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Enantioselective Synthesis of the Tricyclic Core of FR901483 Featuring a Rh-Catalyzed [2+2+2] Cycloaddition

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Abstract

An efficient approach to the tricyclic framework of FR901483 is described. The sequence features a [3, 3]-sigmatropic rearrangement of a cyanate into an isocyanate, followed by its subsequent asymmetric rhodium-catalyzed [2+2+2] cycloaddition with a terminal alkyne for the synthesis of the indolizidine core. The *aza*-tricyclic core is completed using an intramolecular benzoin reaction to close the last ring of the natural product. Through a model study of the key cycloaddition, we evaluated the impact of different substituents on the tether of the alkenyl isocyanate.

Indolizidine alkaloids are ubiquitous natural products isolated from a myriad of sources with wide diversity in their substitution pattern and stereochemistry (Figure 1).¹ FR901483 (**1**) is a fungal metabolite with immunosuppressive activity isolated from the fermentation broth of the fungus *Cladobotryum* sp. No. 11231.^{2,3} Its unprecedented and rigid molecular structure was ascertained by X-ray crystallographic analysis. In its crystal structure, the C-ring exists in a boat conformation and the indolizidine nitrogen lone pair is equatorial resulting in a *cis* fusion for the 6,5-bicycle. There is no data about the preferred conformation in solution.

Biosynthetically, the tricyclic core of FR901483 is most likely derived from an aldol reaction between C6 and C7.³ The *aza*-spiro[4.5]decane (A- and C-rings) may be accessed from an oxidative spiroannulation of a tyrosine dimer. The unique structure of FR901483 has generated tremendous interest from the synthetic community, an interest that has resulted in a number a total syntheses and several synthetic studies.^{4,5} All reported non-racemic syntheses to date involve one or two tyrosine derivatives as the source of chirality.⁶

Recent work from our group has demonstrated that indolizidine-based natural products can be assembled efficiently using a rhodium-catalyzed asymmetric [2+2+2] cycloaddition between alkenyl isocyanates (**2**) and exogenous alkynes (**3**) (Scheme 1).^{7–9} Extensive phosphoramidite ligand (L*) optimizations has led to a broader scope of heterocycles since one can control the selective formation of bicyclic lactams (**4**) or vinylogous amides (**5**), the latter arising from a CO migration. With terminal alkynes (**I**, **II**)⁷ and unsymmetrical

internal alkynes (**III**, **IV**),^{8a} single regioisomeric products are obtained in good yields and excellent enantioselectivities.

One of the main synthetic challenges associated with FR901483 is the stereoselective formation of the quaternary *aza*-stereocenter. A potential approach to this problem would rely on the development of a *vinyllogous amide selective* [2+2+2] cycloaddition between a functionalized alkenyl isocyanate (**6**) and *para*-methoxybenzylacetylene (**7**) (Scheme 2). To date, the effect of substitution on the isocyanate tether had been largely unexplored. In the particular case of FR901483, a carbonyl/alcohol precursor at C2 is desired in order to introduce the secondary methylamine functionality at a later stage in the synthesis.

Inherently, terminal alkyl alkynes such as **7**¹⁰ preferentially afford the lactam products (*cf.* Scheme 1, **4**). To overcome this preference, we have developed phosphoramidite ligands **L1** (GuiPhos) and **L2** as a solution to the selective formation of vinyllogous amide adducts with alkyl acetylenes.^{7d,e} Unfortunately, to date these two ligands have proven inefficient for the synthesis of indolizidines with *aza*-quaternary stereocenters, delivering the vinyllogous amide adducts with moderate product- and enantioselectivities. However, the impact of substitution on the tether was unknown and we speculated that it might play to our advantage. To identify the ideal functional group on the tether for our synthetic plan, we first investigated the cycloaddition of several model 1,1-disubstituted alkenyl isocyanates (Table 1).

As expected with GuiPhos (**L1**) as ligand, the vinyllogous amide products **11a–e** are slightly favored with ratios around 1:2 (entries 1, 3, 5, 7 and 9). Product selectivities may be sometimes improved using phosphoramidite **L2** (entries 2, 4, 6, 8 and 10). As previously observed, GuiPhos (**L1**) leads to higher enantioselectivities in comparison to **L2**.^{7d,e} However, the only substrate that affords a cycloadduct with a useful enantioselectivity (94% ee) is isocyanate **9b** with a *gem*-dimethyl substituent at C2 (entry 3). Alkenyl isocyanates **9c–e**, bearing C2 substituents that could potentially lead to the needed carbonyl/alcohol for the synthesis of FR901483, generate vinyllogous amide products with moderate enantioselectivities (54–65% ee).

At this point, we turned our attention to alkenes as carbonyl precursor on the tether (Table 2). Surprisingly, cycloadditions of isocyanate **12a** in the presence of **L1** or **L2** as ligand slightly favor the lactam product with very low enantioselectivities for the desired vinyllogous amide product **14b** (entries 1 and 2). Fortunately, this selectivity is reversed using tetrasubstituted alkene substituents (**12b–e**) in combination with **L1** or **L2**. More importantly, these dienyl isocyanates offer moderate to good enantioselectivities (entries 4, 5, 7, 8, 10, 11, 13 and 14). The real breakthrough came with the advent of CKPhos (**L3**), which improves upon **L1** and **L2** in both product- and enantioselectivity.^{7f} This electron-deficient TADDOL phosphoramidite ligand greatly overcomes the inherent preference of alkyl alkynes to form lactam indolizinones and mainly provides vinyllogous amide products **14** with excellent control of product- (up to 1:14), regio- (single isomer) and enantioselectivities (up to 99% ee). In this series of dienyl isocyanates, **12b** (entry 6) affords the best combination of results (product selectivity, yield and enantioselectivity).

Having established a vinylogous amide selective cycloaddition for the synthesis of models of the indolizidine core of FR901483, a more functionalized isocyanate was required. We identified two possible dienyl isocyanates (**15a** and **15b**) that could lead to the tricyclic core and ultimately to FR901483 (Scheme 3). These isocyanates would be derived from cyanates **16a** and **16b** respectively via a [3,3]-sigmatropic rearrangement. Cyanates **16a** and **16b** would be rapidly assembled from methallyl alcohol (**17**) and alkylating agents **18a** and **18b** respectively.

Treatment of methallyl alcohol (**17**) with 2 equivalents of *n*-BuLi followed by subsequent C-alkylation with either propargyl bromide **18a** or alkyl iodide **18b** yields allylic alcohols **19a–b** (Scheme 4).¹¹ The latter are then converted to the corresponding allylic bromides **20a–b**. Alkylation of ethyl benzoylacetate with the respective allylic bromide (**20a** or **20b**, neat at 50 °C) gives ketoesters **21a–b**, which are not isolated.¹² Addition of THF, paraformaldehyde and potassium carbonate triggers a cascade of transformations starting with an aldol reaction followed by a benzoyl transfer and a E1_{cb} elimination to afford α,β-unsaturated esters **22a** and **22b**. Double 1,2-addition of methyllithium on the esters leads to allylic alcohols **23a–b**, which are converted to the corresponding carbamates **24a–b** using trichloroacetyl isocyanate and a basic work-up.¹³ Dehydration with trifluoroacetic anhydride^{14f} generates cyanates **16a** and **16b**, which immediately undergo a [3,3]-sigmatropic rearrangement.¹⁴ That completes the synthesis of dienyl isocyanates **15a** and **15b**, which are isolated in very good yields upon distillation.

In a very convergent manner, all atoms of the FR901483 skeleton are brought together using a Rh-catalyzed asymmetric [2+2+2] cycloaddition (Scheme 5). In the presence of CKPhos (**L3**), the enantioselective cycloadditions of dienyl isocyanates **18a** and **18b** afford the desired indolizinones **25** and **26** respectively with excellent control of product- and enantioselectivities.

With the entire carbon scaffold of the target in place, we turned our attention at closing the last ring. Our first strategy was based on a 6-*exo-dig* radical cyclization of epoxyalkyne **27** (Equation 1).¹⁵ Titanocene chloride (TiCp₂Cl) is known to homolyze epoxide C-O bonds. The subsequent radical trapping with alkenes or alkynes (intra- or intermolecular) represents a valuable tool for organic synthesis. In our case, generation of a secondary radical **28** should trigger the ring closing reaction on the alkyne. Unfortunately, all attempts to access epoxide **27** from cycloadduct **25** failed.

Equation 1

En route to epoxide **27**, we observed something very interesting in one of our approaches (Scheme 6). Chlorination of cycloadduct **25** with *N*-chlorosuccinimide followed by a 1,4-

reduction mediated by Red-Al affords a single diastereomer of chloroketone **31**. Treatment of chloroketone **31** with sodium borohydride in a 1:1 mixture of dichloromethane and methanol leads to the formation of secondary alcohol **32** where the chlorine atom has been substituted by a methoxy group. Interestingly, this substitution occurs with retention of configuration at C6. The use of different solvent systems, different alcohol nucleophiles or stronger reducing agents only affords the over-reduced product (C6 = CH₂).

The stereochemistry of the C7-hydroxy can be easily rationalized from conformer *trans*-**31** (Scheme 7).¹⁶ Hydride delivery is clearly favored from the top face, away from the axial substituent at C9. To explain the retention of stereochemistry at C6, we invoke an anchimeric effect (neighboring group participation) from the nitrogen lone pair allowing the formation of aziridinium **34**, which can be opened with methanol to generate the observed product **32** (relative stereochemistry determined by nOe).¹⁷

At this point, we envisaged closing the last ring via an intramolecular benzoin reaction.¹⁸ To test this strategy, we synthesized ketoaldehyde **36** (Scheme 8). The four-step sequence starts with chlorination of cycloadduct **26** followed by a 1,4-reduction. We planned to use the C6-chlorine as a synthetic handle to introduce the secondary alcohol (*cf.* Schemes 6 and 7). Deprotection of the primary alcohol followed by Swern oxidation affords the benzoin precursor **36**.

It has long been known that thiazolylidene carbenes catalyze benzoin reactions of aldehydes via the mechanism proposed by Breslow in 1957.¹⁹ Recently developed, bicyclic triazolylidene carbenes, generated from the corresponding triazolium salts, typically outperform other carbene precursors in this transformation.²⁰ When ketoaldehyde **36** is submitted to pre-catalyst **39**²¹ in the presence of Hünig's base, no benzoin products, intra- or intermolecular (**37** or **38**), are observed (Scheme 8). Fortunately, using free carbene conditions previously developed by our group,^{21a} we were pleased to observe a full conversion of **36** and the formation of the desired benzoin product **37** (41% yield) along with a small amount of benzoin dimer **38**.^{22,23} The structure of **37** was supported by extensive NMR analysis, including COSY, APT, HMQC, and NOESY techniques.

In closing, we have assembled the entire scaffold of the immunosuppressive agent FR901483 with appropriate functionality in place to complete the synthesis. We have successfully developed a highly selective rhodium-catalyzed [2+2+2] cycloaddition of two functionalized alkenyl isocyanates and *para*-methoxybenzylacetylene for the enantioselective construction of the indolizidine core of FR901483. The complete sequence to the *aza*-tricyclic core also stars a [3,3]-sigmatropic rearrangement of a cyanate into an isocyanate and an intramolecular benzoin reaction to close the last ring of the natural product.

Experimental Section

General procedures for the rhodium-catalyzed enantioselective [2+2+2] cycloaddition

a) Less than 0.4 mmol of isocyanate—A flame-dried round bottom flask is charged with [Rh(C₂H₄)₂Cl]₂ (3 mol%) and the phosphoramidite ligand (6 mol%), and is fitted with

a flame-dried reflux condenser in an inert atmosphere (N₂) glove box. Upon removal from the glove box, a solution of alkyne (1.3 equiv.) and isocyanate (1.0 equiv.) in toluene is added via syringe followed by an additional rinse of toluene to wash down the remaining residue and reach the final concentration (0.04 M based on isocyanate). The resulting solution is heated to 110 °C in an oil bath for 16–48 hours. The reaction mixture is cooled to ambient temperature, concentrated in vacuo, and purified by flash column chromatography (gradient elution typically 40:60 Hex:EtOAc for the lactam adduct followed by 100% EtOAc or 20:1 EtOAc:MeOH for the vinylogous amide adduct).

b) From 0.4 to 12 mmol of isocyanate—A flame-dried round bottom flask is charged with [Rh(C₂H₄)₂Cl]₂ (2 mol%) and the phosphoramidite ligand (4 mol%), and is fitted with a flame-dried reflux condenser in an inert atmosphere (N₂) glove box. Upon removal from the glove box, toluene is added (90% of the amount needed to reach 0.08 M). A solution of alkyne (1.3 equiv.) and isocyanate (1.0 equiv.) in toluene is added via syringe followed by an additional rinse of toluene to wash down the remaining residue and reach the final concentration (0.08 M based on isocyanate). The resulting solution is heated to 110 °C in an oil bath for 24–48 hours (the disappearance of the isocyanate is followed by NMR of aliquots).

c) More than 12 mmol of isocyanate—A vial is charged with [Rh(C₂H₄)₂Cl]₂ (2 mol%) and the phosphoramidite ligand (4 mol%) in an inert atmosphere (N₂) glove box. Upon removal from the glove box, the contents of the vial are rapidly transferred into a flame-dried round-bottom flask fitted with a reflux condenser. Toluene (90% of the amount needed to reach 0.08 M) is then added using a funnel and the system is evacuated and refilled with Ar twice. A solution of alkyne (1.3 equiv.) and isocyanate (1.0 equiv.) in toluene is added via syringe followed by an additional rinse of toluene to wash down the remaining residue and reach the final concentration (0.08 M based on isocyanate). The resulting solution is heated to 110 °C in an oil bath for 36–48 hours (the disappearance of the isocyanate is followed by NMR of aliquots).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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22. A screen of pre-catalysts (thiazolium and triazolium salts) did not improve the yield of this cyclization.
23. At lower concentration (0.01 M instead of 0.05 M) only the starting material was observed. Increasing the temperature or the catalyst loading did not affect the yield, while lowering the temperature or the catalyst loading led to no ring-formed product.

Biographies

Stéphane Perreault was born and raised in Thetford Mines (Qc, Canada) and received his BSc in chemistry in 2002 from Université de Sherbrooke. He earned his PhD degree (NSERC scholarship) in 2007 under the direction of Professor Claude Spino from the same institution. He was the recipient of the Governor General's Academic Gold Medal. From 2008 to 2010, he was a FQRNT postdoctoral fellow at Colorado State University with Professor Tomislav Rovis. In 2010, he joined Gilead Sciences where he is currently working as a research scientist in medicinal chemistry.

Tomislav Rovis was born in Zagreb in the former Yugoslavia but was largely raised in Southern Ontario, Canada. Following his undergraduate studies at the University of Toronto, he earned his Ph.D. degree at the same institution in 1998 under the direction of Professor Mark Lautens. From 1998–2000, he was an NSERC postdoctoral fellow at Harvard University with Professor David A. Evans. In 2000, he began his independent career at Colorado State University and was promoted in 2005 to Associate Professor and in 2008 to Professor. His group's accomplishments have been recognized by a number of awards including an NSF CAREER and a Roche Excellence in Chemistry award. He has been named a GlaxoSmithKline Scholar, Amgen Young Investigator, Eli Lilly Grantee, Alfred P. Sloan Fellow, a Monfort Professor at Colorado State University. He currently holds the John K. Stille Chair in Chemistry.

Figure 1.
Structure and conformation of (-)-FR901483.

Alkyne scope

Scheme 1.

Scope of the Rh-catalyzed enantioselective [2+2+2] cycloadditions of alkenyl isocyanates and exogenous alkynes.

Scheme 2.
General approach to FR901483.

Scheme 3.
Retrosynthesis of dienyl isocyanates **15a–b**.

RCH ₂ X	Yield of 19 (%)	Yield of 20 (2 steps, %)	Yield of 22 (%)	Yield of 24 (2 steps, %)	Yield of 15 (%)
18a	23	81	89	96	85
18b	72	82	75	67	92

Scheme 4.

a) i. *n*-BuLi, TMEDA, Et₂O, −78 °C; ii. **18a** or **18b**, −78 to 23 °C. b) MsCl, Et₃N, CH₂Cl₂, 0 °C. c) LiBr, THF, 0 to 23 °C. d) i. ethyl benzoylacetate, K₂CO₃, cat. NaI, neat, 50 °C; ii. K₂CO₃, (CH₂O)_n, THF, 65 °C. e) MeLi, CeCl₃, Et₂O, 0 °C. f) i. trichloroacetyl isocyanate, CH₂Cl₂, 0 °C; ii. K₂CO₃, MeOH, H₂O, −78 to 23 °C. g) TFAA, Me₂NEt, CH₂Cl₂, 0 °C.

Scheme 5.

a) 2 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, 4 mol% **L3**, PhMe (0.08 M), 110 °C, 36–48 hours.

Scheme 6.

a) NCS, CH₂Cl₂, -78 °C. b) Red-Al, THF, -78 °C. c) NaBH₄, MeOH, CH₂Cl₂, -78 to 23 °C (77%, 3 steps).

Scheme 7.
Rationale for the stereochemistry of 32.

Scheme 8.

a) NCS, CH_2Cl_2 , -78°C . b) Red-Al, THF, -78°C (85%, 2 steps). c) 1% HCl in MeOH, 0°C (90%). d) i. $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C ; ii. Et_3N , -78 to 23°C (87%). e) i. **39** (50 mol%), KHMDS (45 mol%), PhMe; ii. high vacuum; iii. **36**, PhMe (0.05 M), 70°C (41%).

Table 1

Model study examining tether substituents.

9a-e	7	10a-e	11a-e
Entry	Isocyanate	Ligand	Ratio (10/11)	Yld 11 ^{b,c} (%)	ee 11 ^d (%)
1		L1	1 : 2.5	50	65
2		L2	1 : 3	52	14
3		L1	1 : 2	44 (70)	94
4		L2	1 : 4	62 (70)	82
5		L1	1 : 1.5	42	55
6		L2	1 : 1.5	42	8
7		L1	1 : 1.5	8 (15) ^e	64
8		L2	1 : 7.5	45 (85) ^e	63
9		L1	1 : 1.5	24	58
10		L2	(dr 11e = 3 : 2) 1 : 1.5	15 29	54 12
			(dr 11e = 1 : 1)	24	8

^{a)} 3 mol% [Rh(C₂H₄Cl)₂], 6 mol% phosphoramidite ligand, 1.3 equiv. of **7**, PhMe (0.04 M), 110 °C, 16 hours.

^{b)} Isolated yield of **11**.

^{c)} 100% conversion of **9** unless specified in parentheses.

d) Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

e) Reaction done at 140 °C in xylene.

Table 2

Model study using allylic isocyanates.

Entry	Isocyanate	Ligand	Ratio 13/14	Yld 14 ^{b,c} (%)	ee 14 ^d (%)
1	$R_1 = R_2 = \text{H}$ 12a	L1	1.3 : 1	27	5
2		L2	1.1 : 1	31	46
3		L3	1 : 13	57	94
4	$R_1 = R_2 = \text{Me}$ 12b	L1	1 : 1.3	44	89
5		L2	1 : 2	52	71
6		L3	1 : 7.5	85	98
7	$R_1 = R_2 = \text{Et}$ 12c	L1	1 : 1.8	48	92
8		L2	1 : 3	53	79
9		L3	1 : 5.5	80	98
10	$R_1 = R_2 = \text{Bu}$ 12d	L1	1 : 2	51	92
11		L2	1 : 3.7	67	81
12		L3	1 : 5	64	99
13	$R_1-R_2 = (\text{CH}_2)_5$ 12e	L1	1 : 1.5	51	91
14		L2	1 : 2.5	60	71
15	$R_1 = \text{H}, R_2 = i\text{-Pr}$ 12f^e	L1	1 : 1.3	31	54
16		L2	1 : 1.7	35	9
17		L3	1 : 14	66	99

^{a)} 3 mol% $[\text{Rh}(\text{C}_2\text{H}_4)\text{Cl}]_2$, 6 mol% phosphoramidite ligand, 1.3 equiv. of **7**, PhMe (0.04 M), 110 °C, 16 hours.

^{b)} Isolated yield of **14**.

^{c)} 100% conversion of **12** unless specified in parentheses.

^{d)} Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

^{e)} 10:1 E/Z (confirmed by nOe).