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SYNTHESIS OF GALANTHAMINE AND RELATED ALKALOIDS - NEW APPROACHES. I.

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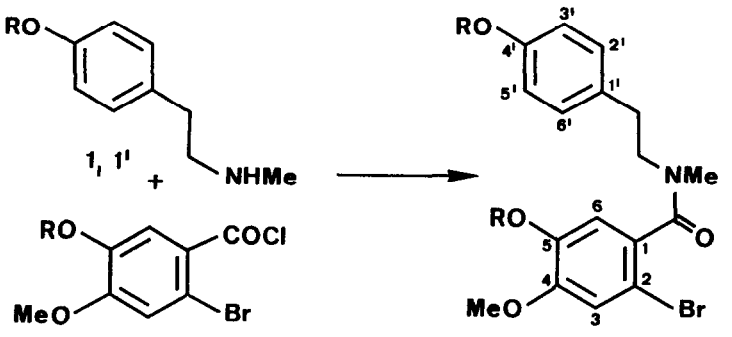
Abstract - Modifications of protecting groups and of the oxidative coupling conditions led to pure crystalline intermediates in the synthesis of galanthamine derivatives and gave dienone **A** in better yields than reported before. The E-configuration of amide **3'** in crystalline state has been determined by X-ray diffraction. Streptomyces affinis 6737 reduces **A** to the optically active (-)-epigalanthamine derivative **C**, whose absolute configuration was determined by Bijvoet's method. Nematospora corylii CBS 2608 reduces to racemic **B**. With Ashbya gossypii IFO 1355 a mixture of racemic **B** and of optically active **C** is obtained. Some other microbial transformations are described.

INTRODUCTION

In one of our previous publications[1] we have reported on the microbial transformation of products which can be used as precursors in the synthesis of galanthamine. In the present work we describe the synthesis of the known narwedine type dienone **A** and its microbial transformation into the two epimeric products galanthamine (**D**) and epigalanthamine (**E**). Furthermore the microbial reduction of the double bond of the same enone **A**, conjugated with a carbonyl group, to an optically active lycoramine derivative **F** has been established.

DISCUSSIONS

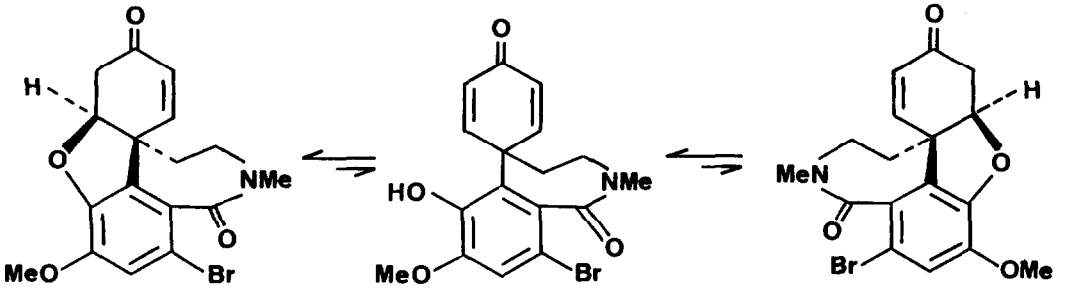
The synthesis of narwedine type enone **A** was realized following the scheme worked out by Kametani et al.,[2] applying however a method improved by us for the oxidative coupling of diol **4** with potassium ferricyanide. We protected the phenolic hydroxyl groups (for the first time in such a case) with the p-methoxybenzyl group, which is hydrolyzed under much



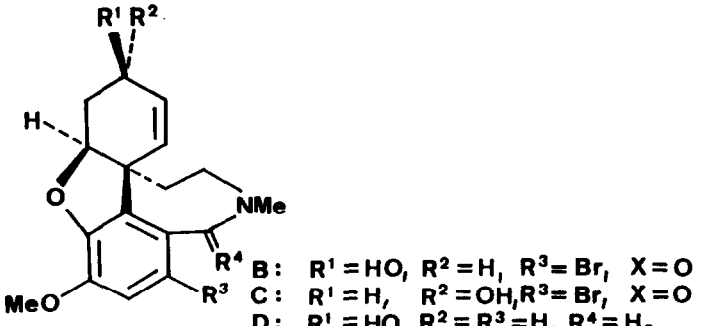
1,2,3: R = MeO — CH_2 —

1',2',3': R = — CH_2 —

4: R = H

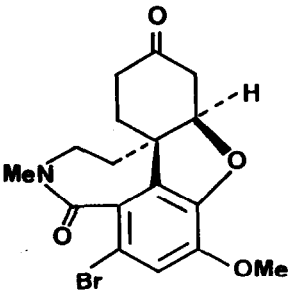


A' A A''

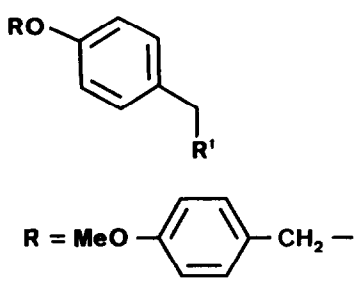


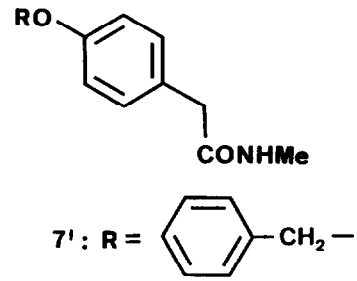
B .... E

B: $R^1 = HO$, $R^2 = H$, $R^3 = Br$, X = O
C: $R^1 = H$, $R^2 = OH$, $R^3 = Br$, X = O
D: $R^1 = HO$, $R^2 = R^3 = H$, $R^4 = H_2$
E: $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = H_2$

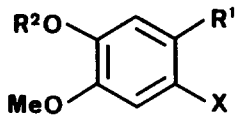


F





	R'
5	COOH
6	COCl
7	CONHMe
8	CSNHMe



	R'	X	R²
9	– CHO	H	H
10	– CHO	H	MeO — CH₂
11	– CH_2OH	H	–"–
12	– CH_2OAc	H	–"–
13	– CH_2OAc	Br	–"–
14	– CH_2OH	Br	–"–
15	– COOH	Br	–"–

milder conditions than the benzyl group.

Amine **1**, which is transformed into ring A of diol **4**, is obtained from p-methoxybenzyl-phenylacetic acid **5**. The amide **7** was prepared by Schotten-Baumann reaction and treating the intermediate acid chloride **6** in DMF with gaseous methylamine (76% yield from **5** to **7**). When the reaction is carried out in pyridine solution, side products are obtained and the yield is low. It is known for similar cases,[3] that pyridine catalyzes the chlorination of the activated methylene group located between the aromatic ring and the carbonyl group. In DMF medium this is, however, avoided. The melting point of the amide **7'** obtained by us (143.5-144.5°C) is distinctly higher than the reported one[2] (103-104°C).

According to the literature[2] the reduction of the amide **7** is carried out with lithium aluminium hydride. We used sodium borohydride instead in the transformation of **7** to **1** via the thioamide **8**. The latter is obtained by heating **7** with phosphorous polysulphide in pyridine solution. Cobalt chloride hexahydrate is added to the thioamide **8** in methanol solution forming a coordination complex between the metal ion and the thioamide. The C=S bond becomes weaker and can be successfully attacked by the hydride ions. Thus a colourless amine is obtained with a yield of 80%. The melting point of the amine hydrochloride salt **1'**, obtained according to the described method, is 208-210°C, whereas 163-165°C was reported for the same salt.[2] This reduction of the thioamide to amine can be carried out under very mild conditions (at room temperature in methanol), is not sensitive towards humidity, and gives high yield.

The acid chloride **2**, forming cycle B of diol **4**, was obtained from isovanillin **9** by the scheme given on the preceding page.

During bromination of compound **10** a mixture of products is obtained and the bromination itself gets difficult due to the electron-accepting effect of the aldehyde group, while the acetate **12** is brominated quantitatively at the required position in glacial acetic acid in the presence of sodium acetate. The reaction sequence from **9** to **14** is practically quantitative. The alcohol **14** is oxidized in water - acetone mixture with potassium permanganate to the acid **15** in a yield of 79%.

The amide **3** is produced by condensation of amine **1** with acid chloride **2**, prepared from **15** with oxalyl chloride. The analogous amide **3'** with benzyl as protecting group and obtained by Kametani et al.[2] through Schotten-Baumann reaction was described as a brown oil, while **3'** obtained by our method is a crystalline product (m.p. 96 - 98°C).

The NMR-spectrum of the amide **3** showed at room temperature ($CDCl_3$ or DMSO-d_6) two singlets (appr. 1:1) for the N-methyl protons, which collapse to a sharp line at higher temperature (120°C), proving thus that an E/Z-equilibrium of the amide group is present in the solution.

The X-ray structural analysis was performed with the amide **3'** and proved that the E-stereoisomer is present in the crystals. The amide grouping is nearly perpendicular to the ring B to avoid severe steric interaction. The distance between the two C-atoms partici-

pating in the coupling reaction is 3.92Å. As can easily be seen from the molecular models, it is only this E-isomer which can give the coupling reaction (Fig. 1).

The amide **3** was hydrolyzed to the crystalline amide **4** (mp. 126-128°C) under very mild conditions with 5 % ethanolic hydrochloric acid. The analogous amide **3'** is hydrolyzed only under much more drastic conditions (boiling with 48 % hydrobromic acid) to give the same amide-diol **4** for which a melting point of 288-289°C (maybe a salt and not free phenol) has been reported.

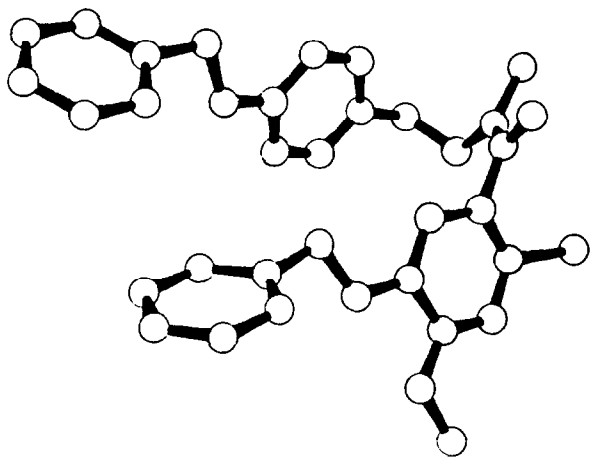


Fig. 1

Conformation of 3' in the crystal

The diol **4** was oxidized with potassium ferricyanide according to the method described by Kametani et al.,[2] but the yield of the purified oxidation product **A** does not exceed 15 %. The obtained narwedine type enone **A** was then subjected to microbial transformation.

About 400 species of microorganisms have been screened for their ability to reduce the synthetic intermediate **A**, from which 60 strains gave reaction products when treated in analytical scale in 100 ml shaker flasks containing 20 ml culture. 5 of those 60 microorganisms were selected because only they gave reproducible results in the microbial transformations when performed preparatively in 2 l shaker flasks with 100 ml substrate.

Septomyxa affinis DSM 6737 gives in the course of microbial reduction to 85 % of complete transformation (-)epigalanthamine derivative **C**. After 96 h of fermentation the compound was isolated yielding 50 % of pure product. The X-ray structure analysis (Fig. 2) also proves its absolute configuration.

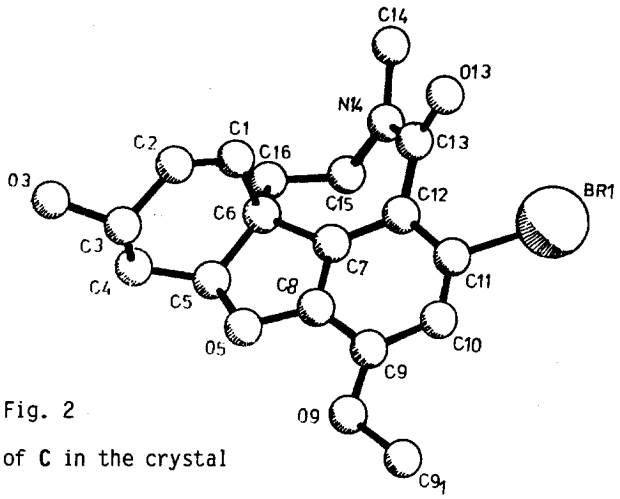


Fig. 2

Conformation of **C** in the crystal

Nematospora corylii CBS 2608 gives the galanthamine derivative **B** with a yield over 50% of racemic product. The X-ray structure analysis (Fig. 3) indicates a racemic mixture, because the elementary cell contains both enantiomers. The presence of a racemate was further proved by esterification with the acid chloride of (-)-camphoric acid, giving rise to two diastereomers.

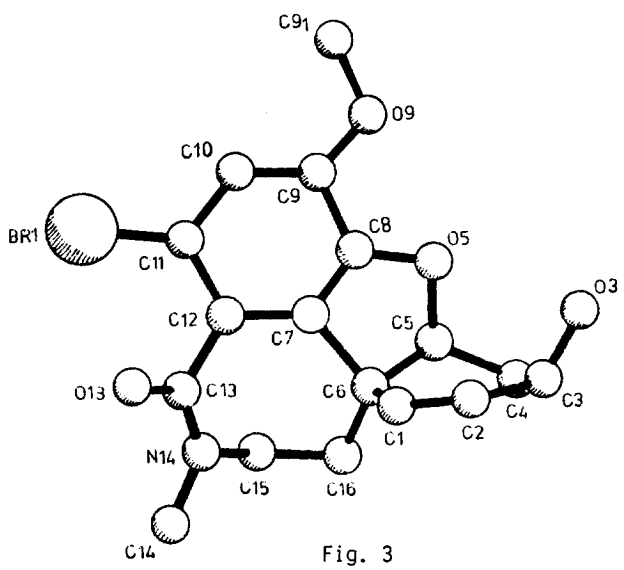


Fig. 3

Conformation of **B** in the crystal

Ashbya gossypii IFO 1355 gives the compounds **B** and **C** in a ratio of 1:2 and a total yield of above 45 %. It was proved as well that **C** is an optically pure compound while the compound **B** remains racemic.

Nocardia alba DSM 43130 and Bacillus cereus DMS 508 show a type of reaction different from mere reduction of the keto group. These bacterial strains, in contrast to the usually used fungi and yeast strains, hydrogenate the double bond in 3,4-position with simultaneous resolution of the racemate to (+)-lycoramine derivate **F**. The remaining starting material has no optical activity.

The formation of a derivative of (-)-epigalanthamine and a derivative of (+)-lycoramine can be explained by the equilibrium between the two forms **A'** and **A"**, which can open to the same achiral dienone **A**. Unreacted starting material is isolated in racemic form when the (+)-lycoramine derivative **F** is obtained, i.e. the two enantiomeric forms are equally consumed, this being due to the mentioned equilibrium.

The microbial reduction with Septomyxa affinis, Nocardia alba, or Bacillus cereus gives either optically active products or only one enantiomeric form of the starting racemate, which indicates the strict stereospecificity of the enzyme present in these microorganisms. The microbial reduction with Nematospora corylii CBS 2608 gives a racemic galanthamine derivative, i.e. the enzyme system has no such specificity with respect to the two starting enantiomeric forms, but shows a stereospecificity only with respect to the carbonyl group which is reduced yielding beta-configuration of the OH-group.

MATERIALS AND METHODS

Microbial transformation of compound **A** (narwedine type enone).

1. The screening medium was composed of 0.5 % glucose, 2 % malt extract, 1 % universal peptone (Merck), and 0.5 % yeast extract.

2. An inoculum was prepared by transferring loopfuls of the strain from the slants into 100 ml shaking flasks containing 20 ml of sterile medium. Then the cultures were incubated at 27°C or 30°C and 100 rpm for 24-72 h. After sufficient time of growth of the cultures, 4 mg of the substrate dissolved in DMF (0.1 ml/20 ml) were added. To analyse the reaction 1 ml culture broth was removed after 24, 48 and 72 h.

3. Chemical analysis. 1 ml culture broth was alkalized with 0.05 ml concentrated NH_3-solution, shaken for 30 s with 0.2 ml chloroform/propanol-2 (3:1) and then centrifuged.

The extract (10-30 µl) was developed on PTLC-plates (Merck) with xylene/butanol-2/methanol/ diethylamine (40/40/6/4). The spots were visible under UV at 254 nm or the plates were sprayed with Ce^{IV} dyeing reagent and heated to 120°C for 2 min: Blue spots on yellow background appeared on the chromatogram.

4. Preparative isolation of microbial products **B** and **C**. Three cultures in 100 ml-flasks were precultivated in the manner as described above, transferred into 2 l-flasks containing 500 ml medium, and grown for 24-72 h. Then 100-150 mg substrate, dissolved in DMF, were added under sterile conditions. The reaction was monitored in the described way. At the end of the fermentation period the broth was alkalized and the mycelia separated by filtration. The liquid phase and mycelium were extracted three times with ethyl acetate. The combined extracts were dried over anhydrous sodium sulphate and the solvent was evaporated. After filtration the extracts were separated by reversed-phase chromatography.

Reduction of the keto group in each of the enone forms **A'** and **A"** can lead to two stereoisomeric alcohols which possess either a ß-hydroxy group (cis relative to the ether bridge) as in **B** or an α -hydroxy group (trans relative to the ether bridge) as in **C**.

Using different microorganisms both epimeric alcohols were obtained and their relative configurations were determined from their 400 MHz ^1H NMR spectra. Table 1 contains the chemical shifts and coupling constants of the products (galanthamine derivative = **B**, epigalanthamine derivative = **C**). Individual signals were identified with the help of double resonance experiments. The signs of the coupling constants were not determined and assumed to be as usual.

In assigning structures **16** and **17** to the products **B** and **C**, respectively, one has to consider that in both **16** and **17** there are two possible conformations of the cyclohexene ring (**16'**, **16"** and **17'**, **17"**). According to Dreiding models, the other parts of the molecules are very rigid.

Coupling constants between protons at C(5) and C(6) are not conclusive because they differ by less than 0.3 Hz for the two epimers. In compound **B** both vicinal couplings between the protons at C(1) and the proton at C(2) are distinctly smaller (1.6 and 5.6 Hz, resp.) than would be expected for an antiperiplanar arrangement. On the other hand one of these couplings is very large in **C** (10.3 Hz). Hence **B** must exist as conformer **16"** or **17'** and **C** as **16'** or **17"**.

This conclusion is supported by the relative magnitudes of the $J_{2,3}$ values: 5.3 Hz in **B**, 1.7 Hz in **C**, i.e. the torsional angle between the C(2)-H and C(3)-H bonds is distinctly closer to the orthogonal arrangement in **C** than it is in **B**. This can also be deduced from the relative magnitudes of the allylic couplings in **B** (0.8 Hz) and **C** (2.1 Hz). The large value in **C** points to approximately parallel orientation of the C(2)-H bond and the p_z-orbitals of the C=C double bond.

The extraordinary large coupling constant (11.7 Hz) between H(2) and the hydroxyl proton in **B** remains as the only criterion to distinguish between structure **16"** and **17'**. Experimentally this coupling was proved by double resonance (irradiation of H(2)) and by H/D-exchange. Its large magnitude can only be explained by a fixed antiperiplanar confor-

Table 1 - ^{1}H-NMR Data of **A** - **F** (400 MHz, $CDCl_3$, TMS as Internal Standard).

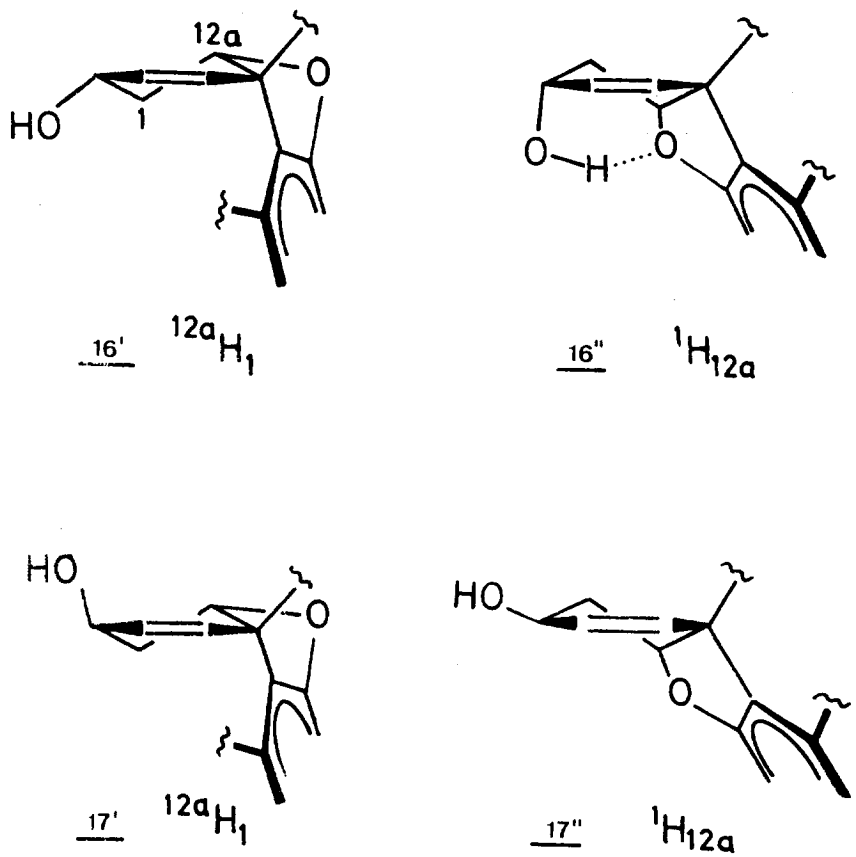
δ or J	A	B	C	D	E	F
H(1')	2.80 dd	2.04 ddd	1.75 ddd	2.02 ddd	1.69 ddd	2.79 dd
H(1")	3.14 ddd	2.65 dddd	2.75 dddd	2.69 dddd	2.77 dddd	2.96 dd
H(2)	-	4.12 comp. m[b]	4.48 comp. m[b]	4.14 comp. m[b]	4.61 dddd	-
H(3)	5.94 dd	5.90 ddd	5.71 dt	6.00 ddd	6.05 dt	
H(4)	6.34 dd	5.50 ddd	5.39 dt	6.06 dd	5.79 dt	1.9-2.2 m
H(5')	1.97 dt	1.73 ddd	1.82 ddd	1.58 ddd	1.63 ddd	
H(5")	2.47 ddd	2.29 ddd	2.41 ddd	2.09 ddd	2.16 dt	2.46 ddd
H(6')	3.88 ddd	3.80 ddd	3.75 ddd	3.28 dt	3.25 dt	3.74 ddd
H(6")	3.29 ddd	3.20 ddd	3.21 ddd	3.06 dt	3.04 bd[b]	3.20 ddd
H(8')	-	-	-	4.09 d	4.06 d	-
H(8")	-	-	-	3.69 d	3.61 d	-
H(9)	-	-	-	6.64[a] ABq	6.55[a] ABq	-
H(10)	7.13 s	7.09 s	7.05 s	6.66[a] ABq	6.61[a] ABq	7.04 s
H(12a)	4.84 ddd	4.71 ddd	4.72 comp.m[b]	4.62 comp. m[b]	4.58 comp. m[b]	4.94 dd
NCH_3	3.23 s	3.19 s	3.19 s	2.40 s	2.56 s	3.16 s
OH	-	2.12 d	1.69 bs	2.36 bs	1.74 bs	-
OCH_3	3.90 s	3.89 s	3.89 s	3.84 s	3.82 s	3.87 s
$J_{1,1"}$	17.7	15.7	14.8	15.6	14.0	17.0
$J_{1,2}$	-	5.0	10.3	4.9	10.6	-
$J_{1',12a}$	3.9	2.7	2.7	2.4	2.2	3.0
$J_{1",2}$	-	1.6	5.6	1.8	5.8	-
$J_{1",3}$	0.9	1.2	1.4	1.0	1.4	-
$J_{1",12a}$	2.5	3.5	3.5	3.3	3.7	4.0
$J_{2,3}$	-	5.3	1.7	4.6	2.2	-
$J_{2,4}$	-	0.8	2.1	-	1.4	-
$J_{2,OH}$	-	11.7	-	-	-	-
$J_{3,4}$	10.2	10.0	10.1	10.5	10.3	
$J_{4,12a}$	2.2	1.5	1.2	1.0	1.4	
$J_{5',5"}$	14.7	14.5	14.4	13.6	14.0	14.0
$J_{5',6'}$	2.5	3.0	3.3	1.8	2.8	4.0
$J_{5',6"}$	2.5	2.2	2.2	3.6	1.4	4.0
$J_{5",6'}$	13.3	13.4	13.5	13.6	14.0	13.0
$J_{5",6"}$	3.7	3.8	4.0	3.0	3.0	5.0
$J_{6',6"}$	14.9	14.9	14.9	13.6	14.0	14.0
$J_{8',8"}$	-	-	-	15.3	16.0	-
$J_{9,10}$	-	-	-	8.2	8.2	-

a) assignments may be interchanged: - b) determined by double resonance technique

mation of the H-C(2)-OH moiety, for which an intramolecular hydrogen bond between OH and the ether oxygen in structure **16"** must be responsible. The observed coupling constant would be unexplainable if the structure were **17'**.

Consequently, compound **B** possesses configuration **16** and prefers conformation **16"**, compound **C** possesses configuration **17** and prefers conformation **17"**. Both conformations **16"** and **17"** are of type $^{1}H_{12a}$, which can also be deduced from the relatively small vicinal constants of coupling $J_{1",12a}$ (3.5 Hz) requiring a synclinal arrangement of the bonds C(1)-H" and C(12a)-H.

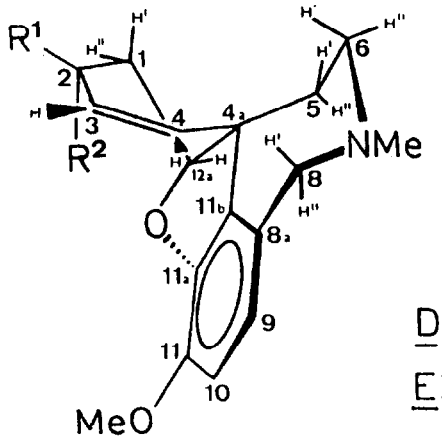
The structures of **B** and **C** were confirmed by their X-ray structural analysis. Crystal and refinement data for **B** and **C** are summerized in Table 2.



16' $^{12a}H_1$ 16" $^{1}H_{12a}$

17' $^{12a}H_1$ 17" $^{1}H_{12a}$

Possible conformations of **16** and **17**



D: $R^1=H$, $R^2=OH$

E: $R^1=OH$, $R^2=H$

Preferred conformation of D and E

Table 2 - Crystal and Refinement Data.

Compound	B	C
Formula	$C_{17}H_{18}NO_4Br.H_2O$	$C_{17}H_{18}NO_4Br$
Space group	$P2_12_12_1$	$P2_1/c$
a (Å)	12.638(3)	7.953(3)
b (Å)	13.279(4)	12.906(4)
c (Å)	9.970(2)	15.632(4)
ß (°)	90	97.93 (4)
Z	4	4
M_r	398.3	380.2
$D_c(g.cm^{-3})$	1.58	1.59
Radiation	Mo Kα	Cu Kα
μ (mm^{-1})	2.40	3.46
2 θ Range (°)	⩽50°	⩽130°
unique reflections	1679	2698
F^2 rejection criterion	<2.0 σ (F^2)	<2.0 σ (F^2)
refinement reflections	1249	2051
R	0.050	0.097
R_w	0.042	0.096
g	0.0002	0.0002

Intensity data collection was carried out on Syntex $P2_1$ four-circle diffractometer using the ω-scan method. The structures were solved with the help of Patterson and difference synthesis and refined by full-matrix least-squares. Positions for the hydrogen atoms were calculated (with the exception of that of the proton at O(3) in **C** which was allowed to refine freely; this proton could not be located for **B**). Anisotropic temperature factors were introduced for the non-hydrogen atoms. The weighting scheme was given by $w = k[\sigma^2(F_o) + gF_o^2]^{-1}$. The relatively high value of the terminal R factor for **B** is a reflection of the poor quality of the crystal used for the data collection. Further details of the crystal structure analysis may be obtained from Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggerstein-Leopoldshafen 2 upon specification of the deposition number CSD 53666, the authors and the journal reference.

The absolute configuration of **C** was assigned as (3S, 5S, 6S) at 99.5 % level of confidence on the basis of a Hamilton R-factor test. C(5) and C(6) display the same absolute configurations as in natural galanthamine. The O(3)•••••O(5) distances are 4.36 and 3.2 Å in **C** and **B**, respectively. The latter distance is significantly longer than would be expected for an intramolecular O-H•••••O hydrogen bond.

(±)-galanthamine derivative **B** and (-)-epigalanthamine derivative **C** obtained by the microbial reduction were reduced with lithium aluminium hydride to (±)-galanthamine **D** and (-)-epigalanthamine **E**, respectively. ^{13}C-NMR data of **A**, **D** and **F** are given in Table 3.

Table 3 - ^{13}C-NMR Data of **A**, **D**, and **F** ($CDCl_3$).

	A	**D**	**F**
C(1)	36.78	29.96	42.5
C(2)	192.92	62.07	207.2
C(3)	126.00	126.86	41.0
C(4)	146.71	127.62	35.8
C(4a)	48.81	48.22	48.6
C(5)	36.78	33.81	35.5
C(6)	48.65	53.81	48.7
C(8)	164.81	60.60	165.4
C(8a)	123.14	129.32	123.8
C(9)	114.22	122.06	113.1
C(10)	118.94	111.18	118.3
C(11)	146.30	145.82	145.9*
C(11a)	145.87	144.10	145.8*
C(11b)	129.57	133.03	120.7
C(12a)	89.42	88.72	91.7
C(13)	34.22	42.07	34.0
C(14)	56.53	55.89	56.4

*assignment may be interchanged

EXPERIMENTAL PART

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 297 or Pye-Unicam SP-200G spectrophotometer, nuclear magnetic resonance spectra on a Jeol JNM-PS-110 (^{1}H, 100 MHz), a Bruker WM 270, or a Bruker WM 400 spectrometer (^{1}H, 250 MHz; ^{1}H, 400 MHz, and ^{13}C, 62.9 MHz). Solutions in deuterochloroform with tetramethylsilane as internal standard were used unless otherwise stated. Chemical shifts are quoted in ppm downfield from TMS. Mass spectra were recorded on a JEOL JMS-D300 or Varian SM1 instrument. HPLC was performed on either a Waters or Knauer instrument using a normal-phase semi-preparative Porasil column, eluting with a mixture of methylene chloride/ethyl acetate 1:1, or a reversed-phase semipreparative C^{18} Bondapak column, eluting with a mixture of methanol/water 1:1 or methanol/water/triethylamine (75/25/0.5), and detecting at 254 nm.

4-(4-Methoxybenzyloxy)-phenyl-N-methylacetamide (7). 10.00 g (36.7 mmol) of 4-(4-methoxybenzyloxy)-phenylacetic acid (5) were dissolved in 50 ml of anhydrous DMF and this solution was cooled in an ice-bath. 5.81 g (48.8 mmol) of thionyl chloride were added dropwise within 45 min with stirring, which continued for one more hour. Gaseous methylamine was slowly passed through the solution for 45 min. The solution became dark and increased viscosity. Then the reaction mixture was stirred at room temperature for 1 h and diluted with water to a volume of 1 l. A light precipitate is produced which was recrystallized from ethanol: m.p. 159-160°C; yield 8.00 g (76%). MS m/e: 285 ($M^{+\cdot}$). IR (KBr):ν* (cm^{-1})= 1520, 1580, 1615 (Ar), 1015, 1035 (OCH_2Ar, $ArOCH_3$), 1640, 1665 (CO), 3100, 3250 (NH). ^{1}H-NMR (250 MHz)*: δ = 2.74 and 2.76 (two s, 3H, NCH_3); 3.52 (s, 2H, $ArCH_2CO$); 3.82 (s, 3H, OCH_3); 4.98 (s, 2H, $ArCH_2OAr$); 5.36 (broadened s, 1H, NH); 6.69 (d, 2H, J = 8.5 Hz, H(2) and H(6)); 6.92 (d, 2H, J = 10 Hz, H(2') and H(6')); 7.16 (d, 2H, H(3) and H(5)); 7.36 (d, 2H, H(3')and H(5')).

4-(4-Methoxybenzyloxy)-phenyl-N-methylthioacetamide (8). A stirred suspension of 30.00 g (10.5 mmol) of amide 7 in 600 ml anhydrous pyridine is cooled in an ice-bath, then 30.00 g (13.4 mmol) of phosphorous pentasulfide were added in portions within 90 min and the stirring was continued for further 6 h at 60-65°C. Then 75% of pyridine were distilled off and the residue was diluted with water to 1.5 l. The produced precipitate was allowed to stay for several h at appr. 5°C, then the crystals were filtered off and washed well with water. Recrystallization from ethanol: m.p. 117-119°C; yield 18.30 g (58%). MS m/e: 301 ($M^{+\cdot}$). IR (KBr): ν* (cm^{-1})= 1520, 1560, 1590, 1620 (Ar), 1015, 1030 (OCH_2 Ar, $ArOCH_3$), 3080, 3250 (NH), 1080 (CS). ^{1}H-NMR (100 MHz): δ = 1.60 (broadened s, 1H, NH); 2.96 and 3.00 (two s, 3H, NCH_3); 3.66 (s, 3H, OCH_3); 3.90 (s, 2H, $ArCH_2CS$); 4.76 (s, 2H, OCH_2Ar); 6.58 and 7.10 (m, 8H, Ar).

* The reported spectra are superpositions for two rotamers.

2-(4-Methoxybenzyloxy)-ethyl-N-methylamine (1). 9.00 g (30 mmol) of thioamide **8** were dissolved in 1100 ml ethanol. The obtained solution was not completely clear and showed opalescence. To this solution were added 14.30 g (60.3 mmol) of cobalt chloride hexahydrate, and the colourless solution turned into violet. The stirred solution was cooled in an ice-bath and 5.60 g (14.7 mmol) of sodium borohydride were added in portions. Then the ice-bath was removed and the stirring continued under reflux for 90 min. The non-organic precipitate was filtered hot, washed twice with hot ethanol, and the combined ethanol extracts were concentrated almost to dryness. The residue was diluted with chloroform and the amine was precipitated as its sulphate with 2% sulphuric acid. The sulphate was filtered off and washed with chloroform. Recrystallization from ethanol: m.p. 181-182°C; yield 8.85 g sulphate (80%). The free base is a crystalline product with m.p. 64 - 66°C (from ethyl ether/petroleum ether). MS m/e = 271 ($M^{+\cdot}$). IR (KBr):ν*(cm^{-1}) = 1520, 1580, 1620 (Ar), 1015, 1035 (OCH_2Ar, $ArOCH_3$). ^{1}H-NMR (250 MHz):δ= 1.62 (broadened s, 1H, NH); 2.43 (s, 3H, NCH_3); 2.74 (t, 2H, J = 4.7 Hz, CH_2N); 2.78 (t, 2H, $ArCH_2C$); 3.81 (s, 3H, OCH_3); 4.96 (s, 2H, $ArCH_2O$); 6.90 (d, 2H, J = 8.5 Hz, H(2') and H(6')); 6.92 (d, 2H, J = 8.5 Hz, H(2) and H(6)); 7.12 (d, 2H, H(3') and H(5')); 7.35 (d, 2H, H(3) and H(5)).

4-Methoxy-5-(4-methoxybenzyloxy)-benzaldehyde (10). 18.00 g (11.8 mmol) of isovanillin (9) were dissolved in 88.00 ml of anhydrous DMF and 40.80 g (29.6 mmol) of anhydrous potassium carbonate were added. The mixture was stirred vigorously and 22.41 g (14.3 mmol) of p-methoxy-benzylchloride, dissolved in 10 ml of DMF, were added. The mixture was stirred for 2 h at 100°C. Then it was allowed to cool and diluted to 1 l with water. The product was separated by cooling until crystallization and purified by recrystallization from ethanol: m.p. 84-85.5°C; yield 30.4 g (95%). MS m/e = 272 ($M^{+\cdot}$). IR (KBr): ν*(cm^{-1})= 1000, 1020 (OCH_2Ar, $ArOCH_3$), 1520, 1580, 1600, 1620 (Ar), 1700 (CO). ^{1}H-NMR (250 MHz): δ = 3.80 (s, 3H, OCH_3 at C(4')); 3.94 (s, 3H, OCH_3 at C(4)); 5.11 (s, 2H, OCH_2Ar); 6.90 (d, 2H, J = 9 Hz, H(2') and H(6')); 6.98 (d, 1H, $J_{5,6}$ = 9 Hz, H(5)); 7.38 (d, 2H, H(3') and H(5')); 7.460 (dd, 1H, $J_{2,6}$ = 2 Hz, H(6)); 7.465 (d, 1H, H(2)); 9.82 (s, 1H, CHO).

4-Methoxy-5-(4-methoxybenzyloxy) benzyl alcohol (11). To 8.00 g (29.4 mmol) of **10**, dispersed in 100 ml ethanol, are added under stirring 1.20 g (31.5 mmol) of sodium borohydride in portions. After addition of the last portion the mixture was stirred for one more hour at room temperature while the suspension turned into a clear solution. 50% of the ethanol was distilled off in vacuo, the rest was cooled, acidified with 10% hydrochloric acid to pH 4-5, and diluted with 250 ml of water. The produced precipitate was filtered off and recrystallized from ethanol: m.p. 118.5-119.5°C; yield 7.73 (96%). MS m/e = 274 ($M^{+\cdot}$). IR (KBr): ν* (cm^{-1}) = 1015, 1030 (CCH_2Ar, $ArCCH_3$), 1510, 1610, 1620 (Ar), 3490 (OH). ^{1}H-NMR (100 MHz): δ = 1.64 (s, 1H, OH); 3.72 (s, 3H, OCH_3 at C(4')); 3.80 (s, 3H, OCH_3 at C(4)); 4.48 (s, 2H, CH_2OH); 4.96 (s, 2H, OCH_2Ar); 6.72 - 6.82 (m, 5H, Ar); 7.22 and 7.30 (m, 2H, Ar).

4-Methoxy-5-(4-methoxybenzyloxy)-benzylacetate (12). 6.00 g (21.8 mmol) of alcohol **11** were dissolved in 30 ml of anhydrous pyridine, the solution was cooled in an ice-bath, and 2.06 g (26.2 mmol) of acetylchloride were added dropwise with stirring. The mixture was

stirred for further 30 min at room temperature, 50% of the pyridine were removed in vacuo and 200 ml of water were added to the mixture. The produced precipitate was filtered off, washed with water and recrystallized from ethanol: m.p. 83-83.5°C; yield 6.57 g (95%). MS m/e = 316 ($M^{+\cdot}$). IR (KBr): ν^* (cm^{-1}) = 1025, 1050 (OCH_2Ar, $ArCCH_3$), 1520, 1615 (Ar), 1740 (CO). ^{1}H-NMR (250 MHz): δ = 2.07 (s, 3H, Ac); 3.81 (s, 3H, OCH_3 at C(4')); 3.87 (s, 3H, OCH_3 at C(4)); 4.99 (s, 2H, OCH_2Ar); 5.07 (s, 2H, CH_2OAc); 6.84 and 6.94 (comp. m, 5H, H(2), H(2'), H(5), H(6), H(6')); 7.37 (d, 2H, J = 8.5 Hz, H(3') and H(5')).

2-Bromo-4-methoxy-5-(4-methoxybenzyloxy)-benzylacetate (13). 14.80 g (46.8 mmol) of 12 were dissolved in 215 g glacial acetic acid containing 4.40 g of sodium acetate and the solution was cooled in a waterbath to about 15°C. To the solution were added dropwise under stirring 9.00 g (56.2 mmol) of bromine. The water-bath was removed and the stirring continued for further 60 min at room temperature. The solution became gradually lighter and a white crystalline product separated. 2 l of water were added slowly under vigorous stirring to the reaction mixture. The produced light precipitate was filtered off, washed with plenty of water and recrystallized from ethanol: m.p. 84-85°C; yield 17.50 g (95%). MS m/e = 394/396 ($M^{+\cdot}$). IR (KBr): ν^* (cm^{-1}) = 990, 1030 (OCH_2Ar, $ArOCH_3$), 1520, 1600, 1610 (Ar), 1730 (CO). ^{1}H-NMR (250 MHz): δ = 2.08 (s, 3H, Ac); 3.80 (s, 3H, OCH_3 at C(4')); 3.06 (s, 3H, OCH_3 at C(4)); 5.05 (s, 2H, OCH_2 at C(1')); 5.08 (s, 2H, OCH_2 at C(1)); 6.89 (d, 2H, J = 8.6 Hz, H(2') and H(6')); 6.96 (s, 1H, H(6)); 7.05 (s, 1H, H(3)); 7.35 (d, 2H, H(3') and H(5')).

2-Bromo-4-methoxy-5-(4-methoxybenzyloxy)-benzyl alcohol (14). 18.00 g (45.5 mmol) of acetate 13 were added to 360 ml of 10% methanolic potassium hydroxide under stirring. The hydrolysis proceeded within 30 min at room temperature under concomitant dissolution of acetate. A part of the solvent was distilled off in vacuo until crystallization began. The reaction mixture was acidified with 10% hydrochloric acid to pH 6 and diluted with 200 ml water. The precipitate was filtered off, washed with water to neutral pH and recrystallized from ethanol/water: m.p. 91-92.5°C; yield 14.97 g (94 %). MS m/e = 352/354 (M^+). IR (KBr): ν^* (cm^{-1}) = 1000, 1020 (OCH_2Ar, $ArOCH_3$), 1500, 1520, 1600, 1610 (Ar), 3490 (OH). ^{1}H-NMR (100 MHz)**: δ = 3.22 (broadened s, 1H, OH), 3.60 (s, 6H, 2 × OCH_3); 4.28 (s, 2H, CH_2O); 4.82 (s, 2H, $Ar'CH_2O$); 6.75 (d, 2H, J = 9Hz, H(2') and H(6')); 6.90 (s, 1H, H(6)); 7.00 (s, 1H, H(3)), 7.14 (d, 2H, H(3') and H(5')).

2-Bromo-4-methoxy-5-(4-methoxybenzyloxy)-benzoic acid (15). 10.00 g (27.3 mmol) of benzyl alcohol 14 were dissolved in 140 ml of hot acetone. To the boiling solution were added dropwise within 30 min 20.00 g (126 mmol) of potassium permanganate in 260 ml of water. The acetone was distilled off in vacuo, MnO_2 was filtered off hot, and the precipitate was washed with a hot 5% potassium hydroxide solution. Then the filtrate was cooled and acidified with 10% hydrochloric acid. The isolated acid was recrystallized from ethanol: m.p. 176-178°C; yield 7.90 g (79%). MS m/e = 366/368 ($M^{+\cdot}$). IR (KBr): ν^* (cm^{-1}) = 1000, 1030, 1040 (CH_2Ar, $ArOCH_3$), 1520, 1560, 1600 (Ar), 1700 (CO). ^{1}H-NMR (250 MHz)**: δ = 3.80 (s, 3H, OCH_3 at C(4')); 3.87 (s, 3H, OCH_3 at C(4)); 5.07 (s, 2H, OCH_2Ar); 6.989 (d, 2H, J = 8.5 Hz, H(2') and H(6')); 7.27 (s, 1H, H(3)); 7.41 (d, 2H, H(3') and H(5')); 7.52 (s, 1H,

H(6)); 13.14 (broadened s, 1H, COOH).

2-Bromo-4-methoxy-5-(4-methoxybenzyloxy)-N-[2-(4-methoxybenzyloxyphenyl)-ethyl]-N-methylbenzamide (3). 5.80 g (15.8 mmol) of the acid 15 were dissolved in 174 ml hot anhydrous benzene containing 1.89 ml (23 mmol) pyridine. The mixture was cooled in an icebath and 2.57 g (20.3 mmol) of oxalyl chloride were added dropwise under stirring for 30 min. Pyridine hydrochloride started precipitating and the stirring was continued for further 30 min. The pyridine hydrochloride was filtered off and 1.88 g of triethylamine was added to the filtrate. This solution was added dropwise during 90 min. to an icecold solution of 4.20 g (15.4 mmol) amine 1 in 210 ml of anhydrous benzene to give a precipitate of triethylamine hydrochloride. The precipitate was filtered off, the filtrate washed consecutively with 5% acetic acid and 5% potassium carbonate, dried ($MgSO_4$) and distilled to give an oil which crystallized from methanol: m.p. 110-112°C; yield 6.37 g (65%). MS m/e = 619/621 ($M^{+\cdot}$). IR (KBr):ν*(cm^{-1}) = 1010, 1030 (OCH_2Ar, $ArOCH_3$), 1520, 1590, 1615 (Ar), 1640 ($CONCH_2$). ^{1}H-NMR (250 MHz)*'**: δ = 2.65 and 2.98 (two s, 3H, NCH_3); 2.81 (m, 2H, $ArCH_2C$); 3.61 (m, 2H, NCH_2C); 3.73 (m, 9H, 3 x OCH_3); 4.89 (m, 4H, 2 OCH_2Ar); 6.49 and 7.33 (m, 14H, Ar).

2-Bromo-4-methoxy-5-hydroxy-N-[2-(4-hydroxyphenyl)-ethyl]-N-methylbenzamide (4). 5.00 g (8 mmol) of the amide 3 were dissolved in 100 ml of hot 80% ethanol and 100 ml of 10% hydrochloric acid were added to the resulting solution under stirring. Stirring was continued under reflux for further 30 min. A part of the solvent was distilled off in vacuo until crystallization started. Extraction was carried out with ethyl acetate, followed by washing with saturated solution of sodium chloride and drying ($MgSO_4$). Methylene chloride was added to the residue and a white crystalline product was obtained. Recrystallization from ethanol gave white crystals with m.p. 126-128°C; yield 2.94 g (96%). MS m/e = 379/381 ($M^{+\cdot}$). IR (KBr):ν* (cm^{-1}) = 1030 ($ArOCH_3$), 1520, 1590, 1620 (Ar), 1640 ($CONCH_3$), 3000 - 3300 (broad OH). ^{1}H-NMR (250 MHz) *'**: δ = 2.72 and 2.98 (two s, 3H, NCH_3); 2.71 and 2.79 (two t, 2H, J = 14 Hz, $ArCH_2C$); 3.23 and 3.60 (two t, 2H, NCH_2C); 3.84 (s, 3H, OCH_3); 6.55 and 6.63 (two s, 1H, H(3)); 6.66 and 6.74 (two d, 2H, J = 8 Hz, H(2') and H(6')); 6.82 and 7.11 (two d, 2H, H(3') and H(5')); 7.15 (s, 1H, H(6)).

Phenol oxidation of diol 4 to dienone A. To a solution of 1.00 g (2.63 mmol) diol 4 in 250 ml chloroform was added a mixture of 4.90 g (14.8 mmol) potassium ferricyanide and 50 ml of a 5% solution of sodium hydrogencarbonate under vigorous stirring at 60°C. The stirring was continued for 90 min. The separated chloroform layer was washed with water, dried ($MgSO_4$) and evaporated to give a brown oil (600 mg) which was chromatographed on 10.00 g silica gel with 10% ethyl acetate/chloroform: m.p. 238-239°C (from ethanol); lit. m.p. 252-253°C (from benzene/hexane);[2] yield 0.14 g (15%) of A. MS m/e = 377/379 ($M^{+\cdot}$). IR ($CHCl_3$): ν* (cm^{-1}) = 1020, 1080 ($ArOCH_3$), 1570, 1600 (Ar), 1640 ($CONCH_3$), 1680 (O=C-C=C).

** in DMSO - d_6

(±)-Galanthamine (D). To a suspension of lithium aluminium hydride (130 mg) in dioxane (8 ml) was added under stirring a solution of alcohol **B** (50 mg, 0.13 mmol) in dioxane (8 ml) within 30 min at room temperature. The stirring was continued under reflux for 2 h. TLC analysis showed that during the stirring the reaction became quantitative. Ethyl acetate and water were added to decompose the excess of the reagent. The ethyl acetate extracts were washed with water, dried ($MgSO_4$) and evaporated to give a colourless oil (50 mg). It was purified by HPLC with eluent methylene chloride/ethyl acetate (1:1) on a "Porasil" column to give optically inactive amine **D**: 37.5 mg (96 %). It was recrystallized from ethyl ether: m.p. 282-284°C (from ethanol). MS m/e = 287 ($M^{+\cdot}$). IR (KBr): ν^* (cm^{-1}) = 1020, 1035, 1050, 1080, 1115 (COC), 1580, 1620 (Ar) 3265 and 3320 (OH).

(-)-Epigalanthamine (E). To a suspension of lithium aluminium hydride (130 mg) in dioxane (8 ml) was added dropwise under stirring a solution of alcohol **C** (50 mg, 0.13 mmol) in dioxane (8 ml) within 30 min at room temperature. The stirring was continued under reflux for 2 h. Ethyl acetate and water were added to decompose the unreacted lithium aluminium hydride. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was distilled off in vacuo to give a colourless oil, crystallizing from ethanol: m.p. 188-189°C; yield 34.8 mg (92 %). $[\alpha]_D^{20°C}$ = -327.4 (c=0.27 in ethanol). MS m/e = 287 ($M^{+\cdot}$). IR (KBr): ν^* (cm^{-1}) = 1030, 1100 (COC), 1580, 1620 (Ar), 3415 (OH).

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