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261. An Enantioselective Total Synthesis of Natural (+)-Luciduline

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Dedicated to Professor *R. B. Woodward* on his 60th anniversary

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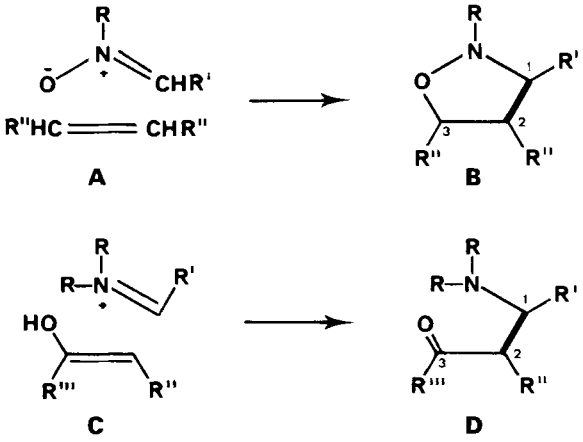
Summary

The naturally occurring Lycopodium alkaloid (+)-luciduline (**1**) has been synthesized from (*R*)-5-methyl-cyclohex-2-en-1-one (**12**) by a sequence of seven steps (s. *Scheme 6)* in 33% overall yield. The key step **4**→**6** presumably involves a transient nitrone **5** which undergoes a highly regioselective intramolecular addition to a non-polarized olefinic bond.

1. Introduction. - A synthetically important feature of nitrone-olefin-cycloadditions **A**→**B** [1] is the formation of a C(1),C(2)-bond with concomitant introduction of nitrogen and oxygen functionality at the positions 1 and 3 *(Scheme 1).* It thus provides a useful alternative to the classical *Mannich* reaction **C**→**D** which plays a pivotal role in the biogenesis and total synthesis of alkaloids [2].

Scheme 1



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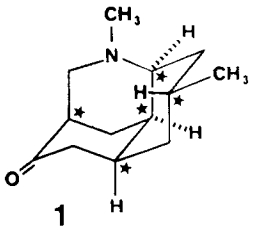
We now wish to report in detail the use of a highly regiocontrolled *N*-alkenyl nitrone addition in the stereoselective synthesis of (+)-luciduline[2])[3]). The natural alkaloid, isolated from *Lycopodium lucidulum*, has been shown by chemical and X-ray evidence to have structure **1** [5] *(Scheme 2)*. Its racemate was first synthesized by a multistep approach *via* the aminoketone **2** which undergoes an internal *Mannich* reaction **2**→**3**→**1** on heating with formaldehyde [6] *(Scheme 3)*.

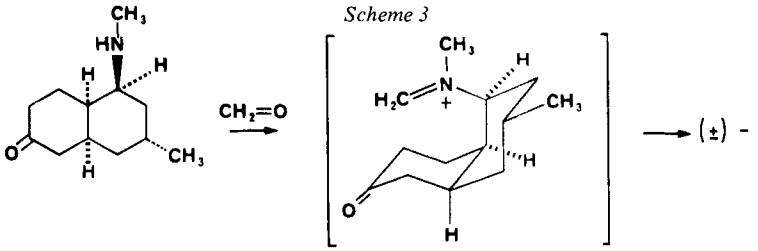
Scheme 2



1

(+)-LUCIDULINE

Scheme 3



2 **3**

Alternatively, the short and efficient synthesis of the optically pure natural alkaloid (+)-**1**, described here, relies on an intramolecular nitrone addition **4**→**5**→**6** taking advantage of the ready accessibility of the *N*-alkenyl-hydroxylamine **4** *(Scheme 4)*.

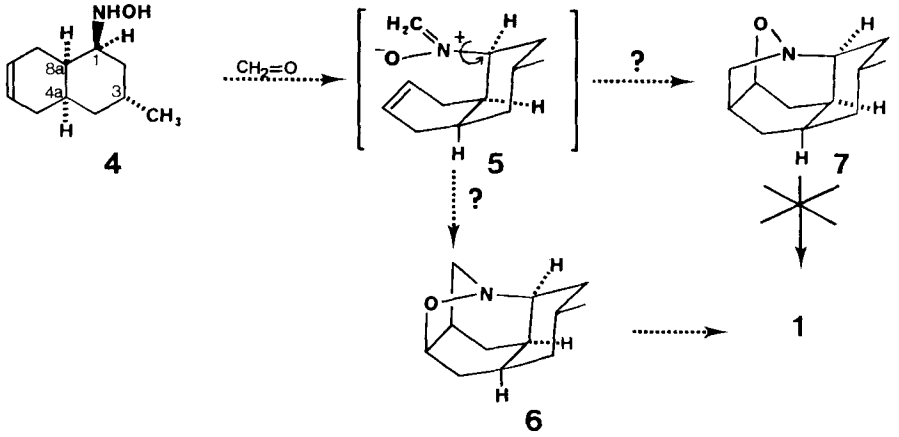
The initial uncertainty as to whether the nitrone **5** would cyclize to **6** and/or to **7** appeared to be less critical in view of the regioselectivity observed in intramolecular *N*-alkenyl-azomethinimine additions involving non-polarized olefinic bonds [4] [7]. For the assembly of the four chiral centers of the hydroxylamine **4**, we chose to use a precursor containing the enantiomerically pure methyl substituted center C(3), which should induce selectively the configuration of the other three chiral carbon atoms. As shown below, these requirements are perfectly met by (*R*)-5-methyl-cyclohex-2-en-1-one (**12**).

2. Preparation of (+)-(*R*)-5-Methyl-cyclohex-2-en-1-one (12, *Scheme 5*). – In order to prepare the enantiomerically pure cyclohexenone (*R*)-**12** the natural, readily

[2]) For a preliminary communication describing the closely related synthesis of (±)-**1** see [3].

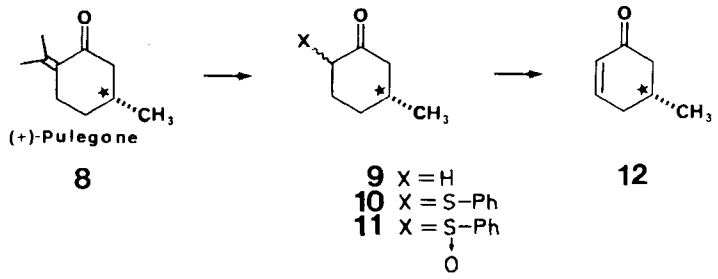
[3]) For a recent review on intramolecular additions of nitrones and azomethinimines to olefinic bonds see [4].

Scheme 4



available monoterpene (+)-pulegone (**8**) was considered to be a particularly attractive chiral starting material of known absolute configuration. Removal of the isopropylidene group by retroaldolization of **8** [8] [9] furnished (*R*)-3-methyl-cyclohexanone (**9**) which is also commercially available. Introduction of C,C-unsaturation into **9** has been described *via* a bromination-dehydrobromination sequence [9]. However, the initial halogenation step proceeded with insufficient site selectivity, giving 2-bromo-5-methyl-cyclohexanone in low yield, after its separation by crystallization from competitively formed 2-bromo-3-methyl-cyclohexanone. On the other hand, we observed a highly regioselective sulfenylation [10] on sequential treatment of **9** with lithium diisopropylamide and diphenyldisulfide to give the thioethers **10** (2:1 mixture of stereoisomers). Oxidation of **10** to the sulfoxides **11** (*m*-chloroperbenzoic acid) and subsequent heating of **11** in refluxing carbon tetrachloride at 65° furnished the pure cyclohexenone (*R*)-**12** in 49% overall yield from **9**.

Scheme 5



3. Conversion of (+)-(*R*)-5-Methyl-cyclohex-2-en-1-one (12) into Natural (+)-Luciduline (1) *(Scheme 6).* – 3.1. *Preparation of the Hydroxylamine* **4**. – (*R*)-**12**, thus readily available, was subjected to a *Diels-Alder* reaction with an excess of butadiene in the presence of $SnCl_4$ at 25°. Under these conditions the addition of butadiene took place exclusively from the side opposite to the methyl substituent to give the octalones **13** in 67% yield. That the correct configuration at the angular

C(4a) has been introduced is based on a close analogy [11] and is ultimately proven by conversion of **13** to the natural product (+)-**1**. This yield and the stereochemical control at C(4a) contrast favorably with those observed in an analogous reaction in the absence of *Lewis* acid [11]; however, during the transformation **12** → **13** *Lewis* acid-promoted epimerization of **13a** at C(8a) could not be avoided.

Since the desired but minor *cis*-fused ketone **13a** was difficult to separate from its more stable isomer **13b** (prep. GC.) recyclization of the latter was unattractive. However, on oximation of the **13a**:**13b** mixture with hydroxylamine hydrochloride in ethanol/water it was noticed that the *cis*-octalone **13a** reacted faster (giving the oxime **14**) than its *trans*-isomer **13b**. Consequently we devised conditions for effecting the rapid epimerization **13a** ⇄ **13b** while simultaneously withdrawing the *cis*-octalone **13a** from the equilibrium mixture by selective transformation to the oxime **14**. Thus, slow addition over 17.5 h (by means of a syringe drive) of hydroxylamine hydrochloride in methanol to a solution of the ketones **13a** and **13b** in methanolic KOH-solution afforded the *cis*-fused (+)-oxime **14** in 60% isolated yield together with a minor amount of its *trans*-fused C(8a) epimer (12%)[4]). Having thus selectively set up the desired *cis*-relationship of H–C(4a), H–C(8a) and the methyl group in **14** reduction with $NaBH_3CN$ (pH = 3 to 4 in methanol) [12] proceeded exclusively from the less hindered *exo* side to give (in 98% yield) the required (−)-hydroxylamine **4**, containing four chiral centers of correct configuration.

3.2. In situ *Preparation and Thermal Cycloaddition of the* N-*Alkenyl Nitrone* **5**. Having a practical and short route to the (−)-hydroxylamine **4** in hand we turned our attention to the crucial conversion of (−)-**4** to the transient nitrone **5** which should spontaneously undergo an intramolecular thermal cycloaddition reaction to yield **6**. Indeed, heating **4** with an excess of paraformaldehyde in the presence of molecular sieves in refluxing toluene gave directly the bridged isoxazolidine **6** in 87% yield. No trace of the corresponding positional isomer **7** *(Scheme 4)* was found indicating a highly regioselective nitrone addition to the non-polarized olefinic bond. The exclusive formation of **6** agrees perfectly with the regiochemistry of model studies which show a striking reversal of selectivity on thermal cycloaddition of *N*-3-alkenyl as compared with *N*-4-alkenyl nitrones; these results imply that in the corresponding transition states the formation of the new C,C-bond is more advanced than that of the C,O-bond [13][5]). Final, unambiguous evidence for the assignment of structure **6** to the adduct was provided by its transformation into naturally occurring (+)-luciduline (**1**) as described below.

3.3. *Conversion of the Adduct* **6** *into (+)-Luciduline* (**1**). This remaining task was accomplished by firstly methylating **6** with methyl fluorosulfonate in ether to obtain the methylammonium salt **15** in 96% yield. Several attempts to transform **15** directly to

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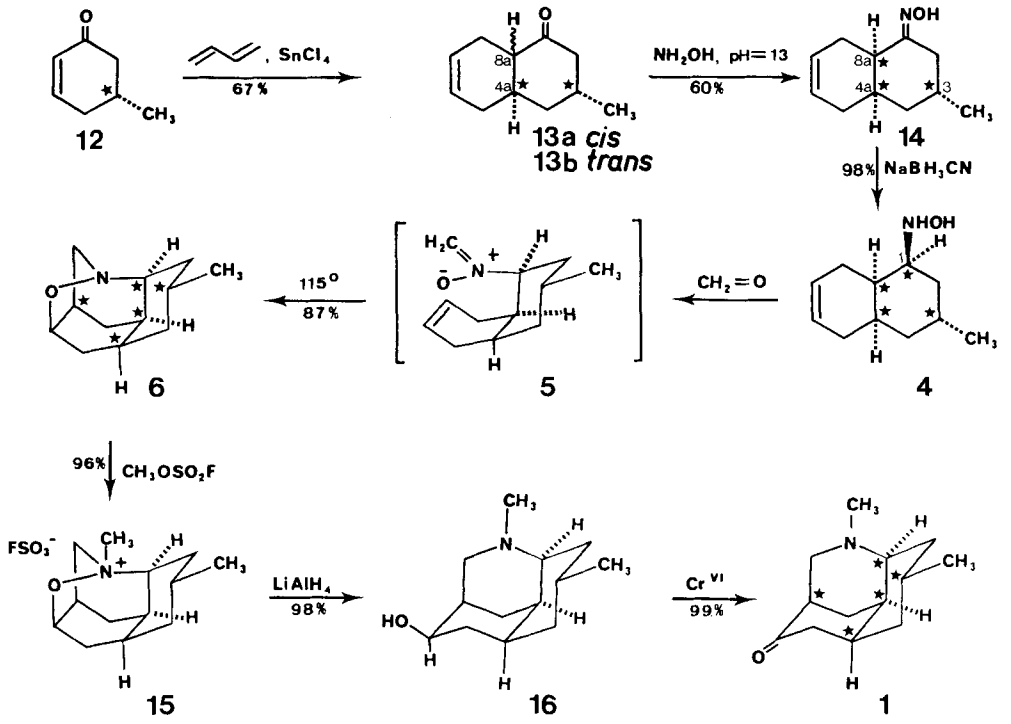
[4]) Whereas purification of the (+)-oxime **14** required simple chromatography, pure racemic **14** (62%) was obtained more readily by direct crystallization (2-propanol) of the crude oxime mixture. No interconversion of **14** and its *trans*-fused C(8a) epimer occurred under these conditions showing the selective conversion **13a** + **13b** → **14** to be kinetically controlled.

[5]) For the analogous regioselectivity of intramolecular *N*-alkenyl-*N'*-acyl-azomethinimine additions see [7].

Scheme 6



1 by base induced fragmentation were unsuccessful[6]) but eventually reductive *N*, *O*-cleavage with lithium aluminium hydride smoothly afforded dihydroluciduline (**16**)[7]) in 98% yield. Finally, oxidation of the alcohol **16** with *Jones'* reagent furnished optically pure (+)-luciduline (**1**) in 99% yield. The IR., ^{1}H-NMR. and mass spectra, as well as the GC. and chiroptic properties of synthetic (+)-**1** are identical with those of natural luciduline. In summary, the above route provides the otherwise scarce alkaloid (+)-luciduline in 33% overall yield from (+)-**12** thus illustrating nicely the utility of intramolecular *N*-alkenyl nitrone additions (as an alternative to the *Mannich* reaction). Using the same reaction sequence the racemic 5-methyl-cyclohex-2-en-1-one (**12**) [15] was converted to the racemic alkaloid **1**.

Financial support of this work by the *Fonds National Suisse de la Recherche Scientifique*, *Sandoz Ltd*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We are indebted to Professor *W.A. Ayer* for kindly providing a sample of (+)-luciduline and thank Mr. *J.P. Saulnier* and Mrs. *F. Klöti* for careful NMR. and mass spectroscopic measurements.

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6) Sec. BuLi/THF/−78 to 25°; LDA/DME/−78 to 25°; 4N aq. NaOH/hexane/25°. For a successful cleavage of an allyloxy ammonium salt see [14].

7) Synthetic **16** displayed ^{1}H-NMR. and mass spectra identical to those of the alcohol obtained by reduction of natural luciduline with $NaBH_4$ [5].

Experimental Part

General. – All reactions were carried out under an argon atmosphere. For tetrahydrofuran the abbreviation THF is used. The usual work-up implies shaking of the crude reaction mixture with ether or CH_2Cl_2 and ice water, washing of the organic layer with water, $NaHCO_3$-solution and/or sat. aq. NaCl-solution, drying over anhydrous Na_2SO_4 and removal of the solvent *in vacuo* (i.V.) using a rotary evaporator (RV.). Preparative chromatography was carried out on silica gel (*Merck* 0.05–0.20 mm) unless otherwise specified. Melting points (m.p.) are not corrected. Gas chromatograms (GC.): steel columns (3 mm, stationary phase on Chromosorb W, 2.5 atm N_2; column A: 5% FFAP, 4 m; column B: 3% KOH, 15% Carbowax, 2 m; column C: 5% OV225, 4 m); retention time in min. IR. spectra: $CHCl_3$ unless otherwise specified, $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR. spectra: in $CDCl_3$ at 100 MHz unless otherwise specified, internal standard tetramethylsilane ($\delta = 0$ ppm); abbreviations: s = singlet, d = doublet, t = triplet, qa = quartet, m = multiplet, br. = broad, J = spin-spin coupling constant (Hz). Mass spectra (MS.): signals are given in *m/e* (rel. %). The racemic compounds reported here show GC., as well as IR., ^{1}H-NMR. and mass spectra, identical with those described for the corresponding, optically pure enantiomers.

Preparation of (+)-(*R*)-5-Methyl-cyclohex-2-en-1-one (12) *(Scheme 5).* – *Sulfenylation of (+)-(R)-3-Methyl-cyclohexanone* (**9**). A 1.2N solution of butyllithium in hexane (160 ml, 192 mmol) was added to a stirred solution of diisopropylamine (28.3 ml, 200 mmol) in dry THF (290 ml) at –78°. After 15 min at –78° (+)-(*R*)-3-methyl-cyclohexanone[8]) (11.5 ml, 96 mmol) was added dropwise to the mixture during 20 min. The resulting solution was stirred for 0.5 h at –78°, then transferred by argon pressure through a steel tube during 0.5 h into a stirred solution (25°) of diphenyldisulfide (43.6 g, 200 mmol) in dry THF (200 ml). Stirring of the mixture at 25° for 1 h, followed by the usual work-up, including washing of the organic layer with 10% aq. HCl-solution and chromatography (ether/hexane) furnished the thioethers **10** (16.8 g, 80% yield, 2:1 mixture of stereoisomers). – IR. (film): 1708, 1585*m*, 750, 700. – ^{1}H-NMR.: 0.99–1.15 (2*d*, $J = 6$, 3 H); 1.5–2.5 (6 H); 2.6–3.0 (1 H); 3.65–4.0 (1 H); 7.1–7.7 (5 H).

(+)-(R)-*5-Methyl-cyclohex-2-en-1-one* (**12**). A solution of *m*-chloroperbenzoic acid (85%, 5.08 g, 25 mmol) in CH_2Cl_2 (150 ml) was added dropwise during 40 min to a stirred solution of the sulfides **10** (5.5 g, 25 mmol) in CH_2Cl_2 (250 ml) at –78°. After 30 min at –78° usual work-up of the reaction mixture gave crude **11** (5.6 g, 95% yield) as a viscous oil. A solution of the crude ketosulfoxides **11** (4.87 g, 20.8 mmol) in CCl_4 (150 ml) was heated in the presence of $CaCO_3$ (2.0 g, 20 mmol) at 65° for 21 h. The filtered *(Celite)* and evaporated reaction mixture[9]) (4.68 g) gave, after chromatography (hexane/ether 2:3) and bulb-to-bulb distillation (60–70°/12 Torr), the optically pure (*R*)-**12** (1.17 g, 49% yield from **9**), $[\alpha]_D^{25°} = -90.2°$ ($c = 2.55$, $CHCl_3$, lit [9]: $[\alpha]_D^{25°} = -90.17°$). – IR. (film): 3030*w*, 1680, 1618*w*, 885, 741. – ^{1}H-NMR.: 1.09 (*d*, $J = 6$, 3 H); 1.8–2.7 (5 H); 6.05 (*d* × *d*, $J = 1$ and 10, 1 H); 7.0 (*m*, 1 H). – MS.: 110 ($C_7H_{10}O^+$, 22), 68 (100), 40 (13), 39 (17).

Conversion of (+)-(*R*)-5-Methyl-cyclohex-2-en-1-one (12) to Natural (+)-Luciduline (1) *(Scheme 6).* – Diels-Alder *Cycloaddition of 5-Methyl-cyclohex-2-en-1-one* (**12**) *to Butadiene.* Freshly distilled $SnCl_4$ (0.91 ml, 7.7 mmol) was added at –78° to a solution of the optically pure (*R*)-**12** (770 mg, 7.0 mmol) in dry acetonitrile (0.5 ml) in a silylated Pyrex tube. The mixture was slowly warmed up to 25°, diluted with dry acetonitrile (3 ml) and recooled to –78°. After addition of butadiene (1.5 ml) the tube was sealed under argon and kept at 25° for 3 days. Usual work-up, followed by chromatography (toluene/ethyl acetate 9:1) and bulb-to-bulb distillation afforded a 1:2.5 mixture[10]) of the *cis*- and *trans*-fused adducts **13a** and **13b** (774 mg, 67% yield)[11]), b.p. 78° (bath)/0.4 Torr. – IR.: 1705, 1658*w*. – ^{1}H-NMR. (60 MHz): 0.8–1.1 (3 H); 1.3–2.95 (11 H); 5.55–5.8 (2 H). – MS.: 164 ($C_{11}H_{16}O^+$, 43), 149 (7), 146 (8), 131 (10), 104 (18), 92 (74), 91 (100), 79 (26).

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[8]) Commercially available *(Aldrich)* (*R*)-**9**, $[\alpha]_D^{20°} = +12.34°$ (lit. [16]: $[\alpha]_D^{20°} = +12.5°$) was used. Alternatively, (*R*)-**9** was prepared conveniently by retroaldolisation of (+)-pulegone [8] [9].

[9]) GC. analysis (column C, 140°) showed the presence of **12** (retention time: 5.34) and 3-methyl-cyclohex-2-en-1-one (8.39) in a ratio of 10:1.

[10]) Analyzed by GC. (column A, 170°), **13a**: retention time 11.3, **13b**: 9.7. Upon prolonged standing at 25° this mixture slowly equilibrated to give a final ratio **13a**:**13b** = 1:3.2.

[11]) No optical rotation of this mixture was measured in view of its direct conversion to **14**.

Following the above procedure treatment of (±)-**12** (1.80 g, 16.4 mmol) with butadiene (3 ml) and $SnCl_4$ (1.5 equiv., 10 days, 25°) furnished a 1:1.7-mixture of racemic **13a** and **13b** (1.81 g, 67%).

(3R,4aS,8aR)-3,4,4a,5,8,8a-Hexahydro-3-methyl-1(2H)-naphthalenone oxime (**14**). Powdered KOH (1.42 g, 25 mmol) was added to a stirred solution of a 1:2.5 mixture of chiral **13a** and **13b** (670 mg, 4.09 mmol) in dry methanol (5 ml) at 25°. After the KOH had dissolved completely a solution of hydroxylamine hydrochloride (313 mg, 4.5 mmol) in dry methanol (7.4 ml) was added very slowly during 17.5 h by means of a syringe drive. Usual work-up and chromatography (toluene/ethyl acetate 9:1) of the reaction mixture furnished the *cis*-fused oxime **14** (436 mg, 60% yield), m.p. 107–108° (2-propanol). $[\alpha]_D^{22°} = +14°$, $[\alpha]_{546\,nm}^{22°} = +14°$, $[\alpha]_{436\,nm}^{22°} = +22°$, $[\alpha]_{365\,nm}^{22°} = +46°$ ($c = 1.0$, ethanol). – IR.: 3580, 3280br., 1657*w*. – ^{1}H-NMR.: 0.75–2.7 (10 H); 1.00 (*d*, $J = 6.5$, 3 H); 3.19 ($d \times d \times d$, $J = 1.5$, 4.5 and 13.5, 1 H); 5.65 (*s* br., 2 H); 8.8–9.5 (1 H). – MS.: 179 ($C_{11}H_{17}NO^+$, 100), 164 (25), 162 (41), 147 (61), 105 (22), 91 (62), 79 (33), 77 (23), and the more polar *trans*-fused C(8a)-epimer of **14** (86 mg, 12%), m.p. 121–127° (2-propanol). $[\alpha]_D^{22°} = -17°$, $[\alpha]_{546\,nm}^{22°} = -37°$, $[\alpha]_{436\,nm}^{22°} = -66°$, $[\alpha]_{365\,nm}^{22°} = -99°$ ($c = 1.0$, ethanol). – IR.: 3580, 3270br., 1657*w*. – ^{1}H-NMR.: 0.96 (*d*, $J = 6.5$, 3 H); 1.2–2.6 (10 H); 3.23 ($d \times d \times d$, $J = 1.5$, 3.0 and 14.0, 1 H); 5.7 (*s* br., 2 H); 9.44 (*s*, 1 H). – MS.: 179 ($C_{11}H_{17}NO^+$, 75), 164 (14), 162 (40), 147 (100), 105 (28), 91 (78), 79 (27), 77 (25).

Following the above procedure a 1:3 mixture of the racemic **13a** and **13b** (670 mg) furnished, after work-up and fractional crystallization from 2-propanol, the *cis*-fused (±)-**14**, m.p. 143–145° (353 mg). Chromatography of the mother liquor followed by crystallization gave another crop of (±)-**14** (total yield: 457 mg, 62%) and its *trans*-fused C(8a)-epimer, m.p. 152–158° (81 mg, 12% yield).

No interconversion of **14** and its *trans*-fused C(8a)-epimer occurred (TLC. evidence) on keeping the isolated stereoisomers (5 mg) in a solution (0.5 ml) of hydroxylamine hydrochloride (300 mg) and KOH (1.42 g) in methanol (5 ml) at 25° for 18 h.

(1S,3R,4aS,8aR)-1,2,3,4,4a,5,8,8a-Octahydro-1-(hydroxyamino)-3-methyl-naphthalene (**4**). A 1:1 mixture of methanol and conc. aq. HCl-solution was added dropwise at 25° to a stirred mixture of (+)-**14** (374 mg, 2.09 mmol), $NaBH_3CN$ (138 mg, 2.2 mmol) and a trace of methyl orange in methanol (10 ml). The rate of the addition was controlled so that the color of the reaction mixture remained reddish – orange (pH = 3 to 4) for a period of 1 h. Subsequent basification of the solution with 6N aq. KOH (20 ml) and usual work-up furnished the free hydroxylamine **4** (369 mg, 98% yield), m.p. 149–150°, $[\alpha]_D^{22°} = -34°$, $[\alpha]_{546\,nm}^{22°} = -58°$, $[\alpha]_{436\,nm}^{22°} = -95°$, $[\alpha]_{365\,nm}^{22°} = -132°$ ($c = 0.62$, ethanol). – IR.: 3580, 3260br. – ^{1}H-NMR.: 1.03 (*d*, $J = 6.5$, 3 H); 0.8–2.5 (11 H); 3.26 ($d \times t$, $J = 10$ and 4.5, 1 H); 5.5–6.1 (4 H). – MS.: 181 ($C_{11}H_{19}NO^+$, 29), 164 (100), 149 (20), 147 (15), 133 (10), 105 (29), 90 (89), 86 (25), 79 (46), 77 (29), 67 (24).

Following the above procedure (±)-**14** (401 mg, 2.24 mmol) afforded (±)-**4** (405 mg, 99% yield), m.p. 133–135°.

(1R,11R)-11-Methyl-6-oxa-5-aza-tetracyclo[7.4.0.0^{3,7}.0^{5,13}]tridecane (**6**). A mixture of (–)-**4** (320 mg, 1.77 mmol), paraformaldehyde (300 mg, 5.7 equiv.), dry molecular sieves (4 A, 10 g) and dry toluene (30 ml) was heated in a sealed Pyrex tube at 115° for 4 h. Subsequent filtration (Celite), washing of the molecular sieves with ethyl acetate, evaporation of the filtrate and chromatography (Al_2O_3, neutral, activity III, $CHCl_3$) furnished the bridged isoxazolidine **6** as a colourless oil (298 mg, 87% yield), GC. (column B): retention time 12.1. – $[\alpha]_D^{22°} = -66°$, $[\alpha]_{546\,nm}^{22°} = -81°$, $[\alpha]_{436\,nm}^{22°} = -136°$, $[\alpha]_{365\,nm}^{22°} = -203°$ ($c = 1.0$, ethanol). – IR.: 1122, 1092, 1042, 1018, 959, 929, 899, 880. – ^{1}H-NMR.: 0.82 (*d*, $J = 6.5$, 3 H); 0.9–2.4 (11 H); 2.53 (*q*, $J = 6$, 1 H); 2.85–3.3 (3 H); 4.43 (*m*, 1 H). – MS.: 193 ($C_{12}H_{19}NO^+$, 76), 176 (100), 150 (10), 148 (10), 133 (11), 105 (16), 92 (35), 91 (38), 85 (27), 83 (42), 67 (15), 55 (20).

Following the above procedure the racemic **4** (160 mg, 0.88 mmol) was converted to (±)-**6** (137 mg, 81% yield) which crystallized at 0°, m.p. 35–37°.

(1R,11R)-5,11-Dimethyl-6-oxa-5-azonia-tetracyclo[7.4.0.0^{3,7}.0^{5,13}]tridecane fluorosulfonate (**15**). Methyl fluorosulfonate (155 µl, 1.9 mmol) was added in one portion to a stirred solution of (–)-**6** (245 mg, 1.27 mmol) in dry ether (20 ml). Immediately a colourless precipitate was formed which, after stirring of the mixture for an additional 30 min at 0°, was separated by filtration, washed with ether and dried to yield the salt **15** (374 mg, 96% yield), m.p. 138–140°. $[\alpha]_D^{22°} = -48°$, $[\alpha]_{546\,nm}^{22°} = -57°$, $[\alpha]_{436\,nm}^{22°} = -98°$, $[\alpha]_{365\,nm}^{22°} = -156°$ ($c = 1.22$, ethanol). – IR.: 3490br., 1070, 988, 905. – ^{1}H-NMR.: 0.93 (*d*, $J = 6$, 3 H); 1.0–2.55 (11 H); 3.28 (*qa*, $J = 6$, 1 H, irradiation at 5.12 → *t*, $J = 6$); 3.57 (*s*, 3 H); 3.96 ($d \times d \times d$, $J = 2.5$, 5 and 11.5, 1 H); 4.2–4.5 (2 H); 5.12 (*m*, 1 H).

Following the above procedure (±)-**6** (106 mg, 0.55 mmol) was converted to the racemic salt **15** (155 mg, 92%), m.p. 128–132°.

Dihydroluciduline (**16**). $LiAlH_4$ (45 mg, 1.19 mmol) was added in one portion to a stirred solution of (−)-**15** (146 mg, 0.47 mmol) in dry THF (5 ml). The mixture was stirred for 4.5 h at 25° then decomposed with sat. aq. Na_2CO_3-solution (40 ml) and subjected to the usual work-up to give **16** as a colorless solid (97 mg, 98% yield), m.p. 70–74° (lit. [5] m.p. 65–70°). $[\alpha]_D^{22°} = +17.5°$, $[\alpha]_{546\,nm}^{22°} = +15.5°$, $[\alpha]_{436\,nm}^{22°} = +25°$, $[\alpha]_{365\,nm}^{22°} = +49°$ ($c = 1.0$, ethanol). – IR.: 3580, 3405br., 1458, 1140, 1072, 1042, 1032, 1020. – ^{1}H-NMR.: 0.84 (*d*, $J = 6.5$, 3 H); 2.09 (*s*, 3 H); 0.8–2.2 (13 H); 2.2–2.8 (2 H); 3.12 ($d \times t$, $J = 11.5$ and 2.5, 1 H); 3.88 (*m*, 1 H). – MS.: 209 ($C_{13}H_{23}NO^+$, 32), 208 (42), 193 (16), 192 (100), 166 (26), 164 (17).

The IR., ^{1}H-NMR. and mass spectra of synthetic (+)-**16** are identical with those of naturally derived dihydroluciduline [5].

Following the above procedure (±)-**15** (43 mg, 0.14 mmol) was reduced to (±)-**16** (28.5 mg, 97% yield), m.p. 75–77°.

Luciduline (**1**). 1.23M *Jones* reagent (0.864 ml, 1.07 mmol) was added at 0° to a stirred solution of (+)-**16** (74 mg, 0.354 mmol) in acetone (5 ml) and the mixture was stirred at 25° for 1 h. Addition of 10% aq. $NaHSO_3$-solution (15 ml) and 4N NaOH (5 ml) followed by the usual work-up and distillation (80–100° (bath)/0.5 Torr) furnished **1** as a colorless oil (73 mg, 99%). – GC. (column B, 200°): retention time 12.38. – $[\alpha]_D^{22°} = +87°$, $[\alpha]_{578\,nm}^{22°} = +91°$, $[\alpha]_{546\,nm}^{22°} = +106°$, $[\alpha]_{436\,nm}^{22°} = +210°$, $[\alpha]_{365\,nm}^{22°} = +456°$ ($c = 2.8$, methanol). – IR. (film): 2775*s*, 1705*s*, 1458, 1385, 1376, 1351, 1305, 1290, 1282, 1265, 1234, 1207, 1137, 1110, 1086, 1065, 1053, 1043, 1030, 895, 844, 757. – ^{1}H-NMR.: 0.89 (*d*, $J = 6.5$, 3 H); 0.8–2.6 (13 H); 2.14 (*s*, 3 H); 2.7–3.3 (2 H). – MS.: 207 ($C_{13}H_{21}NO^+$, 100), 206 (55), 192 (22), 164 (52), 150 (15), 96 (42), 70 (21), 44 (22).

The IR., ^{1}H-NMR. and mass spectra of synthetic (+)-**1** are identical with those of natural luciduline. A redistilled sample of natural luciduline showed the following rotations: $[\alpha]_D^{22°} = +87°$, $[\alpha]_{578\,nm}^{22°} = +91°$, $[\alpha]_{546\,nm}^{22°} = +106°$, $[\alpha]_{436\,nm}^{22°} = +209°$, $[\alpha]_{365\,nm}^{22°} = +444°$ ($c = 2.05$, methanol).

Following the above procedure racemic **16** (70 mg, 0.33 mmol) was oxidized to give racemic **1** as a colorless oil (68 mg, 98% yield). (±)-**1**-hydrochloride (crystallized from CH_2Cl_2/ether) melts at 238–240° (sealed capillary, lit. [6]: 171–172°).

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