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Synthesis of Homochiral Camphor Annulated Pyrrole Derivatives

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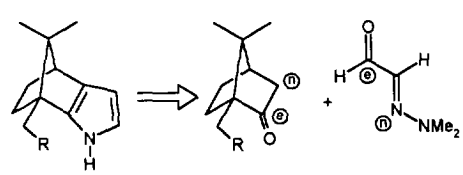
Abstract: Two new derivatives of camphor annulated to pyrrole have been synthesized representing potentially useful mono- and bidentate chiral ligands. A new method for the cleavage of the NN bond in 1-(dimethylamino)pyrroles is described.

A chiral auxiliary should ideally be synthesized in a small number of steps using cheap homochiral precursors, readily available in both enantiomeric forms. Many strategies use homochiral compounds covalently bound to prochiral groups (substrate controlled stereoselective synthesis), and there are numerous examples of chiral auxiliaries based on camphor or its derivatives[1].

Connected with our research on reagent controlled, metal promoted asymmetric synthesis, we wished to use the previously unreported camphor annulated pyrrole derivatives **1a** and **1b** as homochiral ligands. Syntheses of pyrazole derivatives based on camphor (**2a**)[2] or menthone[3] via reaction of suitable 1,3-dicarbonyl compounds with hydrazine have been published.

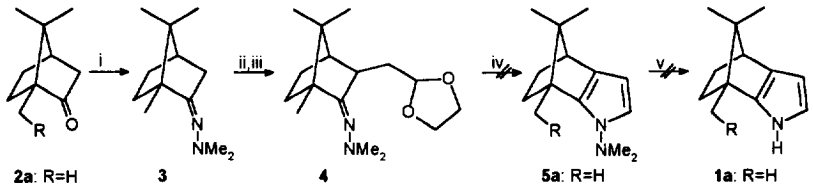
A recent publication about the synthesis of substituted pyrroles[4] prompts us to report our results on pyrrole annulation to camphor including the highly efficient N-deprotection of 1-(dimethylamino)pyrroles[5] using sodium in liquid ammonia at room temperature in an autoclave. We followed a retrosynthetic strategy for the synthesis of **1a** and its bidentate derivative **1b** involving a [3+2] cyclization of a C-C-N (**B**, glyoxal N,N-dimethyl monohydrazone) and a C-C (**A**, lithium enolate of camphor) fragment.



1a: R=H
1b: R=SMe

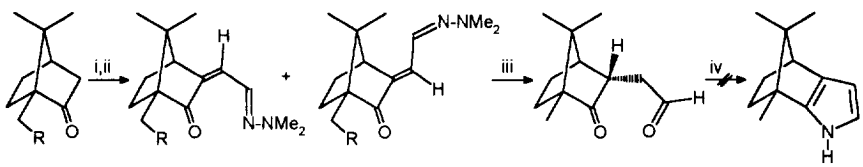
A **B**

An unsuccessful attempt to prepare compound **1a** has been reported[6] (Scheme 1). It had been found that the lithiated camphor N,N-dimethylhydrazone **3** can be alkylated with 2-iodomethyl-1,3-dioxolane. However, the acid catalyzed ring closure to give **5a** remained unsuccessful as well as experiments to cleave off the N-(dimethylamino) group in the analogous menthone based annulated N-(dimethylamino)pyrrole[6].



Scheme 1 (ref.[6]): i, H_2NNMe_2; ii, LDA, THF, HMPA, 0°C; iii, 2-iodomethyl-1,3-dioxolane, -78°C; iv, *p*-TsOH, toluene, reflux; v, Raney nickel, H_2, H_2O, MeOH

10-(Methylthio)camphor **2b** as starting material for **1b** can be synthesized on a multigramme scale from homochiral (+)-camphor-10-sulfonic acid via reduction of the sulfonyl chloride with triphenyl phosphine[7] and subsequent phase-transfer catalyzed S-methylation[8] according to published procedures.



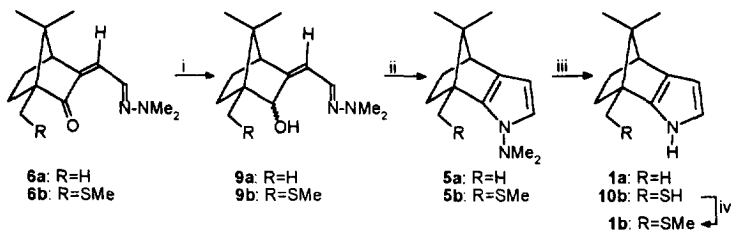
Scheme 2: i, LDA, THF, 0°C; ii, Me_2N-N=CH-CHO, THF, -78°C → +50°C, (**6a**: 86 % for i,ii; **6b**: 63 % for i,ii); iii, $TiCl_3$ [15% (w/v) in 10% HCl], NH_4OAc, dioxan, reflux (41 %); iv, NH_4OAc, EtOH

The Z/E ratio of the hydrazonoethylidene derivatives **6/7** obtained on reaction of the camphor enolate with glyoxal (N,N-dimethyl)monohydrazone is very temperature-dependent as demonstrated for **6a/7a** (Scheme 2). Reaction at -78°C and subsequent equilibration of the intermediate lithium alkoxides at 50°C clearly favours the desired Z-isomer **6a**. The stereochemical assignment can be made unambiguosly by comparing the anisotropy effects on the olefinic proton in the ^{1}H-NMR spectra and is supported by chemical arguments (*vide infra*).

Direct reductive pyrrole cyclization of **6a** with simultaneous NN bond cleavage to give **1a** using sodium dithionite as recommended by Severin et al.[9] failed. Treatment of the mixture **6a/7a** with titanium(III)chloride gives one saturated 1,4-dicarbonyl compound shown to be **8**. Therefore, a separation of the double bond isomers would not be necessary in a hypothetic synthesis via **8**. However, the attempted cyclization (**8→1a**) with ammonium acetate results in decomposition of the starting material.

Reduction of **6/7** giving the epimeric Z/E mixture of the 4-hydroxy hydrazones **9** followed by acid catalyzed cyclization provides the pyrrole precursors **5** which can be easily purified by distillation (Scheme 3). The E-configured 4-hydroxy hydrazones derived from **7** do not cyclize to give pyrroles. This finding supports the stereochemical assignment of **6** and **7**. Many efforts to solve the final preparative problem, the NN bond cleavage, remained unsuccessful (reductive cleavage with Raney-nickel[6,9], even after quaternization[6] with

methyl iodide or triethyloxonium tetrafluoroborate to facilitate hydrogenolysis, treatment with chromium(II)acetate[10], ozonolysis). The only feasible reaction for the cleavage of the NN bond in the 1-(dimethylamino)pyrrole is reduction with sodium / liquid ammonia in an autoclave at room temperature[5,11]. Usually, the conversion is quantitative and no by-products are observed. Similar observations have been made independently by Enders et al.[4]



Scheme 3: i, $NaBH_4$, EtOH, H_2O, reflux (**9a**: 86 %; **9b**: 91 %); ii, *p*-TsOH, toluene, 90°C (**5a**: 66 %; **5b**: 40 %); iii, Na, liquid NH_3, -78°C → r.t. (**1a**: 72 %); iv, MeI, NH_4OH, r.t. (**1b**: 75 % for iii,iv)

However, we found that certain functional groups are labile under these reaction conditions. For instance, the sulfide group in **5b** is completely demethylated to give **10b**[12]. Subsequent methylation of the thiol **10b** is highly chemoselective in the presence of the pyrrole NH yielding **1b**.

Hence, the homochiral compounds (+)-(4S,7R)-4,5,6,7-tetrahydro-7,8,8-trimethyl-1H-4,7-methanoindole **1a**[13] and (-)-(4S,7S)-4,5,6,7-tetrahydro-8,8-dimethyl-7-methylthiomethyl-1H-4,7-methanoindole **1b**[14] are obtained on a multigramme scale via this protocol. The key step of the reaction sequence is the cleavage of the NN bond in 1-(dimethylamino)pyrroles. A new method for this deprotection reaction using sodium in liquid ammonia at room temperature was developed. Details on the application of **1a** and **1b** as ligands for reagent controlled asymmetric syntheses will be published in due course.

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11. *Illustrative procedure for reductive cleavage of the NN bond in 1-(dimethylamino)pyrroles:* Dry ammonia (100 ml) is condensed at -78°C into a dry glass tube fitting into a stainless steel laboratory autoclave (CAUTION: This reaction should be performed only in a well-ventilated hood). Sodium metal (150 mmol, 3.45 g) is slowly added in small pieces. The 1-(dimethylamino)pyrrole (30 mmol, 6.55 g in the case of **5a**), dissolved in absolute tetrahydrofuran (10 ml) is added dropwise at -78°C. The glass tube is then placed in the autoclave. When the reaction mixture has warmed up to room temperature, a pressure of about 10-12 bar is reached. Stirring is continued under these conditions for 24 h. The autoclave is then cooled to -78°C, the remaining pressure relieved and the glass tube removed from the autoclave. Ammonium chloride is slowly added in small portions with vigourous stirring to decolourize the deep blue solution. The cooling bath is removed and the ammonia is allowed to evaporate overnight. The residue is dissolved in 2 N hydrochloric acid (30 ml); the solution is extracted three times with dichloromethane and the organic layers are discarded. Aqueous sodium hydroxide [10 % (w/v), 100 ml] is added to the aqueous layer and the alkaline solution is extracted four times with dichloromethane. The organic layers are pooled, washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated. Further purification of **1a** is achieved by sublimation of the solid residue (0.1 mbar, 60°C) to give 3.8 g (72 %) of **1a** as an off-white powder (m.p. 43-45 °C). It should be handled under argon atmosphere, because it is slightly oxygen-sensitive.
12. The formation of a small amount of **1a** (< 10 %) according to dethiomethylation of **5b** is also observed under the reaction conditions applied.
13. *Selected data* for **1a**: $[\alpha]_D^{22}$ = +34.3 (c=1.33, MeOH). - ^{1}H-NMR (200 MHz, DMSO-D_6, TMS): δ 0.68-0.90 (m, 2H); 0.75 (s, 3H); 0.85 (s, 3H); 1.20 (s, 3H); 1.64 (m, 1H); 1.88 (m, 1H); 2.66 (d, ^3J 3.5 Hz, 1H); 5.74 (t, $^3J \approx {}^4J$ 2.0 Hz, 1H); 6.36 (t, ^3J 2.0 Hz, 1H); 10.37 (br. s, 1H). - ^{13}C-NMR (50 MHz, $CDCl_3$, TMS): δ 12.0; 20.3; 20.9; 28.8; 34.5; 50.4; 52.3; 60.9; 103.6; 116.3; 129.4; 143.0. - $C_{12}H_{17}N$ [175.27]. - GC-MS: m/z = 175 (23%, M^+); 160 (73%, M^+-Me); 132 (100%); 117 (27%).
14. *Selected data* for **1b**: $[\alpha]_D^{25}$ = -41.1 (c=2.76, CH_2Cl_2). - ^{1}H-NMR (200 MHz, $CDCl_3$, TMS): δ 0.91 (s, 3H); 0.93 (m, 1H); 0.94 (s, 3H); 1.25 (m, 1H); 1.76 (m, 1H); 2.00 (m, 1H); 2.27 (s, 3H); 2.78 (d, ^2J 11.6 Hz, 1H); 2.78 (d, ^3J 3.7 Hz, 1H); 2.98 (d, ^2J 11.6 Hz, 1H); 5.95 (t, $^3J \approx {}^4J$ 2.4 Hz, 1H); 6.53 (t, ^3J 2.4 Hz, 1H); 8.44 (br. s, 1H). - ^{13}C-NMR (50 MHz, $CDCl_3$, TMS): δ 17.9; 20.6; 21.1; 28.9; 32.6; 35.6; 50.2; 56.8; 61.8; 103.0; 116.9; 129.8; 141.1. - $C_{13}H_{19}NS$ [221.37]. - GC-MS: m/z = 221 (21%, M^+); 174 (100%, M^+-SMe); 146 (38%); 130 (73%).

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