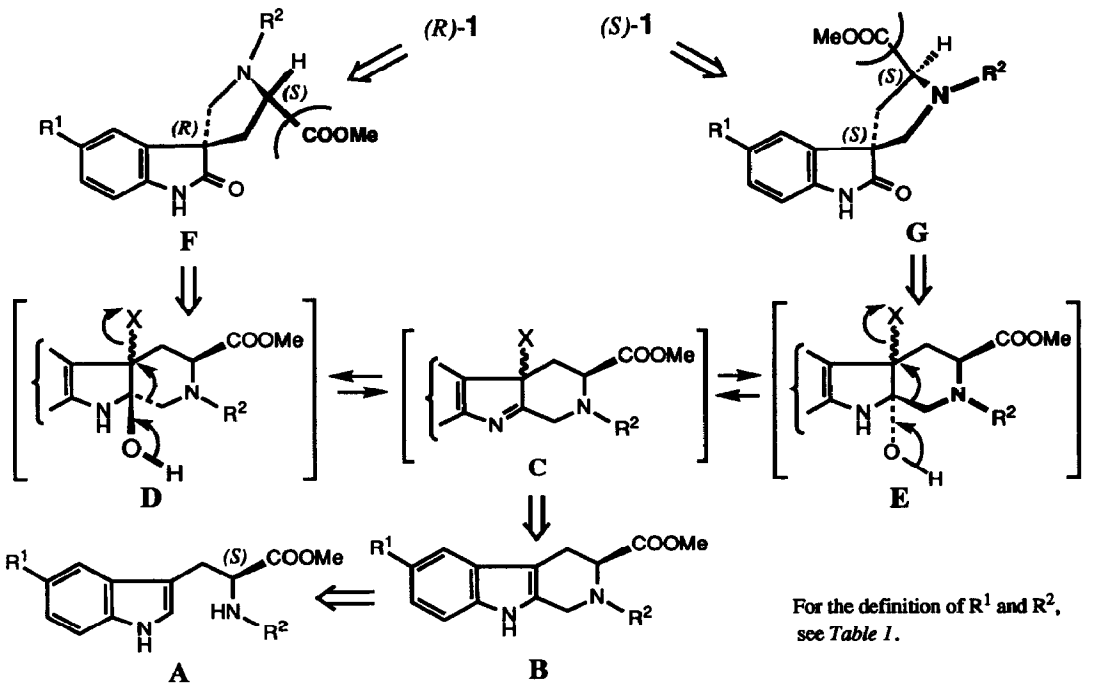


Since the absolute configuration of (–)-**1** was not known at the time we initiated the project outlined below, it was planned to develop an unambiguous enantioselective synthesis which should furnish both optical antipodes of horsfiline with established absolute configuration [4]. To solve this problem, we decided to take recourse to a chiral handle which would eventually be removed at a later stage of the synthesis, namely subsequent to creation of the chiral spiro centre. This strategy circumvents the problem of an enantioselective oxidation of **2** and merely calls for control over the diastereoselectivity in the crucial rearrangement step.

RESULTS AND DISCUSSION

The retrosynthetic scheme presented below illustrates the chosen approach. Provided that the diastereoisomeric oxindole intermediates **F** and **G** can be separated or prepared diastereoselectively, a single optically pure tetrahydro-β-carboline derivative **B** could serve as the common precursor for both optical antipodes of horsfiline (**1**). This approach seemed all the more attractive because the required compounds of type **B** can readily be prepared by means of a *Pictet-Spengler* condensation between commercially available L-tryptophan derivatives of general structure **A** and formaldehyde [5].

Scheme 2



Model studies with the more readily available demethoxy compounds **4**, **5**, and **6** allowed us to draw the following conclusions (see *Scheme 3* and *Table 1*, entries 1-3): a) the one-pot oxidation-rearrangement sequence (*N*-bromosuccinimide / H_2O / AcOH) [6] furnishes the desired oxindoles in fair to good yields, b) the resulting mixtures of the **F**- and **G** type isomers can readily be analyzed by ^{1}H-NMR spectroscopy, c) the relative configuration (and therefore also the absolute configuration at the crucial spiro centre) can be deduced unambiguously by means of NOE difference experiments, and d) the diastereoselectivity of the reaction sequence depends critically on the nature of the *N*-substituent R^2 (for a discussion, see below).

The required intermediates (+)-**7** and (–)-**8** were prepared in optically pure form as shown in *Scheme 4*. Using a slightly modified version of *Brossi*'s protocol [7], we transformed the hydrochloride of the commercially available (*S*)-5-hydroxytryptophan into (–)-**20** in virtually quantitative yield. The method of choice for the *O*-methylation of the derived protected compound (+)-**21** turned out to be treatment with TMS-diazomethane in the presence of *Hünig*'s base, which furnished (+)-**7** in very high yield [8]. The *N*-methyl analogue (–)-**8** was prepared from (+)-**7** through deprotection, followed by the reductive amination [9]. Surprisingly, this reaction led to a 1:3-mixture of two compounds, the minor component representing the desired target (–)-**8**. The NMR- spectroscopic data obtained for the major product points to structure **23** for this compound, and it turned out that treatment of the alleged betain with Et_3N in boiling THF led to quantitative formation of (–)-**8** [10].

Scheme 3

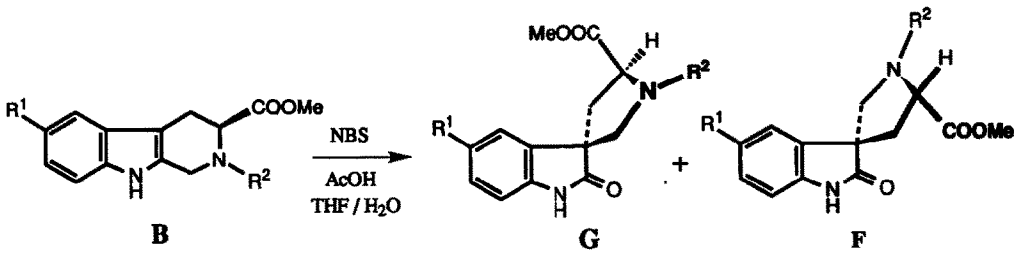


Table 1. Diastereoselectivity of the Oxidative Rearrangement of Indole Precursors 4-8.

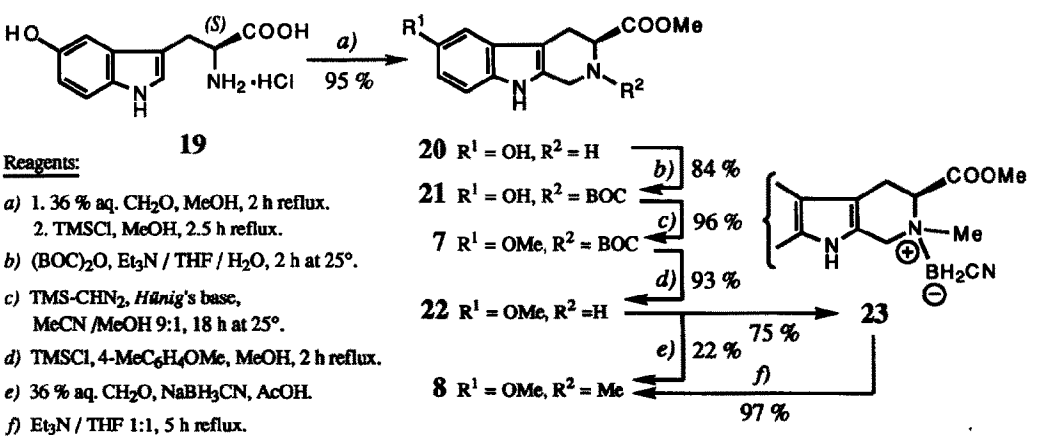
Entry	B	R^1	R^2	Conditions	G			F	Comb. Yield
1	**4**	H	H	2 h at 0°	**9**	3.1	: 1	**14**	81 %
2	**5**	H	Z	5 min at – 5°	**10**	1	: 4.2	**15**	84 %
3	**6**	H	Me	1 h at 0°	**11**	> 95	: 5	**16**	50 %
4	**7**	OMe	BOC	40 min at – 15°	**12**	1	: 12	**17**	83 %
5	**8**	OMe	Me	20 min at – 10°	**13**	> 95	: 5	**18**	50 %

Z = $C(=O)OCH_2Ph$
BOC = $C(=O)OC(CH_3)_3$

(*S*)-**1** (*R*)-**1**

As in the above-mentioned model experiments, the diastereoselectivity of the oxidative rearrangement of (+)-**7** and (–)-**8** was remarkably divergent (see *Table 1*, entries 4 and 5). In the former case the stereochemistry at the spiro centre relative to the pre-existing chiral centre could be determined for both epimers formed with the aid of NOE difference experiments. The major diastereoisomer ((–)-**17**) was analyzed after deprotection and *N*-methylation. The resulting oxindole (–)-**18** (*Scheme 5*) was shown to represent the *unlike* (3*R*, 3'*S*)-isomer (see *Figure 1*). The data presented in *Tables 2* and *3* shows that while the ^{13}C-NMR chemical shifts are of little use for assigning the relative configuration, the difference between the ^{1}H-NMR δ-values of the two methylene protons at C(1') seems to be of diagnostic value: in the G-series Δδ ranges from 0.10 to 0.29 ppm, as compared to 0.42-0.94 ppm in their F-type counterparts.

Scheme 4



Reagents:

a) 1. 36 % aq. CH_2O, MeOH, 2 h reflux. 2. TMSCl, MeOH, 2.5 h reflux.

b) $(BOC)_2O$, Et_3N / THF / H_2O, 2 h at 25°.

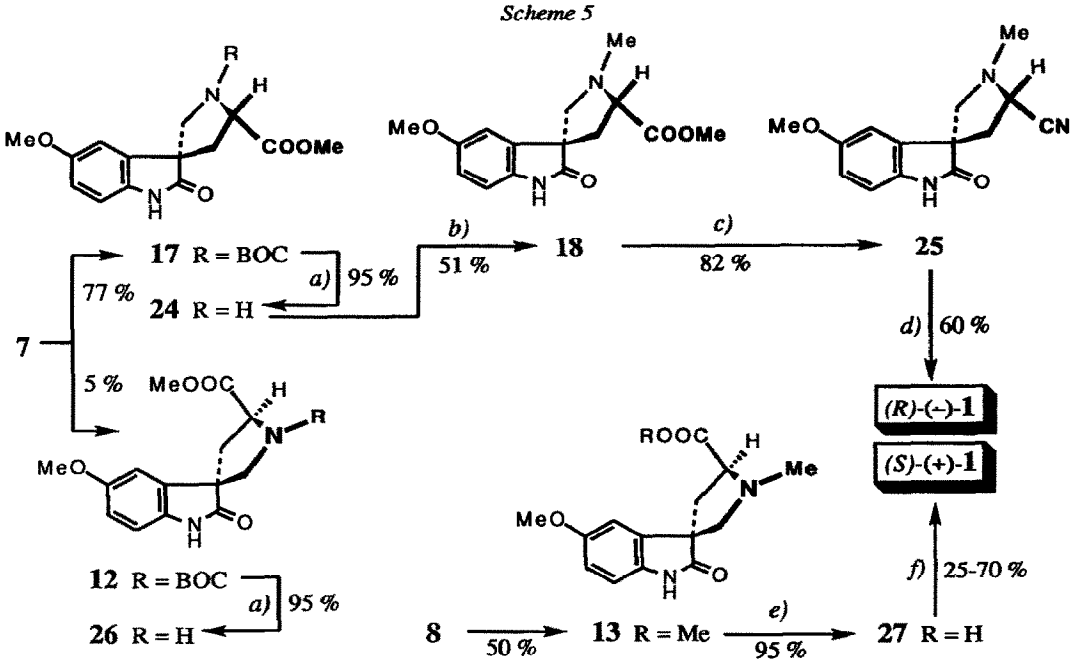
c) TMS-CHN_2, *Hünig*'s base, MeCN /MeOH 9:1, 18 h at 25°.

d) TMSCl, 4-MeC_6H_4OMe, MeOH, 2 h reflux.

e) 36 % aq. CH_2O, $NaBH_3CN$, AcOH.

f) Et_3N / THF 1:1, 5 h reflux.

Scheme 5



Reagents: a) TMSCl, MeOH, 2 h refl. b) 1. 5 eq. 36 % aq. CH_2O, $NaBH_3CN$, AcOH, 25°; 2. MeOH/2N HCl 5:1, 3 h refl. c) 1. NH_3, MeOH, 48 h 25°; 2. $(CF_3CO)_2O$, dioxane, pyridine 2 h 25°; d) $NaBH_4$, EtOH, pyridine, 12 h at 40°. e) 1N NaOH, MeOH. f) 1. $ClCOOCH_2CHMe_2$, N-Me-morpholine; 2. 2-mercaptopyridine-N-oxide, Me_3CSH, hv.

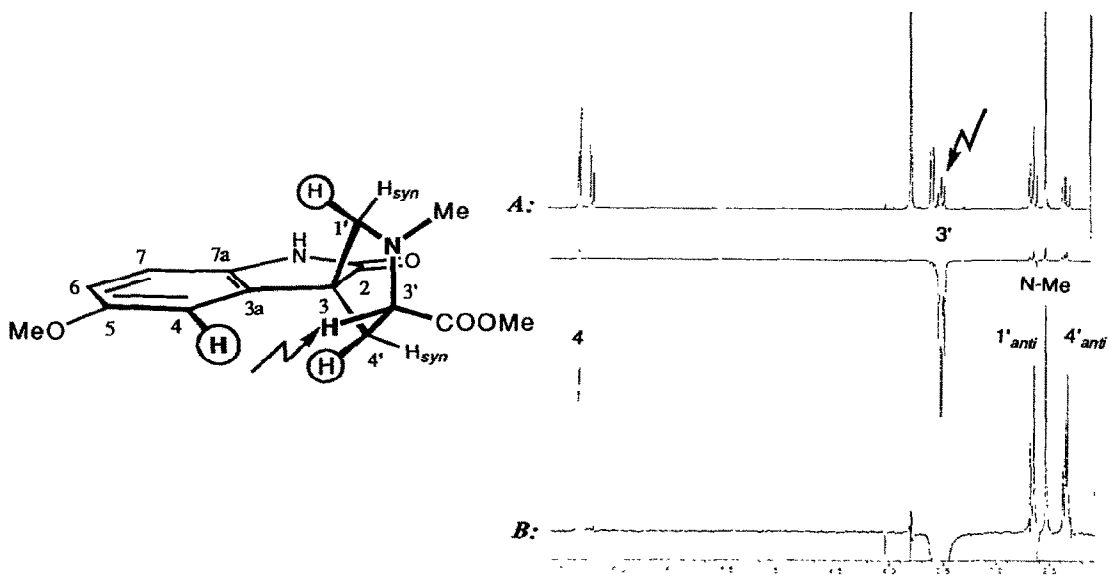
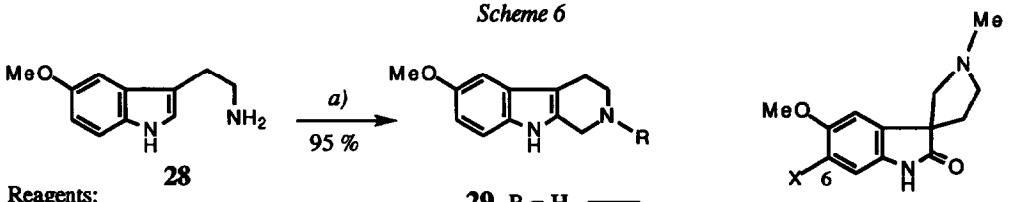


Figure 1. ^{1}H-NMR Spectra of 18, A: Regular, B: NOE Difference Spectrum upon Irradiation at 3.51 ppm.

The removal of the now uncalled-for carbomethoxy group in the intermediates (–)-**13** and (–)-**18** presented some problems: whereas the *Barton* method [11] worked reasonably well in the former case and finally furnished the unnatural enantiomer (+)-horsfiline ((+)-**1**), the same procedure, when applied to (–)-**18**, produced very disappointing results (at most 5 % yield) [12]. However an alternative method that involves reductive removal of the cyano group in the corresponding nitrile **25** proved quite satisfactory [13], giving (*R*)-(–)-**1** in reasonable overall yield. The material obtained this way was identical with a sample of natural horsfiline [14], thus defining the absolute configuration of the natural product to be as shown in *Scheme 1* [4].

Since the final products are expected to racemize under acidic or basic conditions [15], the optical purity of both samples of horsfiline was checked through ^{1}H-NMR spectroscopy of their salts with *Mosher's* acid and shown to exceed 95 % e.e. (see *Exper. Part, Figure 2)* [16]. The required reference sample of racemic **1** was prepared as shown in *Scheme 6*. Whereas the *Pictet-Spengler* condensation between 5-methoxytryptamine (**28**) and CH_2O proceeded in very high yield [17], the oxidative rearrangement of **30** led to an unseparable mixture of (±)-**1** and the corresponding 6-bromo derivative (±)-**31** which, however, could be quantitatively debrominated by means of catalytic hydrogenation to give (±)-**1** [6].

Scheme 6



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Reagents:

a) 38 % aq. CH_2O, TMSCl.

b) 1. 38 % aq. CH_2O, $NaBH_3CN$.

2. *N*-methylmorpholine, THF, 12 h reflux.

c) NBS, H_2O / AcOH, -10°.

d) H_2, Pd / C.

The observed changes of the diastereoselectivity during the oxidative rearrangement of the indole precursors deserve some comment: it seems as if the hybridization of the piperidine *N*-atom would dictate the stereochemical outcome, because it determines the ground-state conformation of the starting materials; in the case of **6** or its protonated form **6'** (*Scheme 7*) the carbomethoxy group presumably occupies preferentially an equatorial position, whereas the corresponding carbamates are present as 1:1-mixtures of two rotamers around the amide bond (**7** and **7'**, for instance), in both of which the ester group is axially oriented [18]. Maximum overlap of the relevant orbitals during the bromination step would lead to the axial *trans*- or *cis*-3-bromo-indolenines **34** and **37**, respectively [19].

Seemingly, the following addition of water to the imine group also proceeds under stereoelectronic control, requiring a previous conformational change of ring C. In both series the resulting *cis*-bromohydrins have perfectly aligned bonds for the subsequent pinacol-type rearrangement that leads to the observed major products **11** and **17**, respectively.

CONCLUSION

Both optical antipodes of horsfiline (**1**) have been synthesized in about 10 steps and satisfactory overall yields from the same enantiomer of the starting tryptophan derivative. The success of the chosen approach bodes well for analogous preparations of alkaloids endowed with similar structures.

Scheme 7

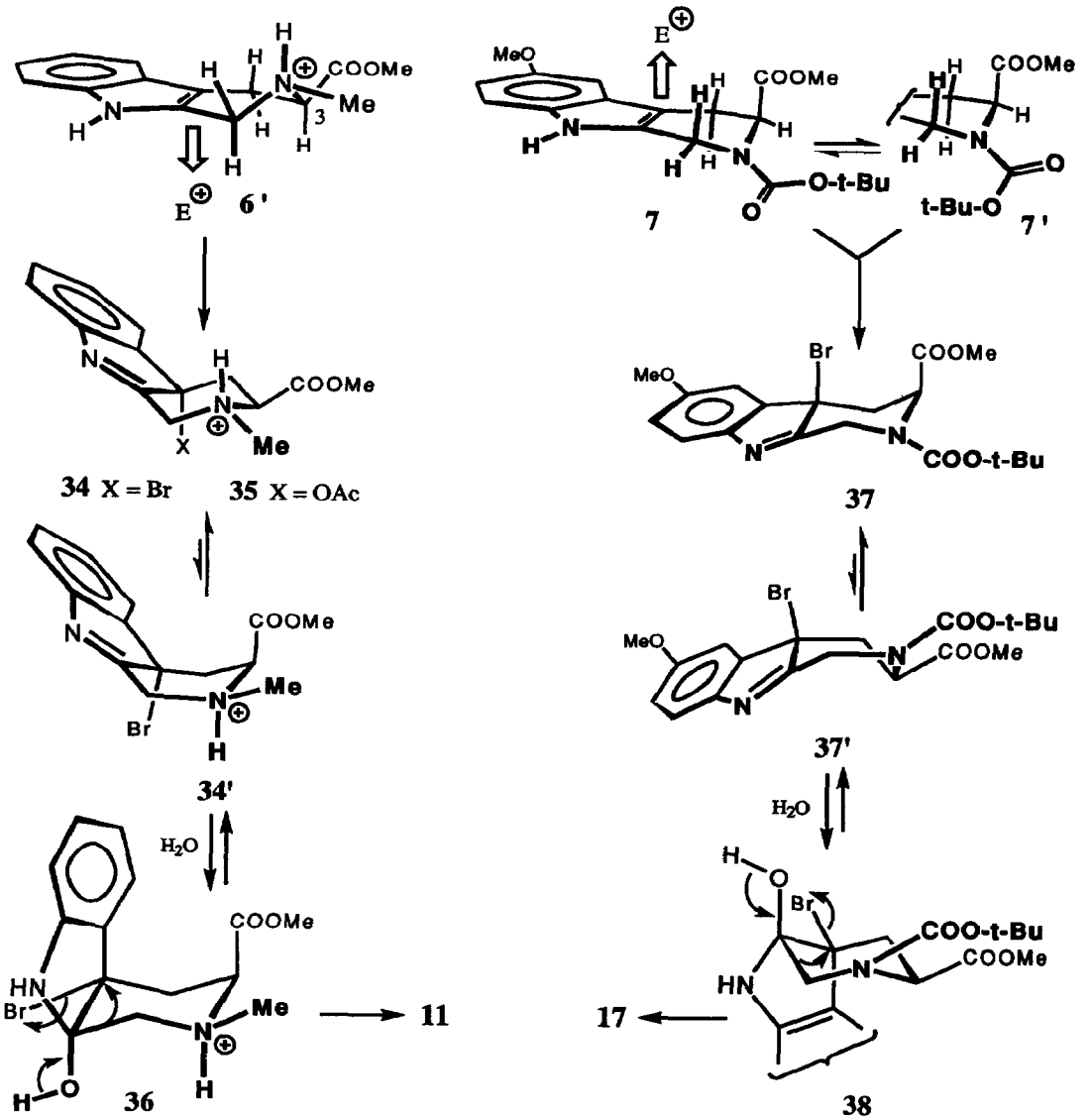

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Table 2. ^{13}C-NMR Chemical Shifts (ppm, rel. to TMS) of Some Spiro-Oxindoles in $CDCl_3$.

Series		G-Type					F-Type					
Cpd. / Carbon	1[a]	9	11	13	26	27	14	16	17	18	24	25
2	182.6	182.2	181.4	181.1	182.2	181.3	182.4	181.1	176.3	181.7	181.7	180.2
3	54.1	55.3	52.6	52.9	55.8	53.1	54.6	52.1	52.8	52.8	55.0	53.1
3a	137.6	132.5	135.3	136.0	134.0*	135.8	133.0	134.4	134.2	136.0	134.5	136.5
4	110.4	123.0*	124.2*	110.7	110.2°	111.9*	122.8*	123.2*	110.1	110.7*	110.0*	110.6*
5	156.2	122.8*	123.2*	156.4	156.4	157.6	122.7*	122.9*	155.1	156.1	156.3	156.4
6	112.5	128.1	128.0	113.4	112.9	115.5	128.2	128.3	112.7	112.4	112.7	112.8
7	109.8	109.8	109.5	109.8	110.0°	111.1*	110.0	109.7	109.3	110.4*	110.2*	110.5*
7a	133.4	140.4	139.9	133.0	133.9*	130.7	140.7	140.3	134.2	134.0	133.8	133.6
1'	66.3	58.9	65.9	65.6	59.0	63.4	58.3	65.5	54.7	65.5	58.3	64.1
3'	56.7	61.1	67.3	67.2	61.1	69.1	61.4	67.8	58.2	67.8	61.4	55.9
4'	38.1	41.4	41.1	41.3	41.5	41.1	41.6	41.6	39.3	41.7	41.7	41.8
COOMe	–	174.6	173.1	b)	174.6	169.0[c]	173.6	172.5	172.1	172.6	173.4	116.9[d]
COO*Me*	–	52.4	52.0	52.1	52.4	–	52.4	52.1	52.0	52.1	52.4	–
Ar-OMe	55.9	–	–	55.9	55.9	56.1	–	–	55.4	55.9	55.9	55.7
N-Me	41.8	–	40.8	40.7	–	42.6	–	40.2	–	40.2	–	38.3

* / ° Assignments may be interchanged.

[a] Assignments by *Bodo* and coworkers [1]. [b] Not detected. [c] COOH. [d] CN.

Table 3. ^{1}H-NMR Chemical Shifts (ppm, rel. to TMS) of Some Spiro-Oxindoles in $CDCl_3$.

Series		G-Type					F-Type				
Cpd. / H[a]	1	9	11	13	26	27[b]	14	16	18	24	25
4	6.97	7.28	7.59	7.28	6.92	7.23	7.25	7.27	6.86	6.88	6.99
5	–	7.06	7.06	–	–	–	7.04	7.06	–	–	–
6	6.67	7.22	7.21	6.74*	6.74	6.80	7.22	7.22	6.74	6.75	6.76
7	6.78	6.92	6.91	6.77*	6.83	6.88	6.94	6.90	6.87	6.83	6.90
1'*syn*	2.85	3.36	3.20	3.22	3.36	4.14	3.51	3.60	3.60	3.52	3.14
1'*anti*	2.81	3.26	2.91	2.92	3.24	3.64	3.09	2.70	2.66	3.08	2.95
3'	2.75/2.96	4.30	3.51	3.53	4.29	4.87	4.19	3.55	3.51	4.18	4.16
4'*syn*	2.05	2.31	2.26	2.26	2.28	2.61	2.44	2.66	2.65	2.49	2.73
4'*anti*	2.63	2.70	2.75	2.72	2.70	2.85	2.44	2.37	2.34	2.43	2.50
COOMe	–	3.82	3.79	3.80	3.81	–	3.79	3.80	3.80	3.80	–
Ar-OMe	3.73	–	–	3.78	3.79	3.78	–	–	3.79	3.79	3.79
N-Me	2.41	–	2.52	2.52	–	3.22	–	2.55	2.53	–	2.60

[a] Convention: *syn* means on the same side of the ring as the carbomethoxy group.

[b] As hydrochloride in CD_3OD.

EXPERIMENTAL PART

General. All solvents employed as reaction media were reagent grade *(Fluka, puriss.)* and were stored over molecular sieves (4Å). M.p. (not corrected): *Tottoli* apparatus, sealed evacuated capillaries, unless mentioned otherwise. Optical rotations: *Perkin-Elmer 241* at 25° and 589 nm (Na_D). IR spectra: *Perkin-Elmer 781*, ν_{max} in cm^{-1}. ^{1}H-NMR spectra (δ [ppm] from TMS, apparent coupling constants *J* [Hz]): 300 MHz: *Varian Gemini 300*; 400 MHz: *Bruker AMX 400*; 500 MHz: *Bruker AMX 500*. ^{13}C-NMR spectra (δ [ppm] from TMS, multiplicities as determined from DEPT spectra): 75 MHz: *Varian Gemini 300*; 100 MHz: *Bruker AMX 400*; 125 MHz: *Bruker AMX 500*. NOE: *Bruker WM 300* (300 MHz); irradiated proton → affected signal(s). Mass spectra (m/z [amu] (% base peak)): *Hitachi-Perkin-Elmer, VG TRIBRID* (EI: 70 eV, unless stated otherwise; FAB: in 3-nitrobenzyl alcohol as matrix).

A) Synthesis of (–)-(R)-Horsfiline ((–)-1)

(3S)-3-Carbomethoxy-6-hydroxy-1,2,3,4-tetrahydro-β-carboline ((–)-20). To a soln. of 3 g (13.6 mmol) of (L)-5-hydroxytryptophan (**19**) (*Fluka, puriss.*) in 40 ml of MeOH were added 15 ml of 2 N HCl. After stirring at 25° for 5 min the mixture was evaporated under reduced pressure. The residue was dissolved in 70 ml of MeOH and 1.32 ml (15 mmol) of 36% aq. formaldehyde were added. After 2 hours reflux the mixture was evaporated to yield 3.65 g of a buff foam which was dissolved in 80 ml of MeOH containing 3.6 ml of TMSCl. The mixture was refluxed for 150 min and evaporated to give 3.84 g (13.6 mmol, 99 %) of the hydrochloride of **20**.

M.p.: > 275° (dec.). $C_{13}H_{14}N_2O_3 \cdot HCl$ (282.73)

$[\alpha]_D$: - 37.1 (c=1.1, MeOH).

IR (KBr): 2954, 2743, 1739, 1598, 1438, 1354, 1262, 1214, 1137, 802.

^{1}H-NMR: (300 MHz, CD_3OD) 7.17(*dd*, *J*= 8.7, 0.3, 1H); 6.82(*dd*, *J*= 2.3, 0.3, 1H); 6.69(*dd*, *J*= 8.7, 2.3, 1H); 4.43(*m*, 2H); 4.40(*dd*, *J*= 10.4, 5.3, 1H); 3.90(*s*, 3H); 3.30(*dd*, *J*= 16.0, 5.3, 1H); 3.05(*dd*, *J*= 16.0, 10.4, 1H).

^{13}C-NMR: (75 MHz, CD_3OD) 170.8(*s*), 152.0(*s*), 133.2(*s*), 128.1(*s*), 127.4(*s*), 113.3(*d*), 112.8(*d*), 105.4(*s*), 103.3(*d*), 56.4(*d*), 53.8(*q*), 42.1(*t*), 23.6(*t*).

MS (FAB): 274(100, M^++1), 246(63, M^+), 176(24), 160(48), 154(59), 136(51), 89(25), 77(25).

(3S)-2-tert.-Butyloxycarbonyl-3-carbomethoxy-6-hydroxy-1,2,3,4-tetrahydro-β-carboline ((+)-21). To a soln. of 1.52 g (5.4 mmol) of (–)-**20** in a mixture of 20 ml of THF, 5 ml of H_2O and 1.65 ml of Et_3N that had been stirred at –15° for 5 min, were added 1.52 g (7 mmol) of di-*tert.*-butyl dicarbonate (*Fluka, purum*). After stirring at 25° for 2 h the mixture was worked up with aq. Na_2CO_3 and CH_2Cl_2 and the residue chromatographed (silica gel, hexane/EtOAc, gradient 4:1 to 1:1) to yield 1.57 g of a yellow solid (4.54 mmol, 84 %).

M.p.: 118° (dec.). $C_{18}H_{22}N_2O_5$ (346.41)

$[\alpha]_D$: + 97.1 (c=0.9, MeOH).

IR ($CHCl_3$): 3600, 3460, 1735, 1682, 1605, 1452, 1400, 1332, 1097, 1022, 900.

^{1}H-NMR: (300 MHz, $CDCl_3$) 8.16(br. *s*, 0.5H); 7.84(br.*s*, 0.5H); 7.09(*d*, *J*= 8.6, 0.5H); 7.05(*d*, *J*= 8.6, 0.5H); 6.91(*d*, *J*= 2.7, 0.5H); 6.90(*d*, *J*= 2.7, 0.5H); 6.71(*dd*, *J*= 8.6, 2.7, 0.5H); 6.68(*dd*, *J*= 8.6, 2.7, 0.5H); 5.58(br.*s*, 0.5H); 5.51(br.*s*, 0.5H); 5.40(*dd*, *J*= 6.2, 0.8, 0.5H); 5.19(*dd*, *J*= 6.2, 0.8, 0.5H); 4.84(*d*, *J*= 16.2, 0.5H); 4.78(*d*, *J*= 16.2, 0.5H); 4.54(*d*, *J*= 16.2, 0.5H); 4.47(*d*, *J*= 16.2, 0.5H); 3.61(*s*, 1.5H); 3.57(*s*, 1.5H); 3.32(*dm*, *J*=15.5, 1H); 3.02(*dd* , *J*= 15.5, 6.2, 1H); 1.53(*s*, 9H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 172.3(*s*), 172.2(*s*), 155.9(*s*), 155.7(*s*), 149.8(*s*), 149.6(*s*), 131.5(*s*), 130.8(*s*), 127.5(*s*), 127.3(*s*), 111.4(2x*d*), 111.3(*d*), 111.2(*d*), 105.8(*s*), 104.8(*s*), 103.1(*d*), 103.0(*d*), 81.4(s), 81.1(s), 53.8(*d*), 52.5(*d*), 52.4(*q*), 40.7(*t*), 40.3(*t*), 28.4(2x*q*), 23.4(*t*), 23.1(*t*).

MS (FAB): 347(15, M^++1), 346(22, M^+), 345(19), 289(23), 245(100), 231(14), 185(40), 160(31), 57(62).

(3S)-2-tert.-Butyloxycarbonyl-3-carbomethoxy-6-methoxy-1,2,3,4-tetrahydro-β-carboline ((+)-7). To a soln. of 1.22 g (3.53 mmol) of (+)-**21** in a mixture of 9 ml of acetonitrile and 1 ml of MeOH were added 1.82 ml (10.6 mmol) of ethyldiisopropylamine (*Fluka, purum*) and 5.3 ml (10.6 mmol) of a 2 N soln. of TMS-diazomethane in hexane (*Fluka, purum*). After stirring at 25° for 18 h in the dark there were added 0.7 ml of AcOH and stirring continued for 10 min. Then the mixture was evaporated under reduced pressure and the residue chromatographed (silica gel; hexane/EtOAc, gradient 4:1 to 1:1) to yield 1.15 g of a yellow solid (3.40 mmol, 96 %).

M.p.: 59-61°. $C_{19}H_{24}N_2O_5$ (360.41)

$[\alpha]_D$: + 127.2 (c=0.95, MeOH).

IR ($CHCl_3$): 3460, 3330, 1735, 1685, 1605, 1482, 1168, 1098, 1025.

^{1}H-NMR: (400 MHz, $CDCl_3$) 8.35(br.*s*, 0.5H); 7.82(br.*s*, 0.5H); 7.18(*d*, *J*= 8.7, 0.5H); 7.16(*d*, *J*= 8.7, 0.5H); 6.94(*s*, 0.5H); 6.93(*s*, 0.5H); 6.80(*d*, *J*= 8.7, 0.5H); 6.79(*d*, *J*= 8.7, 0.5H); 5.42(*dd*, *J*= 6.4, 1.2, 0.5H); 5.20(*dd*, *J*= 6.3, 1.3, 0.5H); 4.88(*d*, *J*= 16.2, 0.5H); 4.80(*d*, *J*= 16.2, 0.5H); 4.55(*d*, *J*= 16.2, 0.5H); 4.50(*d*, *J*= 16.2, 0.5H); 3.85(*s*, 3H); 3.63(*s*, 1.5H); 3.61(*s*, 1.5H); 3.40(*s*, 0.5H); 3.36(*s*, 1.5H); 3.09(*dt*, *J*=6.3, 1.3, 0.5H); 3.06(*dt*, *J*=6.4, 1.2, 0.5H); 1.53(*s*, 9H).

^{13}C-NMR: (125 MHz, $CDCl_3$) 172.1(2x*s*), 155.8(*s*), 155.6(*s*), 154.1(*s*), 154.0(*s*), 131.5(*s*), 131.4(*s*), 130.6(*s*), 130.5(*s*), 111.6(d), 111.5(d), 111.4(2xd), 106.2(s), 105.3(s), 100.5(2xd), 81.1(s), 80.9(s), 55.9(q), 53.8(*d*), 52.5(*q*), 52.4(*q*), 40.7(*t*), 40.4(*t*), 28.4(2x*q*), 23.5(*t*), 23.2(*t*).

MS (FAB): 361(44, M^++1), 360(55, M^+), 359(30), 305(38), 304(34), 303(33), 260(51), 259(100), 199(42), 174(43), 57(74).

*(3*R*, 3'*S*)-Oxindole (+)-24*. To a soln. of 2.3 g (6.4 mmol) of (+)-7 in a mixture of 140 ml of THF/AcOH/H_2O 3:2:2 which was stirred under Ar at –15° were added 1.2 g (6.7 mmol) of *N*-bromosuccinimide (*Fluka, purum*) in small portions. After stirring at –10° for 40 min in the dark there were added 150 ml of sat. aq. Na_2CO_3 soln. and the mixture was extracted with CH_2Cl_2 (3 x 100 ml). Chromatography (silica, hexane/EtOAc, gradient 4:1 to 1:1) gave 2.0 g (83 %) of a 8:1-mixture of **17** and **12** which was deprotected using *p*-methylanisole as scavenger [20]: the above mixture and 0.81 ml (6.4 mmol) of *p*-methylanisole (*Fluka, purum*) were dissolved in 100 ml of MeOH and treated with 0.81 ml (6.4 mmol) of TMSCl. The mixture was refluxed for 30 min and then allowed to stand at 25° for 12 h. Evaporation under reduced pressure, followed by workup with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 and chromatography (silica gel; EtOAc, gradient with 0-20 % of MeOH) furnished 1.3 g (74 % over both steps) of (+)-**24** as colorless crystals.

M.p.: 128°. $C_{14}H_{16}N_2O_4$ (276.29)

$[\alpha]_D$: + 61.2 (c=0.96, MeOH).

IR ($CHCl_3$): 3425, 1735, 1695, 1597, 1478, 1433, 1295, 1172, 1024.

^{1}H-NMR: (300 MHz, $CDCl_3$) 8.50(br. *s*, 1H); 6.88(*d*, *J*= 2.4, 1H); 6.83(*d*, *J*= 8.4, 1H); 6.75(*dd*, *J*= 8.4, 2.4, 1H); 4.18(*dd*, *J*= 8.4, 7.5, 1H); 3.80(*s*, 3H); 3.79(*s*, 3H); 3.52(*d*, *J*= 11.4, 1H); 3.05(*d*, *J*= 11.4, 1H); 2.69(br. *s*, 1H); 2.47(*dd*, *J*= 13.3, 7.5, 1H); 2.45(*dd*, *J*= 13.3, 8.4, 1H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 181.7(*s*), 173.4(*s*), 156.3(*s*), 134.5(*s*), 133.8(*s*), 112.7(*d*), 110.2(*d*), 110.0(*d*), 61.4(*d*), 58.3(*t*), 55.9(*q*), 55.0(*s*), 52.4(*q*), 41.7(*t*).

MS (EI): 276(31, M^+), 218(22), 217(81), 188(17), 177(21), 176(100), 160(20), 101(22).

*(3*R*, 3'*S*)-Oxindole (–)-18*. To a soln. of 0.30 g (1.09 mmol) of (+)-**24** in 10 ml of acetonitrile were added 0.46 ml of 36 % aq. CH_2O soln., 138 mg (2.2 mmol) of $NaBH_3CN$ (*Fluka, purum*), and 0.31 ml (5.5 mmol) of AcOH. The mixture was stirred at 25° for 2 h and then worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 to give the N(1)-hydroxymethyl derivative of **18** (93 % yield), which was cleaved through treatment with aq. 2 N HCl/MeOH 1:5 (3 h reflux). Evaporation under reduced pressure, followed by workup with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 and chromatography (silica gel; EtOAc) furnished 160 mg (0.55 mmol, 51 %) of (–)-**18** as a slightly yellow solid.

M.p.: 163°. $C_{15}H_{18}N_2O_4$ (290.32)

$[\alpha]_D$: – 9.5 (c=0.9, MeOH).

IR ($CHCl_3$): 3430, 1720, 1660, 1490, 1435, 1297, 1174, 1030.

^{1}H-NMR: (300 MHz, $CDCl_3$) 9.22(br. *s*, 1H); 6.87(*d*, *J*= 8.6, 1H); 6.86(*d*, *J*= 2.4, 1H); 6.74(*dd*, *J*= 8.6, 2.4, 1H); 3.80(*s*, 3H); 3.79(*s*, 3H); 3.60(*d*, *J*= 9.7, 1H); 3.51(*dd*, *J*= 8.9, 7.6, 1H); 2.66(*d*, *J*= 9.7, 1H); 2.65(*dd*, *J*= 12.9, 8.9, 1H); 2.53(*s*, 3H); 2.34(*dd*, *J*= 12.9, 7.6, 1H).

NOE: a) Irrad. at 3.51 (H-C(3')) → 4 signals at 6.86 (H-C(4)), 2.66 (H_{anti}-C(1')), 2.53 (CH_3-N), and 2.34 (H_{anti}-C(4')).
b) Irrad. at 2.34 (H_{anti}-C(4')) → 4 signals at 6.86 (H-C(4)), 3.51 (H-C(3')), 2.66 (H_{anti}-C(1')), and 2.65 (H_{syn}-C(4')). *(See Figure 1).*

^{13}C-NMR: (75 MHz, $CDCl_3$) 181.7(*s*), 172.6(*s*), 156.1(*s*), 136.0(*s*), 134.0(*s*), 112.4(*d*), 110.7(*d*), 110.4(*d*), 67.8(*d*), 65.5(*t*), 55.9(*q*), 52.8(*s*), 52.1(*q*), 41.7(*t*), 40.2(*q*).

MS (EI): 290(4, M^+), 231(100), 188(27), 175(15), 160(23), 115(13), 100(35).

*(3*R*, 3'*S*)-Oxindole (+)-25*. *A* soln. of 160 mg (0.55 mmol) of (–)-**18** in 12 ml of MeOH was saturated with gaseous NH_3 at 20° and stirred at 25° under an NH_3-atmosphere for 48 h. The mixture was evaporated and chromatographed (silica; EtOAc/MeOH 5:1) to yield 150 mg (0.54 mmol, 98 %) of the oily primary amide; 145 mg (0.53 mmol) of this material was suspended in 15 ml of 1,4-dioxane containing 0.13 ml of pyridine. The mixture was placed in an ultrasonic bath for 3 min and then were added 0.08 ml (0.58 mmol) of $(CF_3CO)_2O$ and stirring was continued for 90 min at 25°. Workup with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 gave a crude material which was chromatographed (silica; EtOAc, gradient with 0-20 % of MeOH) to yield 45 mg (0.16 mmol, 31 %) of the intermediate amide and 80 mg (0.31 mmol, 59 %) of (+)-**25** as a white solid.

M.p.: 115-116°. $C_{14}H_{15}N_3O_2$ (257.28)

$[\alpha]_D$: + 18.4 (c=1.1, MeOH).

IR ($CHCl_3$): 3420, 1710, 1472, 1432, 1297, 1171, 1035.

^{1}H-NMR: (300 MHz, $CDCl_3$) 9.18(br. *s*, 1H); 6.99(*d*, *J*= 2.6, 1H); 6.90(*d*, *J*= 8.5, 1H); 6.76(*dd*, *J*= 8.5, 2.6, 1H); 4.16(*dd*, *J*= 8.2, 3.3, 1H); 3.79(*s*, 3H); 3.14(*d*, *J*= 9.5, 1H); 2.95(*d*, *J*= 9.5, 1H); 2.73(*dd*, *J*= 13.6, 3.3, 1H); 2.60(*s*, 3H); 2.50(*dd*, *J*= 13.6, 8.2, 1H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 180.2(*s*), 156.4(*s*), 136.5(*s*), 133.6(*s*), 116.9(*s*), 112.8(*d*), 110.6(*d*), 110.5(*d*), 64.1(*t*), 55.9(*d*), 55.7(*q*), 53.1(*s*), 52.1(*q*), 41.8(*t*), 38.3(*q*).

MS (FAB): 257(2, M^+), 230(6), 202(32), 187(55), 175(34), 160(37), 82(53), 42(74), 27(100).

(R)-Horsfiline (–)-1. To a soln. of 60 mg (0.23 mmol) of (+)-25 in 3 ml of EtOH and 1 ml of pyridine were added 50 mg (1.31 mmol) of $NaBH_4$ (Fluka, purum) at 25° under Ar. The mixture was stirred at 40° for 12 h and then worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 to give a crude material that was chromatographed (silica; EtOAc/MeOH 5:1) to give 32 mg (0.138 mmol, 60 %) of (–)-1 as a colorless solid that was recrystallized from acetone.

M.p.: 123-125°. Lit.: 125-126° [1].

$[\alpha]_D$: – 7.0 (c=2.7, MeOH). Lit.: – 7.2 (c=1, MeOH) [1]. Hydrochloride: – 28 (c=0.6, MeOH).

IR-, ^{1}H-NMR-, and ^{13}C-NMR spectra agree with the ones of natural (–)-1 within experimental error [1,14].

B) Synthesis of (+)-(S)-*Horsfiline ((+)-1)*

(3S)-3-Carbomethoxy-6-methoxy-1,2,3,4-tetrahydro-β-carboline ((–)-22). To a soln. of 100 mg (0.28 mmol) of (+)-7 (see above) in 12 ml of MeOH were added 0.105 ml (0.83 mmol) of TMSCl and 0.105 ml (0.83 mmol) of p-methylanisol. The mixture was refluxed for 150 min and then evaporated under reduced pressure. Workup with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 furnished 67 mg (0.26 mmol, 93 %) of a as a white solid.

M.p.: 157°. $C_{14}H_{16}N_2O_3$ (260.29)

$[\alpha]_D$: - 40.2 (c=0.9, MeOH).

IR ($CHCl_3$): 3455, 1730, 1594, 1476, 1451, 1435, 1264, 1130.

^{1}H-NMR: (300 MHz, $CDCl_3$) 7.93(br. *s*, 1H); 7.15(*d*, *J*= 8.8, 1H); 6.92(*d*, *J*= 2.4, 1H); 6.79(*dd*, *J*= 8.8, 2.4, 1H); 4.05(*m*, 2H); 3.84(*s*, 3H); 3.79(*s*, 3H); 3.78(*dd*, *J*= 9.6, 4.8, 1H); 3.08(*dd*, *J*= 15.2, 4.8, 1H); 2.85(*ddt*, *J*= 15.2, 9.6, 1.8, 1H); 2.13(*s*, 3H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 173.8(*s*), 154.2(*s*), 132.9(*s*), 131.1(*s*), 127.7(*s*), 111.2(*d*), 111.1(*d*), 100.4(*d*), 56.0(*q*), 55.9(*d*), 52.2(*q*), 42.2(*t*), 25.4(*t*).

MS (EI): 260(27, M^+), 201(39), 184(10), 174(34), 173(100), 158(75), 130(15).

(3S)-3-Carbomethoxy-6-methoxy-2-methyl-1,2,3,4-tetrahydro-β-carboline ((+)-8). To a soln. of 388 mg (1.49 mmol) of (–)-22 in 10 ml of acetonitrile were added 0.62 ml (7.46 mmol) of 36 % aq. CH_2O soln., and after stirring at 25° for 15 min 220 mg (2.98 mmol) of $NaBH_3CN$ (*Fluka, purum*) and 0.43 ml (7.5 mmol) of AcOH were added. Stirring was continued for 1 h and then the mixture was evaporated under reduced pressure and worked up with sat. aq. Na_2CO_3 soln. The resulting BH_2CN-complex of (+)-8 was refluxed for 2 h in 12 ml of THF containing 20 % of triethylamine. The crude material was chromatographed (silica gel; EtOAc, gradient with 0-20 % of MeOH) to yield 325 mg (1.19 mmol, 80 %) of (+)-8 as a slightly yellow oil.

M.p.: Oil. $C_{15}H_{18}N_2O_3$ (274.31)

$[\alpha]_D$: + 40.7 (c=0.85, MeOH).

IR ($CHCl_3$): 3470, 1765, 1482, 1454, 1435, 1171, 1151, 1034, 1025.

^{1}H-NMR: (400 MHz, $CDCl_3$) 7.81(br. *s*, 1H); 7.14(*d*, *J*= 8.7, 1H); 6.92(*d*, *J*= 2.4, 1H); 6.78(*dd*, *J*= 8.7, 2.4, 1H); 4.05(*d*, *J*= 15.2, 1H); 3.84(*s*, 3H); 3.79(*d*, *J*= 15.2, 1H); 3.72(*t*, *J*= 5.5, 1H); 3.70(*s*, 3H); 3.12(*ddt*, *J*= 15.5, 5.5, 1.5, 1H); 3.06(*ddt*, *J*= 15.5, 5.5, 1.5, 1H); 2.58(*s*, 3H).

^{13}C-NMR: (100 MHz, $CDCl_3$) 173.0(*s*), 154.0(*s*), 132.0(*s*), 131.2(*s*), 127.5(*s*), 111.4(*d*), 111.2(*d*), 105.7(*d*), 100.3(*d*), 61.5(*d*), 55.9(*q*), 51.7(*q*), 49.3(*t*),41.9(*q*), 23.5(*t*).

MS (FAB): 275(27, M^++1), 274(100, M^+), 215(53), 213(26), 174(42), 173(32).

(3R, 3'R)-Oxindole (–)-13. To a soln. of 85 mg (0.31 mmol) of (+)-8 in a mixture of 4.5 ml of THF/AcOH/H_2O 5:6:4 which was stirred under Ar at – 5° were added 61 mg (0.34 mmol) of *N*-bromosuccinimide (*Fluka, purum*) in small portions. After stirring at – 5° for 20 min in the dark the mixture was worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2. Chromatography (silica, EtOAc, gradient with 0-20 % of MeOH) gave 50 mg (56 %) of (–)-13 as a yellowish oil.

M.p.: Oil. $C_{15}H_{18}N_2O_4$ (290.29)

$[\alpha]_D$: – 44.8 (c=2.5, MeOH).

IR ($CHCl_3$): 3680, 3440, 1720, 1605, 1485, 1447, 1300, 1178, 1035, 905.

^{1}H-NMR: (500 MHz, $CDCl_3$) 7.93(br. *s*, 1H); 7.28(*d*, *J*= 2.5, 1H); 6.77(*dd*, *J*= 8.4, 0.5, 1H); 6.74(*dd*, *J*= 8.4, 2.5, 1H); 3.80(*s*, 3H); 3.78(*s*, 3H); 3.53(*m*, 1H); 3.22(br. *d*, *J*= 9.2, 1H); 2.92(*d*, *J*= 9.2, 1H); 2.72(*dd*, *J*= 13.2, 8.8, 1H); 2.52(*s*, 3H); 2.26(*d*, *J*= 13.2, 7.9, 1H).

NOE: a) Irrad. at 3.22 (H_{syn}-C(1')). → 3 signals at 7.28 (H-C(4)), 2.92 (H_{anti}-C(1')), and (weak) 2.52 (CH_3-N).
b) Irrad. at 2.92 (H_{anti}-C(1')) → 4 signals at 7.93 (H-N(1)), 3.53 (H-C(3')), 3.22 (H_{syn}-C(1')), 2.66 (H_{anti}-C(1')), and 2.52 (CH_3-N).
c) Irrad. at 2.26 (H_{syn}-C(4')). → 3 signals at 7.28 (H-C(4)), 3.53 (H-C(3')), 2.72 (H_{anti}-C(4')).

^{13}C-NMR: (125 MHz, $CDCl_3$) 181.1(*s*), 177.0(*s*), 156.4(*s*), 136.0(*s*), 133.0(*s*), 113.4(*d*), 110.7(*d*), 109.8(*d*), 67.2(*d*), 65.6(*t*), 55.9(*q*), 52.9(*s*), 52.1(*q*), 41.3(*t*), 40.7(*q*).

MS (FAB): 291(100, M^++1), 290(37, M^+), 289(44), 231(70), 107(24), 77(21).

(3R, 3'R)-Oxindole (+)-27. To a soln. of 50 mg (0.17 mmol) of (–)-13 in 2 ml of MeOH were added 0.27 ml of 1 N NaOH. After stirring at 25° under Ar the mixture was concentrated and the residue dissolved in 0.5 ml of 2 N HCl. After filtration and evaporation of the filtrate 39 mg (0.12 mmol, 70 %) of the hydrochloride of (+)-27 were obtained (colorless crystals).

M.p.: > 200°, dec. $C_{14}H_{16}N_2O_4 \cdot HCl$ (312.6)

$[\alpha]_D$: + 14.8 (c=2.1, MeOH).

^{1}H-NMR: (300 MHz, CD_3OD) 7.23(*d*, *J*= 2.0, 1H); 6.88(*dd*, *J*= 9.0, 1.0, 1H); 6.83(*dd*, *J*= 9.0, 2.0, 1H); 4.87(*dd*, *J*= 11.4, 6.9, 1H); 4.14(*d*, *J*= 12.7, 1H); 3.77(*s*, 3H); 3.65(*d*, *J*= 12.7, 1H); 3.22(*s*, 3H); 2.85(*dd*, *J*= 13.7, 6.9, 1H); 2.61(*dd*, *J*= 13.7, 11.4, 1H).

NOE: a) Irrad. at 4.14 (H_{syn}-C(1')). → 2 signals at 7.23 (H-C(4)) and 3.65 (H_{anti}-C(1')).
c) Irrad. at 2.61 (H_{syn}-C(4')). → 3 signals at 7.23 (H-C(4)), 4.87 (H-C(3')), and 2.85 (H_{anti}-C(4')).

^{13}C-NMR: (50 MHz, CD_3OD) 181.3(*s*), 169.0(*s*), 157.6(*s*), 135.8(*s*), 130.7(*s*), 115.5(*d*), 111.9(*d*), 111.1(*d*), 69.1(*d*), 63.4(*t*), 56.1(*q*), 53.1(*s*), 42.6(*q*), 41.1(*t*).

MS (FAB): 277(100, M^++1), 276(16, M^+), 232(14), 231(36), 107(10), 77(13).

(S)-Horsfiline (+)-1. A mixture of 20 mg (0.06 mmol) of (+)-27, 20 mg (0.2 mmol) of *N*-methylmorpholine (*Fluka, purum*), and 28 mg (0.2 mmol) of isobutyl chloroformate (*Fluka, purum*) in 3 ml of THF was stirred at 25° for 1 h. Then was added 0.2 ml of THF, containing 36 mg (0.36 mmol) of triethylamine and 45 mg (0.36 mmol) of 2-mercaptopyridine-1-oxide (*Fluka, purum*). After stirring at 25° for 1 h 0.2 ml of *tert.*-butyl mercaptane was added to the yellow mixture which was irradiated with a tungsten lamp (250 W) for 3 h. Work-up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 gave a crude material that was chromatographed (silica gel; EtOAc, gradient with 0-50 % of MeOH) to give 10 mg (0.043 mmol, 72 %) of (+)-1 as an oil that solidified in the refridgerator.

M.p.: insufficient material for recrystallization.

$[\alpha]_D$: + 5.2 (c=0.5, MeOH). Hydrochloride: + 28.0 (c=0.6, MeOH).

IR-, ^{1}H-NMR-, and ^{13}C-NMR spectra agree with the ones of (–)-1 within experimental error [1,14].

C) Synthesis of (±)-Horsfiline ((±)-1)

A soln. of 310 mg (1.43 mmol) of **32**, prepared from 5-methoxytryptamine (**30**) acc. to ref. 17, in 24 ml of THF/AcOH/H_2O 10:7:7 was cooled to – 5°. Following portionwise addition of 281 mg (1.58 mmol) of NBS stirring was continued for 30 min. Then were added 50 mg of NBS and after 1 h an addtitional 50 mg (total amount: 2.14 mmol, 1.5 eq.). Work-up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 gave a crude material that was dissolved in 200 ml of MeOH and hydrogenated (25°, 1 atm of H_2) for 12 h over 100 mg 5 % Pd on charcoal in the presence of 1 ml of AcOH and 500 mg of NaOAc. Filtration, followed by chromatography (silica gel; EtOAc, gradient with 0-50 % of MeOH) furnished 180 mg (54 %) of (±)-1 as a solid that was recrystallized from acetone.

M.p.: 154-156° Lit.: 155-156° (acetone) [1], 153-154° (acetone) [3].

IR-, ^{1}H-NMR-, and ^{13}C-NMR spectra agree with the ones of (–)-1 within experimental error [1,14].

D) Preparation of Model Compounds

(3S, 3'S)-Oxindole 9. To a soln. of 100 mg (0.38 mmol) of (–)-4 [21,22] in a mixture of 1 ml of H_2O and 1.5 ml of AcOH which was stirred under Ar at 0° were added 80 mg (0.45 mmol) of *N*-bromosuccinimide (*Fluka, purum*) in small portions. After stirring at 0° for 2 h in the dark the mixture was evaporated and worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2. Chromatography (silica gel; EtOAc) furnished 76 mg (81 %) of a 3:1-mixture of **9** and **14** as a colorless oil.

Data of the major product **9**:

M.p.: Oil $C_{13}H_{14}N_2O_3$ (246.16)

IR ($CHCl_3$): 3420, 1720, 1670, 1485, 1470, 1447, 1341, 1236, 908.

^{1}H-NMR: (300 MHz, $CDCl_3$) 8.50(br. *s*, 1H); 7.28(*dm*, *J*= 8.0, 1H); 7.22(*td*, *J*= 8.0, 1.3, 1H); 7.06(*td*, *J*= 8.0, 1.0, 1H); 6.92(*dm*, *J*= 8.0, 1H); 4.30(*dd*, *J*= 9.1, 6.1, 1H); 3.82(*s*, 3H); 3.36(*d*, *J*= 11.8, 1H); 3.26(*d*, *J*= 11.8, 1H); 2.70(*dd*, *J*= 13.5, 9.1, 1H); 2.47(*m*, 1H); 2.31(*dd*, *J*= 13.5, 6.1 1H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 182.2(*s*), 174.6(*s*), 140.4(*s*), 132.5(*s*), 128.1(*d*), 123.0(*d*), 122.8(*d*), 109.8(*d*), 61.1(*d*), 58.9(*t*), 55.3(*s*), 52.4(*q*), 41.4(*t*).

MS (EI): 246(31, M^+), 214(11), 188(13), 187(100), 158(25), 146(78), 130(17), 101(24).

Data of the minor product **14**, prepared from **15** through hydrogenolysis (H_2 /Pd), as described for **16** below:

M.p.: Oil $C_{13}H_{14}N_2O_3$ (246.1)

IR ($CHCl_3$): 3415, 1720, 1614, 1462, 1430, 1382, 1100.

^{1}H-NMR: (300 MHz, $CDCl_3$) 9.34(br. *s*, 1H); 7.25(*dm*, *J*= 7.6, 1H); 7.22(*td*, *J*= 7.6, 1.3, 1H); 7.04(*td*, *J*= 7.6, 1.0, 1H); 6.94(*dm*, *J*= 7.6, 1H); 4.19(*t*, *J*= 8.0, 1H); 3.79(*s*, 3H); 3.51(*d*, *J*= 11.5, 1H); 3.09(*d*, *J*= 11.5, 1H); 2.90(*m*, 1H); 2.44(*m*, 2H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 182.4(*s*), 173.6(*s*), 140.7(*s*), 133.0(*s*), 128.2(*d*), 122.8(*d*), 122.7(*d*), 110.0(*d*), 61.4(*d*), 58.3(*t*), 54.6(*s*), 52.4(*q*), 41.6(*t*).

MS (EI): 246(6, M^+), 214(3), 188(12), 187(81), 158(51), 146(81), 130(100), 101(45).

(3S, 3'S)-Oxindole (–)-11. To a soln. of 1.1 g (4.5 mmol) of (+)-**6** [22] in 65 ml of a mixture of THF/AcOH/H_2O 20:27:18 which was stirred under Ar at 0° were added 800 mg (4.5 mmol) of *N*-bromosuccinimide (*Fluka, purum*) in small portions. After stirring at 0° for 20 min in the dark the mixture was evaporated and worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2. Chromatography (silica gel; EtOAc, gradient with 0-20 % of MeOH) furnished 640 mg (55 %) of (–)-**11** containing less than 5 % of **16**.

M.p.: Oil $C_{14}H_{16}N_2O_3$ (260.18)

$[\alpha]_D$: – 65.1 (c=1.6, MeOH).

IR ($CHCl_3$): 3420, 1720, 1618, 1482, 1438, 1347, 1178, 1100, 907.

^{1}H-NMR: (300 MHz, $CDCl_3$) 8.68(br. *s*, 1H); 7.59(*dm*, *J*= 7.6, 1H); 7.21(*td*, *J*= 7.6, 1.3, 1H); 7.06(*td*, *J*= 7.6, 1.0, 1H); 6.91(*dm*, *J*= 7.6, 1H); 3.79(*s*, 3H); 3.51(*dd*, *J*= 9.0, 7.6, 1H); 3.20(*d*, *J*= 9.1, 1H); 2.91(*d*, *J*= 9.1, 1H); 2.75(*dd*, *J*= 13.3, 9.0, 1H); 2.52(*s*, 3H); 2.26(*dd*, *J*= 13.3, 7.6 1H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 181.4(*s*), 173.1(*s*), 139.9(*s*), 135.3(*s*), 128.0(*d*), 124.2(*d*), 123.2(*d*), 109.5(*d*), 67.3(*d*), 65.9(*t*), 52.6(*s*), 52.0(*q*), 41.1(*t*), 40.8(*q*).

MS (EI): 261(95, M^++1), 260(13, M^+), 259(52), 202(16), 201(100), 158(14), 130(19).

(3R, 3'S)-Oxindole 16. To a soln. of 500 mg (1.88 mmol) of (–)-**4** [22] in 29 ml of CH_2Cl_2 which was stirred under Ar at –10° were added 0.32 ml (2.26 mmol) of benzyl chloroformate (*Fluka, purum*). After stirring at –10° for 15 min the mixture was worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2. Chromatography (silica gel; EtOAc/pet. ether, gradient from 1:4 to 1:1) furnished 645 mg (94 %) of **5**. To a soln. of 620 mg (1.7 mmol) of **5** in 23 ml of a mixture of H_2O/AcOH/THF 8:12:3 which was stirred under Ar at –5° were added 333 mg (1.87 mmol) of *N*-bromosuccinimide (*Fluka, purum*) in small portions. After stirring at 0° for 15 min in the dark the mixture was evaporated and worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2. Chromatography (silica gel; EtOAc/pet. ether, 1:1) furnished 545 mg (84 %) of a 4:1-mixture of **15** and **10** as a white foam. To 250 mg (0.66 mmol) of this mixture in 15 ml of MeOH were added 20 mg of 10 % Pd on charcoal. After stirring for 2 h under an atmosphere of H_2 the mixture was filtered through Celite ® and the filtrate evaporated. The residue (150 mg, 92 %) was an oily 4:1-mixture of **14** and **9** which was N-methylated as follows: To a soln. of this mixture (0.61 mmol) in 15 ml of CH_3CN were added 0.25 ml (3.05 mmol) of 36 % aq. formaldehyde, 90 mg (1.22 mmol) of $NaBH_3CN$ and 0.3 ml of AcOH. After stirring at 25° for 1 h the mixture was worked up as usual. The residue, consisting mostly of the N(1)-hydroxymethyl derivative of **16**, was dissolved in 11 ml of a 10:1-mixture of 2N aq. HCl and MeOH and stirred at 80° for 12 h. Workup, followed by chromatography (silica gel, gradient: EtOAc containing 0-20 % of MeOH) furnished 110 mg (61 %) of **16** as a colorless oil.

M.p.: Oil $C_{14}H_{16}N_2O_3$ (260.16)

IR ($CHCl_3$): 3420, 1725, 1620, 1486, 1446, 1331, 1175, 1105, 904.

^{1}H-NMR: (300 MHz, $CDCl_3$) 8.36(br. *s*, 1H); 7.27(*d*, *J*= 7.7, 1H); 7.22(*td*, *J*= 7.7, 1.3, 1H); 7.06(*td*, *J*= 7.7, 1.0, 1H); 6.90(*d*, *J*= 7.7, 1H); 3.80(*s*, 3H); 3.60(*d*, *J*= 9.8 1H); 3.55(*d*, *J*= 8.7, 7.6, 1H); 2.70(*d*, *J*= 9.8, 1H); 2.66(*dd*, *J*= 13.0, 8.7, 1H); 2.55(*s*, 3H); 2.37(*dd*, *J*= 13.0, 7.6 1H).

^{13}C-NMR: (75 MHz, $CDCl_3$) 181.1(*s*), 172.5(*s*), 140.3(*s*), 134.4(*s*), 128.3(*d*), 123.2(*d*), 122.9(*d*), 109.7(*d*), 67.8(*d*), 65.5(*t*), 52.1(*s*), 52.1(*q*), 41.6(*t*), 40.2(*q*).

Acetoxyindolenine 35. To a soln. of 30 mg (0.12 mmol) of (+)-**6** [22] in 3 ml of CH_2Cl_2 which was stirred under Ar at –10° were added 60 mg (0.13 mmol) of $Pb(OAc)_4$ (*Fluka, purum*). After stirring at –10° for 3 h the mixture was diluted with EtOAc and filtered through silica gel. The filtrate was evaporated and chromatographed (silica gel, gradient: EtOAc containing 0-20 % of MeOH) to give 28 mg (79 %) of **35** as a rather unstable yellow oil.

M.p.: Oil $C_{16}H_{18}N_2O_4$ (302.18)

IR ($CHCl_3$): 1752, 1730, 1602, 1486, 1451, 1433, 1367, 1112, 1088, 1061, 902.

$[\alpha]_D$: +94.5 (c=1.1, MeOH).

^{1}H-NMR: (300 MHz, $CDCl_3$) 7.60(*dm*, *J*= 7.9, 1H); 7.41(*m*, 2H); 7.23(*td*, *J*= 7.5, 1.0, 1H); 3.88(*d*, *J*= 12.5, 1H); 3.77(*s*, 3H); 3.53(*dd*, *J*= 12.0, 2.3, 1H); 3.37(*d*, *J*= 12.5, 1H); 2.92(*dd*, *J*= 14.3, 2.3, 1H); 2.39(*s*, 3H); 2.07(*s*, 3H); 1.68(*dd*, *J*= 14.3, 12.0, 1H).

NOE: a) Irrad. at 2.92 (H_{anti}-C(4)). → 3 signals at 7.41 (H-C(5)), 3.53(H-C(3)), and 1.68 (H_{syn}-C(4)).
b) Irrad. at 3.53 (H_{ax}-C(3)). → 4 signals at 3.37 (H_{anti}-C(1)), 2.92 (H_{anti}-C(4)), 2.39(N-Me), and 2.07 (OAc).

^{13}C-NMR: (75 MHz, $CDCl_3$) 175.5(*s*), 171.8(*s*), 168.5(*s*), 154.3(*s*), 136.2(*s*), 130.2(*d*), 126.4(*d*), 122.5(*d*), 121.7(*d*), 83.9(*s*), 61.8(*d*), 54.5(*t*), 52.5(*q*), 41.9(*q*), 38.8(*t*), 20.9(*q*).

E) Determination of the Optical Purity of (+)- and (–)-*Horsfiline (1)*

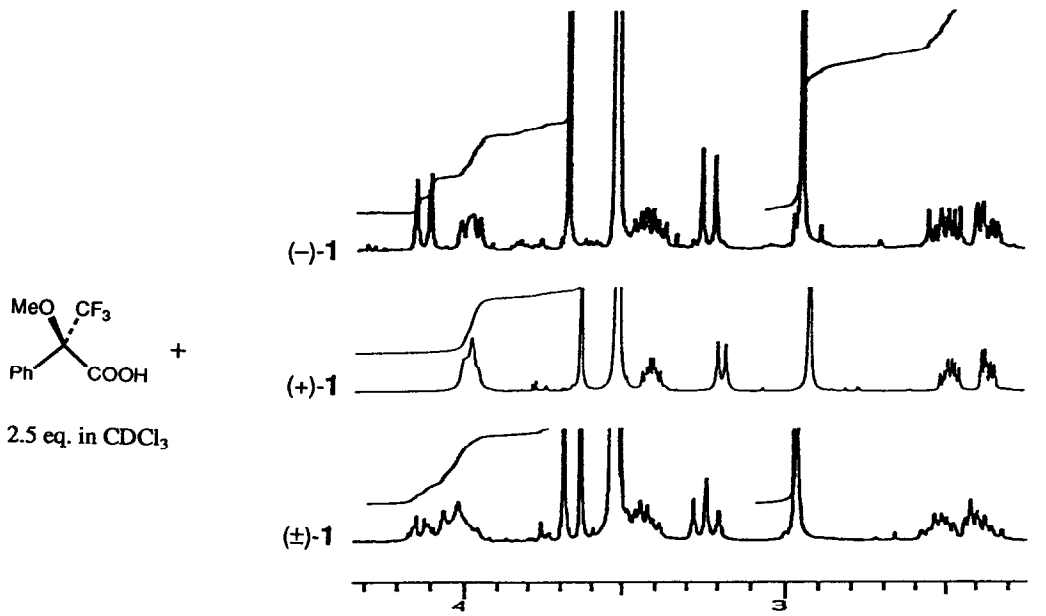

Figure 2. ^{1}H-NMR spectra of the salts of (±)-1 and (–)-1 with 2. 5 eq. of (R)-*2-methoxy-2-trifluoromethyl-2-phenylacetic acid ($CDCl_3$, 300 MHz).*

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