CHAPTER 2

SYNTHESIS OF 5,6-$(OH)_2$-PTAT: A POTENTIAL MIXED D_1/D_2-RECEPTOR AGONIST*

2.1 INTRODUCTION

In vivo studies performed during the 1980's showed that animals with normosensitive dopamine receptors display locomotor activity and stereotyped behaviour through functional synergism between D_1 and D_2 receptors,** while animals with supersensitive dopamine receptors display such behaviours through functionally uncoupled D_1 and D_2 receptors (see **1.4.3**) [1]. If this concept is extrapolated to man, it implies that in conditions with normosensitive or slightly supersensitive dopamine receptors, as is probably the case in the early stages of Parkinson's disease, stimulation of both D_1 and D_2 receptors would be needed for a good clinical result. On the contrary, in conditions with supersensitive dopamine receptors, as is probably the case in the later stages of Parkinson's disease, selective stimulation of either D_1 or D_2 receptors would be sufficient for a clinical effect [1,2]. Based on this hypothesis, we initiated a study to develop a novel mixed D_1/D_2-receptor agonist, which could ultimately be used clinically in conditions where stimulation of both D_1 and D_2 receptors is needed.

2.2 5,6-$(OH)_2$-PTAT: A POTENTIAL MIXED D_1/D_2-RECEPTOR AGONIST

Typically, the development of dopamine-receptor agonists has proceeded along two main routes, *i.e.* rigidification of the dopamine molecule (**1**) and molecular dissection of the classical dopamine-receptor agonist apomorphine (**7**), as exemplified in Chart 2.1 for 5,6-dihydroxy- and 5-hydroxy-2-aminotetralins, important classes of dopamine-receptor agonists [3-8]. 5,6-Dihydroxy-2-aminotetralin (5,6-$(OH)_2$-AT, **8**), suggested by Pinder and colleagues to be the dopaminergic pharmacophore in apomorphine (**7**) [9], can be viewed as a combination of both approaches [10-12]. Based on structural

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* This chapter is partially based on:

Copinga S, Dijkstra D, De Vries JB, Grol CJ, Horn AS (1993) Synthesis and pharmacological evaluation of 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1,2-naphthalenediol: a novel non-selective dopamine-receptor agonist. *Recl Trav Chim Pays-Bas* **112**, 137-142.

** As described in **1.2.4** the dopamine-receptor family has expanded recently by the use of molecular cloning techniques. Five different dopamine receptors, termed D_1 through D_5, have so far been documented. Based on molecular biological properties and present pharmacological characterization these dopamine receptors can be classified in two dopamine-receptor subfamilies, *i.e.* "D_1-like" receptors (D_1 and D_5) and "D_2-like" receptors (D_2, D_3 and D_4). Consequently, this study dealing with D_1 and D_2 receptors, may involve any or all of the members within these particular subfamilies of dopamine receptors.

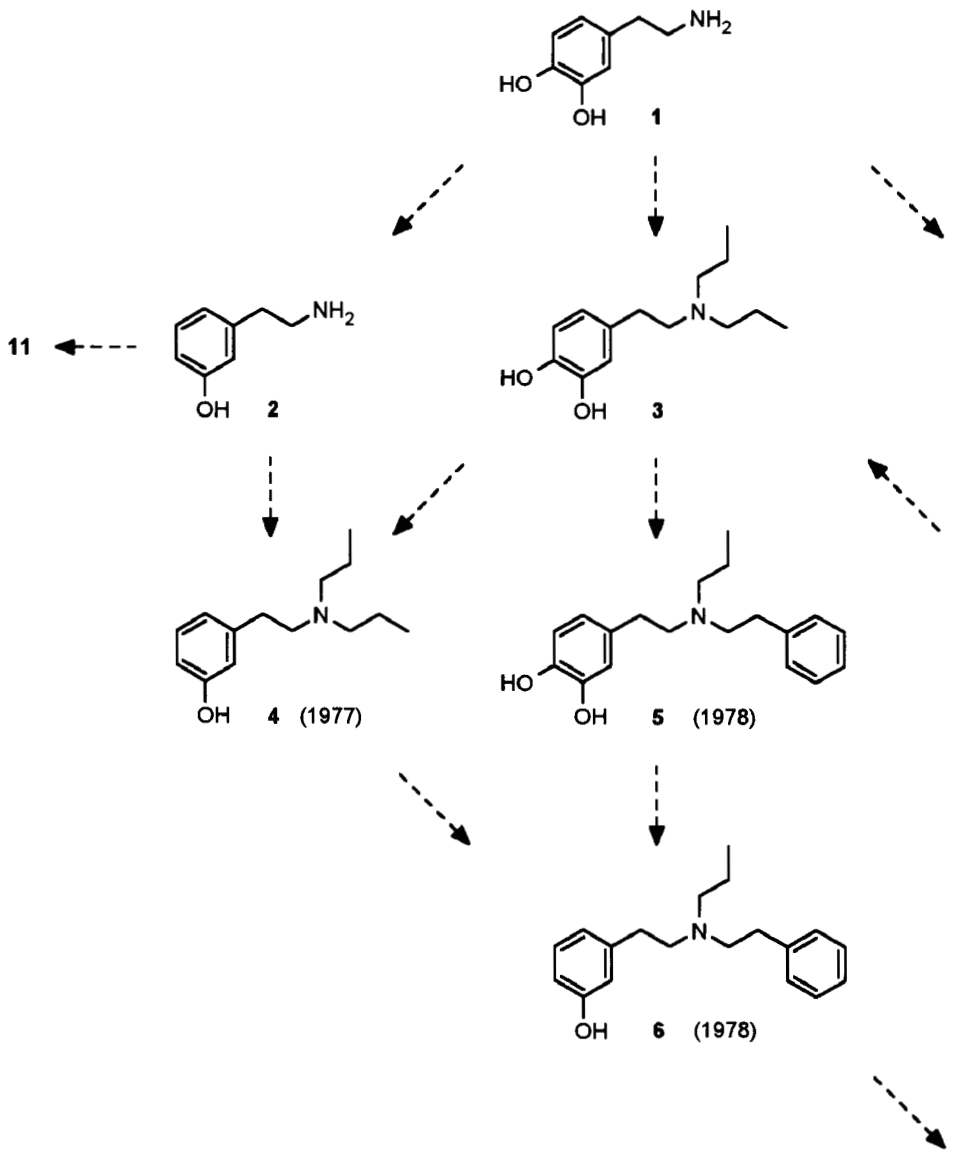
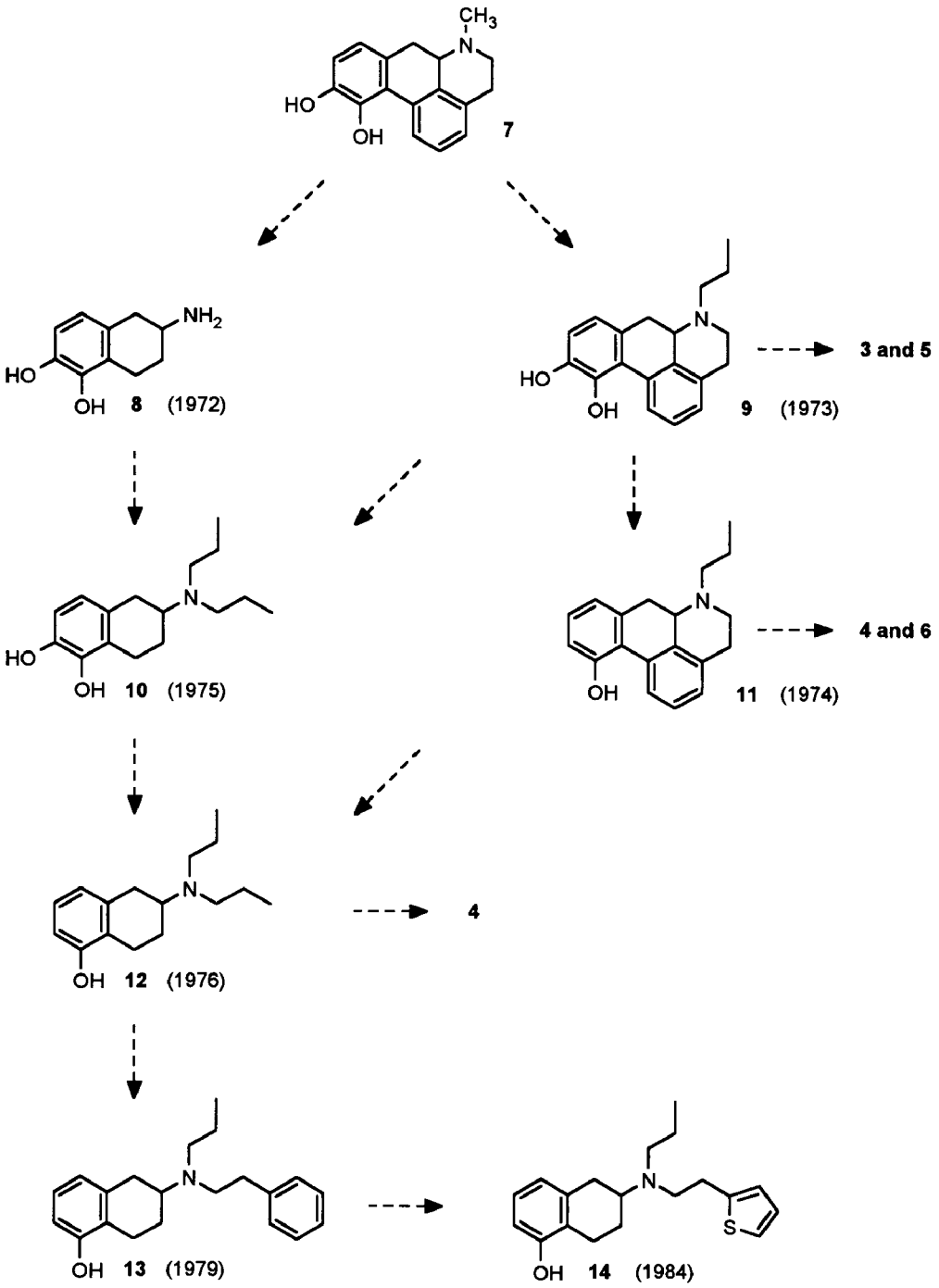


Chart 2.1 5,6-Dihydroxy- and 5-hydroxy-2-aminotetralins: dopamine-receptor agonists resulting from rigidification of the dopamine molecule (**1**), molecular dissection of apomorphine (**7**) and structural modification of the lead compounds dopamine (**1**), apomorphine (**7**) and 5,6-dihydroxy-2-aminotetralin (5,6-$(OH)_2$-AT, **8**).


CH3
N
HO
OH
7
NH2
HO
OH
8 (1972)
N
HO
OH
9 (1973)
3 and 5
N
HO
OH
10 (1975)
N
OH
11 (1974)
4 and 6
N
OH
12 (1976)
4
N
OH
13 (1979)
N
S
OH
14 (1984)

modifications of dopamine (1) and apomorphine (7), which led to compounds with dopaminergic activity –*e.g.* *m*-tyramine (2) [13,14], N-*n*-propylnorapomorphine (9) [15-19], and 11-hydroxy-N-*n*-propylnoraporphine (11) [16,20]–, 5,6-dihydroxy-2-(N,N-di-*n*-propylamino)tetralin (5,6-$(OH)_2$-DPAT, **10**) [11,12,21] and 5-hydroxy-2-(N,N-di-*n*-propylamino)tetralin (5-OH-DPAT, **12**) [22,23] were developed from 5,6-$(OH)_2$-AT (**8**). Pharmacological evaluation of these two 2-aminotetralins in dopamine-receptor subtype-selective bioassays revealed that 5,6-$(OH)_2$-DPAT (**10**) is a mixed D_1/D_2-receptor agonist and that 5-OH-DPAT (**12**) has a lower activity at D_1 receptors than 5,6-$(OH)_2$-DPAT (**10**) and a higher activity at D_2 receptors than 5,6-$(OH)_2$-DPAT (**10**) [24,25]. Beaulieu and colleagues even designated 5-OH-DPAT (**12**) as a selective D_2-receptor agonist due to the fact that this 2-aminotetralin failed to display appreciable D_1-receptor agonist activity [26]. These data are indicative of the importance of the catechol function of 2-aminotetralins, such as 5,6-$(OH)_2$-DPAT (**10**), for activity at D_1 receptors.

Structure-activity-relationship studies, set up to elucidate the receptor-preferred conformation of dopamine at D_1 and D_2 receptors, showed that of the monohydroxylated 2-(N,N-di-*n*-propylamino)tetralins 5-OH-DPAT (**12**), mimicking rigidly the α-rotameric conformation of dopamine,* is the most active one at both subtypes of dopamine receptors, followed by 7-OH-DPAT, mimicking rigidly the β-rotameric conformation of dopamine,* and finally 6-OH-DPAT, a compound only with a para-hydroxy [24,25]. 8-OH-DPAT, a compound without a meta- or para-hydroxy, shows no dopaminergic activity at all, but acts as a potent and selective 5-HT_{1A}-receptor agonist [4,24,25,27]. In addition, these studies revealed that of the dihydroxylated 2-(N,N-di-*n*-propylamino)tetralins 5,6-$(OH)_2$-DPAT (**10**), an α-rotameric dopamine-receptor agonist, displays higher activity at both D_1 and D_2 receptors than 6,7-$(OH)_2$-DPAT, a β-rotameric dopamine-receptor agonist [24,25].

Based on the above described structure-activity relationships and the fact that N-*n*-propyl-N-phenethyl-2-(3-hydroxyphenyl)ethylamine (RU 24213, **6**) [28], developed from 11-hydroxy-N-*n*-propylnoraporphine (**11**) through molecular dissection and from N,N-di-*n*-propyl-2-(3-hydroxyphenyl)ethylamine (**4**) [29,30] and N-*n*-propyl-N-phenethyl-2-(3,4-dihydroxyphenyl)ethylamine (**5**) [28,31] through structural modification, behaves pharmacologically as a selective D_2-receptor agonist [32], Horn and co-workers, in search of clinically applicable, selective D_2-receptor agonists, developed 5-hydroxy-2-[N-*n*-propyl-N-2-(phenyl)ethylamino]tetralin (N-0434, **13**), first described by a combination of Swedish research groups [23], and 5-hydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin (N-0437, **14**), in which the 2-(phenyl)ethylamine side chain of N-0434 (**13**) is replaced isosterically by a 2-(2-thienyl)ethylamine side chain, as extremely potent and selective D_2-receptor agonists [26,33-40].

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* See footnote on α- and β-rotameric conformations of dopamine on page 25.

Considering the pharmacological profiles of 5,6-$(OH)_2$-DPAT (**10**), a mixed D_1/D_2-receptor agonist, and N-0437 (**14**), a selective D_2-receptor agonist, in combination with the importance of a catechol function, present in many selective D_1-receptor agonists, *e.g.* SKF 38393 (**15**), for D_1-receptor activity (see **1.3.2**), we suggested 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin (5,6-$(OH)_2$-PTAT, **16**), the catechol analogue of N-0437 (**14**), as a potential mixed D_1/D_2-receptor agonist, as outlined in Chart 2.2.

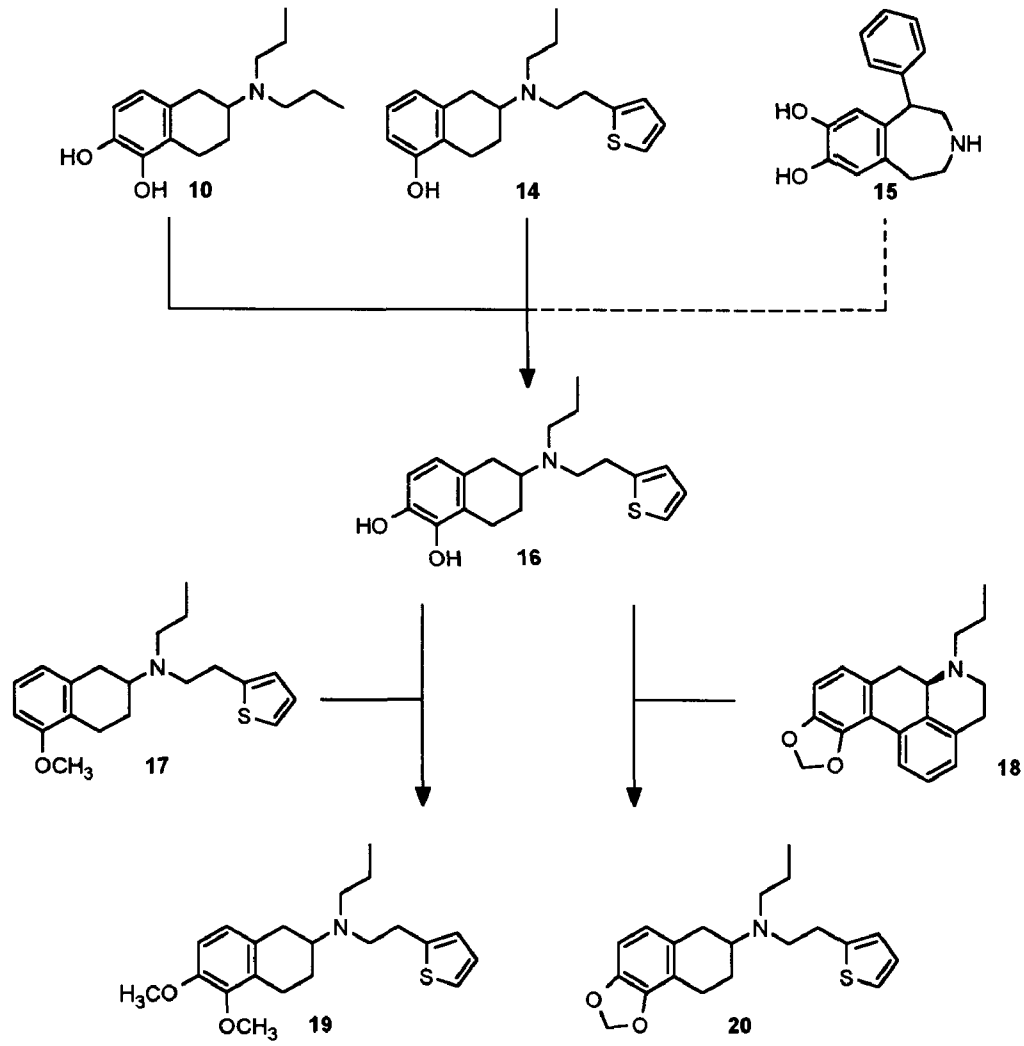


Chart 2.2 Chemical structures of 5,6-$(OH)_2$-PTAT (**16**), a potential mixed D_1/D_2-receptor agonist, and 5,6-$(OCH_3)_2$-PTAT (**19**) and 5,6-OCH_2O-PTAT (**20**), potential prodrugs of 5,6-$(OH)_2$-PTAT (**16**). **10**: 5,6-$(OH)_2$-DPAT, **14**: N-0437, **15**: SKF 38393, **17**: N-0724, and **18**: (–)-MDO-NPA.

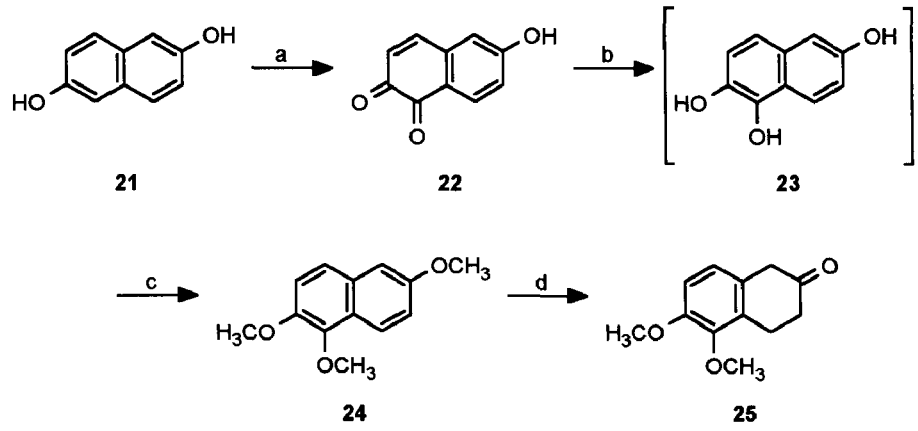
Due to the presence of a catechol function, 5,6-$(OH)_2$-PTAT (**16**) will be rapidly metabolized, or stated differently, will have a low biostability and, notably, a short duration of action. These shortcomings may be circumvented by the development of a prodrug. The prodrug approach is based on the concept of metabolic activation, *i.e.* the active parent compound is liberated from the prodrug by enzymatic activity. As outlined in Chart 2.2, we proposed 5,6-dimethoxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]-tetralin (5,6-$(OCH_3)_2$-PTAT, **19**) and 5,6-methylenedioxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin (5,6-OCH_2O-PTAT, **20**) as potential prodrugs of 5,6-$(OH)_2$-PTAT (**16**), analogous to 5-methoxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]-tetralin (N-0724, **17**), a possible prodrug of N-0437 (**14**) [41], and (–)-10,11-methylene-dioxy-N-*n*-propylaporphine ((–)-MDO-NPA, **18**), an orally effective, long-acting prodrug of (–)-NPA (**9**) [42-44]. These prodrugs of 5,6-$(OH)_2$-PTAT (**19** and **20**) can probably metabolically be activated by the oxidative ether-cleavage action of a cytochrome-P450 isoenzyme [45,46].

2.3 SYNTHESIS OF 5,6-DISUBSTITUTED 2-[N-*N*-PROPYL-N-2-(2-THIENYL)ETHYL-AMINO]TETRALINS

2.3.1 5,6-DIMETHOXY- AND 5,6-DIHYDROXY-2-[N-*N*-PROPYL-N-2-(2-THIENYL)-ETHYLAMINO]TETRALIN

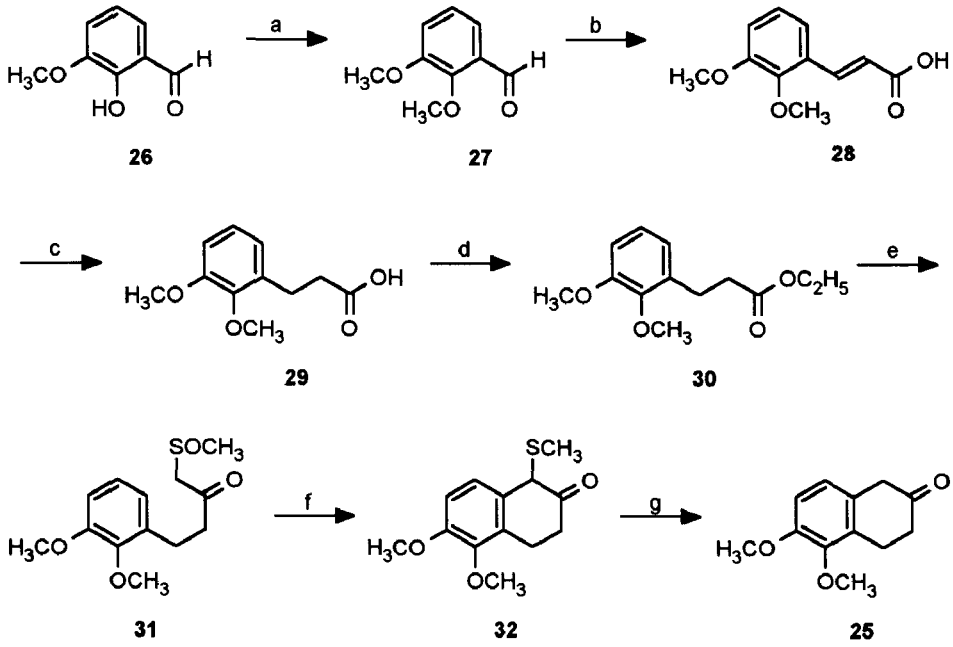
In 1969 Sprenger and colleagues reported for the first time the synthesis of a 5,6-dimethoxy-2-(dialkylamino)tetralin [47]. Important intermediates in this synthetic route were 5,6-dimethoxy-1-tetralone, prepared in seven steps from 2-hydroxy-3-methoxy-benzaldehyde according to the method of Elmore and King [48], and 5,6-dimethoxy-2-amino-1-tetralone, prepared from 5,6-dimethoxy-1-tetralone in three steps including a Neber rearrangement. Cannon and colleagues showed that the ether links in this compound can be cleaved to obtain a 5,6-dihydroxy-2-(dialkylamino)-tetralin [10].

In 1975 McDermed and co-workers demonstrated that 5,6-dimethoxy-2-tetralone (**25**) offers greater versatility as an intermediate to synthesize a wide variety of 5,6-dimethoxy- and 5,6-dihydroxy-2-aminotetralins [11]. They prepared 5,6-dimethoxy-2-tetralone (**25**), synthesized earlier through isomerization of 5,6-dimethoxy-1-tetralone [49], in four steps, as outlined in Scheme 2.1. This synthesis included as the first step the oxidation of 2,6-dihydroxynaphthalene (**21**) to 6-hydroxy-1,2-naphtoquinone (**22**) by the use of Fremy's radical [50,51], a difficult reaction to perform. Subsequently, this napthoquinone **22** was reduced to 1,2,6-trihydroxynaphthalene (**23**) by sodium hydro-sulfite. The trihydroxynaphthalene **23** was not isolated due to its sensitivity to air oxidation, but was immediately methylated to the known trimethoxynaphthalene **24** [52]. This compound **24** was converted to 5,6-dimethoxy-2-tetralone (**25**) by a Birch reduction and an acid hydrolysis, for the first time utilized sequentially by Robinson and co-workers [53].



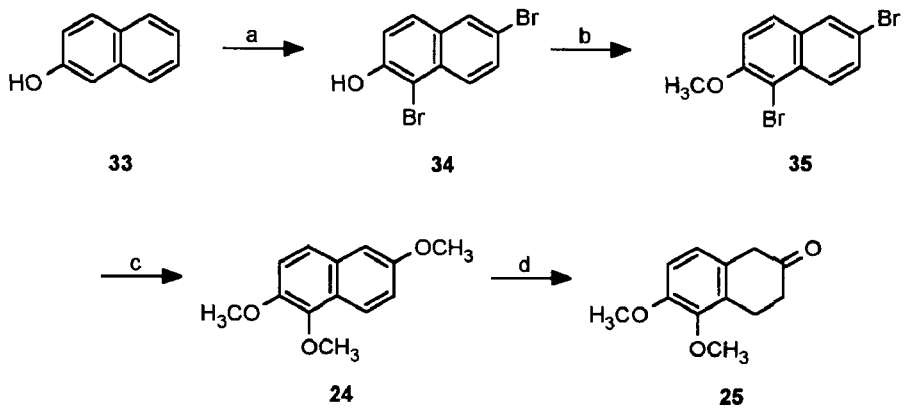
Scheme 2.1 Reagents: (a) $K_2(SO_3)_2NO^{\bullet}$ (Fremy's radical), pH 4.5; (b) $Na_2S_2O_4$; (c) $(CH_3)_2SO_4$, K_2CO_3; (d) Na, C_2H_5OH, H_2O, 36% HCl.

In 1977 5,6-dimethoxy-2-tetralone (**25**) was prepared differently by Cannon and colleagues *via* a multi-step synthetic pathway [12], as outlined in Scheme 2.2. The most important reaction in this pathway was the acid-catalyzed cyclisation of β-ketosulfoxide **31** to 1-methylthio-2-tetralone **32**, involving a Pummerer rearrangement, as described by Oikawa and Yonemitsu [54].



Scheme 2.2 Reagents: (a) $(CH_3)_2SO_4$, KOH; (b) $CH_2(COOH)_2$, pyridine, piperidine; (c) Na-Hg; (d) C_2H_5OH, H^+; (e) NaH, DMSO; (f) CF_3COOH; (g) Pd-on-C (5%), H_2, CH_3COOH.

In 1978 Horn and co-workers described a facile synthesis of 5,6-dihydroxy-2-aminotetralin (**8**), also involving as key intermediate 5,6-dimethoxy-2-tetralone (**25**) [55]. They prepared this tetralone **25** in three steps from commercially available 1,6-dibromo-2-hydroxynaphthalene (**34**) *via* 1,2,6-trimethoxynaphthalene (**24**), as McDermed and colleagues did [11]. This synthetic route to 5,6-dimethoxy-2-tetralone (**25**), as outlined in Scheme 2.3, was found in practice to be more convenient than the above-mentioned methods of McDermed and colleagues and Cannon and colleagues [11,12].

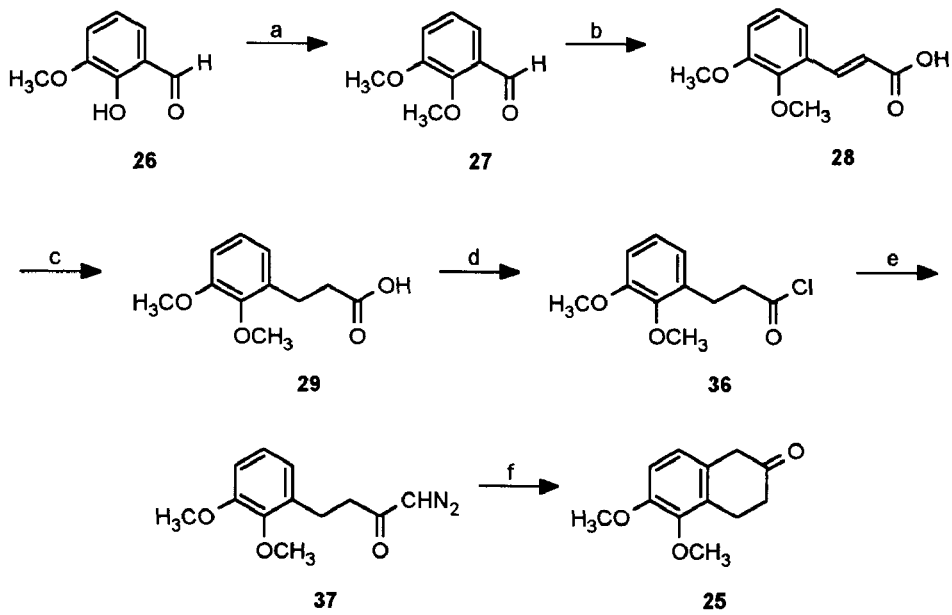


Scheme 2.3 Reagents: (a) Br_2, CH_3COOH; (b) $(CH_3)_2SO_4$, NaOH; (c) $NaOCH_3$, CuI, 2,4,6-trimethylpyridine; (d) Na, C_2H_5OH, H_2O, 36% HCl.

In view of the synthesis of 5,6-dimethoxy- (5,6-$(OCH_3)_2$-PTAT, **19**) and 5,6-dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin (5,6-$(OH)_2$-PTAT, **16**) the method, which was used previously by our group [55], was chosen to prepare the key intermediate 5,6-dimethoxy-2-tetralone (**25**) (Scheme 2.3). Difficulties were encountered in this synthetic route at different stages. The first two steps, *i.e.* the bromination of hydroxynaphthalene **33** [56-58] and the methylation of dibromohydroxynaphthalene **34** [57], were uneventful. Contrarily, the methoxylation of 1,6-dibromo-2-methoxynaphthalene (**35**), using sodium methoxide in the presence of copper(I) iodide by a method of Bacon and co-workers [59,60], gave very unpredictable results. If the methoxylation, an aromatic nucleophilic substitution, succeeded, the yield was often very low. Major by-products, resulting from competition between reductive and nucleophilic substitution, were 2-methoxynaphthalene and 2,6-dimethoxynaphthalene. These by-products were removed by purification through column chromatography. The highest yield, as described in the experimental section (see **2.4.2**), was approximately 60% of pure 1,2,6-trimethoxynaphthalene (**24**). In attempting to improve the results of this reaction, the solvent 2,4,6-trimethylpyridine was replaced by dimethylformamide or a mixture of toluene and dimethylformamide (13:4), as performed by the group of Cannon [61,62]. Although the workup procedure of the reaction was now less laborious,

these replacements failed to give better results. The conversion of pure 1,2,6-trimethoxynaphthalene (**24**) by a Birch reduction and an acid hydrolysis [53] to the desired 2-tetralone **25** always produced 6-methoxy-2-tetralone as a by-product. Removal of this impurity by bisulfite adduct formation, followed by vacuum distillation or column chromatography, was not successful. In the best case, the yield was almost 70% of crude 5,6-dimethoxy-2-tetralone (**25**), containing significant amounts of 6-methoxy-2-tetralone (see **2.4.2**). If this crude tetralone was used in the next reactions to prepare 5,6-$(OCH_3)_2$-PTAT (**19**) and 5,6-$(OH)_2$-PTAT (**16**), the impurity, resulting from 6-methoxy-2-tetralone, could be removed by the column chromatography of the residual oil, which was yielded by the reductive alkylation of contaminated secondary 2-aminotetralin **46** (see **2.4.4** and Scheme 2.5).

Due to the encountered difficulties in the synthetic route to 5,6-dimethoxy-2-tetralone (**25**) *via* 1,2,6-trimethoxynaphthalene (**24**), an alternate synthetic pathway, as outlined in Scheme 2.4, was attempted. This pathway was used previously by Nichols and co-workers to synthesize 5,6-methylenedioxy- and 6,7-methylenedioxy-2-tetralone [63]. Although cinnamic acid **28** is commercially available, this acid was synthesized for economic reasons from 2-hydroxy-3-methoxybenzaldehyde (**26**) in two steps, namely a methylation [64] and a condensation, *i.e.* the Doebner modification of the Knoevenagel reaction [63,65-67]. Cinnamic acid **28** was almost converted quantitatively to α-diazoketone **37** *via* propanoic acid **29** and acyl chloride **36** [63,68,69]. The next step in this synthetic pathway is the crucial conversion of α-diazoketone **37**, reported



26 **27** **28** **29** **36** **37** **25**

Scheme 2.4 Reagents: (a) $(CH_3)_2SO_4$, KOH; (b) $CH_2(COOH)_2$, pyridine, piperidine; (c) Pd-on-C (10%), H_2; (d) $SOCl_2$; (e) CH_2N_2; (f) $[Rh(CH_3COO)_2]_2$, CF_3COOH.

earlier by Elmore and King [48], to 2-tetralone **25** *via* a rhodium(II) acetate-catalyzed cycloaddition, *i.e.* an intramolecular Buchner reaction, followed by a transformation under influence of trifluoroacetic acid. This conversion, as reported firstly by McKervey and colleagues [70,71] and recently reinvestigated by Cordi and colleagues [72], is very interesting from a mechanistic point of view. The postulated mechanism, as outlined in Chart 2.3, involves initially an intramolecular attack of a rhodium(II) carbenoid [73,74] onto the benzene ring of α-diazoketone **37** to form cyclopropanated tricyclic intermediate **38**, a norcaradiene-like intermediate. This intermediate **38** is in equilibrium with 3,8a-dihydroazulen-1(2H)-one **39**. Under acidic conditions, cyclopropanated tricyclic intermediate **38** can be protonated to ion **40**, which rearranges by the opening of a C–C bond to allow re-aromatization. This re-aromatization gives 3,4-dihydro-2-naphthalenol **41**, which tautomerizes to 5,6-dimethoxy-2-tetralone (**25**). The overall yield of this six-step synthesis of 5,6-dimethoxy-2-tetralone (**25**) was almost 50%. Although this synthetic route had two steps more than the above-described one *via* 1,2,6-trimethoxynaphthalene (**24**), the overall yield was higher (50% *vs.* 30%) and above all the desired 2-tetralone **25** was completely pure.

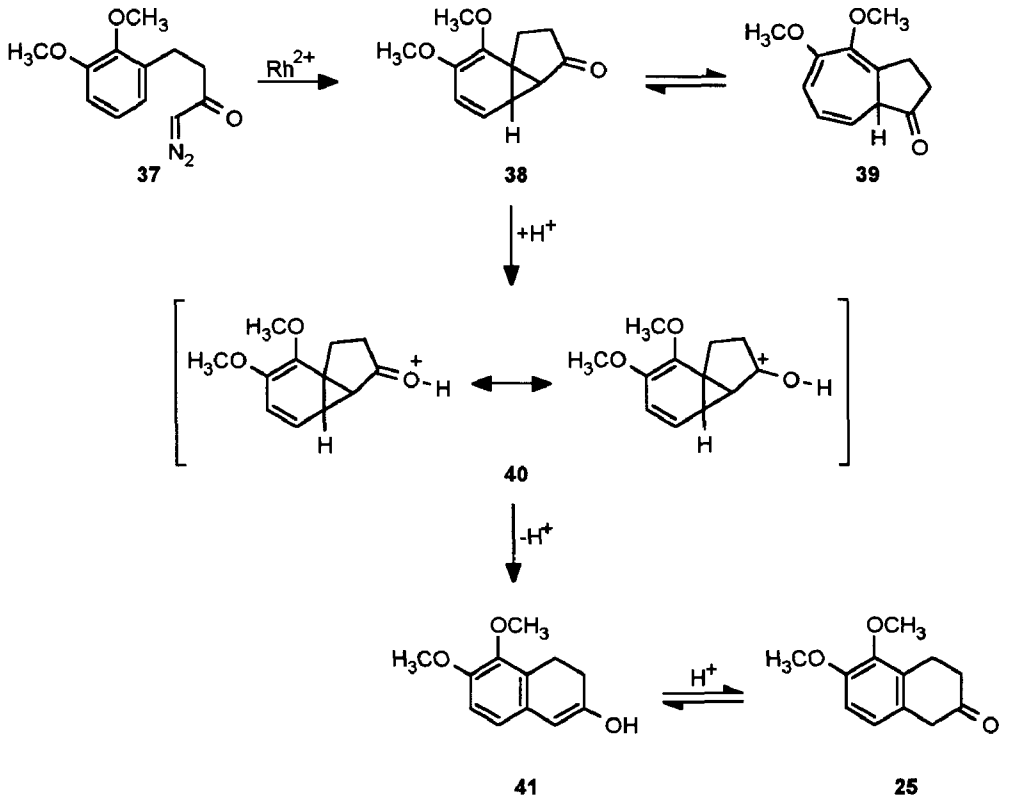
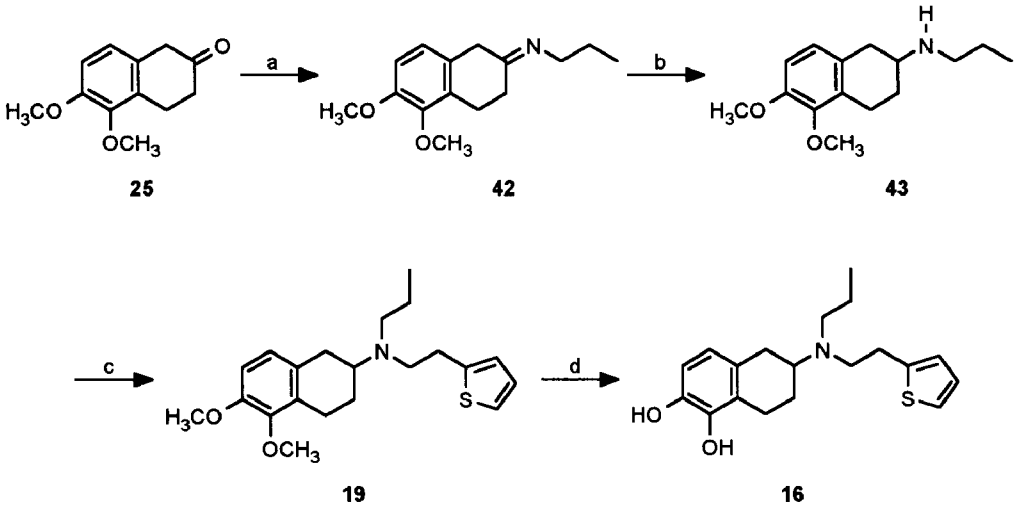


Chart 2.3 Postulated mechanism for rhodium(II) acetate-catalyzed cyclisation, followed by a rearrangement under acidic conditions [70-72].

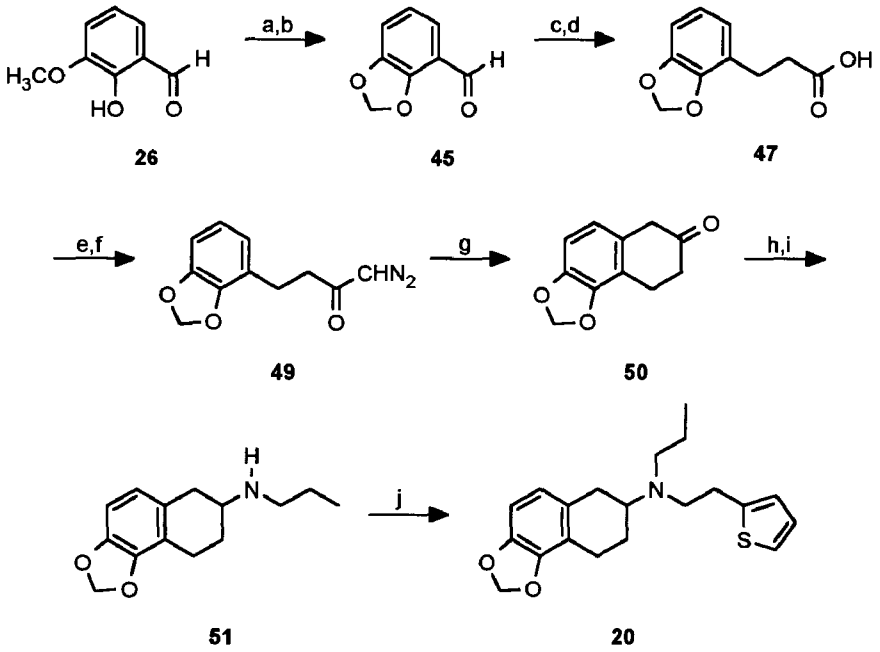
The synthetic route, used to obtain 5,6-$(OCH_3)_2$-PTAT (**19**) from 5,6-dimethoxy-2-tetralone (**25**), consisted of three steps, as outlined in Scheme 2.5. The first step was an acid-catalyzed condensation between 2-tetralone **25** and *n*-propylamine, yielding imine **42** [11,55]. This imine **42** was instantaneously catalytically hydrogenated in the second step to secondary 2-aminotetralin **43** [11,55]. Subsequently, the third step involved a reductive N-alkylation of secondary 2-aminotetralin **43** with 2-thiopheneacetic acid in the presence of trimethylamineborane in refluxing xylene [36], according to the method of Trapani and co-workers [75]. These three steps, yielding 5,6-$(OCH_3)_2$-PTAT (**19**), were straightforward. Ultimately, the conversion of 5,6-$(OCH_3)_2$-PTAT (**19**) to 5,6-$(OH)_2$-PTAT (**16**) comprised a demethylation, as outlined in Scheme 2.5. This demethylation was difficult to perform. Initially, the ether cleavage was attempted with 48% hydrobromic acid [10,12,76]. This method failed because complete ether cleavage was accompanied by total N-dethienylethylation. A milder method of ether cleavage was tried by using boron tribromide in dichloromethane [36,77]. However, complete demethylation of both methoxy groups could not be accomplished. Thus, this reaction always gave the two possible hydroxy-methoxy-2-aminotetralins as by-products, which were difficult to separate from catechol **16**. Finally, the ether cleavage succeeded, albeit in low yield (26%), by using boron tribromide-methyl sulfide complex as demethylating agent [78,79]. The hydrochloride salt of 5,6-$(OH)_2$-PTAT (**16**) could only be obtained by working under an atmosphere of nitrogen and was stored in a vacuum desiccator until use.



Scheme 2.5 Reagents: (a) *n*-$C_3H_7NH_2$, p-TsOH·H_2O; (b) PtO_2, H_2; (c) $(CH_3)_3N{\cdot}BH_3$, 2-thiophene-acetic acid; (d) $BBr_3{\cdot}(CH_3)_2S$.

2.3.2 5,6-METHYLENEDIOXY-2-[N-*N*-PROPYL-N-2-(2-THIENYL)ETHYLAMINO]-TETRALIN

Key intermediate in the synthesis of 5,6-methylenedioxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin (5,6-OCH_2O-PTAT, **20**) was 5,6-methylenedioxy-2-tetralone (**50**). This 2-tetralone **50** was synthesized from 2-hydroxy-3-methoxybenzaldehyde (**26**) *via* α-diazoketone **49**, as described previously by Nichols and co-workers [63]. As outlined in Scheme 2.6, the first step of this synthetic pathway involved the demethylation of 2-hydroxy-3-methoxybenzaldehyde (**26**) by the use of 48% hydrobromic acid in glacial acetic acid in accordance with the method of Pauly and colleagues [80,81]. The 37% yield of this reaction was lower than the previously described yields [81,82]. The next step, the conversion of 2,3-dihydroxybenzaldehyde (**44**) to 2,3-methylenedioxybenzaldehyde (**45**), was accomplished by the method of Tomita and Aoyagi [83]. The methylenation, involving two sequential, aliphatic nucleophilic substitutions [84], was carried out using dibromomethane as methylenating agent (instead of diiodomethane [82]) in the presence of potassium carbonate as ionizing base, copper(II) oxide as catalyst, and dimethylformamide as solvent [85-87]. Subsequently, methylenedioxybenzaldehyde **45** was converted to 5,6-methylenedioxy-



Scheme 2.6 Reagents: (a) 48% HBr, CH_3COOH; (b) CH_2Br_2, K_2CO_3, CuO, DMF; (c) $CH_2(COOH)_2$ pyridine, piperidine; (d) Pd-on-C (10%), H_2; (e) $SOCl_2$; (f) CH_2N_2; (g) $[Rh(CH_3COO)_2]_2$, CF_3COOH; (h) *n*-$C_3H_7NH_2$, p-TsOH·H_2O; (i) PtO_2, H_2; (j) $(CH_3)_3N{\cdot}BH_3$, 2-thiopheneacetic acid.

2-tetralone (**50**) by the same sequence of smoothly executed reactions as used for the conversion of 2,3-dimethoxybenzaldehyde (**27**) to 5,6-dimethoxy-2-tetralone (**25**) (see **2.3.1** and Scheme 2.4) [63,67,88,89]. The crucial reaction in this sequence, the conversion of α-diazoketone **49** to the desired 2-tetralone **50**, proceeded in modest yield.

5,6-OCH_2O-PTAT (**20**) was obtained from 5,6-methylenedioxy-2-tetralone (**50**) in three straightforward steps, as outlined in Scheme 2.6. These three steps involved a condensation, a catalytic hydrogenation and a reductive N-alkylation, as already described for the synthesis of 5,6-$(OCH_3)_2$-PTAT (**19**) from 5,6-dimethoxy-2-tetralone (**25**) (see **2.3.1** and Scheme 2.5) [11,36,55,75].

2.4 EXPERIMENTAL SECTION

2.4.1 GENERAL ASPECTS

Melting points were determined in open glass capillaries on an Electrothermal digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Philips PU 9706 spectrophotometer or on a Beckman AccuLab 2 spectrophotometer, and only the important absorptions are given. ^1H NMR spectra were recorded on a 60 MHz Hitachi Perkin-Elmer R-24 B spectrometer or on a 300 MHz Varian VXR-300 spectrometer. Chemical shifts (δ) are reported in ppm (parts per million) relative to $(CH_3)_4Si$ as an internal standard or via $\delta(CDCl_3)$ (7.24) or $\delta[(CD_3)_2SO]$ (2.49). Chemical-ionisation (CI) mass spectra, using NH_3 as reactant gas, were obtained with a Finnegan 3300 system. Elemental analyses for new substances were performed by the Department of Chemistry, University of Groningen, The Netherlands. Where elemental analyses are indicated, obtained results were within 0.4% of theoretical values.

2.4.2 PREPARATION OF 5,6-DIMETHOXY-2-TETRALONE *VIA* 1,2,6-TRIMETHOXYNAPHTHALENE

1,6-Dibromo-2-naphthalenol (34)
To a vigorously stirred solution of 2-naphthol (**33**) (144.0 g, 1.00 mol) in glacial acetic acid (0.75 l) was added dropwise over a period of 1.5 h a solution of bromine (105 ml, 2.05 mol) in glacial acetic acid (360 ml). After the addition was complete, the reaction mixture was refluxed until the evasion of hydrogen bromide, which was removed by a constant stream of nitrogen and absorbed in H_2O, stopped (after approx. 1.5 h). During cooling of the reaction mixture a pink solid precipitated. To the cooled reaction mixture was added slowly ice-water until the formation of precipitate ended. After stirring for 2 h, the pink solid was collected by suction filtration and dissolved in CH_2Cl_2. This solution was washed with a 2.5% aqueous solution of $Na_2S_2O_3$ and saturated aqueous solutions of $NaHCO_3$ and NaCl and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded 284.0 g (0.94 mol, 94%) of naphthalenol **34** as a slightly pink solid: mp 104-106 °C ([56] mp 106 °C, 80% acetic acid; [57] mp 106 °C, benzene); IR (cm^{-1}, KBr) 3420 (OH), 1580 (Ar), 920, 870, 800 (ArH); ^1H NMR (60 MHz, $CDCl_3$) δ 5.90 (s, 1H, OH), 7.15-8.00 (m, 5H, ArH); ^1H NMR (60 MHz, $CDCl_3$+D_2O) δ 7.15-8.00 (m, 5H, ArH).

1,6-Dibromo-2-methoxynaphthalene (35)
Dimethyl sulphate (40 ml, 0.42 mol) was added dropwise over a period of 30 min to a vigorously stirred solution of naphthalenol **34** (100.1 g, 0.332 mol) in 2N NaOH (250 ml). The temperature of the reaction

mixture raised to 35 °C and a cream-coloured precipitate appeared. After 15 min 2N NaOH (100 ml) was added to the reaction mixture and the basic reaction mixture was stirred for 1 h at 55 °C. Subsequently another amount of dimethyl sulphate (15 ml, 0.16 mol) was added dropwise over a period of 10 min. The basic reaction mixture was stirred for 30 min at 55 °C and heated at reflux for 1 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 (3 x 100 ml). The CH_2Cl_2 layer was washed with 2N NaOH (3 x 100 ml) and a saturated solution of NaCl (1 x 100 ml) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, recrystallization (hexane) yielded 78.0 g (0.247 mol, 74%) of methoxynaphthalene **35** as light-gray crystals: mp 102-103 °C ([57] mp 102 °C, Et_2O); IR (cm^{-1}, KBr) 1580 (Ar), 890, 870, 840, 795; ^1H NMR (60 MHz, $CDCl_3$) δ 4.00 (s, 3H, OCH_3), 7.10-8.25 (m, 5H, ArH).

1,2,6-Trimethoxynaphthalene (24)

Freshly cut sodium (16.5 g, 0.7 g atom) was added under an atmosphere of nitrogen to dry MeOH (200 ml). When dissolution was complete, the warm solution was diluted with dry 2,4,6-trimethylpyridine (100 ml), and subsequently vacuum-dried CuI (20.6 g, 108 mmol) and methoxynaphthalene **35** (30.0 g, 99.4 mmol) were added. The reaction mixture was diluted with an additional amount of dry 2,4,6-trimethylpyridine (200 ml) and was stirred for 20 h under an atmosphere of nitrogen while being maintained at reflux temperature. Initially the colour of the reaction mixture was pale green, but turned during the reaction to deep orange-brown. After cooling, the reaction mixture was filtered through Celite, the filtrate carefully acidified with 6N HCl (480 ml), and the resulting mixture extracted with Et_2O (4 x 150 ml). The combined Et_2O extracts were washed with 2N HCl (1 x 200 ml) and a saturated aqueous solution of NaCl (2 x 200 ml) and then dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel 60 (Merck) using toluene as the eluent. The fractions containing pure trimethoxynaphthalene **24** (determined by TLC) were pooled and the solvent was evaporated under reduced pressure to yield 13.2 g (60.5 mmol, 61%) of trimethoxynaphthalene **24** as a nearly white powder: mp 54-55 °C ([11] mp 55 °C; [52] mp 55 °C, MeOH/light petroleum; [55] mp 54-55 °C); ^1H NMR (60 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.00-8.25 (m, 5H, ArH); MS (CI with NH_3) *m/z* 219 (M+1).

3,4-Dihydro-5,6-dimethoxy-2(1H)-naphthalenone
(5,6-Dimethoxy-2-tetralone, 25)

Trimethoxynaphthalene **24** (10.9 g, 50 mmol) was dissolved in boiling absolute EtOH (125 ml) under mechanically stirring. Sodium (9.0 g, 0.4 g atom), cut in little pieces, was added as rapidly as possible (30 min) to the nitrogen flushed solution. After addition of another amount of absolute EtOH (25 ml), refluxing was continued until all the sodium had disappeared (1 h). The reaction mixture was cooled in an ice bath and then diluted with chilled H_2O (40 ml) and 36% HCl (45 ml) added dropwise as rapidly as possible to avoid the formation of "tetralone-blue". The yellow reaction mixture was stirred for 1 h at reflux temperature. After cooling, the reaction mixture was extracted with Et_2O (50 ml) and the H_2O/EtOH layer was concentrated under reduced pressure until only H_2O remained. This H_2O layer was extracted with Et_2O (3 x 50 ml) and the Et_2O extracts were combined. The resulting Et_2O layer was washed with a saturated aqueous solution of NaCl (3 x 50 ml) and dried over $MgSO_4$. After *in vacuo* evaporation of the solvent, a viscous, brownorange oil was afforded, which solidified in the refrigerator. From the crude oil a $NaHSO_3$ adduct was prepared. Decomposition of this adduct by an aqueous solution of Na_2CO_3 yielded, after extraction with Et_2O, drying over $MgSO_4$ and evaporation of the solvent under reduced pressure, 7.0 g (34 mmol, 68%) of tetralone **25**, contaminated with 6-methoxy-2-tetralone, as a yellow solid: IR (cm^{-1}, neat) 2840 (OCH_3), 1710 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.50 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), 3.50 (s, 2H, CH_2), 3.75 (s, 0.3H, OCH_3 of 6-methoxy-2-tetralone), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.80 (s, 2H, ArH) ([49] ^1H NMR ($CDCl_3$)); MS (CI with NH_3) *m/z* 177 (M−30+1), 207 (M+1), 224 (M+18). Attempts to remove 6-methoxy-2-tetralone

by vacuum distillation or column chromatography (silica gel 60 (Merck) using CH_2Cl_2 as the eluent) failed.

2.4.3 PREPARATION OF 5,6-DIMETHOXY-2-TETRALONE *VIA* 1-DIAZO-4-(2,3-DIMETHOXYPHENYL)-2-BUTANONE

2,3-Dimethoxybenzaldehyde (27)

2-Hydroxy-3-methoxybenzaldehyde (**26**) (38.0 g, 0.250 mol) was melted by warming on a water-bath. To this vigorously stirred melt was added dropwise a solution of KOH (20.5 g, 0.365 mol) in H_2O (30 ml) at such a rate that the addition was complete after 15 min. 30 Seconds after the beginning of this addition dimethyl sulphate (30.0 ml, 0.317 mol) was added dropwise at the same rate. After 5 min the external heating was stopped and the pale reddish-brown reaction mixture continued to reflux gently from the heat of the reaction. When the colour of the reaction mixture changed to green (indication of an acid reaction), the rate of addition of the alkali was slightly increased. When the additions were complete, the brown reaction mixture was poured into a porcelain basin and allowed to cool overnight without disturbance. The resulting crystalline aldehyde **27** was collected by suction filtration and ground in a mortar with ice-cold H_2O (100 ml). After suction filtration and drying in a vacuum desiccator, recrystallization (hexane) yielded 35.0 g (0.211 mol, 84%) of aldehyde **27** as colourless, long needles: mp 50-51 °C ([81] mp 54 °C, ligroine; [90] mp 51-52 °C, EtOH/H_2O; [91] mp 52-54 °C, Et_2O/ petroleum ether); IR (cm^{-1}, KBr) 1685 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.10-7.60 (m, 3H, ArH), 10.45 (s, 1H, CHO).

(E)-3-(2,3-Dimethoxyphenyl)-2-propenoic Acid
*(2,3-Dimethoxy-*trans*-cinnamic Acid, 28)*

A well stirred mixture of aldehyde **27** (21.6 g, 0.130 mol), malonic acid (27.0 g, 0.259 mol), and piperidine (1.9 ml) in pyridine (60 ml) was heated for 2 h at 80 °C and then refluxed for 2 h at 115 °C. The mixture was chilled and poured under stirring into an excess of cold aqueous 1N HCl (0.80 l). The flocculent white precipitate was collected by suction filtration and washed by resuspension and stirring for 15 min in cold H_2O (300 ml). The precipitate was collected by suction filtration and dried in a vacuum desiccator. The yield was 26.0 g (0.125 mol, 96%) of cinnamic acid **28**. An analytical sample was recrystallized from 2-butanone to provide white crystals: mp 181-182 °C ([66] mp 179-180 °C, 2-butanone; [68] mp 180-181 °C, benzene; [69] mp 180 °C, EtOAc); IR (cm^{-1}, KBr) 1690 (C=O), 1635 (C=C); ^1H NMR [60 MHz, $(CD_3)_2SO$] δ 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.40 (d, 1H, =CHCO, J = 17 Hz), 6.75-7.25 (m, 3H, ArH), 7.75 (d, 1H, =CHAr, J = 17 Hz), 12.3 (bs, 1H, OH).

3-(2,3-Dimethoxyphenyl)propanoic Acid (29)

Cinnamic acid **28** (15.9 g, 76.4 mmol) was dissolved in 96% EtOH (500 ml) and hydrogenated overnight over 10% Pd-on-C (1.5 g) in a Parr apparatus under a H_2 pressure of 3.5 atmospheres. The mixture was filtered and the solvent was evaporated *in vacuo* to yield 15.7 g (74.8 mmol, 98%) of propanoic acid **29** as a light-yellow solid. An analytical sample was recrystallized from benzene to provide white crystals: mp 68-69 °C ([65] mp 68 °C, H_2O; [69] mp 69-70 °C, benzene/petroleum (bp 50-60 °C)); IR (cm^{-1}, KBr) 1700 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.50-3.15 (m, 4H, CH_2CH_2), 3.90 (s, 6H, OCH_3), 6.65-7.15 (m, 3H, ArH), 10.9 (bs, 1H, OH); ^1H NMR [60 MHz, $(CD_3)_2SO$] δ 2.40-3.15 (m, 4H, CH_2CH_2), 3.90 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.80-7.25 (m, 3H, ArH).

3-(2,3-Dimethoxyphenyl)propanoyl Chloride (36)

Thionyl chloride (2.45 ml, 33.6 mmol) was added under an atmosphere of nitrogen to a stirred solution of propanoic acid **29** (6.40 g, 30.5 mmol) in benzene (200 ml). After refluxing for 4 h and cooling of the

reaction mixture, the volatiles were evaporated under reduced pressure to yield the crude acyl chloride **36**, which was purified by vacuum distillation. The yield was 6.55 g (28.6 mmol, 94%) of acyl chloride **36** as a colourless, viscous oil: bp 97-98 °C (0.005 mbar) ([68] bp 165-166 °C (15 mmHg); [48] bp 106-107 °C (2 mmHg)); IR (cm^{-1}, neat) 2840 (OCH_3), 1800 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.90-3.40 (m, 4H, CH_2CH_2), 3.90 (s, 6H, OCH_3), 6.65-7.10 (m, 3H, ArH).

1-Diazo-4-(2,3-dimethoxyphenyl)-2-butanone (37)

A solution of acyl chloride **36** (6.52 g, 28.5 mmol) in anhydrous Et_2O (75 ml) was added dropwise over a period of 15 min to a stirred solution of freshly prepared CH_2N_2 (approx. 3.8 g) (**caution**: highly explosive and highly toxic gas) in dry Et_2O (185 ml) [92] at 5 °C and under an atmosphere of nitrogen. After the reaction mixture had reached room temperature, it was allowed to stand overnight under an atmosphere of nitrogen. Removal of the solvent under reduced pressure yielded 6.60 g (28.2 mmol, 99%) of α-diazoketone **37** as a yellow oil: IR (cm^{-1}, neat) 2850 (OCH_3), 2105 (CHN_2), 1645 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.50-3.15 (m, 4H, CH_2CH_2), 3.90 (s, 6H, OCH_3), 5.25 (s, 1H, CHN_2), 6.70-7.15 (m, 3H, ArH) ([48] no data reported).

3,4-Dihydro-5,6-dimethoxy-2(1H)-naphthalenone
(5,6-Dimethoxy-2-tetralone, 25)

α-Diazoketone **37** (6.57 g, 28.0 mmol) was dissolved in CH_2Cl_2 (50 ml) and this solution was added over a period of 10 min to a rapidly stirred solution of $[Rh(CH_3COO)_2]_2$ (50 mg) in CH_2Cl_2 (40 ml) under an atmosphere of nitrogen. After refluxing for 10 min, 1 drop of CF_3COOH was added and refluxing was continued for 15 min. After cooling, the reaction mixture was washed with saturated aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. *In vacuo* evaporation of the CH_2Cl_2 yielded a brown-orange oil. The crude oil was purified by vacuum distillation to yield 3.80 g (18.4 mmol, 66%) of tetralone **25** as a light-yellow oil, which crystallized on standing: bp 105-110 °C (0.01 mbar). An analytical sample was recrystallized from hexane to provide white needles: mp 63-64 °C ([11] mp 61-63 °C, hexane; [12] mp 62-64 °C, cyclohexane; [49] mp 64-65 °C, cyclohexene); IR (cm^{-1}, neat) 2840 (OCH_3), 1710 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.50 (t, 2H, CH_2, J = 7 Hz), 3.15 (t, 2H, CH_2, J = 7 Hz), 3.50 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.80 (s, 2H, ArH) ([49] ^1H NMR ($CDCl_3$)); MS (CI with NH_3) *m/z* 207 (M+1), 224 (M+18).

2.4.4 PREPARATION OF 5,6-DIMETHOXY- AND 5,6-DIHYDROXY-2-[N-*N*-PROPYL-N-2-(2-THIENYL)ETHYLAMINO]TETRALIN WITH 5,6-DIMETHOXY-2-TETRALONE AS STARTING MATERIAL

*1,2,3,4-Tetrahydro-5,6-dimethoxy-N-*n*-propyl-2-naphthalenamine*
*(5,6-Dimethoxy-2-(N-*n*-propylamino)tetralin, 43)*

Under an atmosphere of nitrogen, a solution of tetralone **25** (3.30 g, 16.0 mmol), *n*-propylamine (1.60 ml (1.15 g), 19.5 mmol), and a couple of p-toluenesulphonic acid monohydrate crystals in dry benzene (50 ml) was refluxed for 5 h under continuous removal of H_2O using a Dean-Stark apparatus. The benzene and the excess *n*-propylamine were removed under reduced pressure and the residue, *i.e.* crude imine **42**, was dissolved in absolute EtOH (75 ml). After transferring the solution to a Parr hydrogenation flask, PtO_2 (approx. 30 mg) was added as a catalyst and the mixture was hydrogenated overnight under a H_2 pressure of 3 atm. The catalyst was filtered off and the solvent was evaporated under reduced pressure to yield amine **43** as a dark brown oil. After converting the crude amine to its HCl salt by the use of dry ethereal HCl, the salt was dissolved in EtOH and decolourized with charcoal. Recrystallization (EtOH/Et_2O) gave 2.34 g (8.2 mmol, 51%) of **43**·HCl as fine white platelets: mp 239-241 °C dec ([11]

mp 227-229 °C, MeOH/EtOAc; [12] mp 237-239 °C, MeOH/Et_2O); IR (cm^{-1}, KBr) 2880-2580, 2540, 2460 (NH_2^+); ^1H NMR [60 MHz, $(CD_3)_2SO$] δ 1.05 (t, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 7.00 (s, 2H, ArH); MS (CI with NH_3) *m/z* 250 (M+1) (M: free amine).

*1,2,3,4-Tetrahydro-5,6-dimethoxy-N-*n*-propyl-N-[2-(2-thienyl)ethyl]-2-naphthalenamine (5,6-Dimethoxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin, 5,6-$(OCH_3)_2$-PTAT, 19)*

A mixture of secondary amine **43** (1.50 g, 6.01 mmol), 2-thiopheneacetic acid (2.56 g, 18.0 mmol) and trimethylamineborane (1.30 g, 17.8 mmol) in dry xylene (60 ml) was refluxed under an atmosphere of nitrogen for 4 h. After cooling, the reaction mixture was washed with aqueous 10% $NaHCO_3$ (3 x 50 ml), H_2O (1 x 50 ml) and a saturated aqueous solution of NaCl (1 x 50 ml) and dried over $NaSO_4$. After removal under reduced pressure of the xylene, the residual oil was purified by column chromatography on silica gel 60 (Merck) using a mixture of EtOAc and petroleum ether 40-60 (1/4) as the eluent. The fractions containing pure tertiary amine **19** (determined by TLC) were combined and the solvent was evaporated under reduced pressure. The residual pure tertiary amine **19** was dissolved in dry Et_2O and precipitated as its HCl salt by treatment with dry ethereal HCl. Recrystallization (2-PrOH) yielded 1.56 g (3.94 mmol, 66%) of **19**·HCl as white crystals: mp 189.5-191.0 °C dec; IR (cm^{-1}, KBr) 2700-2200 (NH^+); ^1H NMR (300 MHz, CD_3OD) δ 1.06 (t, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.87 (dd, 2H, ArH, J = 9 Hz), 6.97-7.33 (m, 3H, ArH); MS (CI with NH_3) *m/z* 360 (M+1) (M: free amine); Anal. calcd. for $C_{21}H_{29}NO_2S$·HCl (395.99): C 63.70, H 7.64, N 3.54, S 8.10; found C 63.69, H 7.59, N 3.72, S 7.92.

*1,2,3,4-Tetrahydro-5,6-dihydroxy-N-*n*-propyl-N-[2-(2-thienyl)ethyl]-2-naphthalenamine (5,6-Dihydroxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]tetralin, 5,6-$(OH)_2$-PTAT, 16)*

BBr_3·Me_2S (1.40 g, 4.5 mmol) was added to a solution of **19**·HCl (0.75 g, 1.9 mmol) in 1,2-dichloroethane (25 ml), under an atmosphere of nitrogen . After refluxing for 0.5 h, the reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ and the 1,2-dichloroethane layer was dried over $MgSO_4$. After evaporation under reduced pressure of almost all the 1,2-dichloroethane, Et_2O was added under stirring and some crystals precipitated. The liquid was decanted and treated with dry ethereal HCl to precipitate the HCl-salt of **16**. After removal of almost all the solvent, very dry Et_2O was added and this mixture was stirred under an atmosphere of nitrogen for 5 min. This treatment was repeated twice before careful suction filtration under an atmosphere of nitrogen yielded 0.18 g (0.5 mmol, 26%) of **16**·HCl as a slightly pink solid: IR (cm^{-1}, KBr) 3500-3000 (OH), 2800-2200 (NH^+); ^1H NMR (300 MHz, CD_3OD) δ 1.05 (t, 3H, CH_3), 6.50 (d, 1H, ArH, J = 8 Hz), 6.66 (d, 1H, ArH, J = 8 Hz), 6.95-7.31 (m, 3H, ArH); MS (CI with NH_3) *m/z* 332 (M+1) (M: free amine); Anal. calcd. for $C_{19}H_{25}NO_2S$ ·HCl (367.94): C 62.02, H 7.12, N 3.81, S 8.71; found C 61.97, H 7.09, N 4.01, S 8.67.

2.4.5 PREPARATION OF 5,6-METHYLENEDIOXY-2-TETRALONE *VIA* 1-DIAZO-4-(2,3-METHYLENEDIOXYPHENYL)-2-BUTANONE

2,3-Dihydroxybenzaldehyde (44)

To a solution of 2-hydroxy-3-methoxybenzaldehyde (**26**) (75.3 g, 0.495 mol) in glacial acetic acid (450 ml) was added 48% HBr (450 ml). The stirred reaction mixture was heated to boiling as rapidly as possible and a distillate was slowly removed at a temperature of approx. 115 °C. After 6 h the reaction was discontinued (250 ml distillate) and the reaction mixture was cooled. The cooled reaction mixture was poured into a vigorous stirred mixture of ice (750 g) and water (500 ml) and the resulting aqueous layer was extracted three times with Et_2O. Subsequently the Et_2O extracts were combined, washed with saturated aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the solid residue was dissolved in CH_2Cl_2. After removal by filtration of

insoluble brown material and *in vacuo* evaporation of the CH_2Cl_2, recrystallization (hexane) and drying in a vacuum desiccator afforded 25.3 g (0.183 mol, 37%) of aldehyde **44** as fine yellow needles: mp 109-111 °C ([80] mp108 °C; [86] mp 105-107 °C, benzene; [93] mp 105-106 °C, benzene); IR (cm^{-1}, KBr) 3350 (OH), 1660 (C=O); ^1H NMR [60 MHz, $(CD_3)_2SO$] δ 6.65-7.30 (m, 3H, ArH), 9.95 (bs, 2H, $(OH)_2$), 10.25 (s, 1H, CHO); ^1H NMR [60 MHz, $(CD_3)_2SO+D_2O$] δ 6.65-7.30 (m, 3H, ArH), 10.25 (s, 1H, CHO).

2,3-Methylenedioxybenzaldehyde (45)

A mixture of aldehyde **44** (19.5 g, 141 mmol), CH_2Br_2 (29.6 g, 170 mmol), K_2CO_3 (20.0 g, 145 mmol) and CuO (1.3 g) in DMF (130 ml) was heated under an atmosphere of nitrogen at 130 °C for 2.5 h. After cooling to room temperature, the mixture was diluted with H_2O (400 ml) and toluene (200 ml). The solids were removed by filtration through Celite and were washed with toluene. The filtrate was separated into an aqueous layer and a toluene layer, and then the aqueous layer was extracted with toluene (3 x 200 ml). The toluene layers were combined, washed with H_2O (3 x 250 ml) and dried over $MgSO_4$. After evaporation of the toluene under reduced pressure, purification of the residue by vacuum distillation yielded 12.6 g (83.9 mmol, 59%) of aldehyde **45** as a light-yellow oil, which crystallized in the receiver: bp 95-96 °C (0.01 mbar). An analytical sample was recrystallized from EtOAc/hexane to provide fine light-yellow crystals: mp 34-35 °C ([82] mp 32-34 °C, Et_2O; [86] mp 32-33 °C; [87] mp 35-36 °C; [88] mp 34 °C, EtOH or Et_2O; [89] mp 35 °C, petroleum ether (bp 40-60 °C); [94] mp 33-34 °C, Et_2O/light petroleum); IR (cm^{-1}, neat) 1690 (CHO); ^1H NMR (60 MHz, $CDCl_3$) δ 6.15 (s, 2H, OCH_2O), 6.85-7.45 (m, 3H, ArH), 10.10 (s, 1H, CHO).

(E)-3-(2,3-Methylenedioxyphenyl)-2-propenoic Acid
*(2,3-Methylenedioxy-*trans*-cinnamic Acid, 46)*

This cinnamic acid **46** was prepared from aldehyde **45** (12.4 g, 82.6 mmol) by essentially the same procedure as described for the preparation of cinnamic acid **28** from aldehyde **27**. The yield was 15.3 g (79.6 mmol, 96%) of cinnamic acid **46**. An analytical sample was recrystallized from 2-butanone to provide white crystals: mp 193-195 °C ([63] mp 194-195 °C, MeOH; [82] mp 194-196 °C, MeOH; [88] mp 194 °C, H_2O/MeOH or H_2O/EtOAc; [94] mp 194-196.5 °C); IR (cm^{-1}, KBr) 1710 (C=O), 1640 (C=C); ^1H NMR [60 MHz, $(CD_3)_2SO$] δ 6.15 (s, 2H, OCH_2O), 6.55 (d, 1H, =CHCO, J = 16 Hz), 6.85 -7.25 (m, 3H, ArH), 7.55 (d, 1H, =CHAr, J = 16 Hz) ([63] ^1H NMR ($CDCl_3$))

3-(2,3-Methylenedioxyphenyl)propanoic Acid (47)

This propanoic acid **47** was prepared from cinnamic acid **46** (7.9 g, 41.1 mmol) by essentially the same procedure as described for the preparation of propanoic acid **29** from cinnamic acid **28**. The yield was 7.6 g (39.1 mmol, 95%) of propanoic acid **47** as a green crystalline product. An analytical sample was recrystallized from CH_2Cl_2/hexane to provide white crystals: mp 77-79 °C ([63] 79-80 °C, benzene; [82] 80-82 °C; [89] mp 76-78 °C, ether/petroleum ether (bp 40-60 °C); [94] mp 78-79 °C); IR (cm^{-1}, KBr) 1700 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.70 (t, 2H, CH_2CO, J = 8 Hz), 2.95 (t, 2H, CH_2Ar, J = 8 Hz), 5.90 (s, 2H, OCH_2O), 6.70 (s, 3H, ArH), 9.60 (bs, 1H, OH) ([63] ^1H NMR ($CDCl_3$)).

3-(2,3-Methylenedioxyphenyl)propanoyl Chloride (48)

This acyl chloride **48** was prepared from propanoic acid **47** (7.5 g, 38.6 mmol) by essentially the same procedure as described for the preparation of acyl chloride **36** from propanoic acid **29**. The yield was 7.8 g (36.7 mmol, 95%) of acyl chloride **48** as a colourless, viscous oil: bp 88-89 °C (0.005 mbar) ([63] no bp reported); IR (cm^{-1}, neat) 2800 (OCH_2O), 1800 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 3.00 (t, 2H, CH_2CO, J = 7 Hz), 3.25 (t, 2H, CH_2Ar, J = 7 Hz), 5.95 (s, 2H, OCH_2O), 6.75 (s, 3H, ArH).

1-Diazo-4-(2,3-methylenedioxyphenyl)-2-butanone (49)
This α-diazoketone **49** was prepared from acyl chloride **48** (2.30 g, 10.8 mmol) by essentially the same procedure as described for the preparation of α-diazoketone **37** from acyl chloride **36**. The yield was 2.33 g (10.7 mmol, 99%) of α-diazoketone **49** as yellow-green oil: IR (cm^{-1}, neat) 2800 (OCH_3), 2110 (CHN_2), 1640 (C=O); ^1H NMR (60 MHz, $CDCl_3$) δ 2.70 (t, 2H, CH_2CO, J = 7 Hz), 2.95 (t, 2H, CH_2Ar, J = 7 Hz), 5.25 (s, 1H, CHN_2), 6.00 (s, 2H, OCH_2O), 6.75 (s, 3H, ArH) ([63] no spectral data reported).

3,4-Dihydro-5,6-methylenedioxy-2(1H)-naphthalenone
(5,6-Methylenedioxy-2-tetralone, 50)
This tetralone **50** was prepared from α-diazoketone **49** (2.33 g, 10.7 mmol) by essentially the same procedure as described for the preparation of tetralone **25** from α-diazoketone **37**. The only difference was that this tetralone **50** was purified by $NaHSO_3$ adduct formation instead of vacuum distillation. The yield was 0.55 g (2.9 mmol, 27%) of tetralone **50** as a light-yellow solid: mp 88-89 °C ([63] 88-91 °C; [95] no mp reported); IR (cm^{-1}, KBr) 1710 (C=O) ([63] IR (KBr)); ^1H NMR (60 MHz, $CDCl_3$) δ 2.55 (t, 2H, $COCH_2$, J = 6.5 Hz), 3.05 (t, 2H, $ArCH_2$, J = 6.5 Hz), 3.55 (s, 2H, $ArCH_2CO$), 6.05 (s, 2H, OCH_2O), 6.60-6.80 (m, 2H, ArH) ([63] ^1H NMR ($CDCl_3$)); MS (CI with NH_3) *m/z* 191 (M+1), 208 (M+18).

2.4.6 PREPARATION OF 5,6-METHYLENEDIOXY-2-[N-*N*-PROPYL-N-2-(2-THIENYL)-ETHYLAMINO]TETRALIN WITH 5,6-METHYLENEDIOXY-2-TETRALONE AS STARTING MATERIAL

*1,2,3,4-Tetrahydro-5,6-methylenedioxy-N-*n*-propyl-2-naphthalenamine*
*(5,6-Methylenedioxy-2-(N-*n*-propylamino)tetralin, 51)*
This secondary amine **51** was prepared from tetralone **50** (0.53 g, 2.8 mmol) by essentially the same procedure as described for the preparation of secondary amine **43** from tetralone **25**. The yield was 0.22 g (0.8 mmol, 29%) of **51**·HCl as fine white platelets: IR (cm^{-1}, KBr) 2900-2600, 2540, 2460 (NH_2^+); MS (CI with NH_3) *m/z* 234 (M+1) (M: free amine).

*1,2,3,4-Tetrahydro-5,6-methylenedioxy-N-*n*-propyl-N-[2-(2-thienyl)ethyl]-2-naphthalenamine*
*(5,6-Methylenedioxy-2-[N-*n*-propyl-N-2-(2-thienyl)ethylamino]-tetralin, 5,6-OCH$_2$O-PTAT, 20)*
This tertiary amine **20** was prepared from secondary amine **51** (0.15 g, 0.64 mmol) by essentially the same procedure as described for the preparation of tertiary amine **19** from secondary amine **43**. Differences were the use of a mixture of EtOAc and hexane (1/4) instead of a mixture of EtOAc and petroleum ether 40-60 (1/4) as the eluent for the purification by column chromatography and the omission of the recrystallization. The yield was 0.12 g (0.32 mmol, 50%) of **20**·HCl as a white powder: mp 180-182 °C dec; IR (cm^{-1}, KBr) 2700-2200 (NH^+); ^1H NMR (300 MHz, CD_3OD) δ 1.06 (t, 3H, CH_3), 5.93 (d, 2H, OCH_2O), 6.67 (s, 2H, ArH), 6.98-7.34 (m, 3H, ArH); MS (CI with NH_3) *m/z* 344 (M+1) (M: free amine); Anal. calcd. for $C_{20}H_{25}NO_2S$·HCl (379.95): C 63.22, H 6.90, N 3.69, S 8.44; found C 63.17, H 6.88, N 3.73, S 8.46.

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