Synthesis of Terpene Diamines Based on Camphor-Derived Dinitriles

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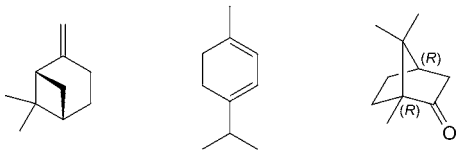
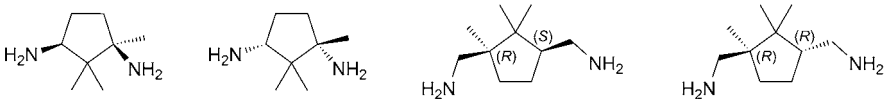
Diamines are useful as additional ligands in enantioselective hydrogenations. A new route for synthesizing such a rigid diamine from naturally available camphor *via* camphor oxime/camphor furoxan/deoxygenation in large scale was developed. The resulting dinitriles were subjected to hydrogenation with *Raney* Ni or other heterogenous catalysts. In most cases, the reduction resulted in complex mixtures. The best results were obtained with *Raney* Ni in THF/H_2O in strongly basic media (NaOH), which affords compound **5b** only in good yield. Homogenous catalyst like *Grubbs* 2nd generation reduced only the less hindered CN group to yield an amino nitrile.

Introduction. – Among the terpenes with economic potential, pinene (**1**), terpinene (**2**), and camphor (**3**) can be envisioned as potential starting materials for synthesis of ligands with C-atom frameworks providing sterical shielding of reactivity. So, camphor-based amines **4a** and **4b** had been prepared as ligands for transition metal complexes. *Jaramillo et al.* synthesized chiral Pt^{II} complexes with these diamines, prepared from camphoric acid [1]. *Yang et al.* used diamines, based on camphor, as intermediates for the preparation of chiral *Schiff*-base ligands [2]. These ligands are sterically strongly congested, and this results in low reaction rates at the respective transition-metal centers. Nevertheless, various diamines have been used as additional chelating ligands for enantioselective hydrogenation of more difficult substrates like tetralones [3]. To end up in high enantioselectivity, it proved to be necessary for the diamines to have a rigid backbone distant from the N-atoms involved in chelation. This might enable the molecule to adopt '*a conformation dictated by the (…) phosphine ligand*' [4]. Such a



1 **2** **3**

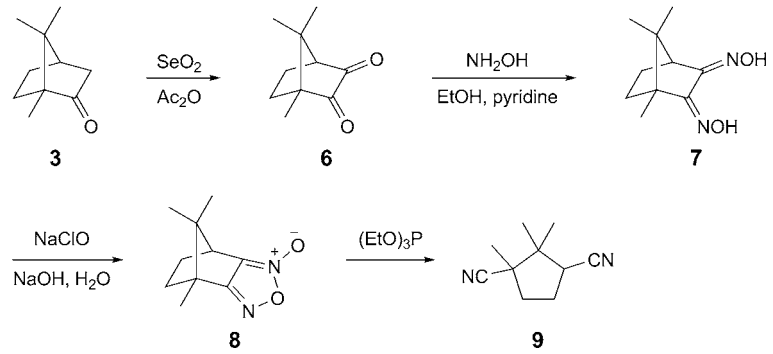


4a **4b** **5a** **5b**

feature might be realized by using other backbone molecules where the N-atom is not directly attached to the C-atom ring, *e.g.*, our target molecules **5a**/**5b**, where two adjacent Me groups at C(2) and additionally one more Me group in α-position to C(2) provides a very similar steric environment. Despite that, **5a** might be able to chelate by forming a seven-membered ring. With respect to enantioselectivity in catalysis, it will be interesting to see if these diamines are advantageous with transition metals of the second and third row. The bicyclic system of camphor can be cleaved by various methods to yield a cyclopentane with a required C-atom framework. Oximes of terpene-ketones often react anomalously to yield nitriles, which are suitable precursors for amines [5]. Such a process is related to furoxans obtained from camphor dioxime. We present here a new synthetic route of diamines **5a**/**5b** in large scale from naturally available camphor.

Results and Discussion. – Furoxans (=1,2,5-oxadiazole 2-oxides) are a neglected class of heterocycles, but very reactive. They are formed easily from dioximes by a fast and clean oxidation, *e.g.*, with NaClO. *Dornow et al.* tried to reduce furoxan **8** with $LiAlH_4$ and obtained an amine in poor yield (not characterized) [6]. Dicarbonitrile **9** could be obtained by other means and reduced with elemental Na to **5** [7]. We tried both routes with no satisfactory results. It was advantageous then to have a suitable method at hand for the deoxygenation of furoxan **8** with $(EtO)_3P$ to **9** [8] (*Scheme 1*). This could be reduced to the target product **5**. Dicarbonitrile **9** was obtained usually as pure stereoisomer **9a** (*cf. Scheme 2*) by ring cleavage of **8**. In need of large amounts of nitrile, we reworked the process of exothermic phosphite deoxygenation, and found it safe and advantageous to use trialkyl phosphates as a solvent. The furoxan is soluble to the extent of 1.5 g furoxan per 10 ml of $(EtO)_3PO$. The final hydrogenation of the nitrile proved to be a difficult process. In simple assets of hydrogenation procedures of **9** to **5**, at least five products (stereoisomers not included) were found to be present, often in equal concentrations. Several catalysts were tried (*Table*), including *Raney* Ni, Rh on alumina [9], Pd on charcoal, Pt on charcoal, and *Grubbs* 2nd-generation catalyst [10]. The compositions of the reduced solutions are compiled in the *Table*. In the worst case, compound **11** or **12**, or both were the main product (*Entries 9* and *10*). One could isolate **12** to reduce it in a second stage to **5**, but formation of **11** was a dead end. This is

Scheme 1



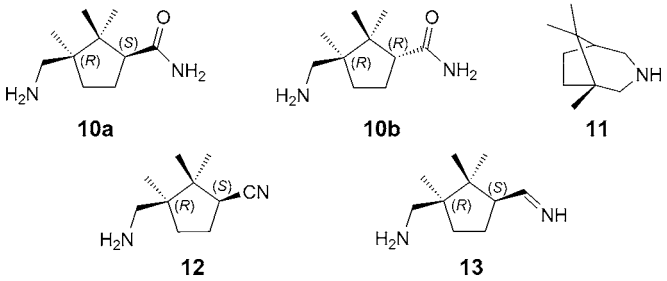
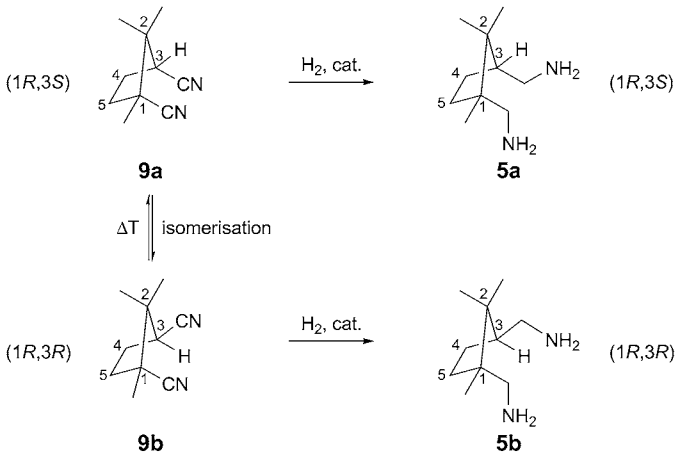


Table. *Hydrogenation of the Dinitrile* **9** *under Different Reaction Conditions*

Entry	Catalyst	Reaction conditions	Yields of products [%]				
			9	**5**	**10**	**11**	**12**
1	*Raney* Ni	EtOH, 6M NaOH (aq.), 60 bar, 110°, 20 h		34		4	29
2	*Raney* Ni	EtOH, 6M NaOH (aq.), 75 bar, 80°, 20 h		86		6	
3	*Raney* Ni	1,4-Dioxane, 6M NaOH (aq.), 50 bar, 110°, 20 h		21	20	5	
4	*Raney* Ni	1,4-Dioxane, 6M NaOH (aq.), 65 bar, 80°, 20 h		24		4	28
5	*Raney* Ni	1,4-Dioxane, 6M NaOH (aq.), 50 bar, 105°, 20 h		38			
6	*Raney* Ni	1,4-Dioxane, 6M NaOH (aq.), 85 bar, 100°, 20 h		61			
7	*Raney* Ni	THF, 6M NaOH (aq.), 70 bar, 70°, 20 h	4	79		6	
8	*Raney* Ni	EtOH 120 bar, 90°, 20 h		67		3	
9	*Raney* Ni	EtOH 70 bar, 70°, 20 h		9			31
10	*Raney* Ni	1,4-Dioxane 65 bar, 90°, 20 h		15	20	20	
11	*Raney* Ni	1,4-Dioxane 60 bar, 140°, 20 h		44		17	19
12	*Raney* Ni	1,4-Dioxane 60 bar, 100°, 20 h		42	10	18	
13	*Grubbs II*	Toluene 80 bar, 50°, 72 h	61				37

due to the sterical hindrance which slows down the reaction rate of hydrogenation at CN group at the tertiary C(1) (*Scheme 2*). The cyclic amine **11** may be formed through deamination of the aldimine **13**, which is an intermediate during the reduction of **9a**. The difficulty encountered here was to find conditions under which hydrogenation is rapid enough to overcome the formation of secondary amine **11**. This was partly achieved by higher pressure to make H_2 readily available at the heterogeneous reaction site. Conversely, racemization at C(3) was crucial, since complete inversion yielded **10b**

Scheme 2



which is scarcely involved in ring closure. Due to the acidity of the C(3)-atom, one can expect isomerization/racemization to occur in further manipulation with protic solvents/basic reaction media involved. Already when pure dinitrile **9** was heated in such solutions, an isomerisation at C(3) took place, and two stereoisomers **5a** and **5b** were formed (*Scheme 2*). Isomer **9b** was reduced to **10b** and thus to **5b** properly. Reactions in EtOH/H_2O/NaOH gave good results, but the yields of diamine **5** varied strongly (34 and 86%; *Table*, *Entries 1* and *2*). 1,4-Dioxane/H_2O/NaOH as reaction media produced moderate yields of diamine **5** (21–61%; *Table*, *Entries 3–6*). The best results were obtained with *Raney* Ni in THF/H_2O/NaOH, which furnished compound **5** in good yield (79% of **5** and only small amounts of by-products; *Table*, *Entry 7*). Temperatures of 70°–80° were optimal for the reaction in THF/H_2O/NaOH. H_2 Pressures of 60 bar and above were required. Small amounts of additional compound **11** were still present, but not in the same quantities as when other means of reduction were employed. Hydrogenation in solvents, without additional NaOH/H_2O, such as EtOH (*Table*, *Entries 8* and *9*) or 1,4-dioxane (*Table*, *Entries 10–12*) gave only poor yields of diamine **5** and a lot of by-products **10**, **11**, or **12**. Even variation of the reaction conditions like temperature or pressure did not improve yields of **5**. Despite an acceptable outcome has been obtained with *Raney* Ni, still a plenty of catalyst was required. Several attempts have been made to use a homogenous reduction system, *e.g.*, such as Ru complexes with NHC ligands. Reduction of the dinitrile **9** with *Grubbs* catalyst (2nd generation) [10] gave only amino carbonitrile **12** in poor yield with plenty of unreacted starting material (*Table*, *Entry 13*). Formation of compound **11** was not observed.

Conclusions. – The aim of our work was to synthesize diamines **5** from naturally available camphor in large scale. After several modifications, furoxan/dinitrile were obtained in quantities of as much as 40 g. Hydrogenation of the intermediate dinitrile was performed best with the inexpensive catalyst *Raney* Ni in basic media to yield **5b**. The best solvent system was THF/H_2O/6M NaOH (*Table*, *Entry 7*).

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Experimental Part

General. Yields were calculated from the area analyses of the gas chromatograms. Quantification was accomplished for **5** only with the isolated pure compound as reference. The reductions were performed in a 50-ml steel autoclave from *Premex* with glass beaker inside. Another problem was to purify the amine from the by-products; several methods were tried, including distillation, salting out, or chromatography on silica gel, ion-exchange resins, and alumina. The best separation results were achieved by chromatography on basic alumina with MeOH/NH_3 100:1. IR Spectra: *Nicolet 380* FT-IR with a *Smart Diamond ATR* (*Thermo Scientific*); $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *JEOL ECS 400* spectrometer; δ in ppm rel. to Me_4Si as internal standard; *J* in Hz. GC/MS: *HP 6890* with MS detector *HP MS 5973* and *HP-5MS* column (*Hewlett Packard*); in *m*/*z*.

*(1*R,*4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptane-2,3-dione* **6** was obtained by oxidation of camphor (**3**) with SeO_2 [11]. *(1*R,*4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptane-2,3-dione dioxime* (**7**) was prepared by reaction of a threefold excess of $NH_2OH \cdot HCl$ with **6** [11][12]. *(4*R,*7*S*)-4,5,6,7-Tetrahydro-4,8,8-trimethyl-4,7-methano-2,1,3-benzoxadiazole 1-oxide* **8** was synthesized from **7** with NaClO [8].

1,2,2-Trimethylcyclopentane-1,3-dicarbonitrile (**9**). $(EtO)_3P$ (15 ml) was heated to 100°, then 7 g (36 mmol) furoxan **8** were added in small portions (*Caution:* large amounts of furoxan can decompose explosively if heated in one portion!). After complete addition, the soln. was refluxed at 150° for 5 h. After cooling to r.t., the soln. was poured into 70 ml of H_2O, and 1 ml HCl (37%) was added. Overnight, white crystals precipitated, and they were separated by vacuum filtration (4.2 g, 81%).

An alternative route was to use trialkylphosphates as solvents. Furoxan **8** (1.6 g, 8.2 mmol), dissolved in 20 ml of $(EtO)_3PO$ was slowly added *via* a dropping funnel to 20 ml of $(EtO)_3P$, which was preheated to 100°. Next, the mixture was heated to 150° for 3 h. Then, $(EtO)_3PO$ and $(EtO)_3P$ were distilled off in vacuum (0.4 mbar). The distillation residue was treated with 10 ml of H_2O and 0.5 ml of HCl (37%) to precipitate **9**, which was collected by vacuum filtration (0.8 g, 60%). IR (ATR): 2885–2977, 2228, 1475, 1454, 1397, 1385, 1370, 1300, 1243, 1206, 1180, 1149, 1128, 1093, 1041, 952, 579, 470. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.2 (*s*, 3 H); 1.3 (*s*, 3 H); 1.4 (*s*, 3 H); 1.8–1.9 (*m*, 1 H); 2.1–2.2 (*m*, 1 H); 2.2–2.3 (*m*, 1 H); 2.4–2.5 (*m*, 1 H); 2.7 (*dt*, *J* = 1.8, 9.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.0; 22.0; 23.4; 25.7; 35.7; 38.2; 44.8; 47.4; 119.8; 122.5. GC/EI-MS: 161, 147, 135, 119, 108, 95, 82, 68, 53, 41, 28, 15.

Hydrogenations with Raney *Ni* (*Table*, *Entries 1–7*). Dinitrile **9** (1.5 g, 9.3 mmol) was dissolved in 8 ml of EtOH, THF, or 1,4-dioxane (better solubility in dioxane and THF), and 8 ml of NaOH (aq., 6M) were added. To this soln. was slowly added Ni/Al alloy (0.4–0.7 g; *Sigma–Aldrich*). Rapid evolution of H_2 occurred while Al dissolved. Next, the autoclave was purged twice with N_2 to remove O_2. Then, the vessel was pressurized with H_2 (55–75 bar). The mixture was stirred overnight at 80–140°. After cooling to r.t., *Raney* Ni was filtered off. The org. solvent was removed by rotary evaporation, und the remaining H_2O phase was extracted with Et_2O (3 × 20 ml). Extraction with AcOEt was unsuitable, because ethyl amides were formed. The org. layer was separated, dried (Na_2SO_4), and the solvent was evaporated. The resulting mixture was purified by CC (basic alumina; with MeOH/25% $NH_3 \cdot H_2O$ 100:1; 10.5 cm × 4.5 cm; TLC (aluminium oxide 60 neutral): R_f 0.4).

Hydrogenations with Raney *Ni* (*Table*, *Entries 8–12*). *Raney* Ni was freshly prepared from Ni/Al alloy (0.5 g) with NaOH (aq., 6M), filtered off, and rinsed with H_2O. Dinitrile **9** was dissolved in 10 ml of EtOH, THF, or 1,4-dioxane, and *Raney* Ni was added. Next, the autoclave was purged twice with N_2 to remove O_2. Then, the vessel was pressurized with H_2 (55–120 bar). From this point on, the procedure was the same as in *Entries 1–7*.

(1,2,2-Trimethylcyclopentane-1,3-diyl)bis[methanamine] (**5**). IR (ATR): 3288, 2940, 2868, 1567, 1453, 1372, 1314. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.6 (*s*, 3 H); 0.8 (*s*, 3 H); 0.9 (*s*, 3 H); 1.2 (*m*, 1 H); 1.4–1.5 (*m*, 2 H); 1.8–1.9 (*m*, 3 H); 2.4 (*t*, *J* = 9.6, 1 H); 2.5 (*s*, 2 H); 2.7 (*dd*, *J* = 3.7, 4.1, 11.9, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.4; 20.3; 23.2; 26.4; 34.7; 44.0; 44.3; 48.52; 49.0; 51.7. GC/EI-MS: 170, 153, 141, 126, 109, 95, 81, 69, 56, 41, 30.

*(1*R,*5*S*)-1,8,8-Trimethyl-3-azabicyclo[3.2.1]octane* (**11**). IR: (ATR): 2923, 2870, 1567, 1557, 1454, 1381, 1312, 1169, 1089, 1047, 978, 881, 815, 686, 620, 433. ^{1}H-NMR (400 MHz, CD_3OD): 0.8 (*s*, 3 H); 0.9 (*s*,

3 H); 1.0 (*s*, 3 H); 1.5–1.7 (*m*, 4 H); 1.9–2.0 (*m*, 1 H); 2.3 (*d*, *J* = 12.8, 1 H); 2.5 (*dd*, *J* = 2.8, 3.2, 10.1, 1 H); 2.9 (*d*, *J* = 12.8, 1 H); 3.1 (*d*, *J* = 13.3, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 16.2; 17.1; 23.6; 24.7; 33.7; 41.5; 42.3; 45.2; 46.5; 52.6. GC/EI-MS: 153, 138, 122, 107, 98, 91, 81, 67, 55, 44, 30.

(1S,3R)-3-(Aminomethyl)-2,2,3-trimethylcyclopentane-1-carbonitrile (**12**). IR (ATR): 3234, 2927, 2873, 1661, 1557, 1471, 1456, 1393, 1379, 1354, 1318, 1227, 1158, 1221, 1066, 1043, 941, 881, 813, 619, 560, 483, 459, 421. ^{1}H-NMR (400 MHz, CD_3OD): 0.7 (*s*, 3 H); 1.2 (*s*, 3 H); 1.3 (*s*, 3 H); 1.4 (*m*, 1 H); 1.8 (*m*, 1 H); 2.0 (*m*, 1 H); 2.1 (*m*, 2 H); 2.4 (*dd*, *J* = 10.7, 11.9, 1 H,); 2.8 (*dd*, *J* = 3.6, 12.4, 1 H). ^{13}C-NMR (100 MHz, CD_3OD): 14.8; 17.7; 22.1; 25.6; 35.2; 42.5; 44.9; 51.2; 125.0. GC/EI-MS: 166, 149, 134, 122, 109, 97, 77, 67, 53, 41, 30.

Hydrogenations with Grubbs *2nd-Generation Catalyst* (*Table*, *Entry 13*). Dinitrile **9** (0.5 g, 3 mmol), ^{t}BuOK (0.11 g, 1 mmol), and *Grubbs* 2nd-generation catalyst (7.3 mg, 0.009 mmol) were dissolved in 15 ml of toluene under Ar and transferred into an autoclave. Then, 80 bar pressure of H_2 was applied, and the soln. was stirred at 50° for 72 h.

Hydrogenations with Pd. Dinitrile **9** (0.25 g, 1.5 mmol) and Pd/C (10% Pd) (0.14 g) were dissolved in 50 ml of EtOH. The soln. was pressurized with 50 bar of H_2 in an autoclave and stirred at 70° for 5 h. No products were formed.

Hydrogenations with Pt. Dinitrile **9** (0.25 g, 1.5 mmol) and Pt/C (5% Pt) (0.06 g) were dissolved in 60 ml of EtOH. The soln. was pressurized with 70 bar of H_2 in an autoclave and stirred at 70° for 5 h. No products were formed.

Hydrogenations with Rh. In an autoclave, dinitrile **9** (0.5 g, 3 mmol) and Rh/Al_2O_3 (5% Rh; 14 mg, 0.1 mmol) were dissolved in 50 ml of MeOH sat. with NH_3; 25/55 bar of H_2 pressure were applied, and the soln. was stirred for 20 h at r.t. or at 100°. No products were formed.

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