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- [15] Crystallographic data collection for $[1\mathbf{a} \cdot (\text{H}_2\text{O}) \cdot ((\text{CH}_3)_2\text{O})_3]$ (**2**): $\text{C}_{15}\text{H}_{48}\text{B}_{30}\text{Hg}_3\text{O}_4$, $M_r = 1218.6$, crystal dimensions = $0.2 \times 0.25 \times 0.5 \text{ mm}^3$, rhombohedral, space group $R\bar{3}$, $a = 21.565(3)$, $c = 15.455(3) \text{ \AA}$, $V = 6225(2) \text{ \AA}^3$, $Z = 6$, $\rho_{\text{calc}} = 1.951 \text{ mg cm}^{-3}$, $T = 100(2) \text{ K}$, absorption coefficient $\mu = 11.098 \text{ mm}^{-1}$. Data were collected on a Bruker SMART CCD diffractometer, using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). Unit cell parameters were determined from a least-squares fit of 976 accurately centered reflections ($6.345^\circ < 2\theta < 55.785^\circ$). A total of 3361 unique reflections were measured, of which 2990 reflections were considered observed with $I > 2\sigma(I)$. All reflections were used for structure analysis. The intensity data were corrected for Lorentz and polarization effects, absorption, and secondary extinction. Atoms were located by use of statistical methods. All non-hydrogen atoms were refined with anisotropic parameters. With the exception of the hydrogen atoms of water (not located), all hydrogen atoms were included in structure factor calculations but parameters were not refined. The hydrogen atoms were assigned isotropic displacement values based approximately on the value for the attached atom. The final discrepancy index was $R = 0.032$, $R_w = 0.074$ ($w = 1/\sigma^2(|F_o|)$) for 2990 independent reflections with $I > 2\sigma(I)$. The largest peak maximum and minimum on a final difference electron density map were 2.19 and $-3.43 \text{ e \AA}^{-3}$, both near Hg. Data were processed by using programs supplied with the Bruker SMART CCD diffractometer.^[19b]
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- [19] a) Crystallographic data collection for $[(1 \cdot \text{H}_2\text{O})_2 \cdot \text{C}_6\text{H}_6]$ (**3**): $\text{C}_{15}\text{H}_{45}\text{B}_{30}\text{Hg}_3\text{O}$, $M_r = 1167.58$, crystal dimensions = $0.15 \times 0.15 \times 0.05 \text{ mm}^3$, rhombohedral (obverse), space group $R\bar{3}$, $a = 20.763(3)$, $c = 15.944(4) \text{ \AA}$, $V = 5953(2) \text{ \AA}^3$, $Z = 6$, $\rho_{\text{calc}} = 1.954 \text{ mg cm}^{-3}$, $T = 100(2) \text{ K}$, absorption coefficient $\mu = 11.594 \text{ mm}^{-1}$. Data were collected on a Bruker SMART CCD diffractometer, using $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). Unit cell parameters were determined from a least-squares fit of 959 accurately centered reflections ($6.794^\circ < 2\theta < 56.532^\circ$). A total of 3202 unique reflections were measured, of which 2505 reflections were considered observed with $I > 2\sigma(I)$. All reflections were used for structure analysis. The intensity data were corrected for Lorentz and polarization effects, absorption, and secondary extinction. Atoms were located by use of statistical methods. All non-hydrogen atoms were refined with anisotropic parameters. With the exception of the hydrogen atoms of water (not located), all hydrogen atoms were included in structure factor calculations but parameters were not refined. The hydrogen atoms

were assigned isotropic displacement values based approximately on the value for the attached atom. The final discrepancy index was $R = 0.041$, $R_w = 0.105$ ($w = 1/\sigma^2(|F_o|)$) for 2505 independent reflections with $I > 2\sigma(I)$. The largest peak maximum and minimum on a final difference electron density map were 3.37 and $-3.41 \text{ e \AA}^{-3}$, both near Hg. Data were processed using programs supplied with the Bruker SMART ccd diffractometer. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-160758 (**2**) and CCDC-160759 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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An Efficient Synthesis of (±)-Narwedine and (±)-Galanthamine by an Improved Phenolic Oxidative Coupling

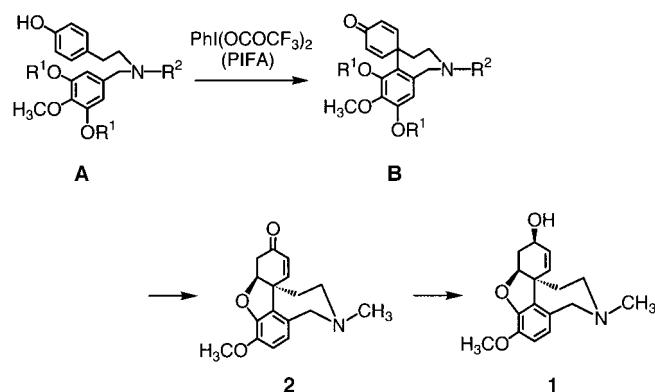
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(–)-Galanthamine (**1**; Scheme 1),^[1] an alkaloid isolated from the *Amarylidiaceae* family, has been approved in Austria and the United Kingdom for the treatment of Alzheimer's disease as a selective acetylcholinesterase inhibitor.^[2, 3] Because of the limited supplies and the high cost of its isolation from natural sources^[4], several syntheses of galanthamine have been reported which use a phenolic oxidative coupling.^[5] Recent syntheses make use of an asymmetric Heck reaction.^[6a] (–)-Galanthamine (**1**) is considered to be synthesized biologically by the phenolic oxidative coupling^[7] of norbelladine derived from L-tyrosine. Since the first synthesis of galanthamine by Barton and Kirby^[8a] in 1960 by the biomimetic phenolic oxidative coupling of the biogenetic precursor norbelladine by using potassium ferricyanide, several methods have been designed to improve the low yield of this coupling reaction: for example, blocking one of the *ortho* positions on the norbelladine derivative with a bromo^[5b,e-g,i,j, 8b] or a trimethylsilyl^[5h] group, which could be easily be substituted by a hydrogen atom, changing the oxidant,^[5c,d,h] and using symmetrical substrates.^[5c,d] Despite these efforts, the yield of the pivotal step in these syntheses still remains only moderate (~50%). Therefore, an efficient synthesis of **1** is highly desirable and useful.

Since (–)-galanthamine (**1**) has been efficiently obtained from (±)-narwedine (**2**)^[8] by crystallization-induced chiral

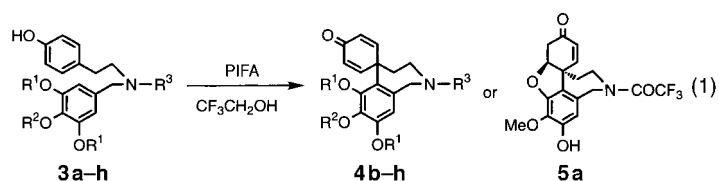
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conversion,^[4, 5i,j] it would seem that an efficient synthesis of **1** should involve an improvement in the phenolic oxidative coupling of the norbelladine derivative **A** to form **2**. We describe herein an efficient formal synthesis of **1** by using an improved phenolic oxidative coupling reaction that uses **A** as the symmetrical substrate^[5c,d] and phenyliodine(III) bis(trifluoroacetate) (PIFA)^[5h] as the oxidant to give spirodienone **B** (Scheme 1).



Scheme 1. Synthetic strategy for (–)-galanthamine (**1**).

For the substrate in the coupling reaction, we chose the norbelladine-type derivatives **3a–h**,^[9] which contain a pyrogallol moiety [Eq. (1)]. The oxidizing agent, PIFA (1.1 equivalents), is degraded to iodobenzene and trifluoroacetic



acid. These byproducts can be removed from the product mixture under reduced pressure and thus an extraction procedure is not required. Results of the oxidative coupling reaction of **3a–h** with PIFA are summarized in Table 1. The reaction of the ideal substrate **3a** with a 2-methoxyresorcinol moiety which can give the narwedine-type product **5a** directly, was carried out in trifluoroacetic acid at -20°C ; however, the yield of **5a** was low (Table 1, entry 1). To increase the

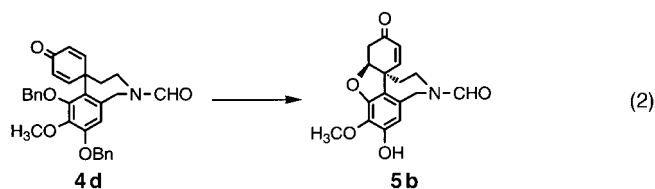
Table 1. Phenolic oxidative coupling of **3** with PIFA.

Entry	Substrate				Product			
	R ¹	R ²	R ³	Temp. [°C]	Time [min]	Yield [%] ^[a]		
1 ^[b]	3a	H	Me	COCF ₃	−20	20	5a	12
2	3b	Bn	Bn	CHO	−40	120	4b	90
3	3c	Me	Me	CHO	−40	15	4c	95
4	3d	Bn	Me	CHO	−40	60	4d	82
5	3d	Bn	Me	CHO	RT	15	4d	85
6	3e	Allyl	Me	CHO	−40	30	4e	48
7	3f	MOM	Me	CHO	−40	10	4f	43
8	3g	Me	Me	COCF ₃	−40	120	4g	75
9	3h	Bn	Me	COCF ₃	−40	60	4h	53

[a] Yield of isolated product. [b] The reaction was carried out in CF₃CO₂H.

solubility of the substrates in trifluoroethanol, we protected the two phenolic hydroxy moieties as the Me, Bn (benzyl), allyl, and MOM (methoxymethyl) ethers **3b–h** (Table 1, entries 2–9). Substrates **3b–d** afforded the desired spirodienones **4b–d** in excellent yields (Table 1, entries 2–4). The formyl group was a better protecting group than the trifluoroacetyl group for the secondary amine (Table 1, entries 3, 8 and 4, 9). The allyl ether (**3e**) and the MOM ether (**3f**) gave the corresponding spirodienones **4** in moderate yields (Table 1, entries 6, 7). Product **4d** was especially easy to crystallize, and was separated mainly by crystallization from the reaction mixture.^[10] Even at room temperature, the coupling reaction of **3d** proceeded successfully and showed a shorter reaction time than those carried out at a lower temperature (Table 1, entries 4 and 5). The yield of the phenolic oxidative coupling reaction of **3c** (95%) is the highest recorded to date among such reactions.

Because selective demethylation of the spirodienone **4c** was difficult, compound **4d** was consequently chosen as the suitable substrate for conversion into the narwedine-type compound **5b** [Eq. (2)]. The use of relatively weak acids was



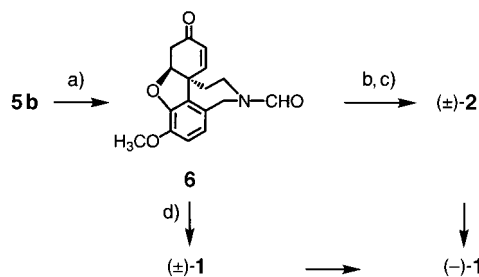
considered to avoid a dienone–phenol rearrangement^[11] and to allow the two benzyl ethers to be dealkylated in the presence of the methyl ether. Trifluoroacetic acid in dimethyl sulfide^[12] required a long reaction time, but the yield was satisfactory (Table 2, entry 1). Methanesulfonic acid^[13] gave the desired product **5b**; however, the yield was only moderate (Table 2, entry 2). The reaction with boron trichloride^[14] at low temperature afforded the desired product **5b** in excellent yield (Table 2, entry 3).

Table 2. Debenzylation of **4d** to form narwedine-type compound **5b**.

Entry	Reagent	Temp.	Time	Yield [%] ^[a] of 5b
1	CF ₃ CO ₂ H in Me ₂ S (2:1)	RT	4 d	81
2	CH ₃ SO ₃ H (10 equiv) in Me ₂ S	RT	2 h	62
3	BCl ₃ (3 equiv) in CH ₂ Cl ₂	-78°C	20 h	95

[a] Yield of isolated product.

The extra hydroxy group on **5b** was reduced quantitatively by its conversion into a triflate group, followed by the palladium(0)-catalyzed reduction with formic acid^[15] (Scheme 2). Although the above synthetic route to **6** from **3d** requires four steps, the overall yield (77%) represents a significant improvement over the reported yield.^[5] The narwedine-type compound **6** was converted efficiently into (±)-narwedine (**2**) by protection of the ketone group, followed by reduction of the *N*-formyl group to an *N*-methyl group. Furthermore, compound **6** was transformed into (±)-galanthamine (**1**) by the diastereoselective reduction of the



Scheme 2. a) 1) TiF_2O , pyridine, 99%; 2) $\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , HCO_2H , 97%; b) ethylene glycol, PPTS, 92%; c) 1) LiAlH_4 , 2) HCl , 83% (2 steps); d) 1) L-Selectride, 2) LiAlH_4 , 61% (2 steps). PPTS = pyridinium *p*-toluenesulfonate.

carbonyl group, as previously reported.^[5g] (±)-Galanthamine has been optically resolved previously,^[5g] and (±)-narwedine (2) has been converted into (–)-galanthamine (1).^[5i, 8c] Therefore, the described efficient route to (±)-narwedine (2) and (±)-galanthamine implies a formal total synthesis of (–)-galanthamine (1).

In conclusion, we were able to improve the pivotal phenolic oxidative coupling reaction of norbelladine-type derivatives, which had been limited to moderate yields over 40 years, and have provided an efficient synthetic route for the industrial production of (–)-galanthamine (1).

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- [9] The norbelladine-type derivatives **3a–h** were easily prepared from methyl gallate and tyramine in high yields, according to ref. [5d] and [5e].
- [10] Typical procedure for the improved phenolic oxidative coupling: To a solution of **3d** (2.0 g, 4.0 mmol) in 2,2,2-trifluoroethanol (100 mL) was added a solution of PIFA (1.9 g, 4.4 mmol) in 2,2,2-trifluoroethanol (10 mL) at -40°C under nitrogen, and the resulting mixture was stirred for 1 h. After the evaporation of the solvent under reduced pressure, the product **4d** (1.29 g, 65%) was isolated by crystallization of the residue from ethyl acetate. The additional crop of **4d** (341.5 mg, 17%) was obtained by column chromatography (chloroform/methanol 20:1) of the condensed mother liquor, followed by crystallization from ethyl acetate. **4d**: colorless needles; m.p. $187\text{--}189^\circ\text{C}$ (dec.) (ethyl acetate); ^1H NMR spectra of a mixture of two conformational isomers were measured. The signals for the minor isomer are shown in parentheses. ^1H NMR (400 MHz, CDCl_3 , 25°C , TMS): δ = (8.21) 8.19 (s, 1H; CHO), 7.47–7.22 (m, 10H), (7.05) 6.98 (d, J = 10.2 Hz, 2H), (6.76) 6.57 (s, 1H; Ar-H), 6.14 (d, J = 10.2 Hz, 2H), 5.15 (5.14) (s, 2H), 4.88 (4.84) (s, 2H), (4.69) 4.60 (s, 2H), 3.75 (3.74) (s, 3H), 3.71 (3.65) (t, J = 6.2 Hz, 2H), (2.29) 2.26 (t, J = 6.2 Hz, 2H); IR (CHCl_3): $\tilde{\nu}$ = 1663 ($\text{C}=\text{O}$, dienone), 1620 and 1593 ($\text{C}=\text{O}$, formyl), 1123 cm^{-1} ($\text{C}-\text{O}$); EI-MS (70 eV): m/z (%): 465 (7) [M^+], 404 (6), 91 (100), 65 (7); HRMS calcd for $\text{C}_{31}\text{H}_{29}\text{NO}_5$ [M^+]: 495.2045, found: 495.2052; elemental analysis: calcd (%) for $\text{C}_{31}\text{H}_{29}\text{NO}_5$: C 75.13, H 5.90, N 2.83; found: C 75.26, H 5.98, N 2.92.
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Aqueous One-Pot Synthesis of Derivatized Cyclopentadienyl–Tricarbonyl Complexes of $^{99\text{m}}\text{Tc}$ with an In Situ CO Source: Application to a Serotonergic Receptor Ligand**

Joachim Wald, Roger Alberto,* Kirstin Ortner, and Lukas Candreia

The radionuclide $^{99\text{m}}\text{Tc}$ is among the most widely used isotopes in diagnostic nuclear medicine.^[1] It is cheap, exhibits good decay characteristics, and typically burdens the patient with a low radiation dose. Whereas in the past $^{99\text{m}}\text{Tc}$ -complexes were preferentially applied as perfusion agents,^[2] a challenge now lies in combining a $^{99\text{m}}\text{Tc}$ complex with a targeting molecule such as a tumor-specific peptide or a small

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