Stereochemical aspects of the “*tert*-amino effect”. Controlled cycloreversion of pyrrolo[1,2-*a*]quinoline derivatives and enantioselective introduction of two new optically active centers

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Abstract. Conversion of 2-vinyl-*N,N*-dialkylanilines **2**, **3** (**a–o**) to pyrrolo[1,2-*a*]quinolines **4–13** (**a–o**) occurs via an irreversible suprafacial 1,5 hydrogen shift to a dipolar intermediate which subsequently cyclizes. In refluxing acetonitrile in the presence of zinc chloride, pyrrolo[1,2-*a*]quinoline derivatives having two electron-withdrawing groups (EWG) at C(4) show cycloreversion. Because of the longer lifetime of the stabilized dipolar intermediate, epimerization at C(4) and/or C(3a) can occur. Epimerization at C(3a) is prevented by a large methoxymethyl substituent at this stereocenter. Since the initial 1,5 hydrogen shift is irreversible, the stereochemistry at C(5) remains unchanged. In product **4j**, two new optically active centers at C(5) and C(4) were introduced in a controlled manner and at C(3a) “self-reproduction of chirality” was obtained without the use of auxiliary chiral reagents.

Introduction

The formation of heterocycles by ring closure of *ortho*-substituted tertiary anilines (the “*tert*-amino effect”) has been reviewed^{1,2}. Depending on the structure of the *ortho* substituent, three different modes of reaction are observed. The rate-determining step is either a 1,5 or a 1,6 hydrogen shift, to give two different types of dipolar intermediates that subsequently undergo (electro)cyclization to give 6- and 5-membered rings, respectively³. When the *ortho* substituent is a vinyl group, 6-membered rings are formed in the case that two electron-withdrawing groups are present at the β -carbon atom of the vinyl moiety (Scheme 1). Previously, we have shown that the rate-determining step

for the formation of the 6-membered ring is an intramolecular suprafacial 1,5 hydrogen shift to a unique helical dipolar intermediate⁴. The transfer of the hydrogen atom creates⁵ a new optically active center at C(5) when $R^2 \neq H$, and the original optically active center C(3a) shows “self-reproduction of chirality”⁶ upon cyclization. In addition to this enantioselectivity, we found that most reactions are also regioselective. When the *N,N*-dialkyl group is not symmetrical, electron-donating substituents R^2 stabilize the iminium group formed upon hydrogen transfer⁷. The R^2 substituent will, therefore, favorably end up at the bridgehead carbon atom C(3a) in the ring-closed products. The rate of formation of the dipolar intermediate is very much dependent on the polarity of the solvent. This can be explained by the

Scheme 1

fact that the dipolar intermediate formed upon the 1,5 hydrogen shift is stabilized in (more) polar solvents. In 1-butanol, the reaction proceeds about 100 times faster than in toluene⁴.

In the present paper, we show that the dipolar intermediate is stabilized by zinc chloride in refluxing acetonitrile, and that cycloreversion of cyclized products takes place. The consequences of the increased lifetime of the dipolar intermediate on the stereo- and regioselectivity are discussed. The introduction of two different electron-withdrawing groups (EWG) creates a prochiral center at the β -carbon atom of the vinyl moiety (Scheme 1). The stereochemistry of this new center and its dependence on the lifetime of the dipolar intermediate are also discussed. The results are in line with steric-energy calculations on the diastereomers.

Results and discussion

Synthesis of the 2-vinyl-*N,N*-dialkylanilines

The 2-vinyl-*N,N*-dialkylanilines **2a–j** and **3f,h,j** were synthesized via a Knoevenagel reaction of the alkyl cyanomalonate esters with the corresponding aldehydes or ketones **1** in toluene (Chart 1)^{5,7}.

Chart 1

Knoevenagel condensation of aldehydes **1** at room temperature yielded exclusively *E*-isomers, but ketones **1f,h,j** required elevated temperatures and gave *E/Z* mixtures⁸. In Table I, the results of the Knoevenagel condensations are summarized. *E*-isomers **2** and *Z*-isomers **3** could not be separated. In some cases, the reaction was slow and cyclization accompanied the condensation.

Thermal isomerization of the 2-vinyl-*N,N*-dialkylanilines

Ring closure reactions of the 2-vinyl-*N,N*-dialkylanilines **2a–j** and **3f,h,j** were performed in refluxing 1-butanol,

Table I Results of Knoevenagel condensations of **1a–j**^a.

Starting compd.	Time (h)	Yield (%)	Products ^b
1a	57	70	2a
1b	48	86	2b
1c	19	64	2c
1d	2	85	2d
1e	2	90	2e
1f	24	45	2f and 3f (2:1)
1g	14	83	2g
1h	72	40	2h and 3h (2:1)
1i	22	77	2i
1j	24	50	2j and 3j (1:1)

^a All condensations took place in toluene at room temperature except for **1f** and **1h** (70°C) and **1j** (110°C, reflux). ^b M.p. and spectral data of **2** and **3** are given in Table VI.

toluene, or in refluxing acetonitrile in the presence of zinc chloride. Cyclization of the *E*-isomers **2a–e** ($R^1 = R^2 = H$), for 4 to 5 h in refluxing acetonitrile in the presence of zinc chloride yielded exclusively pyrrolo[1,2-*a*]quinolines **4a–e** (Table II, Chart 2).

Table II Reaction times and ratios of products obtained from *E*-isomers **2a–e** under different conditions.

Starting compd.	Solvent (reflux)	Ratio (4/5) ^a	Reaction time
2a	CH ₃ CN/ZnCl ₂	100/0	4 h
	1-butanol	100/0	7 h
	toluene	100/0	2 d
2b	CH ₃ CN/ZnCl ₂	100/0	4 h
	1-butanol	80/20	7 h
	toluene	70/30	2 d
2c	CH ₃ CN/ZnCl ₂	100/0	4 h
	1-butanol	80/20	7 h
	toluene	80/20	2 d
2d	CH ₃ CN/ZnCl ₂	100/0	5 h
	1-butanol	75/25 ^b	3 d
	toluene	67/33	8 d
2e	CH ₃ CN/ZnCl ₂	100/0	5 h
	1-butanol	60/40	3 d
	toluene	70/30	8 d

^a All conversions were $\geq 95\%$. ^b Products **4e** and **5e**, formed by transesterification, were also obtained in a 75:25 ratio, respectively.

Cyclization of **2** and **3** in refluxing 1-butanol or toluene is slower than in refluxing acetonitrile in the presence of zinc chloride. Derivative **2a** ($R^3 = \text{CO}_2\text{Me}$) also gave, upon cyclization in refluxing toluene and 1-butanol, exclusively **4a**³. However, in these two solvents, derivatives **2b–e** gave mixtures of **4** and their diastereomers **5**. The difference between **4** (bridgehead substituent and ester moiety are *cis* related) and **5** (bridgehead substituent and ester moiety are *trans* related) is the stereochemistry at carbon atom C(4). The structure of **4b** has been established previously by X-ray analysis⁴. Diastereomers **4** and **5** could not be separated and showed similar peaks in the ¹H- and ¹³C-NMR spectra. The characteristic difference between all diastereomers **4** and **5** is the 0.1 ppm higher chemical shift of the doublet of H(9) for **5** in the ¹H NMR spectra.

We found that, in refluxing toluene or 1-butanol, ring clo-

Chart 2

sure is too slow to avoid *E/Z* isomerization of **2** to **3**. The absorptions of the *Z*-isomers **3b** and **3d** were present in the ¹H NMR spectra when conversion to the cyclized products was not complete (Table VI). Cyclization of the dipolar intermediate, formed upon 1,5 hydrogen shift in the *Z*-isomers **3b–e**, consequently gives derivatives **5b–e**. Surprisingly, when the reaction of **2b** in refluxing acetonitrile in the presence of zinc chloride was stopped after 1.3 h, the conversion was 42%, and compounds **3b/4b/5b** were present in a 1/12/2 ratio. (The same result was obtained after 8-days reaction at room temperature.) After another 2.7 h refluxing of this mixture in acetonitrile in the presence of zinc chloride, however, only **4b** was obtained (Table II). These experiments show *E/Z* interconversion of **2** and **3** in acetonitrile in the presence of zinc chloride and suggest conversion of **5** (*trans*) into **4** (*cis*) under the influence of zinc chloride. This was confirmed by quantitative conversion of a 3:1 mixture of **4d** and **5d** into **4d**, in refluxing acetonitrile in the presence of zinc chloride. A 1:1 *E/Z* mixture of **2d** and **3d**⁹ also yielded quantitatively **4d**, after 5-h refluxing in acetonitrile in the presence of zinc chloride. We can explain this result by assuming that the chelating Lewis acid, zinc chloride, coordinates to the negative pole of the dipolar intermediate, which is formed upon 1,5 hydrogen shift (Scheme 1). This will extend the lifetime to such an extent that, ultimately, the thermodynamically favored products **4a–e** will be formed. Derivatives **5** (*trans*)

can be converted to **4** (*cis*) via the dipolar intermediate either by stereomutation of the negative pole, which ultimately gives epimerization at C(4), or by interconversion of the helix that gives epimerization at C(3a) to give **10** (also *cis*), which is the enantiomer of **4** when R¹ = H. For derivatives **4a–e** where R¹ = R² = H, these two pathways can not be distinguished.

The assumption that *cis* compounds **4** (R¹ = R² = H) are, in fact, thermodynamically more stable diastereomers is supported by the steric energy difference of almost 5 kcal/mol calculated for the *cis* and *trans* derivatives **4b** and **5b** (Table III). An energy difference of 5 kcal/mol means that, in the thermodynamic product ratio, derivative **5b** will be present at less than 0.1%.

Cycloreversion has, thus far, not been observed for this type of compound; zinc-chloride-induced cycloreversion might be a suitable tool for selectively controlling stereochemistry at C(4). In order to understand the consequences of the longer lifetime of the dipolar intermediate on the enantio- and regioselectivity of these reactions, we first studied the more simple dicyano derivatives **4k–o**, because they have two identical (cyano) groups at C(4). We first investigated these model compounds because the energy difference for the two possible extra diastereomers, when R³ at C(4) is an ester moiety, might significantly determine the ultimate product ratio.

Table III Relative steric energies for diastereomers of cyclic ethyl ester cyano derivatives^{a,b,c}.

Substituents			Diastereomers			
	R ¹	R ²	4	5	10	13
b	H	H	0	4.7	0	4.7
f	CH ₃	H	1.3	10.4	0	2.8
g	H	CH ₃	0.1	0.0	0.1	0.0
h	CH ₃	CH ₃	0	3.2	3.3	3.4
i	H	CH ₂ OCH ₃	0	4.2	0	4.2
j	CH ₃	CH ₂ OCH ₃	0	4.3	3.5	3.9

^a Energy differences in kcal/mol. ^b Energies relative to lowest energy diastereomer of a set of substituents. ^c R³ = CO₂Et.

Lewis-acid-catalyzed cycloreversion of cyclic dicyano derivatives

Reaction of dicyano derivative **4k** (R¹ = CH₃, R² = H, R³ = CN), in refluxing acetonitrile in the presence of zinc chloride for 24 h gave diastereomers **4k** and **10k** (R¹ = CH₃, R³ = CN) in a 3:2 product ratio⁹. From this experiment, we concluded that, after cycloreversion, interconversion of the helical dipolar intermediate takes place with epimerization at C(3a) upon subsequent cyclization. All derivatives formed upon epimerization at C(3a) in refluxing acetonitrile in the presence of zinc chloride, with R¹ = CH₃, exhibit a high-field shift for the CH₃ doublet of 0.2 ppm in the ¹H NMR spectrum¹⁰.

From the previous experiments, it is not clear whether the 1,5 hydrogen shift is also reversible. The optically active derivative **6o**⁵ [with a hydrogen atom at C(3a) and a C(1)

center bearing the R² = CH₂OCH₃ group] may be used to answer this question. If the 1,5 hydrogen shift is reversible in refluxing acetonitrile in the presence of zinc chloride, then alkene **2o** will be formed. From previous experiments by Nijhuis et al.⁷, we know that upon cyclization of **2o**, the derivatives **4o**, **6o** and **8o** will be formed in a 33:35:6 yield ratio. After reacting **6o** in refluxing acetonitrile in the presence of zinc chloride for one night, we observed, however, a 1:1 mixture of **6o** and **12o**¹¹. Product **12o** is formed upon cycloreversion of **6o** to the dipolar intermediate, followed by interconversion of the helix, to give, ultimately upon cyclization, epimerization at C(3a)¹⁰. The stereochemistry of derivative **12o** was confirmed by ¹H NOE spectroscopy (Chart 3)¹². The same epimerizations at C(3a) were obtained for derivatives **6n**⁵ and **8o**⁵. Therefore, the stereochemistry at C(5) is determined by the initial 1,5 hydrogen shift and is retained upon cycloreversion and cyclization.

From these experiments, we conclude that the 1,5 hydrogen shift is irreversible and that epimerization at C(3a) takes place when the bridgehead atom substituent is a hydrogen atom.

The following experiments were performed in order to investigate whether interconversion of the helical dipolar intermediate with subsequent epimerization at C(3a) can be prevented when larger R² substituents are attached to this stereogenic carbon atom. The optically active derivative **4l** (R¹ = H, R² = CH₃, R³ = CN) racemized to a 1:1 mixture of **4l** and its enantiomer **10l** after refluxing for 6 h in acetonitrile in the presence of zinc chloride, as was shown by the disappearance of the optical rotation and by ¹H NMR spectroscopy with chiral shift reagents¹³. However, epimerization at C(3a) was not observed for **4m** (R¹ = R² = CH₃). This aberration is explained by the calculated large steric

Chart 3

energy difference between **4m**, and the diastereomer **10m** expected upon C(3a) epimerization (*vide infra*). The reaction of optically active **4n** ($R^1 = H$, $R^2 = CH_2OCH_3$) in acetonitrile in the presence of zinc chloride also showed no epimerization to **10n** after 24 h, as shown by 1H NMR spectroscopy with chiral shift reagents¹³. The bulkiness of the methoxymethyl group obviously prevents interconversion of the helical dipolar intermediate and, consequently, prevents epimerization at C(3a). We found that **4o** ($R^1 = CH_3$, $R^2 = CH_2OCH_3$) also did not give diastereomer **10o** after 24 h refluxing in acetonitrile in the presence of zinc chloride. In the latter case, epimerization is prevented by the bulkiness of the methoxymethyl group as well as by the large steric energy difference between diastereomers **4o** and **10o**. In order to understand the different product distributions upon changing the bridgehead substituent R^2 and/or R^1 , we have calculated the steric energy differences between the cyclic dicyano diastereomers **4k,m,o** and **10k,m,o** ($R^1 = CH_3$). Derivatives **4k** and **10k**, bearing a hydrogen atom at C(3a), exhibit a difference of less than 1 kcal/mol. This agrees well with the presence of both diastereomers in the equilibrium mixture. Derivatives **4m** and **4o** and their diastereomers **10m** and **10o**, bearing more bulky substituents, differ by about 5 kcal/mol. This means that the product ratios for **4m/10m** and **4o/10o** are about 99.9/0.1. The theoretically formed 0.1 percent is not detectable with 1H NMR spectroscopy. The observed results are in good agreement with the calculated data (Table IV).

Table IV Relative steric energies for cyclic dicyano diastereomers **10k-o**^{a,b,c}.

Derivatives	R^1	R^2	ΔE^a
10k	CH ₃	H	0.7
10l	H	CH ₃	0
10m	CH ₃	CH ₃	4.6
10n	H	CH ₂ OCH ₃	0
10o	CH ₃	CH ₂ OCH ₃	5.1

^a Energy differences in kcal/mol. ^b Corresponding compounds **4** have energy of 0. ^c $R^3 = CN$.

Summarizing the influence of zinc chloride on the stereochemistry of the dicyano pyrrolo[1,2-*a*]quinolines, we found that:

- Epimerization at C(3a) takes place when the bridgehead substituent is a hydrogen atom or a methyl group, but is prevented by a large methoxymethyl substituent.
- Epimerization at C(3a) is also not observed when the steric energy of the diastereomer that would be formed upon epimerization at C(3a) (**10m,o**) is much higher than the steric energy of the starting derivative (**4m,o**).

Lewis-acid-catalyzed cycloreversion of the ethyl ester cyano derivatives with R^1 and/or $R^2 \neq H$

When the reaction of **2** (and **3**) **f-j**, compounds that have both a cyano and a ethyl ester group (R^3) attached to the vinyl group and substituents R^1 and/or $R^2 \neq H$, was investigated, we observed more complex results. Derivatives **4-9** (**f-j**) were obtained by refluxing of *E/Z* alkenes **2, 3** (**f-j**) in toluene. *Cis* products **4,6,8** (**f-j**) were formed upon cyclization of *E*-alkenes **2f-j**, whereas *trans* diastereomers **5,7,9** (**f-j**) were formed upon cyclization of *Z*-alkenes **3f-j** already present or formed *in situ*. The *cis* and *trans* products **4-9** (**f-j**) retain the stereochemistry at C(3a) and induced stereochemistry at C(5), as found for the dicyano derivatives obtained in toluene (*vide supra*). All the

structures of derivatives **4-13** (**f-j**) were assigned by comparison with the spectra of **4b** and **5b**, and by comparison with the cyclized dicyano analogs⁵. Structures **4i**, **4j**, **6j** and **12j** were assigned by 1H NOE spectroscopy (Chart 3)¹². From the experiments with the alkyl ester cyano derivatives **4, 5** (**a-e**) ($R^1 = R^2 = H$), it was not possible to determine whether derivatives **5** (*trans*) were converted to derivatives **4** (*cis*) by stereomutation which leads to epimerization at C(4) or by helical interconversion which leads to epimerization at C(3a) (*vide supra*). Investigation of the derivatives obtained upon reaction of ethyl ester cyano derivatives **4-9** (**f-j**) (R^1 and/or $R^2 \neq H$, $R^3 = CO_2Et$) with zinc chloride in refluxing acetonitrile could discriminate whether the epimerization takes place at C(3a) or at C(4). It will also be possible to determine whether substitution of a cyano group by the ester moiety significantly influences the observed C(3a) epimerization and, consequently, the ultimate product ratio. Epimerization at C(3a) with as bridgehead substituents H (**4f**, **6j**), CH₃ (**4g**) or CH₂OCH₃ (**4i**, **4j**) was investigated for derivatives **4-9** (**f-j**).

Reaction of a 9:1 mixture of **4f** (*cis*) and **5f** (*trans*) ($R^1 = CH_3$, $R^2 = H$), in refluxing acetonitrile in the presence of zinc chloride for one night yielded a 15:1 mixture of **4f** and its diastereomer **10f** (both *cis*). Consequently, the energetically disfavored **5f** (*trans*) is converted in almost equal amounts into **4f** and **10f** (both *cis*) by stereomutation, to give epimerization at C(4) or by interconversion of the helix to give epimerization at C(3a), respectively. Steric energy difference calculations indicate that diastereomers **4f** and **10f**, in which the ester moiety and the hydrogen atom at C(3a) are *cis* oriented, are favored over *trans* diastereomers **5f** and **11f** (Table III).

Reaction of optically active **6j** (*cis*), in which the bridgehead substituent is a hydrogen atom and $R^2 = CH_2OCH_3$ is attached at C(1), in refluxing acetonitrile in the presence of zinc chloride, did not show epimerization at C(3a) after 24 h. This is expected when C(4) is not inverted because of the large energy difference of about 5 kcal/mol for the *cis* and *trans* diastereomers as calculated for derivatives **4b** versus **5b** (Table III)¹⁴. When optically active derivative **7j** (*trans*), that has, compared with **6j** (*cis*), an inverted stereochemistry at C(4), was refluxed in acetonitrile in the presence of zinc chloride, epimerization at C(4) to **6j** (*cis*) as well as epimerization at C(3a) to diastereomer **12j** (also *cis*) took place. The structures of **6j** and **12j** were determined by 1H NOE spectroscopy (Table V and Chart 3)¹².

Table V Optical rotations of compounds **4i**, **5i**, **4j**, **6j** and **12j**.

Compd.	$[\alpha]_D^{25}$	(c, CHCl ₃)
4i	-21.5°	(1.0)
5i	+9.6°	(0.2)
4j	+56°	(0.7)
6j	-118°	(0.7)
12j	+117°	(0.4)

From the experiments with the dicyano derivative **4l**, we know that a methyl moiety at C(3a) cannot prevent epimerization at this center. When a 10:1 mixture of optically active **4g** (*cis*) and **5g** (*trans*) ($R^1 = H$, $R^2 = CH_3$) was refluxed in acetonitrile in the presence of zinc chloride for 18 h, complete epimerization occurred at C(3a) to mixtures of **4g** and its enantiomer **10g** (both *cis*), and **5g** and its enantiomer **11g** (both *trans*). The epimerization at C(3a) is the same as observed for the dicyano analog **4l**. Epimerization was shown by 1H NMR spectroscopy experiments with chiral shift reagents¹³. The calculated energy difference between the two

diastereomers **4g** (*cis*) and **5g** (*trans*) is small enough to allow the formation of both **5g** and **4g** (Table III)¹⁵. Reaction of optically active **4i** ($R^1 = H$, $R^2 = CH_2OCH_3$), in refluxing acetonitrile in the presence of zinc chloride gave no epimerization of C(3a), as expected with a methoxymethyl moiety at the bridgehead and similar to the dicyano analog **4n**. Optically active derivative **5i** (*trans*) gave, after 2-h refluxing in acetonitrile in the presence of zinc chloride, exclusively optically active **4i** (*cis*), as was shown by optical rotation and ¹H NMR spectroscopy experiments with chiral shift reagents and ¹H NOE spectroscopy^{12,13}. The corresponding optically active derivative **4j** ($R^1 = CH_3$, $R^2 = CH_2OCH_3$), showed no epimerization at C(3a) in refluxing acetonitrile in the presence of zinc chloride. This was also found in the case of dicyano analog **4o**. Under these reaction conditions, optically active **5j** (*trans*) was converted quantitatively into the optically active **4j** (*cis*), as was shown by ¹H NMR spectroscopy and ¹H NOE spectroscopy^{12,13}. The latter result is important, because cyclization of an optically active mixture of *E*-isomer **2j** and *Z*-isomer **3j**, yielded **4j** containing two new optically active centers and shows, in addition, "self-reproduction of chirality" at the original optically active center C(3a), after refluxing in acetonitrile in the presence of zinc chloride. This means that we observe the same process of the epimerization at C(3a) for both ethyl ester cyano derivatives and dicyano derivatives. When the bridgehead substituent is a methoxymethyl group, epimerization at C(3a) does not take place. A methyl group at the bridgehead cannot prevent

epimerization at C(3a). Surprisingly, a hydrogen atom bridgehead substituent does not show epimerization at C(3a) when this hydrogen atom and the ester moiety are *cis* oriented, but does show epimerization when they are *trans* related. The stability of the *cis* derivative can be explained by the large difference in energy between the *cis* and *trans* diastereomers as found with the steric energy calculations. In conclusion, the Lewis acid, zinc chloride, is able to render the formation of the pyrrolo[1,2-*a*]quinolines **4-13** (**a-o**) reversible, presumably by stabilization of the negative pole of the dipolar intermediate formed. The increased lifetime of the dipolar intermediate in refluxing acetonitrile in the presence of zinc chloride gives rise to thermodynamic product distribution of the cyclic derivatives, except for derivatives with a methoxymethyl group at C(3a). This result is different from the kinetic product distribution that is obtained upon cyclization in refluxing toluene or 1-butanol. As a consequence of the longer lifetime of the dipolar intermediate, both interconversion of the helix, with subsequent epimerization at C(3a), and/or stereomutation, with ultimately epimerization at C(4), can take place. These epimerization reactions can be prevented for steric (CH_2OCH_3) or thermodynamic reasons. The diastereomers in which the bridgehead substituent and the ester group are *cis* related are always thermodynamically favored over the *trans* diastereomers. Therefore, it is possible to introduce two new optically active centers whilst retaining the original optically active center by selecting the proper reaction conditions without the use of chiral auxiliaries.

Table VI Melting points and characteristic spectral data of compounds **2-3** (**a-j**)^a.

Compd.	M.p. (°C)	Mass spectrum <i>m/e</i> (M^+ , calcd.)	¹ H NMR: δ (s)	¹³ C NMR: δ^p
2a^b	148–149	256.120 (256.121)	8.56 (=CH)	155.9 (=CH)
3b^c			7.32 (=CH)	
2c^d	oil	298.169 (298.168)	8.55 (=CH)	155.4 (=CH)
2d^e	173–174	315.122 (315.122)	8.51 (=CH)	154.6 (=CH)
3d^f			7.84 (=CH)	
2e^g	174–175	343.154 (343.153)	8.50 (=CH)	154.6 (=CH)
2f^h	oil	284.153 (284.153)	2.63 (=CCH ₃)	176.2 (=CCH ₃)
3fⁱ			2.51 (=CCH ₃)	172.6 (=CCH ₃)
2g^j	oil	284.153 (284.153)	8.50 (=CH)	155.0 (=CH)
2h^k	oil	298.169 (298.168)	2.59 (=CCH ₃)	177.4 (=CCH ₃)
3h^l			2.50 (=CCH ₃)	174.3 (=CCH ₃)
2i^m	oil	314.165 (314.163)	8.48 (=CH)	154.9 (=CH)
2jⁿ	oil	328.172 (328.178)	2.58 (=CCH ₃)	177.6 (=CCH ₃)
3j^o			2.49 (=CCH ₃)	174.2 (=CCH ₃)

^a All compounds **2** exhibit in IR an absorption between 2220–2230 cm⁻¹ (CN) and 1710–1740 cm⁻¹ (C=O). Satisfactory elemental analyses were obtained for **2a**, **2c**, **2d** and **2e** (C, ± 0.30 ; H, ± 0.10 ; N, ± 0.30). The compounds **3** could not be separated from isomers **2**. Mass spectrum is valid for **2** as well as for mixtures of **2** and **3**. ^{b-o} ¹H NMR: ^b 3.91 (s, 3H, CH₃); ^c 4.25 (q, 2H, *J* 7.2 Hz, OCH₂CH₃); ^d 0.97 (t, 3H, *J* 7.3 Hz, CH₃); ^e 6.79 (d, 1H, *J* 9.4 Hz, Ar H); ^f 6.72 (d, 1H, *J* 9.4 Hz, Ar H); ^g 0.98 (t, 3H, *J* 7.2 Hz, CH₃); ^h 4.4–4.3 (m, 2H, OCH₂); ⁱ 4.11 (q, 2H, *J* 7.1 Hz, OCH₂); ^j 1.14 (d, 3H, *J* 6.2 Hz, NCHCH₃); ^k 4.32 (q, 2H, *J* 7.2 Hz, OCH₂); ^l 4.15 (q, 2H, *J* 7.0 Hz, OCH₂); ^m 3.28 (s, 3H, OCH₃); ⁿ 6.75–6.65 (m, 1H, Ar H); ^o 6.60–6.55 (m, 1H, Ar H). ^p ¹³C NMR data that are not mentioned were not visible in the spectrum of the mixture.

Experimental

Melting points were determined with a Reichert melting points apparatus and are uncorrected. ^1H NMR, ^1H NOE and ^{13}C NMR spectra were recorded with a Nicolet NT-200 or a Bruker AC 250

spectrometer in CDCl_3 with Me_4Si as internal standard. Mass spectra were obtained using a Finnigan MAT 90 spectrometer and IR spectra using a Nicolet 55XC FT-IR spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter.

Table VII Melting points and characteristic spectral data of products 4–13 (a–j)^a.

Compd.	M.p. (°C)	Mass spectrum <i>m/e</i> (M^+ , calcd.)	^1H NMR: δ	^{13}C NMR: δ (C=O)
4a ^b	149–150	256.122 (256.121)	3.90 (s) (OCH ₃)	168.6
5b ^c			4.11 (q) (OCH ₂)	
4c ^d	oil	298.169 (298.168)	6.7–6.5 (m) (Ar H(9))	168.2
5c ^e			6.50 (d) (Ar H(9))	
4d ^f	114–115	315.123 (315.121)	6.52 (d) (Ar H(9))	167.0
5d ^g			6.45 (d) (Ar H(9))	164.3
4e ^h	150–151	343.154 (343.153)	6.52 (d) (Ar H(9))	167.4
5e ⁱ			6.44 (d) (Ar H(9))	164.5
4f ^j	oil	284.153 (284.153)	4.36 (ABX ₃) (OCH ₂)	168.5
5f ^k			6.48 (m) (Ar H(9))	
10f ^k			4.05 (q) (OCH ₂)	
4g ^l	oil	284.152 (284.153)	6.57 (m) (Ar H(9))	167.0
5g ^m			6.52 (m) (Ar H(9))	
6,8,12,13g ⁿ			1.24 (d) (NCHCH ₃)	
4h ^o	oil	298.169 (298.168)	1.37 (t) (CH ₂ CH ₃)	167.5
5h ^p			1.38 (t) (CH ₂ CH ₃)	
6,8,12,13h ^q			1.39 (t) (CH ₂ CH ₃)	
4i ^r	80–81	314.165 (314.163)	3.17 (s) (OCH ₃)	166.3
5i ^s			3.29 (s) (OCH ₃)	166.0
6i ^t			3.35 (s) (OCH ₃)	168.2
8i ^t			3.37 (s) (OCH ₃)	167.8
4j ^u	85–87	328.172 (328.179)	3.15 (s) (OCH ₃)	166.6
5j ^v			3.22 (s) (OCH ₃)	162.9
6j ^w	117–119	328.179 (328.179)	3.35 (s) (OCH ₃)	168.7
12j ^x	136–137	328.179 (328.179)	3.36 (s) (OCH ₃)	166.4

^a All compounds 4–13 (a–j) exhibit in the IR an absorption between 2240–2250 cm^{-1} (CN) and 1735–1745 cm^{-1} (C=O). Satisfactory elemental analyses were obtained for all solids. If a melting point or “oil” is not given for a compound, it means that separation of the diastereomer(s) was impossible. When a ^{13}C NMR value is not given, this means that the peak was not visible in the spectrum of the mixture. Overall conversions of 2–3 to 4–13 were almost quantitatively (86–98%) obtained after column chromatography ($\text{SiO}_2/\text{CH}_2\text{Cl}_2$). The mass spectra were taken from the crude reaction mixture and the result is stated for the compounds 4. ^{b–z} ^1H NMR: δ ^b 3.31 and 3.18 (ABq, 2H, J 15.9 Hz, ArCH_2); ^c 1.13 (t, 3H, J 7.1 Hz, CH_2CH_3); ^d 0.97 (t, 3H, J 7.3 Hz, CH_2CH_3); ^e no further peaks were assigned; ^f 1.40 (t, 3H, J 7.1 Hz, CH_2CH_3); ^g 1.18 (t, 3H, J 7.0 Hz, CH_2CH_3); ^h 0.98 (t, 3H, J 7.2 Hz, CH_2CH_3); ⁱ 0.85 (t, 3H, J 7.1 Hz, CH_2CH_3); ^j 1.36 (t, 3H, J 7.1 Hz, CH_2CH_3); ^k 1.18 (d, 3H, J 7.2 Hz, NCHCH_3); ^l 1.02 (s, 3H, NCCH_3) and 1.33 (t, 3H, J 7.2 Hz, OCH_2CH_3); ^m 1.14 (t, 3H, J 7.1 Hz, OCH_2CH_3); ⁿ probably a mixture of these 4 compounds, only this peak was assigned; ^o 1.06 (t, 3H, NCCH_3); ^p 1.06 (s, 3H, NCCH_3); ^q probably a mixture of these 4 compounds; 2 different doublets were visible: 1.47 and 1.45 (d, 3H, J 6.2 Hz and J 6.8 Hz, ArCHCH_3); ^r 1.34 (t, 3H, J 7.2 Hz, CH_2CH_3); ^s 1.14 (t, 3H, J 7.2 Hz, CH_2CH_3); ^t only this peak was assigned; ^u 1.36 (t, 3H, J 7.2 Hz, CH_2CH_3); ^v 1.19 (t, 3H, J 7.2 Hz, CH_2CH_3); ^w 1.36 (t, 3H, J 7.2 Hz, CH_2CH_3); ^x 1.39 (t, 3H, J 7.3 Hz, CH_2CH_3).

Table VIII Yields and reaction times of products obtained by thermal isomerization of condensation compounds 2, 3 (f–j) under different conditions^{a,b}.

Starting compd. (2, 3)	Solvent (reflux)	Reaction time	Product yields (%)								
			4	5	10	6	7	12	8	9	13
f	toluene	6 h	77	9							
f	CH ₃ CN/ZnCl ₂	12 h	83		5						
g	toluene	2 d	81	9		4			4		
g	CH ₃ CN/ZnCl ₂	4 h	81	9	e	4			4		
h	toluene	6 d	67	4		12			12		
h	CH ₃ CN/ZnCl ₂	15 h	71			12			12		
i	toluene	6 d	38	10		19	5		19	5	
i	CH ₃ CN/ZnCl ₂	12 h	48			22		2	22		2
j	toluene	12 d	21	5		42	13				
j	CH ₃ CN/ZnCl ₂	24 h	26			49		6			

^a Refluxing of the in toluene cyclized products in acetonitrile in the presence of zinc chloride gave the same products as upon direct cyclization of the alkenes in acetonitrile in the presence of zinc chloride. ^b Kinetic *trans* products 5, 7 and 9 formed in toluene are converted to the *cis* products 4 and/or 10, 6 and/or 12, and 8 and/or 13, respectively, in refluxing acetonitrile in the presence of zinc chloride, except for 5g. ^c Total exchange between 4g, 5g and the enantiomers 10g and 11g takes place.

2-Fluorobenzaldehyde (Janssen), 2-fluoroacetophenone (Janssen), 2-chloro-5-nitrobenzaldehyde (Janssen), all the cyanoacetic acid esters (Janssen), 2-methylpyrrolidine (Alfa), (*S*)-2-(methoxymethyl)pyrrolidine (Merck), and pyrrolidine (Merck) were used without further purification. (*R,S*)-2-(Methoxymethyl)pyrrolidine and (*R*)-2-methylpyrrolidine were synthesized according to Nijhuis et al.⁷ All reactions were carried out under a nitrogen atmosphere. Compounds 1, 2k–o, 4k–o, 6n, 6o and 8o are described by Nijhuis et al.^{5,7}

General procedure for condensation of cyanoacetic acid esters with benzaldehyde and acetophenone derivatives 1. Synthesis of Knoevenagel products 2a–j and 3f,h,j

To a solution of the aldehyde (10 mmol) or the ketone (10 mmol) 1 in toluene (50 ml) was added the corresponding cyanoacetic acid ester (10 mmol) in one portion. After the reaction was complete, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO₂; CH₂Cl₂). For further experimental conditions and characteristic spectral data, see Tables I and VI.

Cyclization of Knoevenagel products 2a–o and 3f,h,j. Synthesis of pyrrolo[1,2-a]quinoline derivatives 4–13 (a–o)

Compound 2 or a mixture of 2 and 3 (10 mmol) was refluxed in 1-butanol (10 ml), toluene (10 ml), or acetonitrile (20 ml) in the presence of zinc chloride (10 mmol) for several hours. When all the starting material had disappeared according to TLC, the solvent was removed under reduced pressure. In the case of ring closure in acetonitrile in the presence of zinc chloride, the product was taken up in CH₂Cl₂ followed by extraction of the zinc chloride by water. The products were purified by column chromatography (SiO₂; CH₂Cl₂). For melting points and characteristic spectral data, see Table VII. The product ratios and reaction times under different conditions for the *E*-alkenes 2a–e are given in Table II. The yields and reaction times for the formation of derivatives 4–9 (f–j), obtained by refluxing in toluene and acetonitrile in the presence of zinc chloride, are given in Table VIII.

cis-(+)-1,2,3,3a-Tetrahydro-5-methylpyrrolo[1,2-a]quinoline-4,4(5H)-dicarbonitrile (10k). Compound 10k could not be separated from 4k. The following peaks were assigned to 10k: ¹H NMR: δ 1.50 (d, 3H, *J* 7.2 Hz, CH₃), ¹³C NMR: δ 140.9 (s, C(9a)), 129.1, 117.5 and 112.3 (d, Ar C), 56.9 (d, NCH), 40.6 (d, ArCHCH₃), 30.1 and 21.7 (t, CH₂), 15.9 (q, CH₃).

(1αS,3αβ,5β)-(+)-1,2,3,3a-Tetrahydro-1-(methoxymethyl)-5-methylpyrrolo[1,2-a]quinoline-4,4(5H)-dicarbonitrile (12o). M.p. 127–129°C (MeOH); [α]_D²⁵ +38° (c 0.08, CHCl₃). ¹H NMR: δ 7.2–7.0 (m, 2H, Ar H), 6.8–6.6 (m, 2H, Ar H), 4.2–4.0 [m, 1H,

NCH(CH₂OCH₃), 3.76 (dd, 1H, *J* 8.8 and 5.7 Hz, NCH bridge), 3.60 (dd, 1H, *J* 9.3 and 2.2 Hz, CHHOCH₃), 3.57 [q, 1H, *J* 7.2 Hz, ArH(CH₃)], 3.37 (s, 3H, OCH₃), 3.14 (dd, 1H, *J* 9.3 and 9.3 Hz, CHHOCH₃), 2.5–2.1 (m, 4H, CH₂ ring), 1.52 (d, 3H, *J* 7.2 Hz, ArCHCH₃). ¹³C NMR: δ 140.0 [s, C(9a)], 129.8 and 128.7 (d, Ar C), 120.6 [s, C(5a)], 117.8 and 112.5 (d, Ar C), 71.6 (t, CH₂OCH₃), 59.1 (q, OCH₃), 57.2 (d, NCH), 43.6 [s, C(CN)₂], 40.1 (d, ArCH), 27.7 and 27.2 (t, CH₂ ring), 23.1 (q, ArCHCH₃). IR (KBr): 2240 (CN) cm⁻¹. MS: accurate mass theor. 281.153 for C₁₇H₁₉N₃O; exp. 281.152. No satisfactory elemental analysis could be obtained on account of slow decomposition.

[1αS,3αα,5α]-1,2,3,3a-Tetrahydro-1-(methoxymethyl)-5-methylpyrrolo[1,2-a]quinoline-4,4(5H)-dicarbonitrile (13o). Product 13o could not be separated from 8o. The following characteristic peaks were assigned to 13o: ¹H NMR: δ 3.35 (s, 3H, OCH₃), 1.56 (d, 3H, *J* 7.0 Hz, ArCHCH₃). ¹³C NMR: δ 139.7 [s, C(9a)], 129.8 and 129.0 (d, Ar C), 120.6 [s, C(5a)], 116.4 and 112.4 (d, Ar C), 71.6 (t, CH₂OCH₃), 60.5 (q, OCH₃), 59.3 (d, NCH), 40.0 (d, ArCH), 27.7 and 27.2 (t, CH₂ ring), 23.1 (q, ArCHCH₃).

Steric-energy calculations

Steric energies were calculated with the QUANTA/CHARMm package^{16,17}. Minimum energy conformations were obtained by systematic variation of the relevant degrees of freedom (rotatable bonds of substituents, pucker of the 5-membered rings). Force-field parameters were taken from the CHARMm 2.1A parameter set. Values for missing parameters were estimated by comparison with related parameters. Atomic charges were derived from semi-empirical calculations with the AM1 method^{4,18}. With the resulting force field the X-ray structure of 4b⁴ was reproduced with a r.m.s. deviation of 0.14 Å for all non-H atoms (0.10 Å for the heterocyclic skeleton); this was judged a reasonable result for such a heterocyclic system.

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Supplementary Material Available. Extensive spectral data

of all new compounds mentioned are deposited at the editor's office (11 pages).

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- ⁹ All the following (mixtures of) cyclic compounds that were reacted in refluxing acetonitrile in the presence of zinc chloride, were obtained by cyclization of the corresponding alkenes in refluxing toluene and purified by column chromatography ($\text{SiO}_2/\text{CH}_2\text{Cl}_2$) and, if possible, by recrystallization from a suitable solvent. Cyclic products obtained by direct closure of the alkenes in refluxing acetonitrile in the presence of zinc chloride, and cyclic products obtained by cyclization in refluxing toluene and subsequent reaction in refluxing acetonitrile in the presence of zinc chloride were identical.
- ¹⁰ The difference of δ 0.2 ppm shift in the ^1H NMR spectra for the R^1 methyl groups were observed for the diastereomer pairs **4k/10k**, **6o/12o**, **8o/13o**, **4f/10f** and **6j/12j**.
- ¹¹ The reaction of **6o** in refluxing acetonitrile in the presence of zinc chloride would also, in the case of a reversible 1,5 hydrogen shift, have given **8o**, either directly or in a two step process via **12o**, or **13o** after C(3a) epimerization, as an intermediate. The discrepancy for the product ratios of **6o** and **12o** versus **8o** and **13o**, can be accounted for by steric hindrance of the methoxymethyl group with H(9) of the aromatic ring (see also Ref. 5).
- ¹² The ^1H NOE interactions not shown were equal to zero or could not be unambiguously assigned. For compound **4j**, the ^1H NOE difference spectroscopy experiments gave a combined signal of the coalescing singlets of the methylene and methyl group of the methoxymethyl moiety.
- ¹³ The shift reagents were a combination of 1 equiv of AgFod , 1 equiv of $\text{Eu}(\text{tfc})_3$, and 1 equiv of the investigated pyrrolo-[1,2-*a*]quinoline. All racemic mixtures showed splitting of the Ar H(9) "doublet", while the product obtained from the optically pure starting materials showed no splitting.
- ¹⁴ We did not, however, find any product that was formed upon epimerization at C(3a) as well as at C(4).
- ¹⁵ The reaction of a 19:1 mixture of **4h** and **5h** with $\text{R}^1 = \text{R}^2 = \text{CH}_3$, in refluxing acetonitrile in the presence of zinc chloride yielded a mixture of **4h** and a small amount of **5h** or **10h**. From the very complicated ^1H NMR spectra of the mixtures (that were not separable), it was unfortunately impossible to unambiguously characterize the minor product. Because of uncertainty in the correct identification of the minor product, no conclusion can be drawn about epimerization at C(3a) in this case. The calculations do not give a clue as to whether the minor compound is **5h** or **10h** since both are energetically about 3 kcal/mol less favored than **4h**. This energy difference is, on the other hand, very much in agreement with the observed 19:1 ratio for **4h** and the minor product.
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