A New Synthesis of (*R*)-(–)-Sumanirole (PNU-95666E)

Ludivine Jean-Gérard,[a] Frédéric Macé,[a] Hélène Dentel,[a] Anh Ngoc Ngo,[a] Sylvain Collet,*[a] André Guingant,*[a] Michel Evain[b]

[a] Université de Nantes, CNRS, Chimie et Interdisciplinarité: Synthèse, Analyse, Modélisation (CEISAM), UMR CNRS n° 6230, 2 Rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France
Fax +33(2)51125402; E-mail: andre.guingant@univ-nantes.fr; E-mail: sylvain.collet@univ-nantes.fr

[b] Institut des Matériaux Jean Rouxel, 2 Rue de la Houssinière, BP 92208, 44322 Nantes Cedex 03, France

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Dedicated to Professor Jacques Lebreton on the occasion of his 50th birthday

Abstract: A twelve-step synthesis of (*R*)-(–)-sumanirole hydrochloride, starting from quinoline, has been achieved. The key reaction features selective epoxidation of the C3–C4 double bond of a 1,2-dihydroquinoline bearing a chiral auxiliary at N-1.

Key words: quinoline, reduction-acylation, asymmetric epoxidation, (*R*)-(–)-sumanirole

Parkinson's disease is a progressive neurodegenerative disease characterized by deterioration of motor control. The symptoms are caused by loss of cells in the brain that secrete the neurotransmitter dopamine formed by decarboxylation of L-DOPA under the action of L-DOPA decarboxylase. Current treatment consists of administration of L-DOPA which is converted to dopamine in situ. However, loss of L-DOPA effectiveness and apparition of side effects are very common after a period of time. In order to minimize these adverse effects, selective stimulation of D_2 receptors, which are believed to be responsible for the restoration of motor function, is highly desirable. In contrast to currently available drugs [e.g., pergolide (**1**), cabergoline (**2**)], which are not selective and show affinity for other receptor subtypes, sumanirole (**3**, Figure 1) has been shown to display high in vitro and in vivo selectivity for the D_2 receptor subtype.[1]

Owing to these remarkable properties, sumanirole was investigated as a potential candidate for the treatment of Parkinson disease but the phase III clinical development was ceased in 2004 because the molecule failed to provide sufficient distinction from currently available therapies. Nevertheless, we became interested in the synthesis of sumanirole[2] because it represented for us a good model to evaluate the feasibility of new methods aimed at preparing variously substituted chiral N-substituted 1,2,3,4-tetrahydroquinolines in view of further applications in the field of natural products.

Our retrosynthetic approach to sumanirole, as illustrated in Scheme 1, relies on initial disconnection of **3** across the NHCO bond of the imidazolone ring to give N-protected 1,2,3,4-tetrahydroquinoline **4**. Compound **4** should be accessible, via regioselective nitration and stereoselective hydroxyl group substitution, from alcohol **5**, which in turn should be derived from **6** by regioselective opening of its epoxide functionality. Finally, the synthesis of **6** could be envisaged through an asymmetric epoxidation reaction of chiral 1,2-dihydroquinoline **7**, whose preparation should be readily achieved from quinoline.

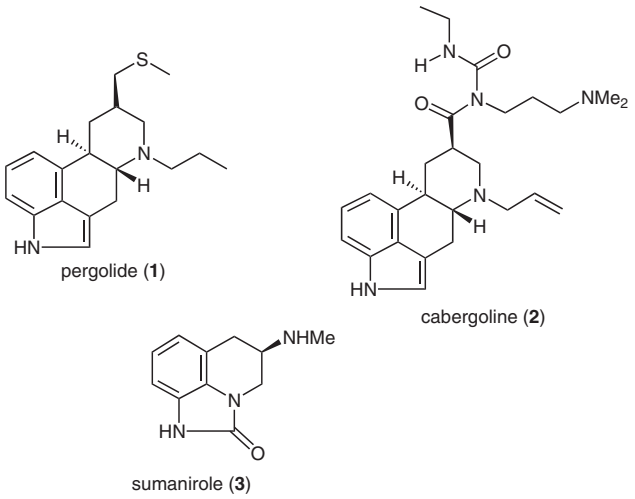
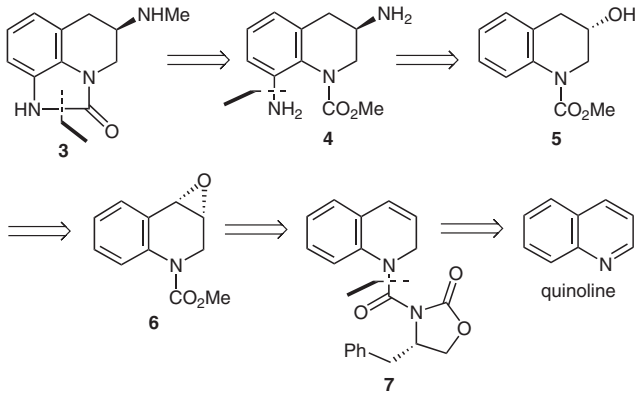


Figure 1



Scheme 1 Retrosynthetic analysis of sumanirole

Our synthetic sequence began with attachment of the (*S*)-4-benzyloxazolidin-2-one-3-carbonyl and 1,2-dihydroquinoline fragments to obtain **7**. This could be realized in a one-pot operation following the method of Minter and

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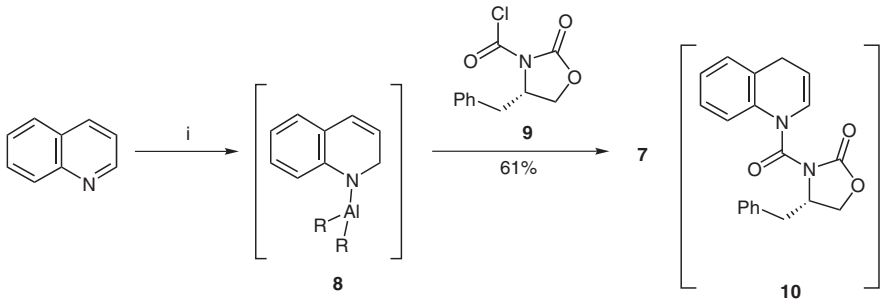
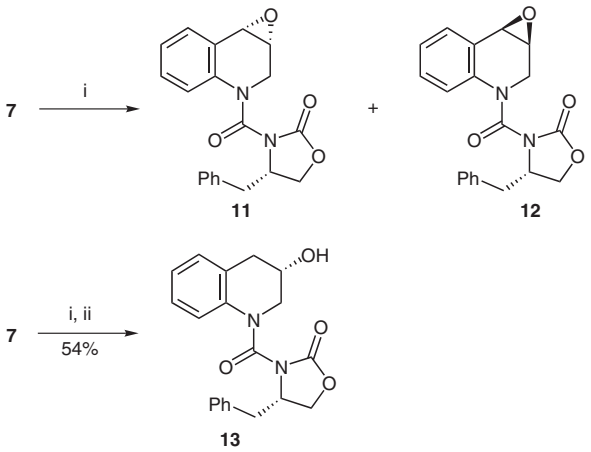


Scheme 2 *Reagents and conditions*: DIBAL-H, (1 equiv), CH_2Cl_2, 1 h, r.t.; then red solution of **8** added to a solution of **9** (0.5 equiv) in CH_2Cl_2 at 0 °C; then stirring for 5 h at r.t.

Stotter[3] who reported the 1,2-reduction of quinoline and trapping of the aminoalane intermediate **8** by use of a large excess of methyl chloroformate. By analogy, capture of **8** with the chiral carbamoyl chloride **9**[4] should lead to the formation of **7** (Scheme 2). However, and for obvious reasons, we searched for conditions avoiding the use of elaborated **9** in excess. The best results were obtained through addition of two equivalents of intermediate **8** onto one equivalent of **9** at 0 °C and subsequent stirring for five hours at 20 °C. Following these conditions, chiral *N*-acyl-1,2-dihydroquinoline **7** was isolated in 61% yield.[5] It should also be noted that these conditions suppress the formation of isomeric 2,3-dihydroquinoline **10**, a byproduct frequently formed in such a reduction–acylation sequence.[3]

Having prepared chiral 1,2-dihydroquinoline **7** we were now in a position to examine the crucial epoxidation step. Although the chiral moiety of the molecule was apparently far remote from the electrophilic double bond, we were pleased to observe that reaction of **7** with MCPBA was significantly diastereoselective, leading to a mixture of epoxides **11** and **12** in a 4:1 to 9:1 ratio. A pure sample of the major epoxide could be obtained after chromatographic separation of the crude mixture and subsequent recrystallization.[6] Its relative and absolute stereochemistry was demonstrated to be that shown in structure **11** by a single-crystal X-ray analysis[7] (Scheme 3 and Figure 2). As **11**is not very stable to silica gel, we found it to be experimentally preferable to hydrogenate the crude mixture of epoxides and effect the separation of the resulting alcohols. Following this protocol,[8] the required alcohol **13** was isolated in 54% yield from **7** (Scheme 3).

Having **13** successfully in hand as a single isomer, we judged preferable to postpone the OH → NHMe transformation to a later stage and to concentrate first on elaboration of the annelated imidazolone ring. In this direction, installation of a NH_2 group at C8 was envisaged via reduction of a nitro-group precursor. Because C6 was the expected most electrophilic center, this latter had to be protected first with a removable group. We thus examined a bromination–nitration sequence[9] as a means of introducing a nitro group cleanly at C8. With the preliminary work having shown the incompatibility of the oxazolidin-2-one moiety with this sequence of reaction, this motif was removed by action of MeOH in the presence of samarium triflate[10] to give the *N*-carbamate-protected 1,2,3,4-tetrahydroquinoline **14**. Bromination of **14** proceeded to give its expected 6-bromo derivative **15**. Subsequent regioselective nitration of **15** was effected by action of $NaNO_3$ in TFA to give compound **16** in good yield (Scheme 4).



Scheme 3 *Reagents and conditions*: i) MCPBA (1 equiv), $NaHCO_3$ (1.6 equiv), CH_2Cl_2, 18 h, 20 °C; ii) H_2 (8 bar), 10% Pd/C, CH_2Cl_2–EtOAc (1:1), 18 h, 20 °C.

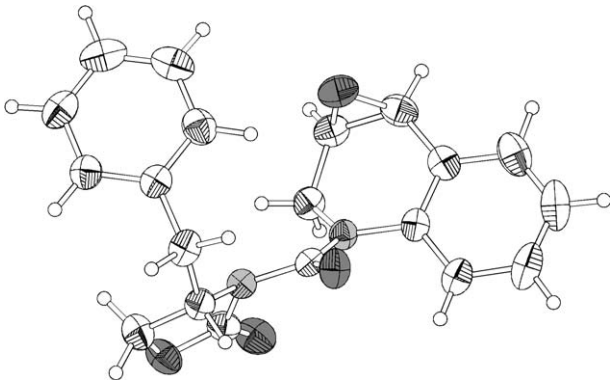
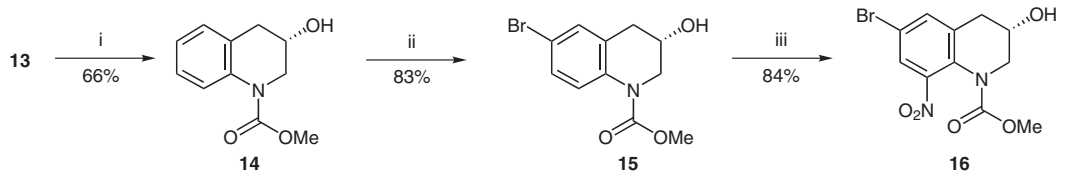
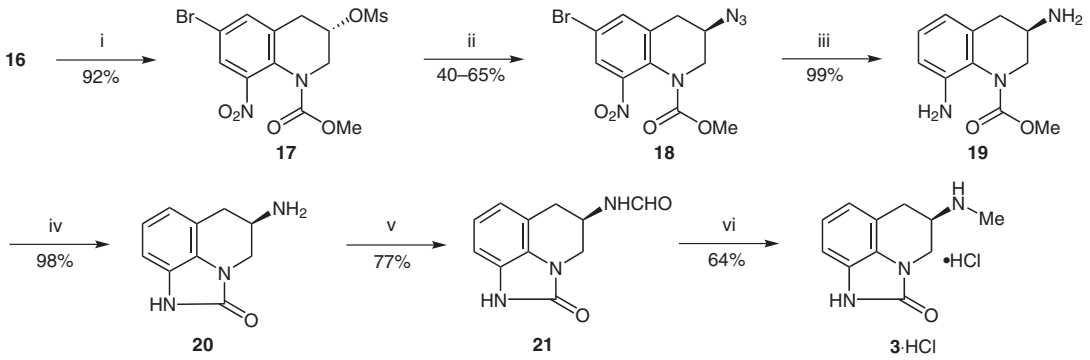


Figure 2 X-ray structure of **11**

At this stage we returned to the installation of the amino substituent at C3. Treatment of **16** with mesyl chloride afforded the corresponding mesylate **17** whose reaction with sodium azide led to azido compound **18** with yields ranging from 40–65%.[11,12] Subsequent hydrogenation of



Scheme 4 *Reagents and conditions*: i) $Sm(OTf)_3$ (0.25 equiv), MeOH, 3 h, 80 °C; ii) Br_2 (1 equiv), AcOH, NaOAc, 1 h, 20 °C; iii) $NaNO_3$ (1 equiv), TFA, 30 min, 20 °C.



Scheme 5 *Reagents and conditions*: i) MsCl (2 equiv), Et_3N (3 equiv), CH_2Cl_2, 45 min, 20 °C; ii) NaN_3 (5 equiv), DMF, 80 °C, 1h; iii) H_2, $Pd(OH)_2$, EtOH, 18 h, 20 °C; iv) KO*t*-Bu (5 equiv), THF, 3.5 h, 20 °C; v) AcOCHO, MeCN, 1 h, 20 °C; vi) $BH_3{\cdot}SMe_2$ (2.3 equiv), THF, reflux, 3 h, then 2 N HCl in MeOH, reflux, 2 h.

18 in the presence of Pearlman'catalyst effected three chemical transformations, that is, hydrogenolysis of the C–Br bond as well as reduction of the nitro and azido groups, to afford compound **19** in almost quantitative yield (Scheme 5). Final transformation of **19** into sumanirole was achieved in three additional steps. Closure of the imidazolone ring, to give the tricyclic compound **20** (nor-Me sumanirole), was realized in excellent yield under the action of KO*t*-Bu in THF. Finally, monomethylation of the amino group at C3 was accomplished via formation of a formamide intermediate[13] **21** whose reduction led to (–)-sumanirole hydrochloride (**3**·HCl).[14]

In conclusion, we have achieved a twelve-step synthesis of (*R*)-(–)-sumanirole hydrochloride **3**·HCl from quinoline. Our work also demonstrates that attachment of a chiral 4-benzyloxazolidin-2-one-3-carbonyl moiety at *N*-1 of 1,2-dihydroquinoline may control the selectivity of the C3–C4 double bond epoxidation. Further manipulations of the epoxide functionality should thus allow the preparation of chiral diversely N-substituted 1,2,3,4-tetrahydroquinolines. Work is in progress to find a coherent explanation of the efficiency of the chiral auxiliary in orienting the sense of epoxidation. We are also currently applying the results of this study in the field of natural product synthesis.

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(5) **Procedure for the Preparation of 7**
To a solution of quinoline (1.6 mL, 13.6 mmol) in CH_2Cl_2 (20 mL), maintained at 0 °C under an argon atmosphere, was added a 1 M solution of DIBAL-H in hexane (13.6 mL, 13.6 mmol). After stirring at 0 °C for 1 h, the red solution was cannulated into a solution of carbamoyl chloride **9** (1.63 g, 6.8 mmol) in 2mL of CH_2Cl_2. The temperature was slowly raised to 20 °C, and stirring was continued for 5 h at this temperature. The reactive mixture was then cannulated into 150 mL of cold H_2O. The resulting emulsion was stirred for 30 min then aq 6 N HCl was added until the aqueous phase reached pH 4. After phase separation, the aqueous phase was extracted with CH_2Cl_2 (4 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel chromatography (toluene–PE–Et_2O = 2:1:1, R_f = 0.26) to afford 1,2-dihydroquinoline **7** as a slightly yellow oil (1.39 g, 61%, calculated based on carbamoyl chloride **9**); $[\alpha]_D^{20}$ +7.7 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.40 (m, 9 H), 6.59 (dd, *J* = 9.6, 2.4 Hz, 1 H), 5.99–6.04 (m, 1 H),

4.73–4.78 (m, 1 H), 4.40 (dd, *J* = 17.0, 5.5 Hz, 1 H), 4.08–4.31 (m, 3 H), 2.92 and 3.26 (ABX system, *J* = 13.5, 8.7, 3.3 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.3, 152.4, 136.0, 134.9, 129.5 (2 C), 129.2, 129.0 (2 C), 128.5, 128.3, 127.5, 126.7, 126.4, 125.5, 122.9, 67.0, 56.5, 45.9, 38.1. IR (KBr): 3060–3028, 3003, 2923–2853, 1722, 1685 cm^{-1}. MS: *m/z* (%) = 334 (<1) [M$^+$], 130 (100), 91 (19). HRMS (EI): *m/z* calcd for $C_{20}H_{18}N_2O_3$: 334.1317; found: 334.1313 [M]$^+$.

(6) Epoxide **11**: recrystallization from $CHCl_3$–PE (1:1); mp 204–203 °C; $[\alpha]_D^{20}$ +54.2 (*c* 0.5, $CHCl_3$).

(7) **Crystal Structure Data for $C_{20}H_{18}N_2O_4$**
Mw = 350.4, colorless block, 0.48 × 0.42 × 0.38 mm^3, orthorhombic, $P2_12_12_1$, *a* = 9.7121 (9)Å, *b* = 12.6679 (16) Å, *c* = 13.6030 (8) Å, *V* = 1673.6 (3) Å^3, *Z* = 4, D_x = 1.390 g cm^{-3}, μ = 0.10 mm^{-1}. 33596 reflections were measured on a Nonius-Kappa CCD diffractometer (graphite monochromator, λ = 0.71073 Å) up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.7 Å^{-1} at r.t.; 4820 reflections were unique (*R*int = 0.038). The structure was solved by direct methods[15] and refined with JANA2006 program[16] against F^2 for all reflections. Nonhydrogen atoms were refined with aniso-tropic displacement parameters. All H atoms were introduced in geometrically optimized positions and refined with a riding model, except for two H atoms (attached to C3 and C4) which positions were refined under constrains. Altogether, 241 parameters were refined. R_1/wR_2 [$I \geq 2\sigma(I)$] = 0.0473/0.1072. R_1/wR_2 [all reflections] = 0.0682/0.1189, *S* = 1.74. Residual electron density is between 0.14 and –0.13 e Å^{-3}. CCDC 769777 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) **Procedure for the Preparation of 13**
Epoxidation
To a solution of 1,2-dihydroquinoline **7** (1.6g, 4.78 mmol) in CH_2Cl_2 (250 mL) were added $NaHCO_3$ (644 mg, 6.22 mmol) and 70–75% MCPBA (1.5g, 6.22 mmol). The mixture was stirred at 20 °C for 18 h under argon, then washed with a sat. $NaHCO_3$ solution (250 mL). After phase separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 160 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product (white powder) was engaged in the reduction process without further purification.
Reduction
To a solution of the above crude epoxide product in a 1:1 mixture of CH_2Cl_2–EtOAc (80 mL) was added 10% Pd/C (668 mg, 9%mol). The mixture was stirred for 18 h at 20 °C under a hydrogen pressure of 8 bar then filtered through a pad of Celite. Celite was rinsed with a 1:1 mixture of CH_2Cl_2–EtOAc, then solvents were concentrated in vacuo. The residue was purified by silica gel chromatography (PE–EtOAc = 1:1, R_f = 0.39) to afford alcohol **13** as a white powder (0.9 g, 54%); $[\alpha]_D^{20}$ –191.0 (*c* 0.34, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00–7.40 (m, 9 H), 4.80 (m, 1 H), 4.28 (m, 1 H), 4.11 and 4.24 (ABX system, *J* = 8.4, 8.4, 7.5 Hz, 2 H), 3.38 and 4.41 (ABX system, *J* = 12.6, <1, <1 Hz, 2 H), 2.99 and 3.15 (ABX system, *J* = 18.0, 5.4, <1 Hz, 2 H), 2.85 and 3.60 (ABX system, *J* = 12.9, 10.2, 3.6 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 152.9, 138.0, 133.9, 129.4 (2 C), 128.1 (2 C), 128.0, 126.5, 125.2, 124.2, 120.3, 67.2, 62.9, 55.2, 50.6, 37.0, 34.7. IR (film): 3452, 3050, 2932, 1772, 1683 cm^{-1}. MS: *m/z* (%) = 323 (9) [M$^+$], 132 (38), 130 (38), 118 (20), 117 (16), 91 (100). HRMS (EI): *m/z* calcd for $C_{20}H_{20}N_2O_4$: 352.1423; found: 352.1427 [M]$^+$.

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(11) Azido compound **18** was isolated along with variable amounts of an elimination product (1,2-dihydroquinoline). Because mesylate **17** is stable in DMF at 80 °C, formation of the elimination byproduct is thus induced by NaN_3. Noteworthy also is the formation of the sole elimination product by treatment of alcohol **16** with DPPA under Mitsunobu conditions.

(12) HPLC profiles showed that azide substitution took place without erosion of enantioselectivity. Mesylate **17**: $[\alpha]_D^{20}$ +34.0 (*c* 0.2, $CHCl_3$; 96% ee determined by chiral HPLC); azido compound **18**: $[\alpha]_D^{20}$ +58.4 (*c* 0.51, $CHCl_3$; 96% ee determined by chiral HPLC).

(13) This two-step N-methylation protocol has already been reported for transforming sumanirole into its *N*,*N*-dimethyl analogue, see ref. 1a.

(14) Hydrochloride of (*R*)-**3**: $[\alpha]_D^{20}$ –29.1 (*c* 0.25, MeOH; 98% ee determined by chiral HPLC), lit.[1a] $[\alpha]_D^{20}$ –30.3 (*c* 1, MeOH).

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