A Novel Synthesis of Substituted 1-Benzyloctahydroisoquinolines by Acid-Catalyzed Cyclization of *N*-[2-(Cyclohex-1-enyl)ethyl]-*N*-styrylformamides

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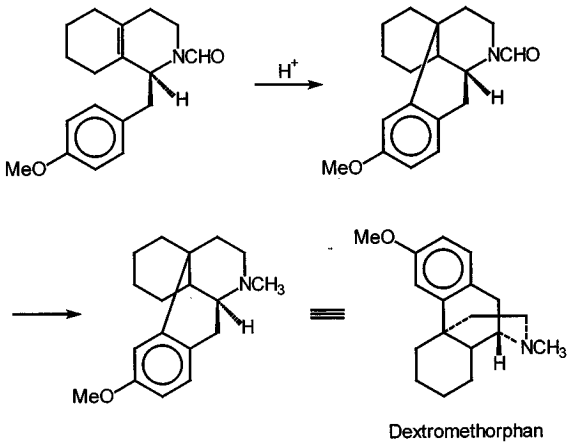
The acid-catalyzed cyclization of *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamides **1**–**5** gave access to 1-benzyl-2-formyloctahydroisoquinolines **6**–**10**. The reactions were performed in the presence of the Lewis acid 9-borabicyclo[3.3.1]non-9-yl triflate. The cyclization of enamide **1** was also studied with Brønsted acid catalysts, such as triflic acid and the heterogeneous catalyst tungstophosphoric acid supported on silica gel. In all cases the 1,2,3,4,5,6,7,8-octahydroisoquinoline formed was accompanied by minor concentrations of one, two, or three isomeric octahydroisoquinolines. 1-Benzyl-2-formyloctahydroisoquinoline (**6**) could also be prepared from *N*-[2-(cyclohex-1-enyl)ethyl]formamide (**11**) by reaction with phenylacetaldehyde in a mixture of acetic acid and trifluoroacetic acid. The octahydroisoquinolines **6**, **8**, **10** as model compounds, were converted into the corresponding *N*-formylmorphinans.

Introduction

The isoquinoline nucleus is the basic structure of a very large family of alkaloids[1]. Most important are the 1-substituted isoquinolines which are either naturally occurring alkaloids or intermediates in both the synthesis and the biosynthesis of e.g. morphinans, protoberberines, and aporphines. Many of these alkaloids exhibit high biological activity and have found important therapeutical use[2]. The 1-benzyl-substituted octahydroisoquinolines are of particular interest as starting materials in the synthesis of the morphinan skeleton. For example, the nonopioid antitussive dextromethorphan is prepared from (1*S*)-1-(*p*-methoxybenzyl)-*N*-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline by acid-catalyzed Grewe cyclization and subsequent reduction of the *N*-formyl group (Scheme 1).

Scheme 1. Synthesis of dextromethorphan from (1*S*)-1-(*p*-methoxybenzyl)-*N*-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline



The synthesis of the isoquinoline ring system is usually achieved by one of the traditional procedures, such as the Bischler-Napieralski reaction[3], the Pictet-Spengler reaction[4], or the Pomeranz-Fritsch reaction[5]. A large number of variations based on the Pictet-Spengler reaction has been reported[6]. Developments in the enantioselective synthesis of isoquinoline alkaloids have been reviewed recently[7]. Most of the research is focused on 1,2,3,4-tetrahydroisoquinolines, whereas the synthesis of octahydroisoquinolines with a double bond common to the two rings has received much less attention. Methods to prepare these octahydroisoquinolines include the Bischler-Napieralski reaction of amides followed by reduction of the cyclic imine[8] or the cyclization of iminium ions[9]. The latter method was successfully applied in the synthesis of octahydroisoquinolines starting from 2-(cyclohex-1-enyl)ethylamine and formaldehyde or benzaldehyde. However, with phenylacetaldehyde the octahydroisoquinoline was obtained only in a very low yield. In contrast, *N*-methylated 2-(cyclohex-1-enyl)ethylamine can be cyclized easily with phenylacetaldehyde via the enamine. The cyclization has been performed with the aid of 50% sulfuric acid or 87% phosphoric acid. The yield of the octahydroisoquinoline could be improved by performing the reaction in an organic solvent in the presence of an excess of *p*-toluenesulfonic acid[10].

It is known that the *N*-formyl group is a versatile protecting group in acid-catalyzed cyclizations which are related to the syntheses described above[11]. Moreover, the *N*-formyl group can be either converted simply into the *N*-methyl group or it can be removed easily by hydrolysis. We here wish to report on a new synthesis of 1-benzyloctahydroisoquinolines starting from *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamides. As the catalyst for the cyclization reactions we studied both Lewis and Brønsted acids. We also

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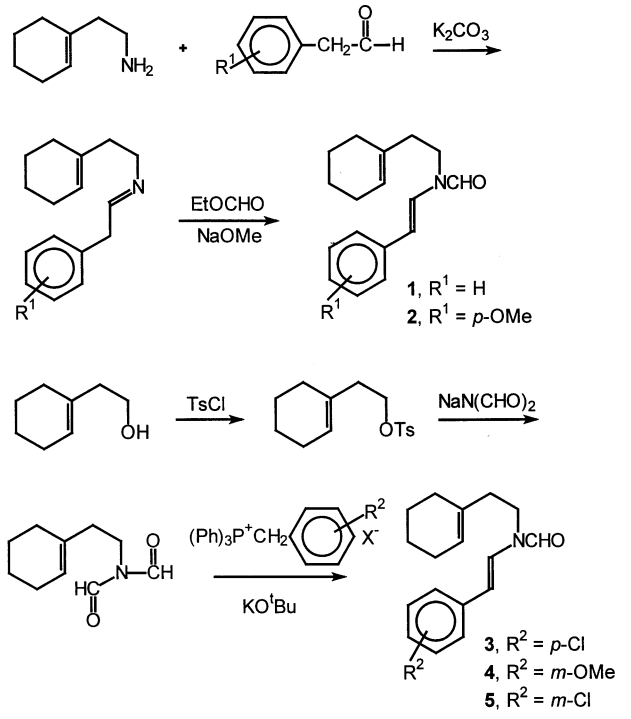
included some heterogeneous examples of the latter type. Finally, some of the octahydroisoquinolines were converted into the corresponding *N*-formylmorphinans, demonstrating the usefulness for the synthesis of morphine alkaloids.

Results and Discussion

Lewis Acid Catalyzed Cyclization Reactions

The substituted *N*-formyl enamines were prepared by two different methods which were recently developed in our laboratory. *N*-[2-(Cyclohex-1-enyl)ethyl]-*N*-styrylformamide (**1**) and the corresponding *p*-methoxyphenyl derivative **2** were synthesized by *N*-formylation of the appropriate imines[12] (Scheme 2). The other method applied, namely the Wittig alkenylation of 2-(cyclohex-1-enyl)ethyl diformamide, gave easy access to phenyl-substituted derivatives **3**–**5**[13].

Scheme 2. Two synthetic pathways to substituted *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamides **1**–**2** and **3**–**5**



The unsubstituted *N*-styryl formamide **1** was used as a model compound to investigate the Lewis acid catalyzed enamide cyclizations. We first studied $AlCl_3$, $AlEtCl_2$, and $TiCl_4$ as catalysts. Under various conditions (solvent, temperature, and catalyst loading) no cyclization of the enamide was observed. When two equivalents of BF_3-Et_2O were used a complete conversion of the enamide was observed on TLC. The main product, isolated by column chromatography, proved to be a cyclized product. Recently, it was shown that trifluoromethanesulfonates (triflates) of titanium, zirconium, or rare earth elements are active Lewis acid catalysts for Diels-Alder reactions and other C–C bond formations[14]. We studied the cyclization reaction of **1** in the presence of these triflates and found here that some of them are also quite active catalysts (Table 1).

Table 1. Activity of (metal) triflates in the cyclization of enamide **1**

Triflate[a]	*T* [°C]	*t* [h][b]
$Cp_2Ti(CF_3SO_3)_2$	93[c]	2
$Cp_2Ti(CF_3SO_3)_2$	80	4
$Yb(CF_3SO_3)_3$	110	—[d]
$Sc(CF_3SO_3)_3$	110	—[d]
$Al(CF_3SO_3)_3$	93[c]	2.5
$B(CF_3SO_3)_3$	50	1
9-BBN(CF_3SO_3)	20	3

[a] Unless otherwise stated 1 equivalent of Lewis acid was used with toluene as solvent. – [b] Time to reach complete conversion as monitored by TLC. – [c] A boiling mixture of THF and toluene was used. – [d] No conversion of enamide after 24 h.

The most active catalysts were boron tris(triflate) [$B(CF_3SO_3)_3$] and 9-borabicyclo[3.3.1]non-9-yl triflate [9-BBN triflate, 9-BBN(CF_3SO_3)]. These triflates have not been previously described as catalysts for cyclization reactions.

The other triflate catalysts were less active than the boron compounds, but they showed the same high selectivity[15]. The activities of the titanium and aluminium triflates were almost equal. We expected that the presence of strong coordinating THF would lower the activity of the Lewis acid. However, in the reaction catalyzed by the titanium compound the presence of THF in the reaction mixture had almost no influence. Surprisingly, the ytterbium and scandium catalysts were completely inactive in the cyclization reaction. These two triflates are active catalysts in various Lewis acid mediated reactions such as Diels-Alder reactions[16], Friedel-Crafts acylation reactions[17], and aldol reactions[18].

The cyclization reaction of **1** catalyzed by 9-BBN triflate was investigated in more detail. When the reaction was carried out at room temperature with one equivalent of Lewis acid the cyclic product was isolated in 72% yield after purification by column chromatography. The product seemed to be uniform on TLC, but a gas chromatogram showed four peaks in a ratio of about 70:20:5:5 with only small differences in retention time. The ^{1}H-NMR spectrum was complex, not only due to the presence of signals of two *N*-formyl rotamers, but also to signals indicating the presence of a mixture of isomeric octahydroisoquinolines. This was confirmed by GC-MS of the mixture since all four products had a molecular mass of 255. Moreover, in each of the four mass spectra a fragment with the highest intensity and a mass of 164 was present indicating the loss of a benzyl group from the octahydroisoquinoline ring. We concluded that the major isomer was the 1,2,3,4,5,6,7,8-octahydroisochinoline from comparison of the ^{1}H-NMR spectrum of the isomeric mixture with the spectrum of pure (1*S*)-1-(*p*-methoxybenzyl)-*N*-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. The latter pure isomer was obtained by formylation of (1*S*)-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline. In $CDCl_3$ at room temperature the ratio

of the *syn/anti* rotamers of the major isomer was approximately 65:35.

The isomer which is present in about 20% shows a proton signal at $\delta = 5.75$ in the ^{1}H-NMR spectrum. From this, combined with other data from the proton spectrum, we found evidence that this isomer is 1-benzyl-2-formyl-1,2,3,5,6,7,8,8a-octahydroisoquinoline. The two other isomers are assumed to be 1-benzyl-2-formyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline and 1-benzyl-2-formyl-1,2,3,4,4a,5,6,7-octahydroisoquinoline. The isomeric mixture of octahydroisoquinolines was reduced to the corresponding *N*-methyl compounds with lithium aluminium hydride. It was possible to isolate pure 1-benzyl-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline as the oxalate salt. This material was identical to the compound obtained from *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-methyl-*N*-styrylamine by acid-catalyzed cyclization[19].

In all cyclization reactions a side product is formed which is more polar than the octahydroisoquinolines. This product was isolated and proved to be *N*-[2-(cyclohex-1-enyl)-1-ethyl]formamide. The cyclization reaction could also be performed with a smaller amount of 9-BBN triflate. Using 50 mol-% of catalyst the conversion of **1** was complete after 6 h at 50°C in toluene. Under reflux conditions in this solvent a complete conversion was observed after 16 h with 20 mol-% of catalyst. In this case the isolated yield of the octahydroisoquinoline was 74%.

To gain more insight into the Lewis acid catalyzed cyclization reactions we applied 9-BBN triflate to different substituted *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamides (Scheme 3). The results are summarized in Table 2.

Scheme 3. Synthesis of phenyl-substituted *N*-[2-(cyclohex-1-enyl)-ethyl]-*N*-styrylformamides

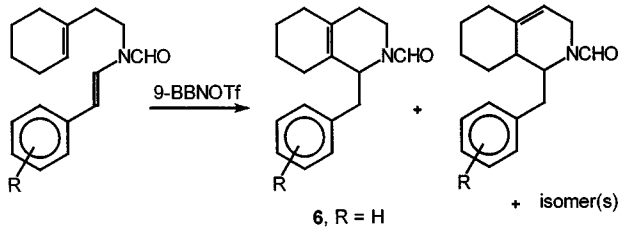


Table 2. Cyclization of substituted *N*-styryl enamides catalyzed by 9-BBN triflate[a]

Entry	Enamide	Isolated yield[b] (%)	Ratio of isomers
1	*p*-OMe (**2**)	67	70:20:5:5
2	*p*-Cl (**3**)	51	90:10
3	*m*-OMe (**4**)	53	80:15:5
4	*m*-Cl (**5**)	54	85:15

[a] Reactions were performed in CH_2Cl_2 with 1 equivalent of catalyst at 20°C. – [b] Products were isolated by column chromatography.

The octahydroisoquinolines were isolated in quite good yields. In all cases the main side-product was the formamide formed after loss of the styryl substituent. The number of isomers proved to be dependent on the substituents at the phenyl ring. Cyclization of the chloro compounds gives only one isomeric side product.

Brønsted Acid Catalyzed Cyclization Reactions

For the cyclization reaction of **1** we also investigated catalysis by Brønsted acids. We observed a complete conversion of **1** after 2 h heating under reflux in the presence of a mixture of acetic acid and trifluoroacetic acid (volume ratio 4:1), previously used in the synthesis[20] of tetrahydroisoquinolines via *N*-formyliminium ions. A mixture of isomeric octahydroisoquinolines was formed which was isolated in 60% yield. Trifluoroacetic acid alone was studied as a catalyst in toluene at 50°C. Even with three equivalents of acid no cyclization was observed on TLC after 6 h. We also performed a reaction with one equivalent of boron tris(trifluoroacetate), prepared in situ from boron tribromide and silver trifluoroacetate, under the same conditions. In this case about 25% conversion of the enamide was observed after 6 h. This indicates a higher activity for the Lewis acid with three trifluoroacetate ligands compared to trifluoroacetic acid.

The strong Brønsted acid trifluoromethanesulfonic acid (triflic acid) was also investigated. This acid proved to be a very active catalyst for the cyclization reaction. Using 50 mol-% of triflic acid the conversion of **1** was complete after 4 h reaction in toluene at 50°C. With 20 mol-% of catalyst the conversion was complete after 16 h reflux in a 1:5 mixture of dichloromethane and toluene. The isolated yield of isomeric octahydroisoquinolines **6** was 82%.

Furthermore, we studied two heterogeneous Brønsted acid catalysts. Firstly Nafion-H, a perfluorinated resinsulfonic acid which is active in many acid-catalyzed reactions[21], was tested. A complete conversion of **1** was observed after 16 h boiling in ethylene glycol dimethyl ether. The activity of Nafion-H in this solvent was higher than in benzene or toluene, probably due to swelling of the polymer in the more polar solvent. The amount of solid acid was high, 160 mg of Nafion-H for only 65 mg of enamide. Secondly, looking for a more active heterogeneous acid, we found that the heteropoly acid tungstophosphoric acid ($H_3PW_{12}O_{40}$) supported on silica gel (40 w-%)[22][23] was more active in the cyclization reaction. Using half the amount of acid (per weight) as **1**, a complete conversion was observed after 20 h heating under reflux in toluene. The isolated yield of the octahydroisoquinoline mixture **6** was 66%. The product was also analyzed by GC and the ratio of isomers was now 60:25:10:5. Although the 1,2,3,4,5,6,7,8-octahydroisoquinoline is formed in a slightly smaller amount there is no substantial difference between the composition of this mixture and the mixture obtained in the Lewis acid catalyzed cyclization reaction.

The cyclization of the *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamide in the presence of acids probably proceeds

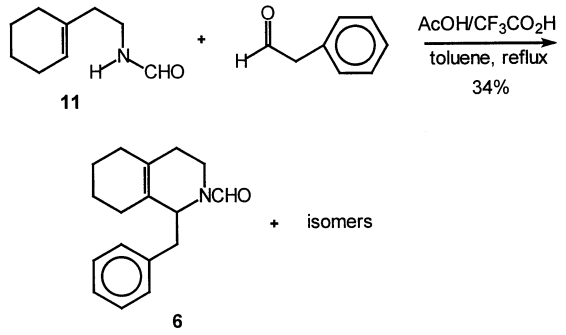
via an *N*-acyliminium ion[24]. In the Brønsted acid catalyzed reactions protonation of the enamide double bond gives a carbocation which is in equilibrium with the *N*-acyliminium ion. After reaction of this cationic intermediate with the olefinic double bond the isoquinoline structure is formed. Proton elimination, followed by acid catalyzed isomerization reactions of the newly formed carbon−carbon double bond, gives the isomeric mixture of octahydroisoquinolines.

In the Lewis acid catalyzed cyclizations the reaction path is less clear. It is known that metal halides are not active in so-called Lewis acid catalyzed reactions of olefins in the absence of a co-catalyst[25]. Therefore, an explanation for the activation of the enamide double bond in the presence of a Lewis acid might be protonation by a superacid which is formed when trace amounts of water or triflic acid are present in the reaction mixture. Another possibility for the formation of the *N*-acyliminium ion is attack of the Lewis acidic cation at the β-carbon atom of the enamide double bond. Cyclization with the olefinic double bond affords the octahydroisoquinolines after proton elimination and isomerization, combined with protonolysis of the alkyl−boron[26] or alkyl−metal bond.

Synthesis of 1-Benzyl-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline and Isomers from *N*-[2-(Cyclohex-1-enyl)ethyl]formamide

According to a procedure described by Lukanov et al.[6b] various 2-formyl-1,2,3,4-tetrahydroisoquinolines can be prepared by an acid-catalyzed cyclization reaction of *N*-formyl-2-phenylethylamines and different aldehydes. The reaction proceeds via the *N*-formyliminium ion which is formed after elimination of water. In order to study the possibility of the 1-benzyloctahydroisoquinoline formation by this method we synthesized *N*-[2-(cyclohex-1-enyl)ethyl]formamide (**11**) by reaction of the amine with ethyl formate. The formamide prepared thus was treated with phenylacetaldehyde in a 4:1 mixture of acetic acid and trifluoroacetic acid (Scheme 4).

Scheme 4. Synthesis of isomeric octahydroisoquinolines **6** from *N*-[2-(cyclohex-1-enyl)ethyl]formamide



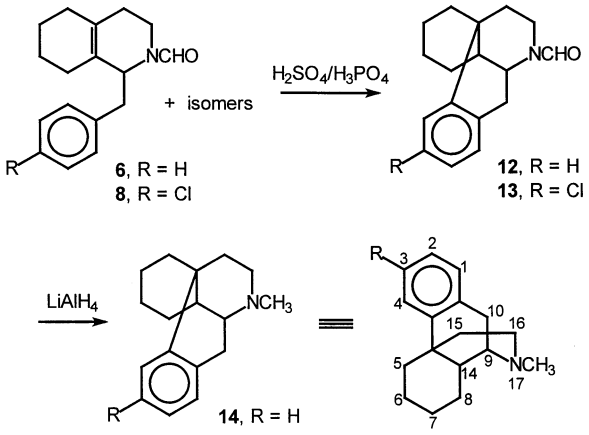
The best results were obtained when the reaction was carried out with an excess (1.1 to 1.3 equivalents) of aldehyde. The formation of the isoquinoline was less selective than from enamide **1** and compound **6** was isolated in 34% yield. Again four isomers were obtained in the same ratio as observed for the mixture formed after the 9-BBN triflate catalyzed cyclization of enamide **1**.

We also investigated the cyclization of **11** in the presence of 9-BBN triflate or CF_3SO_3H in boiling toluene. However, no formation of octahydroisoquinolines was observed on TLC with either of the two acids.

Synthesis of Morphinans

To demonstrate the viability of the *N*-formyloctahydroisoquinolines as starting compounds for the synthesis of *N*-formylmorphinans we applied the acid-catalyzed cyclization of the octahydroisoquinolines to the morphinan skeleton, known as the Grewe cyclization[27]. We found that for these isoquinolines the cyclization is best carried out in a mixture of concentrated sulfuric acid and concentrated phosphoric acid (1:1 in volume) at moderate temperatures. The Grewe cyclization was first performed with the isomeric mixture of unsubstituted *N*-formyl octahydroisoquinolines (**6**, Scheme 5). After 3 h at room temperature the conversion of the isoquinoline was complete. No traces of starting material could be observed with TLC, indicating that all isomers of the octahydroisoquinoline were converted. It is to be expected that acid-catalyzed isomerization takes place under the reaction conditions.

Scheme 5. Synthesis of morphinans from the isomeric octahydroisoquinolines



The morphinan was isolated by column chromatography. TLC showed one spot, but GC analyses indicated the presence of two side products, both in quantities of about 5%. The mixture was further analysed by GC-MS. The major product (90%) shows the appearance of prominent peaks at *m/z* 255, 183, 141, and 73, which are characteristic for a morphinan structure[28]. The other two products also have a molecular mass of 255 and they probably possess an isomorphinan and an apomorphine structure. ^{1}H NMR in $CDCl_3$ at room temperature showed the presence of two *N*-formyl rotamers in the main product in a ratio of 1:1. Reduction of the *N*-formyl group with lithium aluminium hydride gave the *N*-methylmorphinan (**14**, Scheme 5).

The *p*-chlorooctahydroisoquinoline (**8**) was also converted into the morphinan (Scheme 5). At room temperature no conversion was observed, obviously due to deactivation caused by the chloro substituent in the benzene ring. However, at 50°C the *p*-chloroisoquinoline was fully converted in 2 h. In this reaction a crude octahydroisoquinoline was used as starting compound. The yield of isolated morphinan was 35%, based on the *p*-chloro-substituted *N*-styryl enamide. Again two *N*-formyl rotamers were formed with a ratio of 1:1 in $CDCl_3$. The mixture was analyzed by GC and it showed again three compounds in a ratio of 90:5:5. The major component was 3-chloro-*N*-formylmorphinan (**13**) according to the mass spectrum and the NMR spectra.

Cyclization of the *m*-chlorooctahydroisoquinoline **10** in H_2SO_4/H_3PO_4 at 50°C gave a product which was isolated in 57% yield. GC analyses of the product showed that two major components (together 95%) were present in a ratio of 60:40. The mass spectra of both compounds were almost identical and had the characteristic pattern of a morphinan structure. From this, in combination with NMR data, we concluded that 2-chloro-*N*-formylmorphinan as well as 4-chloro-*N*-formylmorphinan were formed in the Grewe cyclization.

In summary, we have shown that substituted *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-formyl-2-phenylethenamines can be converted into the corresponding 1-benzyloctahydroisoquinolines under relatively mild conditions and with catalytic amounts of acid. Lewis and Brønsted acids were both studied and the best results with homogeneous catalysts were obtained with 9-BBN triflate and CF_3SO_3H. With these acids a complete conversion of the enamide was observed with 20 mol-% of catalyst. In addition we showed that the heterogeneous acid $H_3PW_{12}O_{40}$ on silica gel is an active catalyst in this type of cyclization reaction. In all cases a mixture of isomeric octahydroisoquinolines was formed with the 1,2,3,4,5,6,7,8-octahydroisoquinoline as major component. Finally, this mixture of isomeric octahydroisoquinolines was easily converted into the corresponding morphinan by the Grewe cyclization.

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Experimental Section

The *N*-[2-(cyclohex-1-enyl)ethyl]-*N*-styrylformamides were prepared according to known methods[11][12]. $AlCl_3$, $AlEtCl_2$ (1.8 M solution in toluene), $TiCl_4$, and 9-BBN triflate (0.5 M solution in hexanes) were purchased from Aldrich. $BF_3{-}C_4H_{10}O$, $Sc(CF_3SO_3)_3$, and BBr_3 (1 M solution in dichloromethane) were purchased from Fluka. $AgCF_3SO_3$ was purchased from Acros. $Yb(CF_3SO_3)_3$ was prepared from Yb_2O_3 and CF_3SO_3H[29]. The other triflates were prepared in situ from the halides by reaction with silver triflate. Nafion-H was purchased from Fluka. The heteropoly acid $H_3PW_{12}O_{40}/SiO_2$ was prepared by impregnating Aerosil 200 with an aqueous solution of $H_3PW_{12}O_{40}$ followed by drying in a rotary evaporator. Prior to use the HPA was pre-treated at 130°C/0.3 Torr for 1.5 h. Toluene, dichloromethane and tetrahydrofuran of analytical grade were commercial products and were stored over MS 3 Å. Prior to use the solvents were distilled from sodium (toluene and tetrahydrofuran) or CaH_2 (dichloromethane). All reactions were performed under nitrogen.

Mass spectra were determined using a VG70-SE spectrometer. − ^{1}H- (400 MHz) and ^{13}C- (101 MHz) NMR spectra were recorded with a Varian VXR-400S spectrometer with $CDCl_3$ as solvent and tetramethylsilane as reference. − Infrared spectra were recorded using a Beckman IR-4210 spectrophotometer or a Perkin Elmer Spectrum 1000 FT-IR spectrophotometer. − Gas chromatography was performed using a Packard 427 gas chromatograph with a CP Sil5 GB (10 m × 0.53 mm) column. − Samples for GC-MS were chromatographed with a CP Sil 5 GB (25 × 0.25 mm) column and analyzed with a VG70-SE spectrometer. − Column chromatography was performed on silica gel (Merck Kieselgel 60, particle size 63−200 μm) and TLC on deactivated silica gel (0.25 mm, Merck F_{254}).

Cyclization of Substituted N-[2-(Cyclohex-1-enyl)ethyl]-N-styrylformamides. − General Procedure for 9-BBN Triflate Catalyzed Reactions: The enamide was dissolved in toluene (25 ml per mmol of enamide) and the 9-BBN triflate solution was added by syringe. The mixture was stirred in a thermostated flask (50 ml) at 25°C or higher temperatures (less than one equivalent of catalyst). The conversion of the enamide was monitored by TLC with dichloromethane/methanol (95:5) as eluent. At complete conversion a saturated solution of $NaHCO_3$ was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with toluene. The combined organic layers were washed with water and a saturated solution of NaCl. After drying (Na_2SO_4), the solvent was evaporated under reduced pressure. The mixture of isomeric octahydroisoquinolines was purified by column chromatography with dichloromethane/methanol (97:3) as eluent.

1-Benzyl-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**6**) *and Its Isomers:* Compound **6** and its isomers were prepared according to the general procedure with one equivalent of 9-BBN triflate. Enamide **1** (2.10 g, 8.24 mmol) yielded 1.52 g (5.95 mmol, 72%) of octahydroisoquinoline as an oil. − ^{1}H NMR (major isomer): rotamer ratio: 65:35 (value for the minor rotamer in parentheses): δ = 1.65 (m_c, 4 H, 2 × CH_2 in ring), 1.90 (m_c, 4 H, 2 × allylic CH_2), 2.20 (2.05) (m_c, 2 H, CH_2CH_2N in ring), 2.90 (m_c, 3 H, CH_2N and one benzylic proton), 3.31 (dd) and (3.63) (d) [1 H, 1 benzylic proton, J = 10.1 Hz (minor rotamer), J = 6.3 Hz, J = 13.3 Hz (major rotamer)], 4.38 (dd) and (4.72) (m_c) [1 H, CHN, J = 6.9 Hz, J = 13.1 Hz (major rotamer)], 7.20 (m_c, 5 H, aromatic protons), 7.40 (7.95) (s, 1 H, CHO). − ^{13}C NMR (both rotamers of major isomer): δ = 161.03, 160.85, 138.06, 137.86, 129.54, 129.28, 129.07, 128.74, 128.26, 128.17, 127.80, 126.80, 126.40, 60.73, 53.21, 40.40, 37.31, 36.08, 33.30, 30.88, 30.16, 30.00, 29.67, 27.73, 22.90, 22.79, 22.73. − MS (major isomer); *m/z* (%): 255 (16) [M^+], 226 (13), 164 (100), 136 (61), 108 (37), 91 (63), 79 (23), 65 (26). − High-resolution mass; *m/z*: 255.1622; calcd. for $C_{17}H_{21}NO$ 255.1623. − IR: $\tilde{\nu}$ (neat): 1670 cm^{-1} (C=O).

2-Formyl-1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**7**) *and Its Isomers:* Compound **7** and its isomers were prepared according to the general procedure with one equivalent of 9-BBN triflate. Enamide **2** (325 mg, 1.140 mmol) yielded 217 mg (0.761 mmol, 67%) of octahydroisoquinoline as an oil. − ^{1}H NMR (major isomer): rotamer ratio: 65:35 (value for the minor rotamer in parentheses): δ = 1.65 (m_c, 4 H, 2 × CH_2 in ring), 1.90 (m_c, 4 H, 2 × allylic CH_2), 2,20 (2.04) (m_c, 2 H, CH_2CH_2N in ring), 2.84 (m_c, 3

H, CH_2N and 1 benzylic proton), 3.30 (dd) and (3.56) (d) [1 H, 1 benzylic proton, J = 10.4 Hz (minor rotamer), J = 6.6 Hz, J = 13.3 Hz (major rotamer)], 3.77 (s, 3 H, OCH_3), 4.36 (dd) and (4.69) (m_c) [1 H, CHN, J = 6.7 Hz, J = 13.1 Hz], 6.82 (6.97) [dd, 4 H, aromatic protons, J = 8.5 Hz], 7.39 (7.92) (s, 1 H, CHO). − ^{13}C NMR: both rotamers of major isomer: δ = 161.13, 160.89, 158.44, 158.22, 130.43, 130.24, 129.96, 129.83, 129.71, 128.92, 127.87, 127.77, 114.14, 113.60, 60.87, 55.19, 53.28, 41.95, 40.47, 37.57, 36.31, 33.41, 30.85, 30.15, 29.99, 29.68, 27.72, 27.19, 25.67, 22.89, 22.73. − MS (major isomer); *m/z* (%): 285 (1) [M^+], 178 (23), 164 (100), 121 (82), 91 (18), 77 (20). − High-resolution mass; *m/z*: 285.1722; calcd. for $C_{18}H_{23}NO_2$ 285.1729. − IR: ṽ (neat): 1676 cm^{-1} (C=O).

1-(4-Chlorobenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**8**) *and Its Isomers:* Compound **8** and its isomers were prepared according to the general procedure with one equivalent of 9-BBN triflate. Enamide **3** (128 mg, 0.443 mmol) yielded 66 mg (0.228 mmol, 51%) of octahydroisoquinoline as an oil. − ^{1}H NMR (major isomer): rotamer ratio: 60:40 (value for the minor rotamer in parentheses): δ = 1.65 (m_c, 4 H, 2 × CH_2 in ring), 1.84 (m_c, 4 H, 2 × allylic CH_2), 2.38 (2.02) (m_c, 2 H, CH_2CH_2N in ring), 2.75 (m_c, 3 H, CH_2N and 1 benzylic proton), 3.34 (dd) and 3.61 (d) [1 H, 1 benzylic proton, J = 9.8 Hz (minor rotamer), J = 6.4 Hz, J = 12.8 Hz (major rotamer)],4.36 (dd) and (4.68) (m_c) [1 H, CHN, J = 6.6 Hz, J = 13.3 Hz], 7.24 (7.04) [dd, 4 H, aromatic protons, J = 8.5 Hz], 7.41 (7.90) (s, 1 H, CHO). − ^{13}C NMR: both rotamers of major isomer: δ = 161.07, 160.99, 136.49, 136.33, 132.70, 132.26, 130.81, 130.60, 129.36, 128.88, 128.31, 127.45, 60.53, 53.09, 40.41, 37.83, 36.69, 33.50, 30.80, 30.11, 29.97, 29.58, 27.69, 22.84, 22.72, 22.66. − MS (major isomer); *m/z* (%): 289 (1) [M^+], 207 (5), 164 (100), 136 (16), 91 (7). − IR: ṽ (neat): 1664 cm^{-1} (C=O).

2-Formyl-1-(3-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**9**) *and Its Isomers:* Compound **9** and its isomers were prepared according to the general procedure with one equivalent of 9-BBN triflate. Enamide **4** (603 mg, 2.114 mmol) yielded 317 mg (1.112 mmol, 53%) of octahydroisoquinoline as an oil. − ^{1}H NMR (major isomer): rotamer ratio: 65:35 (value for the minor rotamer in parentheses): δ = 1.67 (m_c, 4 H, 2 × CH_2 in ring), 1.90 (m_c, 4 H, 2 × allylic CH_2) 2.20 (2.01) (m_c, 2 H, CH_2CH_2N in ring), 2.82 (m_c, 3 H, CH_2N and 1 benzylic proton), 3.30 (dd) and (3.66) (d) [1 H, 1 benzylic proton, J = 10.4 Hz (minor rotamer), J = 6.4 Hz, J = 13.1 Hz (major rotamer)], 3.78 (s, 3 H, OCH_3), 4.36 (dd) and 4.72 (m_c) [1 H, CHN, J = 6.7 Hz, J = 13.1 Hz], 6.68 (7.18) (m_c, 4 H, aromatic protons), 7.43 (7.92) (s, 1 H, CHO). − ^{13}C NMR: both rotamers of major isomer: δ = 161.08, 160.93, 159.82, 159.42, 139.60, 139.37, 129.72, 129.05, 127.94, 127.75, 122.00, 121.66, 115.20, 115.11, 111.92, 111.83, 60.58, 55.20, 53.01, 40.45, 38.49, 37.29, 33.39, 30.84, 30.16, 29.99, 29.64, 27.70, 27.43, 22.88, 22.79, 22.71. − MS (major isomer); *m/z* (%): 285 (3) [M^+], 207 (5), 164 (100), 136 (15), 91 (15). − High-resolution mass; *m/z*: 285.1714; calcd. for $C_{18}H_{23}NO_2$ 285.1729. − IR: ṽ (neat): 1664 cm^{-1} (C=O).

1-(3-Chlorobenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**10**) *and Its Isomers:* Compound **10** and its isomers were prepared according to the general procedure with one equivalent of 9-BBN triflate. Enamide **5** (713 mg, 2.468 mmol) yielded 386 mg (1.335 mmol, 54%) of octahydroisoquinoline as an oil. − ^{1}H NMR (major isomer): rotamer ratio: 60:40 (value for the minor rotamer in parentheses): δ = 1.68 (m_c, 4 H, 2 × CH_2 in ring), 1.85 (m_c, 4 H, 2 × allylic CH_2), 2.19 (2.02) (m_c, 2 H, CH_2CH_2N in ring), 2.85 (m_c, 3 H, CH_2N and 1 benzylic proton), 3.36 (dd) and (3.64) (d) [1 H, 1 benzylic proton, J = 10.2 Hz (minor rotamer)], 4.38 (dd) and (4.70) (m_c) [1 H, CHN, J = 6.3 Hz, J = 13.2 Hz], 7.10 (m_c, 4 H, aromatic protons), 7.45 (7.92) (s, 1 H, CHO). − ^{13}C NMR: both rotamers of major isomer: δ = 161.00, 140.12, 139.94, 134.48, 133.85, 129.96, 129.59, 129.41, 129.16, 127.69, 127.60, 127.45, 127.02, 126.60, 60.37, 53.02, 40.35, 38.15, 37.02, 33.48, 30.79, 30.11, 29.97, 29.56, 27.68, 22.85, 22.71, 22.65. − MS (major isomer); *m/z* (%): 164 (100) [M^+ − benzyl], 136 (20), 108 (7), 91 (8), 79 (5). − IR: ṽ (neat): 1666 cm^{-1} (C=O).

Cyclization of N-[2-(Cyclohex-1-enyl)ethyl]-N-styrylformamide (**1**) *Catalyzed by Triflates Prepared in situ. − General Procedure:* The boron or metal halide was dissolved in the appropriate solvent and added to a solution of silver triflate. Precipitation of the silver halide formed took place almost immediately. After 5 min stirring at room temperature, enamide **1** was added and the temperature was raised to the value indicated in Table 1. Every 15 min the reaction mixture was analyzed by TLC. At complete conversion of **1** the mixture was allowed to cool and was filtered. The further work-up procedure was similar to the procedure for 9-BBN triflate catalyzed reactions.

Cyclization of N-[2-(Cyclohex-1-enyl)ethyl]-N-styrylformamide (**1**) *in CH_3COOH and CF_3COOH:* Compound **1** (233.4 mg, 0.915 mmol) was dissolved in CH_3COOH/CF_3COOH (5 ml, volume ratio 8:2) and the mixture was heated under reflux for 2 h (complete conversion of **1** observed with TLC). After cooling, water (50 ml) was added and the mixture was extracted with chloroform (3 × 25 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (75 ml), water, a saturated solution of NaCl (75 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the product was purified by column chromatography (dichloromethane/methanol, 97:3) to give **6** (140.0 mg, 0.549 mmol, 60%) as an oil.

Cyclization of N-[2-(Cyclohex-1-enyl)ethyl]-N-styrylformamide (**1**) *Catalyzed by Triflic Acid. − Typical Procedure:* Compound **1** (522 mg, 2.047 mmol) was dissolved in 28 ml of toluene and 7.2 ml of a 0.057 M solution of triflic acid in dichloromethane (0.2 molar equivalents) were added. The mixture was boiled under reflux for 16 h. After cooling, the mixture was washed with a saturated solution of $NaHCO_3$ (30 ml). The aqueous layer was extracted with toluene (2 × 20 ml). The combined organic layers were washed with water (75 ml), a saturated solution of NaCl, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The octahydroisoquinoline was purified by column chromatography (dichloromethane/methanol, 97:3) to yield 426 mg (1.671 mmol, 82%) of **6** as an oil.

Cyclization of N-[2-(Cyclohex-1-enyl)ethyl]-N-styrylformamide (**1**) *Catalyzed by $H_3PW_{12}O_{40}$ on SiO_2. − Typical Procedure:* Compound **1** (500 mg, 1.961 mmol) was dissolved in 25 ml of toluene and $H_3PW_{12}O_{40}$ on silica gel (250 mg) was added. The reaction mixture was heated under reflux for 20 h. After cooling, the catalyst was filtered off and washed thoroughly with toluene. Toluene was evaporated and the crude product was purified by column chromatography (dichloromethane/methanol, 97:3). This gave 328 mg (1.286 mmol, 66%) of **6** as an oil.

N-[2-(Cyclohex-1-enyl)ethyl]formamide (**11**): 2-(Cyclohex-1-enyl)ethylamine (8.98 g, 71.8 mmol) was dissolved in 50 ml of ethyl formate and the mixture was stirred for 65 h at room temperature. The excess of ethyl formate was removed under reduced pressure and the residue was distilled at 2 Torr. This gave 7.20 g (47.1 mmol, 66%) of **11** boiling at 141°C.

Synthesis of 1-Benzyl-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**6**) *and Isomers from N-[2-(Cyclohex-1-enyl)ethyl]formamide: N*-[2-(cyclohex-1-enyl)ethyl]formamide (**11**, 993 mg, 6.49 mmol)

and phenylacetaldehyde (860 mg, 7.17 mmol) were added to a mixture of acetic acid and trifluoroacetic acid (6.5 ml, 4:1). The mixture was heated under reflux for 3 h. Water (200 ml) was added and the mixture was extracted with dichloromethane (4 × 75 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by column chromatography. This gave 566 mg (2.22 mmol, 34%) of **6**.

Cyclization of the N-Formyloctahydroisoquinolines to the Morphinan Skeleton. − General Procedure: The isomeric mixture of octahydroisoquinolines was dissolved in a 1:1 mixture of concentrated sulfuric acid and concentrated phosphoric acid (20 ml per mmol of octahydroisoquinoline). When a complete conversion was observed with TLC, water was added to the reaction mixture. The aqueous phase was extracted five times with chloroform. The combined organic layers were washed with a saturated solution of $NaHCO_3$, water, a saturated solution of NaCl, and dried (Na_2SO_4). Chloroform was removed under reduced pressure and the morphinan was purified by column chromatography with dichloromethane/methanol (96:4) as eluent.

N-Formylmorphinan (**12**): Compound **12** was prepared according to the general procedure. After 3 h of reaction at room temperature, the conversion of **6** was complete. Octahydroisoquinoline **6** (2.05 g, 8.04 mmol) yielded 1.16 g (4.55 mmol, 57%) of **12** as an oil. − ^{1}H NMR: rotamer ratio 50:50: δ = 1.38 (m_c, 8 H, 5-H, 5′-H, 6-H, 6′-H, 7-H, 7′-H, 8-H, 8′-H), 1.67 (m_c, 2 H, 15-H, 15′-H), 2.42 and 2.46 [m_c, 1 H, 14-H, J = 4.1 Hz], 2.48 (m_c) and 2.70 (d) [1 H, 10-H, J = 3.8 Hz, J = 18.7 Hz], 2.75 (d) and 3.22 (dd) [1 H, 10′-H, J = 6.6 Hz, J = 17.9 Hz], 2.95 (ddd) and 3.28 (m_c) [1 H, 16-H, J = 3.7 Hz], 3.25 (m_c) and 3.70 (m_c) (1 H, 16′-H), 4.17 (dd) and 4.66 (m_c) [1 H, 9-H, J = 5.0 Hz], 7.20 (m_c, 4 H, 1-H, 2-H, 3-H, 4-H), 8.00 and 8.16 (s, 1 H, CHO). − ^{13}C NMR: both rotamers: δ = 160.66, 160.59, 138.81, 138.75, 136.01, 135.49, 128.25, 128.12, 127.01, 126.86, 126.12, 126.04, 125.61, 125.57, 53.72, 46.35, 45.13, 43.86, 42.16, 41.09, 40.94, 38.64, 38.49, 36.42, 36.32, 34.88, 33.06, 31.65, 26.33, 26.26, 26.21, 26.18, 21.86, 21.82. − MS; *m/z* (%): 255 (27) [M^+], 183 (19), 141 (38), 73 (100). − High-resolution mass; *m/z*: 255.1630; calcd. for $C_{17}H_{21}NO$ 255.1623. − IR ṽ (neat): 1678 cm^{-1} (C=O).

3-Chloro-N-formylmorphinan (**13**): Compound **13** was prepared from crude compound **8** according to the general procedure. After 2 h of reaction at 50°C, the conversion of **8** was complete. Crude **8** (250 mg) yielded 88.3 mg (0.306 mmol, 35% based on pure enamide **3**) of **13** as an oil which solidified on standing. − ^{1}H NMR: rotamer ratio 50:50: δ = 1.30 (m_c, 5-H, 5′-H, 6-H, 6′-H, 7-H, 7′-H, 8-H, 8′-H), 1.68 (m_c, 2 H, 15-H, 15′-H), 2.36 and 2.40 (m_c, 1 H, 14-H), 2.44 (m_c) and 2.66 (d) [1 H, 10-H, J = 4.0 Hz, J = 18.5 Hz], 2.73 (d) and 3.19 (dd) [1 H, 10′-H, J = 6.0 Hz, J = 18.2 Hz], 2.92 (ddd) and 3.30 (m_c) [1 H, 16-H, J = 3.8 Hz, J = 4.6 Hz, J = 13.2 Hz], 3.21 (m_c) and 3.72 (m_c) [1 H, 16′-H, J = 5.2 Hz], 4.18 (dd) and 4.66 (m_c) [1 H, 9-H, J = 3.7 Hz], 7.05 (dd, 1 H, 4-H, J = 3.9 Hz], 7.14 [m_c, 1 H, 1-H, J = 1.2 Hz, J = 2.1 Hz], 7.28 [m_c, 1 H, 2-H, J = 2.1 Hz], 8.00 and 8.16 (s, 1 H, CHO). − ^{13}C NMR: both rotamers: δ = 159.67, 159.62, 139.99, 139.41, 133.57, 132.98, 131.73, 131.57, 128.65, 128.52, 125.42, 125.34, 124.74, 124.69, 52.37, 45.03, 43.80, 42.51, 40.87, 39.91, 39.67, 37.91, 37.75, 35.34, 35.24, 33.75, 31.55, 30.14, 25.30, 25.14, 25.12, 25.07, 20.81, 20.78. − MS: 289 (14) [M^+], 207 (10), 175 (13), 73 (100). − High-resolution mass; *m/z*: 289.1233; calcd. for $C_{17}H_{20}ClNO$ 289.1232. − IR: ṽ (neat): 1668 cm^{-1} (C=O).

N-Methylmorphinan (**14**): A solution of *N*-formylmorphinan (**12**, 656 mg, 2.573 mmol) in 25 ml of anhydrous (MS 4Å) diethyl ether was added dropwise within 15 min to a suspension of lithium aluminium hydride (122 mg, 3.211 mmol) in 35 ml of diethyl ether. After 1 h, a 15% solution of NaOH (50 ml) was added, followed by addition of water (50 ml) to dissolve all salts. The aqueuos layer was separated and extracted with diethyl ether (2 × 50 ml). The combined organic layers were washed with water (150 ml) and a saturated solution of NaCl (150 ml). After drying (Na_2SO_4), the ether was removed under reduced pressure to yield 531 mg (2.203 mmol, 86%) of **14** as an oil which solidified on standing. An analytically pure sample was obtained by column chromatography (eluent: CH_2Cl_2/MeOH/NH_4OH, 93:7:0.5). − ^{1}H NMR[30]: δ = 1.40 (m_c, 8 H, 5-H, 5′-H, 6-H, 6′-H, 7-H, 7′-H, 8-H, 8′-H), 1.75 [ddd, 1 H, 15-H, J = 4.9 Hz, J = 12.6 Hz], 1.85 [dt, 1 H, 15′-H, J = 3.1 Hz, J = 12.6 Hz], 2.05 [ddd, 1 H, 14-H, J = 3.2 Hz, J = 12.3 Hz], 2.40 (s, 3 H, NCH_3), 2.44 [m_c, 2 H, 16-H, 16′-H, J = 1.8 Hz, J = 4.7 Hz, J = 11.9 Hz], 2.65 [dd, 1 H, 10-H, J = 5.8 Hz, J = 18.2 Hz], 2.82 [dd, 1 H, 9-H, J = 3.2 Hz, J = 5.7 Hz], 3.03 [d, 1 H, 10′-H, J = 18.4 Hz], 7.17 (m_c, 4 H, 1-H, 2-H, 3-H, 4-H). − ^{13}C NMR: δ = 139.34, 136.70, 126.68, 125.18, 124.32, 124.30, 56.99, 46.20, 44.47, 41.79, 41.15, 36.00, 35.50, 25.73, 25.60, 23.21, 21.14. − MS; *m/z* (%): 241 (100) [M^+], 184 (27), 173 (37), 150 (78), 141 (50), 115 (27), 59 (24).

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