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Three-Component (Domino) Reaction Affording Substituted Pyrroloquinazolines: Cyclization Regioselectivity and Stereoselectivity

Oldřich Paleta,*[a] Bohumil Dolenský,[b] Jiří Paleček,[a] and Jaroslav Kvíčala[a]

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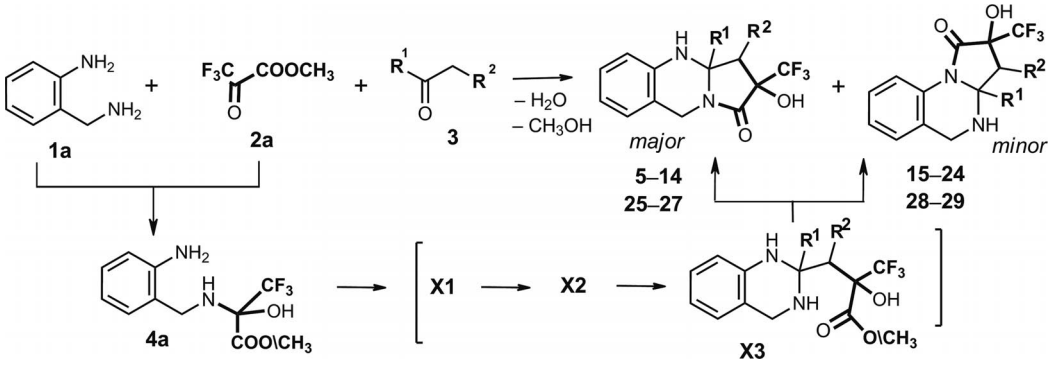
The cyclization involving 2-(aminomethyl)aniline, methyl 3,3,3-trifluoropyruvate, and various oxo compound afforded linearly annulated pyrroloquinazolines, for example, (2*R**,3a*S**)-2-hydroxy-3a-phenyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (*cis*-**8**), as the major product, possessing the skeleton of the alkaloids of the vasicine group, along with angularly annulated products, for example, (2*S**,3a*R**)-2-hydroxy-3a-phenyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (*cis*-**18**). The effects of the nature of the oxo compound and the temperature on the ratio of the linear and angular cyclization products, as well as the diastereoselectivity of the product formation, were studied, with an increase in temperature leading to improved selectivity. Some of the linear pyrroloquinazolines were stereoselectively didehydrogenated at the quinazoline ring by the trifluoropyruvate.

Introduction

Multicomponent reactions (MCRs) are a powerful tool in synthetic organic chemistry: Three or more components mixed together react in one vessel to form several new bonds according to a characteristic chemical algorithm.[1] The three-component Mannich synthesis of (di)alkyl amino ketones[2] or Biginelli cyclization to dihydropyrimidines[3] are well-known reactions. The reaction sequences in MCRs are also known as domino reactions.[4] MCRs offer significant advantages over the usual syntheses of target compounds, which frequently include tedious, several-step isolations: They are time-saving, show bond-forming efficiency (BFE), and are environmentally friendly.[1,4] For the years 2010 and 2011, 40–50 references can be found in a science finder under the entry "Three-component reactions" leading to heterocyclic products.

Recently, we uncovered a new three-component cyclization affording trifluoromethylated dinitrogen tri- or tetracyclic heterocycles (Scheme 1).[5a] The cyclization proceeds with 2-(aminomethyl)aniline (**1a**), methyl trifluoropyruvate (**2a**), and an aldehyde or ketone (**3**) as reactants. All the



Scheme 1. General scheme for the three-component cyclization reaction.

cyclization products possess the quinazoline moiety and, of these, the linearly annulated tricyclic products (**5**–**14** and **25**–**27**; Scheme 1) possess the pyrroloquinazoline skeleton of the alkaloids of the vasicine family (Figure 1). The by-products are isomers in which the lactam ring is angularly attached to the quinazoline moiety (**15**–**24**, **28**, and **29**; Scheme 1). Trifluoropyruvate (**2a**), the key building block,

[a] Department of Organic Chemistry, Institute of Chemical Technology,
16628 Prague 6, Czech Republic
Fax: +420-22044-4284
E-mail: oldrich.paleta@vscht.cz
[b] Department of Analytical Chemistry, Institute of Chemical Technology,
16628 Prague 6, Czech Republic

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was recently used in two-component cyclization reactions that afforded drug-like heterocycles.[5b] In general, quinazoline derivatives display a variety of pharmacological effects,[6] for example, antihypertensive,[7a] bronchodilatory,[7b] anti-HIV,[7c] antiinflammatory,[7d] or antitumor properties.[7e–7g] Vasicine (Figure 1) displays a broad spectrum of bioactivity, for example, as a respiratory stimulator, antihypertensive, and abortivum,[8] and deoxyvasicinone and deoxyvasicine display cytotoxic activity towards leukemia P-338 cells.[9] Some synthetic analogues of alkaloids of the vasicine group were positively tested as antidepressants, neuroleptics, antihypertensives, and anti-Parkinsonica.[10] Alkaloids of the vasicine family are usually synthesized by multistep syntheses.[11] Recently, a two-component synthesis of deoxyvasicinone was carried out.[11f] As is generally known, fluoro substituents, including the trifluoromethyl group, strongly modify the bioactivity.[12] Hence, a modified bioactivity could be achieved for trifluoromethyl derivatives of vasicine and its analogues.

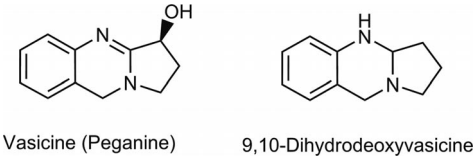


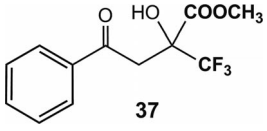
Figure 1. Two alkaloids from the vasicine family.

For the reasons given above, we studied the new cyclization reaction by using a series of oxo compounds having carried out research on the following related topics: An efficient laboratory preparation of methyl trifluoropyruvate (**2a**),[13] trifluoropyruvate hemiaminals formed from aromatic amines or aromatic-aliphatic diamines as the first intermediate in the cyclization is the hemiaminal **4a** (Scheme 1),[14] a synthetically convenient aldolization of enamines with trifluoropyruvate, which is probably the intermediary reaction step in the cyclization reaction,[15] and a method for the structure elucidation of individual compounds in the mixtures of linear (**5**–**14** and **25**–**27**) and angular products (**15**–**24**, **28**, and **29**; Scheme 1) and their stereoisomers (see Figure 2).[16] The method that was developed was applied to a facile assignment of the relative configurations of the stereogenic centers by performing a combination of homo- (proton–proton) and heteronuclear (proton–fluorine) NOE experiments. It was also possible to assign the relative configurations of minor products with a yield of as low as 1%.[16] We applied these results to the structure elucidation in this work. The dependence of the ratio of the main linearly (**5**–**14** and **25**–**27**) and minor angularly (**15**–**24**, **28**, and **29**) annulated products on the structure of the starting aldehyde or ketone was also of interest to us. We also studied the (dia)stereoselectivity of the cyclization reactions and tested the effect of reaction temperature on both the regio- and stereoselectivity of the reactions. In addition, we obtained some information on

Table 1. Isolated yields of the products of linear and angular annulation.[a]

Entry	Oxo compound	*T* [°C]	Products						
			R^1	R^2	Linear cyclization		Angular cyclization		Linear/angular[b]
					Compound	Yield [%]	Compound	Yield [%]	
1	**3a**	r.t.[c]	Me	H	**5**	85.5	**15**	10.2	88.5:11.5
2	**3b**	r.t.	*t*Bu	H	**6**	60.5	**16**	0	100:0
		100				60		0	100:0
3	**3c**	100	Bu	H	**7**	79	**17**	8.3	90.5:9.5
4	**3d**	r.t.[d]	Ph	H	**8**	49	**18**	4	92.5:7.5
		100				86		5	95:5
5	**3e**	r.t.[c]	H	H	**9**	54.2	**19**	16.2	77:23
6	**3f**	r.t.	H	Me	**10**	75	**20**	12	85.5:14.5
		100				68		5	93:7
7	**3g**	r.t.	H	Me_2	**11**	60	**21**	24	76.5:23.5
		100				28		0	100:0
8	**3h**	r.t.	H	Ph	**12**	89.3	**22**	3.1	94:6
		100				85		1	98:2
9	**3j**	r.t.	$–CH_2CH_2CH_2–$		**13**	74	**23**	16	84.5:15.5
		100				78		10	87:13
10	**3k**	r.t.[c]	$–CH_2(CH_2)_2CH_2–$		**14**	67	**24**	3	96:4
		100				87		0	100:0
11	**3l**	r.t.[c]	Et	Me	**25**	48	**28**	19	71.5:28.5
		100				73.5		16.5	81.5:18.5
12	**3m**	100	Et or Me	H or Me	**26**, **27**	55.8	**29**	7.2	88.5:11.5

[a] Oxo compounds used: acetone (**3a**), 3,3-dimethylbutan-2-one (**3b**), hexan-2-one (**3c**), acetophenone (**3d**), acetaldehyde (**3e**), propanal (**3f**), 2-methylpropanal (**3g**), 2-phenylacetaldehyde (**3h**), cyclopentanone (**3j**), cyclohexanone (**3k**), pentan-3-one (**3l**), and butan-2-one (**3m**). [b] Content in final reaction mixture. [c] Ref.[16] [d] Reaction mixture contained 20.6 rel.-% of the aldol **37**.



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the stereoselective didehydrogenation of the primary products by trifluoropyruvate (**2a**).

Results and Discussion

In the first part of our research we studied the regioselectivity of the closure of the lactam ring to which geminal hydroxy and trifluoromethyl groups are attached together with an additional substituent R^1 or R^2 (Table 1, entries 1–4 and 5–8), a vicinally annulated cycle (Table 1, entries 9 and 10), or two substituents R^1 and R^2 (Table 1, entries 11 and 12).

The products **25**–**29** were formed from the starting ketones, which possess two reaction centers. These cyclization reactions offered rich mixtures of products (see below); the reactions at room temperature were slow, whereas at 100 °C they were completed within a few hours.

The following reaction mechanism has been proposed. The first step of the cyclization is a fast reaction of the trifluoropyruvate **2a** with diamine **1a** to form the hemiaminal **4a** at the benzylic amino group (Scheme 1).[16] The following steps could potentially lead to **X1** and **X2**. Probably, the intermediate **X1** includes a Schiff base moiety at the aromatic amino group, which may be in equilibrium with its enamine form **X2**. An intramolecular reaction affording the intermediate **X3** probably follows. The last step of the cyclization is very likely ring closure of the intermediate **X3** to form the lactam (Scheme 1), that is, nucleophilic substitution at the sp^2 carbon atom. Thus, it can be expected that factors such as the nucleophilicity of the nitrogen atom, ring strain during linear or angular lactam ring closure, together with steric effects of the substituents R^1 and R^2 (Scheme 1) would influence the regio- and stereoselectivity of the cyclization.

The isolated yields of the products of linear (**5**–**14** and **25**–**27**) and angular lactam ring closure (**15**–**24**, **28**, and **29**) are summarized in Table 1 together with the ratios of the linear and angular products in the final reaction mixtures. The data reveal that the linear products predominate in all the cyclizations, which can be attributed to the higher nucleophilicity of the original benzylic nitrogen, to which the lactam ring is closed. In the cyclizations involving methyl ketones (entries 1–3), the angular cyclization is increasingly suppressed by the bulkiness of the alkyl R^1 (entry 2) or the benzene ring (entry 4). The same effect of the benzene ring was observed in the reactions of aldehydes (products **12** and **22**). In the reactions of cyclic ketones (entries 9 and 10), the larger cyclohexanone ring markedly suppressed the angular annulation (product **24**) in comparison with cyclopentanone (product **23**).

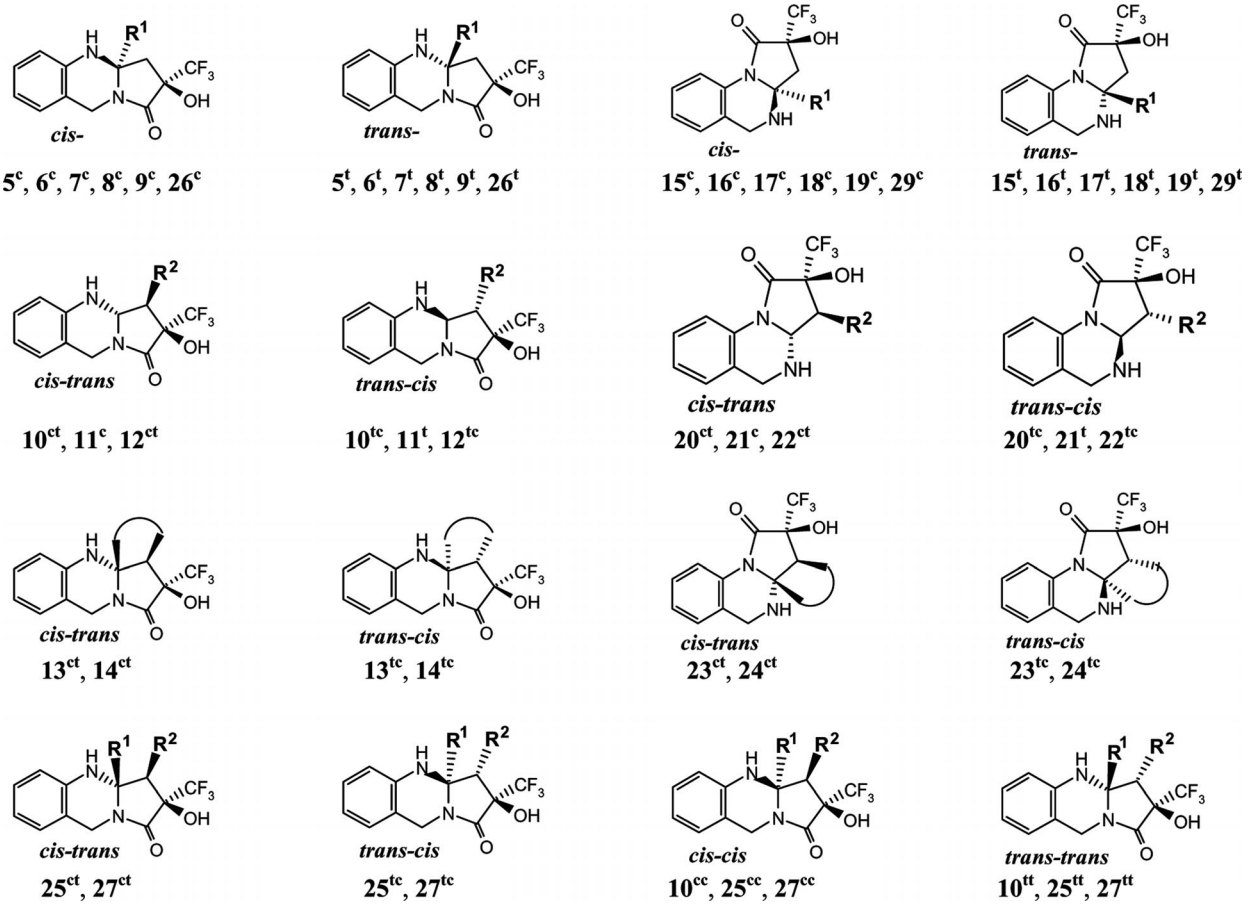


Figure 2. Overview of the diastereoisomers formed in the cyclization reactions.

The effect of a higher reaction temperature on the regioselectivity of the cyclization (Table 1) was the same for all reactions, that is, the suppression of the angular annulation and thus an increase in regioselectivity.

On the basis of the cyclization reactions carried out under analogous conditions, it was possible to estimate a qualitative order of reactivity of the oxo compounds: Cyclopentanone (**3j**) > cyclohexanone (**3k**) > acetone (**3a**) > acetaldehyde (**3e**) > 2-phenylacetaldehyde (**3h**) > propanal (**3f**) > 2-methylpropanal (**3g**) > acetophenone (**3d**).

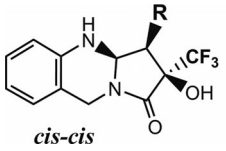
An overview of the diastereoisomers of the cyclization products formed is given in Figure 2. The relative configurations are given with respect to the hydroxy group. Individual diastereoisomers are racemic mixtures of enantiomers.

The linear cyclizations usually afforded mixtures of two diastereoisomers with the *cis* or *cis-trans* configuration prevailing (Table 2). In contrast, in the cyclization of propanal, the product **10** (Table 2) was formed along with an additional two diastereoisomers (5% $\mathbf{10^{cc}}$ and 4% $\mathbf{10^{tt}}$ at room temperature). Similarly, in the cyclization of pentan-3-one (**3l**), four diastereoisomeric linear isomers of **25** (Table 2) were formed both at room temp. and at 100 °C. In contrast, the angular cyclization afforded only two diastereoisomers at room temp. with the *cis-cis* isomer highly prevailing.

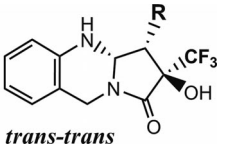
Table 2. Diastereoselectivity in the formation of the products **5**–**14** and **25**–**27** by linear annulation of the lactam ring at room temperature and 100 °C.

	R^1	R^2	*T* [°C]	Isomer 1	Isomer 2	Ratio 1/2
5	Me	H	r.t.	$\mathbf{5^c}$	$\mathbf{5^t}$	65:35
6	*t*Bu	H	r.t.	$\mathbf{6^c}$	$\mathbf{6^t}$	77:23
			100			11:89
7	Bu	H	100	$\mathbf{7^c}$	$\mathbf{7^t}$	77:23
8	Ph	H	r.t.	$\mathbf{8^c}$	$\mathbf{8^t}$	95.5:4.5
			100			97.5:2.5
9	H	H	r.t.	$\mathbf{9^c}$	$\mathbf{9^t}$	56:44
10	H	Me	r.t.	$\mathbf{10^{ct}}$	$\mathbf{10^{tc}}$	26:65[a]
			100			37.5:53[b]
11	H	Me_2	r.t.	$\mathbf{11^c}$	$\mathbf{11^t}$	55:45
			100			65:35
12	H	Ph	r.t.	$\mathbf{12^{ct}}$	$\mathbf{12^{tc}}$	26:74
			100			75.5:24.5
13	$-(CH_2)_3-$		r.t.	$\mathbf{13^{ct}}$	$\mathbf{13^{tc}}$	43:57
			100			80:20
14	$-(CH_2)_4-$		r.t.	$\mathbf{14^{ct}}$	$\mathbf{14^{tc}}$	61:39
			100			80:20
25	Et	Me	r.t.	$\mathbf{25^{tc}}$	$\mathbf{25^{cc}}$	40:27[c]
			100			10:51[d]
26	Et	H	100	$\mathbf{26^c}$	$\mathbf{26^t}$	33:45[e,f]
27	Et	H	100	$\mathbf{27^{ct}}$	$\mathbf{27^{tc}}$	12:9[e,f]

[a] Contains 5% *cis-cis* ($\mathbf{10^{cc}}$) and 4% *trans-trans* ($\mathbf{10^{tt}}$) isomers. [b] Contains 6.5% *cis-cis* ($\mathbf{10^{cc}}$) and 3% *trans-trans* ($\mathbf{10^{tt}}$) isomer. [c] Contains 6% *cis-trans* ($\mathbf{25^{ct}}$) and 27% *trans-trans* ($\mathbf{25^{tt}}$) isomers. [d] Contains 36% *cis-trans* ($\mathbf{25^{ct}}$) and 3% *trans-trans* ($\mathbf{25^{tt}}$) isomers. [e] Contains 0.5% *cis-cis* ($\mathbf{27^{cc}}$) and 0.5% *trans-trans* ($\mathbf{27^{tt}}$). [f] Compounds **26** and **27** are formed in the same mixture (Table 1).

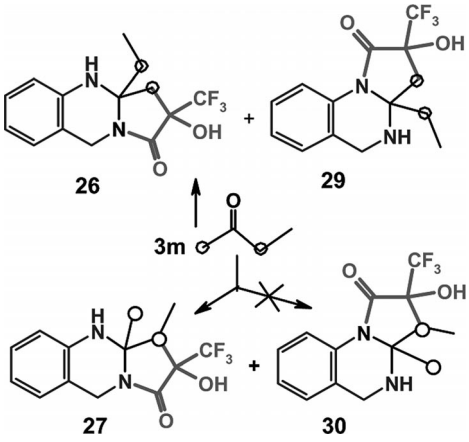


cis-cis



trans-trans

Three regioisomeric cyclization products (**26**, **27**, and **29**; Scheme 2) were formed in the reaction with butan-2-one (**3m**), which possesses two reaction centers (Scheme 2). It was noted that the terminal methyl group in ethyl methyl ketone (**3m**) was more reactive than the interstitial methylene group, being involved in around 70% of the linear cyclization (**26**, **27**) and in 100% of the angular reaction (**29**). No angular cyclization occurred at the methylene group (expected structure **30**). The regioisomers **26**, **27**, and **29** include eight diastereoisomers, but three of them were

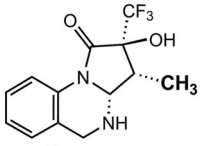


Scheme 2. Regioisomers formed in the cyclization of butan-2-one.

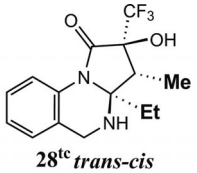
Table 3. Diastereoselectivity in the formation of products **15**–**24**, **28**, and **29** by the angular annulation of the lactam ring at room temperature and 100 °C.

	R^1	R^2	*T* [°C]	Isomer 1	Isomer 2	Ratio of 1/2
15	Me	H	r.t.	$\mathbf{15^c}$	$\mathbf{15^t}$	100:0
16	*t*Bu	H	r.t.	$\mathbf{16^c}$	$\mathbf{16^t}$	0:0
			100			0:0
17	Bu	H	100	$\mathbf{17^c}$	$\mathbf{17^t}$	85:15
18	Ph	H	r.t.	$\mathbf{18^c}$	$\mathbf{18^t}$	28:72
			100			68:32
19	H	H	r.t.	$\mathbf{19^c}$	$\mathbf{19^t}$	90:10
20	H	Me	r.t.[a]	$\mathbf{20^{ct}}$	$\mathbf{20^{tc}}$	32.5:58.5
			100			100:0
21	H	Me_2	r.t.	$\mathbf{21^c}$	$\mathbf{21^t}$	76:24
			100			0:0
22	H	Ph	r.t.	$\mathbf{22^{ct}}$	$\mathbf{22^{tc}}$	85:15
			100			100:0
23	$-(CH_2)_3-$		r.t.	$\mathbf{23^{ct}}$	$\mathbf{23^{tc}}$	75:25
			100			≈99:1
24	$-(CH_2)_4-$		r.t.	$\mathbf{24^{ct}}$	$\mathbf{24^{tc}}$	67:33
			100			100:0
28	Et	Me	r.t.[b]	$\mathbf{28^{tc}}$	$\mathbf{28^{cc}}$	16:84
			100			0:100
29	Et	H	100	$\mathbf{29^c}$	$\mathbf{29^t}$	8:92

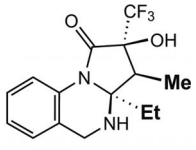
[a] Contains 9% of the *trans-trans* ($\mathbf{20^{tt}}$) isomer. [b] Ref.[16]



$\mathbf{20^{tt}}$ *trans-trans*



$\mathbf{28^{tc}}$ *trans-cis*



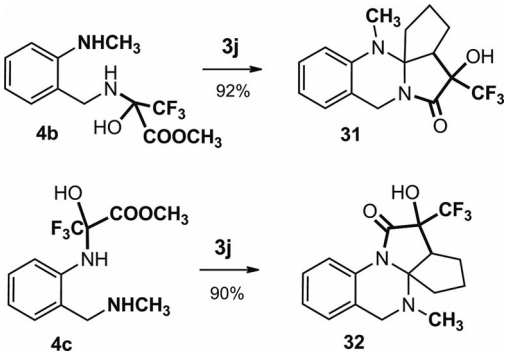
$\mathbf{28^{cc}}$ *cis-cis*

found in yields of only 1% or less (**27^{cc}**, **27^{tt}**, and **29^{c}**; see Tables 2 and 3).

The effect of temperature on diastereoselectivity (Table 2) was analogous to that on the regioselectivity of the cyclization (Table 1), that is, increased selectivity was observed: A higher reaction temperature supported the formation of diastereoisomers with the *cis* configuration (with respect to the OH group) with one exception, for R^1 = *tert*-butyl group (product **6**).

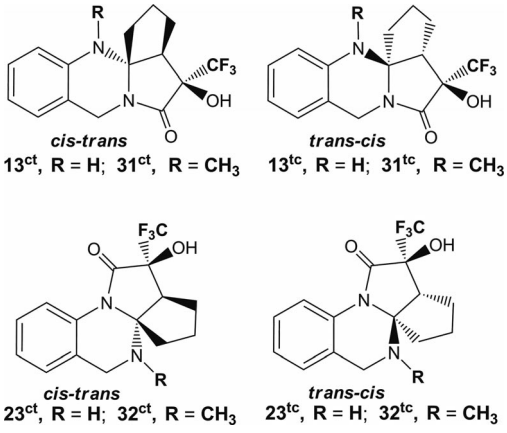
The diastereoselectivity of the angular cyclization (Table 3) was observed to be different to that of the linear reaction (Table 2): It was generally much higher and in particular cyclization reactions, only one or a highly prevalent diastereoisomer was formed (**15**, **20**–**22**, and **24b**; Table 3). A higher reaction temperature supported the formation of diastereoisomers with the *cis* configuration (with respect to the OH group, Table 3).

Complete selectivity of the reaction was achieved by using the *N*-monomethylated 2-(aminomethyl)anilines **1b** and **1c** (see Supporting Information), in which one of the nitrogen atoms was protected against lactamization. The corresponding hemiaminals **4b** and **4c** afforded single regioisomers **31** and **32**, respectively (Scheme 3). The yields were high (92 and 90%), probably as a result of a lower number of potential equilibrium steps in the reaction. The cyclizations were almost completely diastereoselective at 100 °C with the *cis-trans* stereoisomer dominant (Table 4).



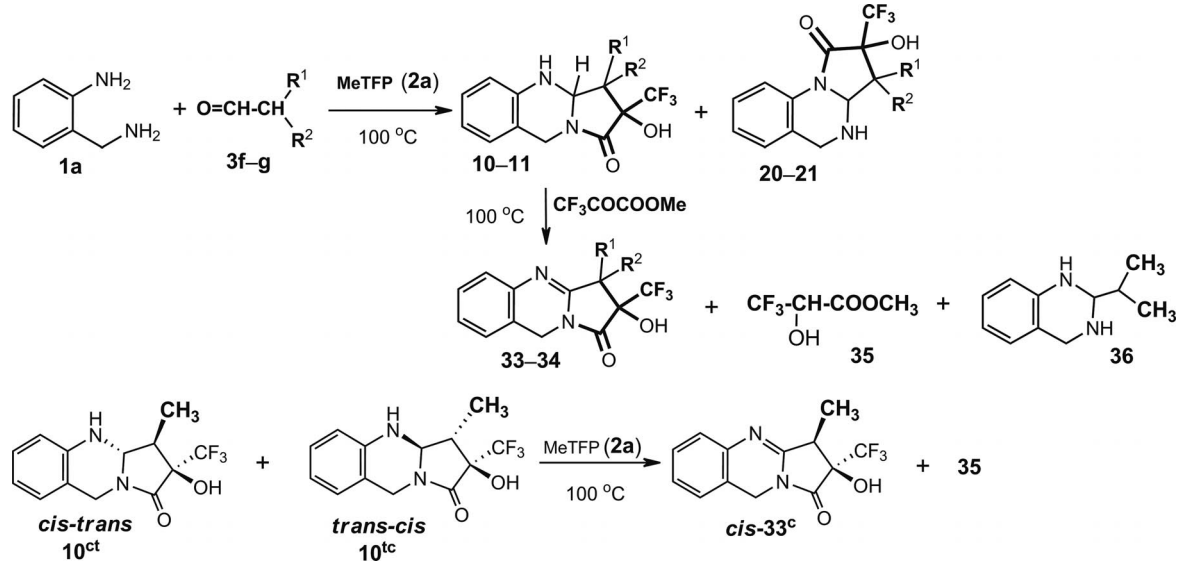
Scheme 3. Regiospecific cyclization reactions involving *N*-monomethylated 2-(aminomethyl)anilines.

Table 4. Diastereoselectivity in the formation of the products **31** and **32** by using *N*-monomethylated 2-(aminomethyl)anilines.



T [°C]		Relative yields of diastereoisomers				
		Linear			Angular	
		c-t	*t-c*		*c-t*	*t-c*
r.t.	**13**	43	57	**23**	75	25
100		80	20		99	1
r.t.	**31**	78	22		–	–
100		99	1		–	–
r.t.		–	–	**32**	32	68
100		–	–		92	8

In the cyclization reactions with particular aldehydes, compounds **33** and **34** were identified as new minor products (Scheme 4), the relative amounts of which increased with increasing temperature (Table 5). They were formed by didehydrogenation of the primary products **10** and **11**,



Scheme 4. Dehydrogenation of products by methyl 3,3,3-trifluoropyruvate (**2a**).

respectively (Scheme 4), with trifluoropyruvate **2a**, which was in turn reduced to methyl 3,3,3-trifluoro-2-hydroxypropanoate (**35**; Scheme 4). The double bond is located between N3a–C4, that is, at the same place as in vasicine (Figure 1). When additional trifluoropyruvate was added to the final reaction mixture, a further portion of the primary product **11** was dehydrogenated to **33**. The quinazoline **36** (the aminal of **3g**) was also formed due to insufficient trifluoropyruvate **2a** in the reaction mixture caused by its hydrogenation. The didehydrogenation reaction was highly stereoselective: When a mixture of *cis*-*trans*-**10** and *trans*-*cis*-**10** was subjected to dehydrogenation, only the *cis*-**33** was formed (Scheme 4). A similar dehydrogenation by trifluoropyruvate was observed in its reaction with substituted tetrahydroquinoline, which was aromatized to the corresponding quinoline.[17] Dehydrogenation was not observed for the angular cyclization products **20** and **21**. The linear products **9** and **12** derived from reactions with acetaldehyde and 2-phenylacetaldehyde did not undergo the dehydrogenation reaction. It can be deduced that the dehydrogenation occurred only in the presence of one or two methyl (alkyl) groups at C3.

Table 5. Yields of the dehydrogenation products in the final mixture of the cyclization reactions (Scheme 4).

Compound[a]	Product	R^1	R^2	Yield [%]	
				r.t.	100 °C
9	–	H	H	0	–
10	**33**[c]	H	Me	0	5
11	**34**	Me	Me	2	29
12	–	H	Ph	0	0

[a] Starting heterocyclic compound.

Conclusions

The new three-component cyclization reaction, which affords substituted pyrroloquinazolines as the major products, including analogues of vasicine, proceeds with high or complete regio- and diastereoselectivity for particular oxo compounds and reaction temperatures. The knowledge gained from this work can be used to control the selectivity of the cyclization reaction and the synthesis of linear and angular target compounds. It was found that 3,3,3-trifluoropyruvate didehydrogenates the linear cyclization products formed from certain aldehydes with complete diastereoselectivity.

Experimental Section

Materials and Methods: All reactions were performed under argon in a well-dried distillation apparatus closed with a drying tube filled with $CaCl_2$ and KOH. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded at frequencies of 300, 282, and 76 MHz, respectively, with a Varian Gemini 300 HC spectrometer. Chemical shifts (δ) are given in ppm relative to TMS for ^1H or ^{13}C NMR and to $CFCl_3$ for ^{19}F NMR. The coupling constants (J) are given in Hz and unless mentioned otherwise, values of J_{HH} are presented. The letters n or p given to NMR shifts denote negative or positive signals in APT. Signal multiplicity: vbr. s = very broad singlet, dt = doublet of triplets, q = quartet, quint = quintet, dquint = doublet of quintets. $CDCl_3$ was used as solvent unless mentioned otherwise. MS spectra were recorded with a Hewlett–Packard MSD 5971A spectrometer (1989, EI 70 eV). IR spectra in KBr pellets were recorded with a NICOLET 740 USA spectrometer. All reagents were purchased from Sigma–Aldrich and used without additional purifications with the exception of aniline. The solvents were purified and dried according to standard procedures, for example, dioxane and methanol were dried with sodium and distilled prior to use. Chloroform was dried with calcium hydride and distilled prior to use.

Preparation of the Starting Compounds: Methyl 3,3,3-trifluoropyruvate (**2a**) was synthesized by the reaction of hexafluoropropene oxide with sulfuric acid according to our procedure.[13] Hemiaminal **4a** [methyl 2-(2-aminobenzylamino)-3,3,3-trifluoro-2-hydroxypropanoate] was synthesized according to our procedure.[14] The preparation of hemiaminal **4b** {methyl 3,3,3-trifluoro-2-hydroxy-2-[2-(methylamino)benzylamino]propanoate} is described below. Hemiaminal **4c** {methyl 3,3,3-trifluoro-2-hydroxy-2-[2-(*N*-methylamino)-anilino]propanoate} was not isolated due to its instability,[14] but used in situ for the preparation of **32**.

General Procedures for Three-Component Cyclization Reactions with 2-(Aminomethyl)aniline (Scheme 1): Detailed procedures together with analytical data are given in Supporting Information. All reactions were performed under a dry inert atmosphere in oven-dried apparatus.

Typical Procedure A: A solution of methyl 3,3,3-trifluoropyruvate (**2a**; 315 mg, 2 mmol) in dioxane (10 mL) was added dropwise to a solution of 2-(aminomethyl)aniline (**1a**; 245 mg, 2 mmol) in dioxane (10 mL) at room temp. with stirring. After 5 min, a solution of an oxo compound (**3**; 2 mmol) in dioxane (6 mL) was added dropwise to the mixture at room temp. with stirring, which was continued until the end of the reaction (100–200 h, NMR monitoring). Volatile components were removed by rotary evaporation and the crude product was separated to yield individual cyclization products by column chromatography (CC) through silica gel. For analytical purposes, some products were further purified by crystallization.

Typical Procedure B: In Procedure B, the same amounts of the reactants **1a**, **2a**, **3**, and solvent as in Procedure A. After mixing **1a** and **2a**, the mixture was heated to 100 °C, the oxo compound **3** was added dropwise and the mixture stirred for 1–2 h (end of the reaction). The resulting reaction mixture was cooled to room temp. and then treated as in Procedure A.

Cyclization with 3,3-Dimethylbutan-2-one (3b): Compound **6** was obtained from this reaction (for experimental details, see the Supporting Information).

(2*R,3a*S**)-3a-*tert*-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (6[c]):** ^1H NMR (300 MHz, CD_3COCD_3): δ = 1.07 (s, 9 H, CH_3), 2.48 (d, $^2J_{HH}$ = 15.4 Hz, 1 H, CH_2), 2.67 (d, $^2J_{HH}$ = 15.2 Hz, 1 H, CH_2), 4.38 (d, $^2J_{HH}$ = 16.8 Hz, 1 H, CH_2), 5.08 (d, $^2J_{HH}$ = 17 Hz, 1 H, CH_2), 6.12 (br. s, 2 H, OH and NH), 6.55–6.65 (m, 2 H, Ph-H), 6.92–7.02 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.5 MHz, CD_3COCD_3): δ = 26.49 [$(CH_3)_3C$], 41.53 (CH_2), 42.92 (CH_2), 43.02 [$C(CH_3)_3$], 77.81 [$CC(CH_3)_3$], 76.73 (q, $^2J_{CF}$ = 30.3 Hz, *C*-CF_3), 126.19 (q, $^1J_{CF}$ = 283.7 Hz, CF_3), 115.21, 116.28, 118.33, 128.01, 129.21, 144.63 (Ph), 169.99 (C=O) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ = –80.75 (s, CF_3) ppm.

(2*R,3a*R**)-3a-*tert*-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (6[t]):** ^1H NMR (300 MHz,

CD_3COCD_3): δ = 1.06 (*s*, 9 H, CH_3), 2.17 (d, $^2J_{HH}$ = 14.9 Hz, 1 H, CH_2), 2.61 (d, $^2J_{HH}$ = 14.9 Hz, 1 H, CH_2), 2.88 (br. s, 1 H, OH or NH), 4.34 (d, $^2J_{HH}$ = 16.5 Hz, 1 H, CH_2), 5.14 (d, $^2J_{HH}$ = 16.5 Hz, 1 H, CH_2), 5.92 (br. s, 1 H, OH or NH), 6.55–6.65 (m, 2 H, Ph-H), 6.92–7.02 (m, 2 H, Ph-H) ppm. ^{13}C NMR (75.5 MHz, CD_3COCD_3): δ = 26.41 [$(CH_3)_3C$], 39.29 (CH_2), 42.69 (CH_2), 43.39 [$C(CH_3)_3$], 77.48 [$CC(CH_3)_3$], 76.63 (q, $^2J_{CF}$ = 30.6 Hz, CCF_3), 126.18 (q, $^1J_{CF}$ = 283.6 Hz, CF_3), 115.69, 116.89, 118.46, 127.98, 129.15, 144.88 (Ph), 171.43 (C=O) ppm. ^{19}F NMR (376.6 MHz, $CDCl_3$): δ = –80.32 (s, CF_3) ppm. IR: $\tilde{\nu}$ = 1702 (s) cm^{-1}. $C_{16}H_{19}F_3N_2O_2$ (328.33): (mixture of **6^c/6^t** = 95:5): calcd. C 58.22, H 5.73, N 8.44; found C 58.53, H 5.83, N 8.53.

Cyclization with Hexan-2-one (3c)

(2*R,3a*R**)-3a-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (7^c):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (t, *J* = 7.7 Hz, 1 H), 7.04 (d, *J* = 7.7 Hz, 1 H), 6.86 (t, *J* = 7.7 Hz, 1 H), 6.63 (d, *J* = 8.2 Hz, 1 H), 5.09 (d, *J* = 17 Hz, 1 H), 4.21 (d, *J* = 17 Hz, 1 H), 4.10 (vbr. s, 1 H), 3.47 (br. s, 1 H), 2.61 (d, *J* = 14.8 Hz, 1 H), 2.18 (d, *J* = 14.8 Hz, 1 H), 1.98–1.86 (m, 1 H), 1.76–1.64 (m, 1 H), 1.35–1.24 (m, 4 H), 0.89 (t, *J* = 7.1 Hz, 3 H) ppm. ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 7.08 (t, *J* = 7.4 Hz, 1 H), 7.02 (d, *J* = 7.7 Hz, 1 H), 6.85 (t, *J* = 7.4 Hz, 1 H), 6.63 (d, *J* = 8.2 Hz, 1 H), 5.07 (d, *J* = 17 Hz, 1 H), 4.20 (d, *J* = 17 Hz, 1 H), 3.84 (br. s, 2 H), 2.60 (d, *J* = 14.8 Hz, 1 H), 2.18 (d, *J* = 14.8 Hz, 1 H), 1.98–1.85 (m, 1 H), 1.75–1.63 (m, 1 H), 1.35–1.25 (m, 4 H), 0.89 (t, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, CD_3COCD_3): δ = 169.1, 143.5, 129.1, 128.1, 126.2 (q, *J* = 283.4 Hz), 119.8, 117.5, 117.5, 77.7 (q, *J* = 30.3 Hz), 72.7, 40.6 (br. s), 40.4, 37.9, 26.6, 24.0, 14.9 ppm. ^{19}F NMR (75 MHz, $CDCl_3$): δ = –80.7 (s) ppm. ^{19}F NMR (75 MHz, CD_3COCD_3): δ = –79.5 (s) ppm. IR: $\tilde{\nu}$ = 1677 (s) cm^{-1}.

(2*R,3a*S**)-3a-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (7^t):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 7.7 Hz, 1 H), 7.02 (t, *J* = 7.3 Hz, 1 H), 6.0 (t, *J* = 7.6 Hz, 1 H), 6.66 (d, *J* = 8.1 Hz, 1 H), 6.09 (br. s, 1 H), 5.82 (br. s, 1 H), 4.88 (d, *J* = 17.2 Hz, 1 H), 4.28 (d, *J* = 17.2 Hz, 1 H), 2.50 (d, *J* = 14.8 Hz, 1 H), 2.43 (d, *J* = 14.8 Hz, 1 H), 1.98–1.78 (m, 2 H), 1.50–1.23 (m, 4 H), 0.88 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.8, 143.4, 129.1, 128.23, 126.2 (q, *J* = 284 Hz), 119.7, 117.2, 117.1, 77.8 (q, *J* = 30.3 Hz), 72.6, 42.0 (br. s), 40.4, 38.5, 26.7, 23.9, 14.9 ppm. ^{19}F NMR (75 MHz, $CDCl_3$): δ = –80.6 (s) ppm. ^{19}F NMR (75 MHz, CD_3COCD_3): δ = –79.2 (s) ppm. $C_{16}H_{19}F_3N_2O_2$ (328.33) (**7^c/7^t** = 97:3): calcd. C 58.53, H 5.83, N 8.53; found C 58.15, H 5.96, N 8.26.

(2*S,3a*S**)-3a-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (17^c):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.1 Hz, 1 H), 7.26 (dd, *J* = 7.2, 2.6 Hz, 1 H), 7.20–7.13 (m, 2 H), 5.99 (br. s, 1 H), 4.14 (d, *J* = 18.1 Hz, 1 H), 4.07 (d, *J* = 18.1 Hz, 1 H), 2.92 (d, *J* = 15.4 Hz, 1 H), 2.92 (br. s, 1 H), 2.07 (dq, *J* = 15.4, *J* = 1.1 Hz, 1 H), 1.95 (td, *J* = 12, 3.8 Hz, 1 H), 1.62–1.25 (m, 5 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 166.5, 135.3, 128.1, 128.0, 127.5, 126.4, 126.2 (q, *J* = 284 Hz), 123.4, 77.4 (q, *J* = 30.7 Hz), 75.4, 43.8, 41.5, 35.4, 26.9, 24.0, 14.9 ppm. ^{19}F NMR (75 MHz, $CDCl_3$): δ = –78.8 (d, *J* = 0.9 Hz) ppm. $C_{16}H_{19}F_3N_2O_2$ (328.33): calcd. C 58.53, H 5.83, N 8.53; found C 58.60, H 6.08, N 8.29.

(2*S,3a*R**)-3a-Butyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (17^t):** Characteristic signals: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.2 Hz, 1 H), 2.61 (d, *J* = 14.4 Hz, 1 H) ppm. ^{19}F NMR (75 MHz, CD_3COCD_3): δ = –78.9 (s) ppm.

The following new cyclization products were prepared and characterized (for experimental details, see the Supporting Information).

Cyclization with Acetophenone (3d) to Give Products 8 and 18: (2*R**,3a*S**)-3a-Phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**8^c**), (2*R**,3a*R**)-3a-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**8^t**), (2*S**,3a*R**)-3a-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**18^c**), and (2*S**,3a*S**)-3a-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**18^t**).

Cyclization with Propanal (3f) to Give Products 10, 20, and 33: (2*R**,3*S**,3a*R**)-2-Hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**10^{tc}**), (2*R**,3*R**,3a*S**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**10^{ct}**), (2*R**,3*S**,3a*S**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]-quinazolin-1(2*H*)-one (**10^{tt}**), (2*R**,3*R**,3a*R**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**10^{cc}**), (2*R**,3*S**,3a*R**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*a*]quinazolin-1(2*H*)-one (**20^{tc}**), (2*S**,3*S**,3a*R**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**20^{ct}**), and (2*R**,3*R**)-2-hydroxy-3-methyl-2-trifluoromethyl-3,9-dihydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**33^c**).

Cyclization with 2-Methylpropanal (3g) to Give Products 11 and 21: (2*R**,3a*R**)-2-Hydroxy-3,3-dimethyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**11^c**), (2*R**,3a*S**)-2-hydroxy-3,3-dimethyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**11^t**), (2*S**,3a*S**)-2-hydroxy-3,3-dimethyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**21^c**), and (2*S**,3a*R**)-2-hydroxy-3,3-dimethyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**21^t**).

Cyclization with Phenylacetaldehyde (3h) to Give Products 12 and 22: (2*R**,3*S**,3a*R**)-3-Phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**12^{tc}**), (2*R**,3*R**,3a*S**)-3-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**12^{ct}**), (2*S**,3*S**,3a*R**)-3-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**22^{ct}**), and (2*S**,3*S**,3a*R**)-3-phenyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**22^{tc}**).

Cyclization with Cyclohexanone (3k) to Give Products 14 and 24: (4a*S**,5*R**,13a*R**)-5-Hydroxy-5-trifluoromethyl-1,2,3,4,4a,5,8,13-octahydroindolo[7a,1-*b*]quinazolin-6-one (**14^{tc}**), (4a*R**,5*R**,13a*S**)-5-hydroxy-5-trifluoromethyl-1,2,3,4,4a,5,8,13-octahydroindolo-[7a,1-*b*]quinazolin-6-one (**14^{ct}**), (2*S**,2a*S**,6a*R**)-2-hydroxy-2-trifluoromethyl-2,2a,3,4,5,6,7,8-octahydroindolo[1,7a-*a*]quinazolin-1-one (**24^{ct}**), and (2*S**,2a*R**,6a*S**)-2-hydroxy-2-trifluoromethyl-2,2a,3,4,5,6,7,8-octahydroindolo[1,7a-*a*]quinazolin-1-one (**24^{tc}**).

Cyclization with Pentan-3-one (3l) to Give Products 25 and 28: (2*R**,3*S**,3a*R**)-3a-Ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**25^{tc}**), (2*R**,3*S**,3a*S**)-3a-ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**25^{tt}**), (2*R**,3*R**,3a*S**)-3a-ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**25^{ct}**), (2*R**,3*R**,3a*R**)-3a-ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**25^{cc}**), (2*S**,3*S**,3a*S**)-3a-ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**28^{cc}**), and

(2*S**,3*R**,3a*S**)-3a-ethyl-2-hydroxy-3-methyl-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**28^{tc}**).

Cyclization with Butan-2-one (3m) to Give Products 26, 27, and 29: (2*R**,3a*R**)-3a-Ethyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**26^{c}**), (2*R**,3a*S**)-3a-ethyl-2-hydroxy-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**26^{t}**), (2*S**,3a*R**)-3a-ethyl-2-hydroxy-2-trifluoromethyl-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1(2*H*)-one (**29^{t}**), and (2*R**,3*S**,3a*R**)-2-hydroxy-3,3a-dimethyl-2-trifluoromethyl-3,3a,4,9-tetrahydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (**27^{tc}**).

Cyclization of Hemiaminal 4b with Cyclopentanone (3j) to Give Product 31: (3a*R**,4*R**,12a*S**)-4-Hydroxy-12-methyl-4-trifluoromethyl-2,3,3a,4,7,12-hexahydrocyklopenta[1′,2′:2,3]pyrrolo[2,1-*b*]-quinazolin-5(1*H*)-one (**31^{ct}**) and (3a*S**,4*R**,12a*R**)-4-hydroxy-12-methyl-4-trifluoromethyl-2,3,3a,4,7,12-hexahydrocyclopenta-[1′,2′:2,3]pyrrolo[2,1-*b*]quinazolin-5(1*H*)-one (**31^{tc}**).

Cyclization with 2-[(Methylamino)methyl]aniline (2c) and Cyclopentanone (3j) to Give Product 32: (2*S**,2a*R**,5a*S**)-2-Hydroxy-6-methyl-2-trifluoromethyl-2a,3,4,5,6,7-hexahydrocyclopenta[1′,2′:2,3]pyrrolo[2,1-*a*]quinazolin-1(2*H*)-one (**32^{ct}**) and (2*S**,2a-*S**,5a*R**)-2-hydroxy-6-methyl-2-trifluoromethyl-2a,3,4,5,6,7-hexahydrocyclopenta[1′,2′:2,3]pyrrolo[2,1-*a*]quinazolin-1(2*H*)-one (**32^{tc}**).

Didehydrogenation of Cyclization Products

(2*R,3*R**)-2-Hydroxy-3-methyl-2-trifluoromethyl-3,9-dihydropyrrolo[2,1-*b*]quinazolin-1(2*H*)-one (33^{c}):** For the general procedure see below for the preparation of **34**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 3 H), 6.99 (d, J = 6.6 Hz, 1 H), 5.31 (br. s, 1 H), 4.71 (d, J = 15.9 Hz, 1 H), 4.54 (d, J = 15.9 Hz, 1 H), 3.03 (q, J = 7.1 Hz, 1 H), 1.41 (d, J = 7.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): characteristic signals: δ = 170.3p, 155.4p, 139.3p, 129.0n, 127.3n, 126.8n, 126.3n, 119.0p, 41.7p, 39.1n, 11.0n ppm. ^{19}F NMR (75 MHz, $CDCl_3$): δ = –80.4 (s) ppm. IR: $\tilde{\nu}$ = 1782 (s), 1656 (s) cm^{-1}. $C_{13}H_{13}F_3N_2O_2$ (284.23): calcd. C 54.93, H 3.90, N 9.85; found C 54.90, H 5.12, N 9.40.

2-Hydroxy-3,3-dimethyl-2-trifluoromethyl-3,9-dihydropyrrolo[2,1-*b*]-quinazolin-1(2*H*)-one (34): In a flask (25 mL), a mixture of **1a** (223 mg, 1.825 mmol), **2a** (593 mg, 3.8 mmol), 2-methylpropanal (**3g**, 134 mg, 1.858 mmol), and dioxane (21 mL) was heated at 100 °C. After 21 h, the mixture contained products **34**:**11^{c}** + **11^{t}** in a ratio of 48.6:51.4 (by ^{1}H NMR). Then **2a** (274 mg, 1.756 mmol) was added the flask and heating at 100 °C was continued for 17 h, which led to a mixture of **34/11^{c}** + **11^{t}** in a ratio of 83.5:16.5 (by ^{1}H NMR). A second portion of **2a** (154 mg, 0.987 mmol) was then added and heating continued for 24 h, after which the reaction mixture no longer contained the initially formed **11^{c}** and **11^{t}** (by ^{1}H NMR). Volatile components were removed (rotary evaporator, 120 °C, 0.66 kPa, 1.5 h) to obtain a crude oily product (1.99 g), which was twice purified by column chromatography, first (SiO_2 2 g, M60, Et_2O/$CHCl_3$, 1:4) afforded an oily material (731 mg), the second (1 g SiO_2, M60, Et_2O/$CHCl_3$, 1:4) afforded again an oily material (550 mg), which was separated by column chromatography (SiO_2 1 g, M60, petroleum ether/acetic acid, 4:1) into two fractions, the first contained pure **34** (254 mg) and the second contained around 50% of **34** (36 mg). Yield of reaction was 272 mg (50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, J = 7.7, 1.7 Hz, 1 H), 7.28 (t, J = 7.4 Hz, 1 H), 7.18 (dt, J = 1.7, 7.1 Hz, 1 H), 7.05 (d, J = 7.7 Hz, 1 H), 4.92 (d, J = 16.2 Hz, 1 H), 4.76 (d, J = 16.2 Hz, 1 H), 4.3 (vbr. s, 1 H), 1.53 (q, J_{HF} = 2.7 Hz, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 158.5, 139.7, 129.0, 127.2, 127.1, 126.3, 123.4 (q, J = 288 Hz), 119.4, 79.1 (q, J = 28.6 Hz), 46.2, 41.6, 23.8, 18.8 (q, J = 2.9 Hz) ppm. ^{19}F NMR (75 MHz, $CDCl_3$): δ = –74.7 (q, J = 2.2 Hz) ppm. IR: $\tilde{\nu}$ = 1768 (m), 1659 (s) cm^{-1}. $C_{14}H_{13}F_3N_2O_2$ (298.26): calcd. C 56.38, H 4.39, N 9.39; found C 56.32, H 4.53, N 9.11.

Supporting Information (see footnote on the first page of this article): Preparation the hemiaminals **4b** and **4c**, detailed procedures for the preparation of **5**–**36**, examples of NMR spectra, X-ray structures, NOE experiments.

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[1] a) A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115–122; b) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; c) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; d) J. Zhu, H. Bienaymé (Eds.), *Multicomponent Reactions*, Wiley-VCH, Weinheim, Germany, **2005**; e) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451–463; f) G. Guillena, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693–700.

[2] a) M. Tramontini, *Synthesis* **1973**, 703–707; b) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; c) A. Córdoba, *Acc. Chem. Res.* **2004**, *37*, 102–112; d) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; e) D. I. McDee, M. Dabiri, P. Salchi, L. Torkian, *ARKIVOC* **2011**, *11*, 156–164.

[3] a) C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937–6963; b) C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879–888.

[4] a) L. F. Tietze, *Synthesis* **1994**, 1185–1194; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) H. Pellisier, *Tetrahedron* **2006**, *62*, 1619–1665; d) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1–21.

[5] a) B. Dolenský, J. Kvíčala, O. Paleta, J. Čejka, J. Ondráček, *Tetrahedron Lett.* **1996**, *37*, 6939–6942; b) S. Ogawa, N. Iida, E. Tokunaga, M. Shiro, N. Shibata, *Chem. Eur. J.* **2010**, *16*, 7090–7095.

[6] a) S. Johne, *Prog. Drug Res.* **1982**, *26*, 259–341; b) A. Kamal, K. L. Reddy, V. Devaiah, N. Shankaraiah, M. V. Rao, *Mini-Rev. Med. Chem.* **2006**, *6*, 71–89.

[7] a) K. Seki, T. Watanabe, T. Suga, *J. Pharm. Pharmacol.* **1987**, *39*, 904–911; b) D. W. Combs, M. S. Rampulla, R. K. Russel, D. H. Klaubert, D. Ritchie, A. S. Meeks, T. Kirchner, *Drug Des. Delivery* **1990**, *6*, 241–254; c) N. R. El-Brollosy, *J. Heterocycl. Chem.* **2006**, *43*, 1435–1440; d) K. M. Amin, M. M. Kamel, M. M. Anwar, M. Khedr, Y. M. Syam, *Eur. J. Med. Chem.* **2010**, *45*, 2117–2131; e) J. B. Garrison, Y.-J. Shaw, C.-S. Chen, N. Kyprianou, *Cancer Res.* **2007**, *67*, 11344–11352; f) V. Chandregowda, A. K. Kush, R. G. Chandrasekara, *Eur. J. Med. Chem.* **2009**, *44*, 3046–3055; g) A. N. de Oliveira, C. C. Bocca, J. E. Carvalho, E. R. Joao, A. L. G. Ruiz, T. P. Silva, R. Rittner, N. F. Hoehr, *Eur. J. Med. Chem.* **2010**, *45*, 4339–4342.

[8] J. Elks, C. R. Ganellin, *Dictionary of Drugs*, *Chemical Data*, *Structures and Bibliographies*, Chapman and Hall, Cambridge, **1991**.

[9] H. Wang, A. Ganesan, *Tetrahedron Lett.* **1998**, *39*, 9097–9098.

[10] a) W. J. Houlihan, US Pat. 3428650, **1969** [*Chem. Abstr.* **1969**, *70*, 77785]; b) T. S. Sulkowski, M. A. Wille, US Pat. 3528981, **1970** [*Chem. Abstr.* **1971**, *74*, 3645].

[11] a) E. Spaeth, F. Keffner, N. Platzer, *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 699–702; b) P. L. Southwick, J. Casanova Jr., *J. Am. Chem. Soc.* **1958**, *80*, 1168–1173; c) N. J. Leonard, M. J. Martell Jr., *Tetrahedron Lett.* **1960**, *25*, 44–47; d) H. H. Wasserman, G. H. Kuo, *Tetrahedron Lett.* **1991**, *32*, 7131–7134; e) M. B. Rubin, R. Gleiter, *Chem. Rev.* **2000**, *100*, 1121–1164; f) J. F. Liu, P. Ye, K. Sprague, K. Sargent, D. Yohannes, C. M. Baldino, C. J. Wilson, S. C. Nag, *Org. Lett.* **2005**, *7*, 3363–3366.

[12] a) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, Chichester, **1991**; b) R. E. Banks, K. C. Lowe (Eds.), *Fluorine in Medicine in the 21st Century (Conference Papers)*, UMIST, Manchester, **1994**; c) A. J. Eliott, in: *Uses of Fluorine in Chemotherapy*, *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**; d) R. Filler, Y. Kobayashi, L. M. Yagupolskii (Eds.), *Organo-fluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, **1993**; e) I. Ojima, J. R. McCarthy, J. T. Welch (Eds.), *Biomedical Frontiers of Fluorine Chemistry*, ACS Symposium Series 639, American Chemical Society, Washington, DC, **1996**; f) V. A. Soloshonok (Ed.), *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*, Wiley, Chichester, **1999**; g) G. Theodoridis, *Fluorine Containing Agrochemicals*, in: *Advances in Fluorine Science*, vol. 2 (Ed.: A. Tressaud), Elsevier, Amsterdam, **2006**, pp. 121–175; h) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; i) J. P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, **2008**; j) A. Tressaud, G. Haufe (Eds.), *Fluorine and Health. Molecular Imaging Biomedical Materials and Pharmaceuticals*, Elsevier, Amsterdam, **2008**, pp. 553–778; k) S. Purser, P. R. Moore, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; l) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; m) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11; n) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081.

[13] B. Dolenský, J. Kvíčala, J. Paleček, O. Paleta, *J. Fluorine Chem.* **2002**, *115*, 67–74.

[14] B. Dolenský, J. Kvíčala, O. Paleta, *J. Fluorine Chem.* **2005**, *126*, 745–751.

[15] J. Paleček, O. Paleta, *Synthesis* **2004**, 521–524.

[16] B. Dolenský, J. Kvíčala, O. Paleta, J. Lang, H. Dvořáková, J. Čejka, *Magn. Reson. Chem.* **2010**, *48*, 375–385.

[17] A. E. Zelenin, N. D. Chkanikov, A. M. Ummov, A. F. Kolomiets, A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, 2074–2081.

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