

Asymmetric synthesis of ephedrine analogs

A. Solladié-Cavallo*, G. Lapitajs*, P. Buchert*, A. Klein**

Laboratoire de Stéréochimie Organométallique, EHICS 1, rue Blaise Pascal, 67008 Strasbourg (France)

S. Colonna* and A. Manfredi

*Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, Via Golgi 19,
20133 Milano (Italy)*

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Abstract

Addition of nitromethane to the chiral chromium tricarbonyl complex of *o*-tolualdehyde (**1**) gives, under conditions of kinetic control, the nitroalcohol **2** with ~ 95% of asymmetric induction. Compound **2** then gives, in 3 steps, the corresponding aminoalcohol in about 40% yield. Use of nitroethane gives the nitroalcohol with a small diastereoselectivity at C(2)-C(3) (d.e. = 30 and 55%), but analogs of ephedrine and pseudoephedrine can be obtained optically pure by chromatography.

Introduction

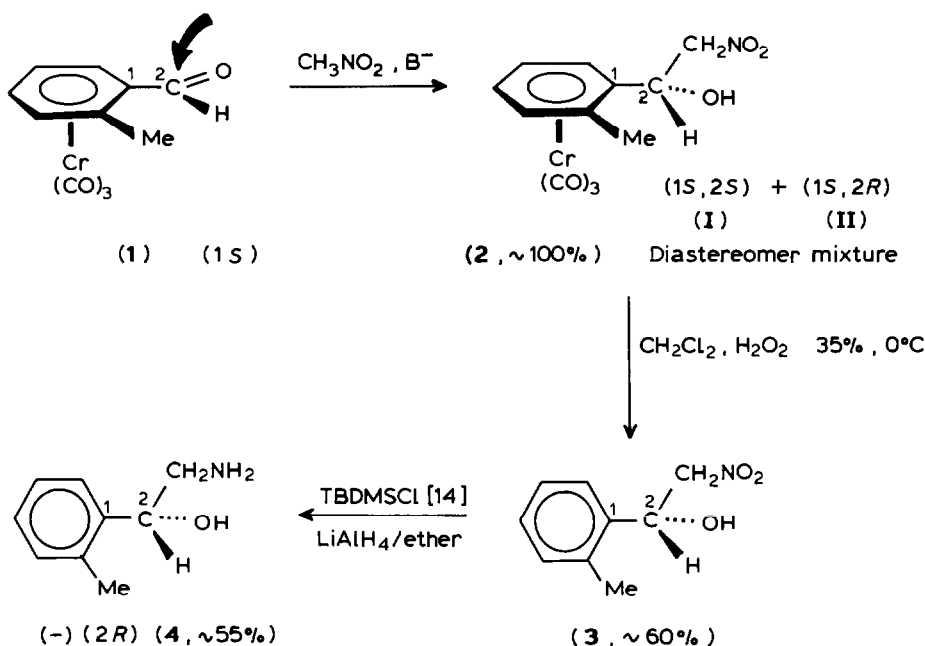
Ephedrine, which is present in the ancient Chinese drug Ma-huang, is extracted from various species of Ephedra. Because of their action on the sympathetic nervous system, natural D(-) ephedrine (2*R*, 3*S*), L(+) pseudoephedrine (2*S*, 3*S*), and analogs constitute an important class of bioactive compounds [1].

The main route to racemic 2-aminoalcohols of this type has been hydride reduction of free or protected cyanohydrins [2] and reduction of free or protected nitroalcohols [3]. Our main objective was to synthesize those aminoalcohols optically pure.

In the course of our study [4–6] on chiral and acyclic arenechromiumtricarbonyl complexes **1** it appeared that condensation of nitroalkanes with chiral and optically pure [7] chromiumtricarbonyl complexes of *ortho*-substituted benzaldehydes could provide a route to optically active 2-aminoalcohols of this type [8]. However, it was necessary to avoid thermodynamic control as far as possible, since work in our

* Undergraduate students from EHICS, Strasbourg.

** Technicienne CNRS.



Scheme 1

group has shown that additions to a carbonyl α to a complexed substituted ring [9*] occur with high degrees of asymmetric induction (90–95%) under kinetic control.

We present here the results of a study of the addition of nitromethane and nitroethane to complex 1 (racemic or optically pure), and hence a three-step route to 2-aminoalcohols which can be considered as an immolative-asymmetric-synthesis.

Results

Addition of nitromethane to complex 1 permits easy determination of the asymmetric induction during creation of the asymmetric carbon C(2). The results are shown in Table 1 and Scheme 1.

Three methods were used: (i) The Henry condensation [10] (Method A), in which the monoanion of nitromethane is generated in the presence of the complex 1 by addition of NaOH (10%) to a mixture of MeNO₂ and 1. (ii) The Seebach condensation [11] (Method B), in which the lithium dianion of nitromethane is added to complex 1. (iii) The Wollenberg nitroalkane synthesis [12] (Method C), in which KF in *i*-PrOH is used to promote condensation of MeNO₂ with 1.

The percentage of asymmetric induction at C(2) is readily determined by ¹H NMR (200 MHz) spectroscopy on the crude products 2 or on the aminoalcohol 4 with Eu(hfc)₃ as shift reagent.

Determination of the yield and of the diastereomer ratio in 2 must be carried out on the crude products as rapidly as possible after isolation (1 to 2 h), as they

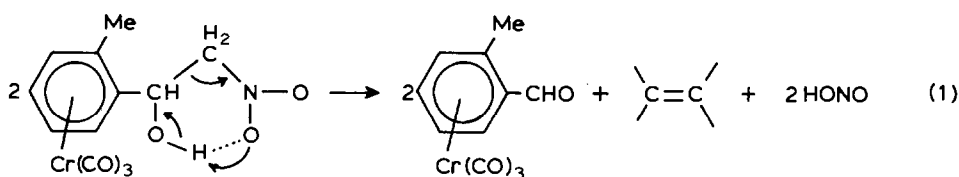
* Reference number with asterisk indicates a note in the list of references.

Table 1
Nitromethane addition to complex **1**

Starting complex 1	Method ^a	T (°C)	2 diastereomer ratio (1 <i>SS</i> , 1 <i>RR</i>)/(1 <i>SR</i> , 1 <i>RS</i>) (yield (%)) (I/II)	4 Enantiomeric purity (%)
racemic	A	r.t.	64/36	(~100)
	A	-20	92/8	(95)
	A	-40	97/3	(90)
(+)-1 <i>S</i>	B	-40		90-92 [α] _D = -14° (c 0.62, CHCl ₃)
racemic	C	20	40/60	(80)
	C	0	88/12	(90)

^a Method A: CH₃NO₂/NaOH (10%) 1 equiv. [10]; Method B: CH₃NO₂/BuLi 2 equiv./THF/30% HMPT [11]; Method C: CH₃NO₂/KF traces, i-PrOH [12].

decompose on standing and regenerate the complexed aldehyde according to the eq. **1** probably because of the increased acidity of the hydroxylic proton due to complexation of the ring by the electron-withdrawing CrCO₃ group.



Because of the instability of **2**, decomplexation (which takes a few hours) gives low yields (~60%).

Because there is a temperature-dependent equilibrium (addition/retroaddition), the percentage of asymmetric induction depends on the temperature (28% at +20°C and 94% at -40°C), and the C(2) absolute configuration obtained at +20°C is the opposite of that obtained at 0°C (method C).

Consistent with these features is the observation in the case of method A that when the addition is performed at -40°C and the reaction then quenched by pouring the mixture rapidly into a cold mixture of ether and aqueous NH₄Cl the asymmetric induction reaches 95% but is 80% or less if the reaction mixture is allowed to warm up to -10 or 0°C before being added to ether/aqueous NH₄Cl mixture.

The (-) sign obtained for the [α]_D of aminoalcohol **4** implies that the absolute configuration is *R* according to Brewster's rules and to our model [13,5a].

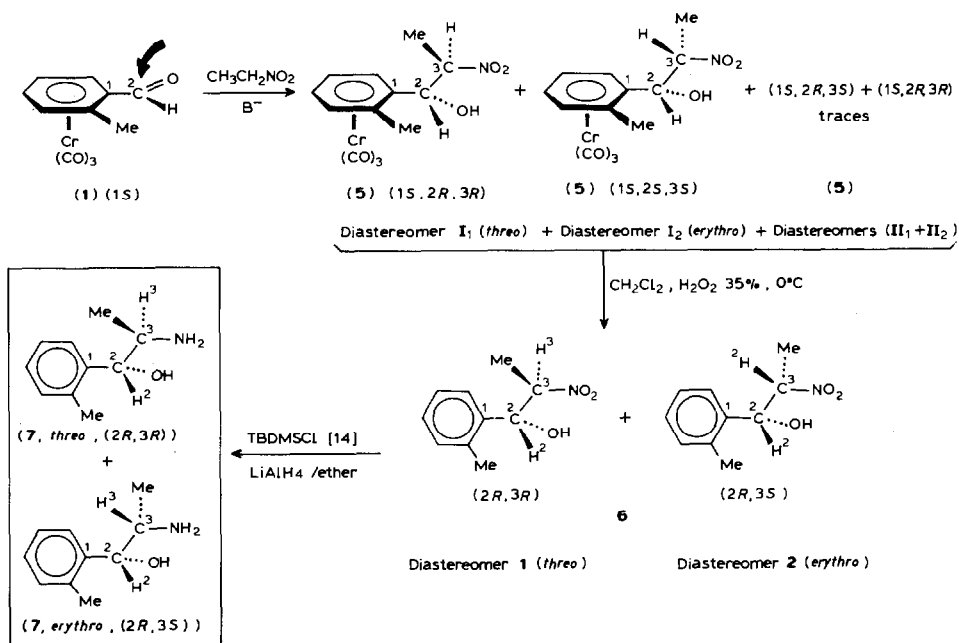
Addition of nitroethane was also examined and the results, shown in Table 2, correspond to the best reaction conditions for asymmetric induction as determined for nitromethane in method A (-40°C) and method B (-40°C).

Only two diastereomers **I**₁ (C(2)-C(3) *threo*) and **I**₂ (C(2)-C(3) *erythro*) were obtained; the two others, **II**₁ and **II**₂, were not detected by ¹H NMR spectroscopy. Assignment of diastereomer **I**₁ to the C(2)-C(3) *threo* isomer and of **I**₂ to the C(2)-C(3) *erythro* isomer in **5** and **6** was based on the 200 MHz ¹H NMR spectrum.

Table 2

Nitroethane addition to complex 1

Starting 1	Method ($T -40^{\circ}\text{C}$)	5 diastereomer ratio (I_1/I_2) (yield (%))	6 diastereomer ratio (1/2)
racemic	A	36/64 (90)	
racemic	B		77/23



Scheme 2

Natural ephedrine (*erythro*) shows a 3J coupling of 4 Hz between H(2) and H(3). The aminoalcohol 4 shows an ABX system with two different coupling constants $^3J(\text{AX})$ 4 and $^3J(\text{BX})$ 8 Hz.

Because NO_2 group will form intramolecular H bonds as NH_2 group, the major conformation in the nitroalcohols and in the aminoalcohols can be expected to be of the same type, and so the ^1H NMR spectra of the nitroalcohols and aminoalcohols can be compared. For compound 5, obtained from method A, the major diastereomer has a 3J -coupling of 3 Hz and hence is assigned to the *erythro* isomer I₂. The minor diastereomer shows a 3J coupling of 7.5 Hz and is *threo*. For compound 6, obtained by method B, the major diastereomer shows a 3J coupling of 9.3 Hz and hence is assigned to the *threo* isomer 1. The minor diastereomer shows a 3J coupling of 3 Hz and is thus *erythro*.

It thus appears that method A leads to 64% of *erythro* and method B to 77% of *threo*, which is consistent with results obtained by Seebach [11]. Hence the com-

plexation of the ring does not drastically change the diastereoselectivities of these condensations.

Protection [14] and reduction [11] will lead to analogs of ephedrine (method A) or pseudoephedrine (method B) as the main compound.

It should be noted that if (+)-(1*S*) complex **1** leads (via method A) to the (2*R*, 3*S*) analog of ephedrine (corresponding to the natural isomer), the (2*S*, 3*S*) analog of pseudoephedrine will be obtained (via method B) from (–)-(1*R*) complex **1**. Optically pure *N*-methyl pseudoephedrine was obtained recently [15] from an arenechromium tricarbonyl complex, but in this case, the chirality comes from the ligand, which is optically pure (+) *N,N*-dimethylamphetamine.

In these three-step immolative asymmetric syntheses a very good asymmetric induction is obtained for the C(2) carbon, 95% e.e., but the asymmetric induction at C(3) is quite poor (28 to 54%) and leads to a mixture of *erythro* and *threo* isomers which must be separated. However, both diastereomers formed are optically pure. This method will thus be best suited for the synthesis of optically pure 2-aminoalcohols of type **4**, as isolation of optically pure analogs of ephedrine and/or pseudoephedrine involves a chromatographic separation.

Experimental

Method A

A mixture of complexed aldehyde **1** (1 mmol) and nitroalkane (2 mmol) in 20 ml EtOH is stirred for a time at –40 °C and aqueous NaOH 10% (2 mmol) is then added dropwise at –40 °C. The red solution rapidly becomes yellow, and is stirred for 30 min at –40 °C, then, still cold, is poured rapidly with stirring into a cold mixture of saturated aqueous NH₄Cl and ether (50/100). The ether layer becomes yellow and is separated from the aqueous layer, which is extracted twice with 20 ml ether. The ethereal layers are combined and dried over Na₂SO₄. After removal of the ether the residue (100% by weight) is checked by 200 MHz NMR and decomplexed without further purification.

Method B

To a stirred cold (–90 °C) solution of nitroalkane (2 mmol) (nitromethane or nitroethane) in 9 ml THF/HMPA (2/1) is slowly added a 1.37 *N* BuLi solution (4.1 mmol) in hexane. The solution is allowed to warm to –60 °C during 1 h then cooled to –78 °C, and the complexed aldehyde **1** (2 mmol in 3 ml THF) is added. After stirring for 1.5 h between –70 and –60 °C and 3 h between –45 and –40 °C, the mixture is cooled rapidly to –90 °C and acidified with 1.5 ml of a 3.5/3 acetic acid/THF mixture, the internal temperature being kept below –85 °C. The acidified mixture is then allowed to warm to room temperature and poured into a mixture of ether (60 ml) and water (20 ml). The organic phase is separated, washed with water (8 × 15 ml) dried (MgSO₄) and evaporated under vacuum to give 100% yield of crude residue, is decomplexed without further purification.

Method C

A mixture of complexed aldehyde **1** (1 mmol) in 6 ml of anhydrous *i*-PrOH and 5 mg of KF is stirred at 0 °C and pure nitromethane (2 mmol) then added dropwise at 0 °C. The red solution is stirred 8 h at 0 °C then kept overnight in the refrigerator

(+5 °C), during which it slowly becomes yellow. The cold solution (+5 °C) is then poured rapidly into a cold mixture of saturated aqueous NH₄Cl and ether (50/100). The yellow ether layer is separated, and the aqueous layer which is extracted twice with 20 ml lots of ether. The ethereal extracts are combined, dried over Na₂SO₄, and evaporated. The residue (100% by weight) is checked by 200 MHz NMR spectroscopy and decomplexed without further purification.

200 MHz ¹H NMR (CDCl₃/TMS) (δ, ppm)

Complex 1. 2.54 (s, 3H, CH₃), 5.04 (d, 1H arom., ³J 6.5 Hz), 5.24 (t, 1H arom., ³J 6.5 Hz), 5.74 (td, 1H arom., H(1), ³J 6.5, ⁴J 1 Hz), 6.06 (dd, 1H arom., H(3), ³J 6.5, ⁴J 1 Hz), 9.82 (s, 1H).

Complex 2. Diastereomer I: 2.27 (s, 3H, CH₃), 2.9 (b, 1H, OH), 4.5 (AB from ABX, 2H, CH₂), 5.17 (d, 1H arom., ³J 6.5 Hz), 5.28 (t, 1H arom., ³J 6.5 Hz), 5.40 (X from ABX, 1 H, CH), 5.46 (td, 1H arom., ³J 6.5, ⁴J 1 Hz), 5.82 (dd, 1H arom., ³J 6.5, ⁴J 1 Hz).

Diastereomer II: 2.35 (s, 3H, CH₃), 3.1 (b, 1H, OH), 4.65 (AB from ABX, 2H, CH₂), 5.11 (d, 1H arom., ³J 6.5 Hz), 5.45 (X from ABX, 1H, CH and 1H arom.), 5.55 (t, 1H arom., ³J 6.5 Hz), 5.73 (d, 1H arom., ³J 6.5 Hz).

Aminoalcohol 4. 2 (s, b, 1H, OH), 2.31 (s, 3H, CH₃), 2.86 (AB from ABX, 2H, CH₂), 4.86 (dd, 1H, CH), 7.2 (m, 3H arom.), 7.5 (m, 1H arom.).

Complex 5. Diastereomer I₂ (erythro): 1.05 (d, 3H, CH₃), 2.26 (s, 3H, CH₃), 4.56 (qd, 1H, CH₃, ³J₂₃ 3, ³J 6.5 Hz), 5.16 (d, 1H arom.), 5.27 (t, 1H arom.), 5.37 (d, 1H, CH(2), ³J₂₃ 3 Hz), 5.45 (t, 1H arom.), 5.80 (d, 1H arom.).

Diastereomer I₁ (threo): 1 (d, 3H, CH₃, ³J 7 Hz), 2.27 (s, 3H, CH₃), 4.68 (quint., 1H, CH(3), ³J 7, ³J₂₃ 7.5 Hz), 5.04 (d, 1H, CH(2), ³J₂₃ 7.5 Hz), 5.11 (d, 1H arom.), 5.25 (t, 1H arom.), 5.51 (t, 1H arom.), 5.71 (d, 1H arom.).

300 MHz ¹H NMR (CDCl₃/TMS) (δ, ppm)

Nitroalcohol 6. Diastereomer 2 (erythro): 1.4 (d, 3H, CH₃, ³J 6.5 Hz), 2.55 (s, 3H, CH₃), 4.54 (qd, 1H, CH(3), ³J 6.5, ³J₂₃ 3 Hz), 5.16 (d, 1H, CH(2), ³J₂₃ 3 Hz), 7.08 (m, 3H, arom.), 7.21 (m, 1H, arom.).

Diastereomer 1 (threo): 1.2 (d, 3H, CH₃, ³J 7 Hz), 2.33 (s, 3H, CH₃), 4.76 (qd, 1H, CH(3)), ³J 7, ³J₂₃ 9.3 Hz), 5.25 (d, 1H, CH(3), ³J 9.3 Hz), 7.08 (m, 3H arom.), 7.21 (m, 1H arom.).

Acknowledgments

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