Enantioselective Synthesis of the Tricyclic Core of FR901483 Featuring a Rhodium-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 to 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 azatricyclic 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.

Key words: [3,3]-sigmatropic rearrangement, isocyanate, [2+2+2] cycloaddition, indolizidine, FR901483

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.

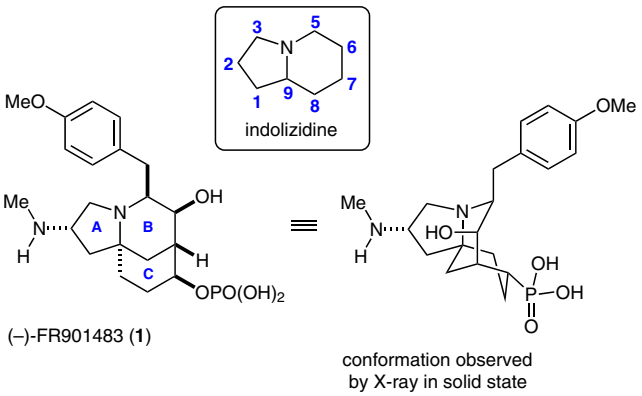
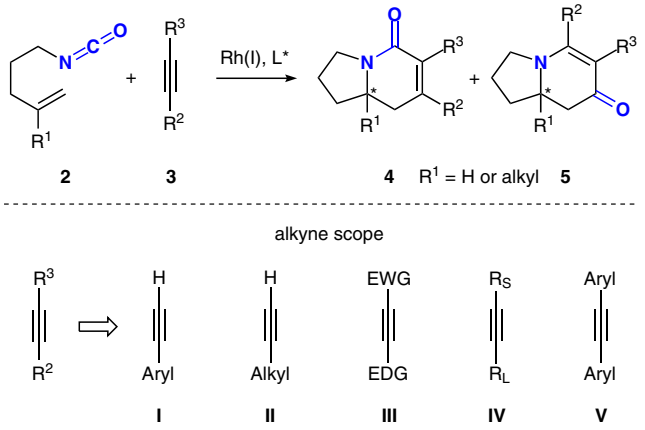


Figure 1 Structure and conformation of (–)-FR901483

Biosynthetically, the tricyclic core of FR901483 is most likely derived from an aldol reaction between C6 and C7.[3] The azaspiro[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 nonracemic 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 have 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** and **II**[7] and unsymmetrical internal alkynes **III** and **IV**,[8a] single regioisomeric products are obtained in good yields and excellent enantioselectivities.



Scheme 1 Scope of the rhodium-catalyzed enantioselective [2+2+2] cycloadditions of alkenyl isocyanates and exogenous alkynes

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 vinylogous amide selective [2+2+2] cycloaddition between a functionalized alkenyl isocyanate **6** and 4-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.

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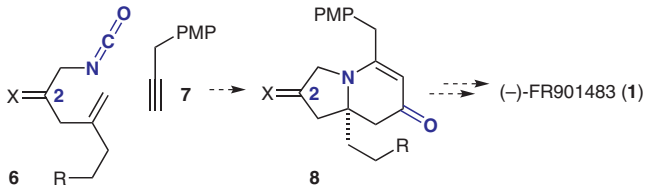


Scheme 2 General approach to FR901483; PMP = 4-MeOC$_6$H$_4$

Inherently, terminal 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** (Figure 2) as a solution to the selective formation of vinylogous amide adducts with alkyl-substituted acetylenes.[7d,e] Unfortunately, to date these two ligands have proven inefficient for the synthesis of indolizidines with aza-quaternary stereocenters, delivering the vinylogous 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 vinylogous amide products **11a–e** are slightly favored with ratios **10**/**11** 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 vinylogous 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, cycload-

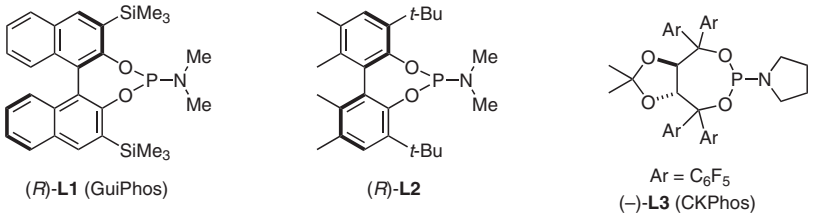


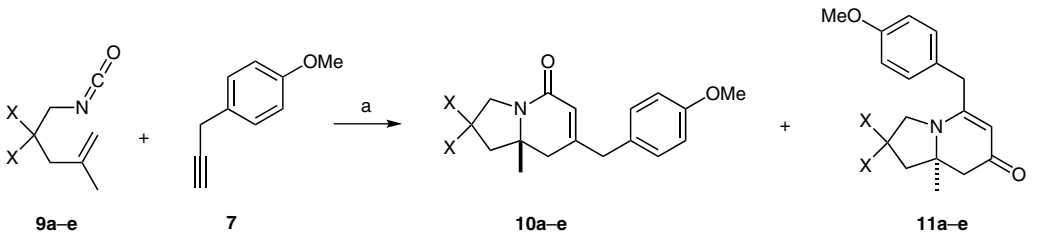
Figure 2 Ligands **L1**, **L2**, and **L3**

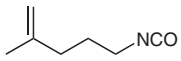
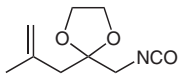
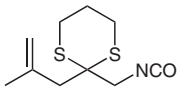
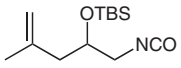
Biographical Sketches

Stéphane Perreault was born and raised in Thetford Mines (Quebec, Canada) and received his B.Sc. in chemistry in 2002 from Université de Sherbrooke. He earned his Ph.D. 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 to 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.

Table 1 Model Study Examining Tether Substituents[a]



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

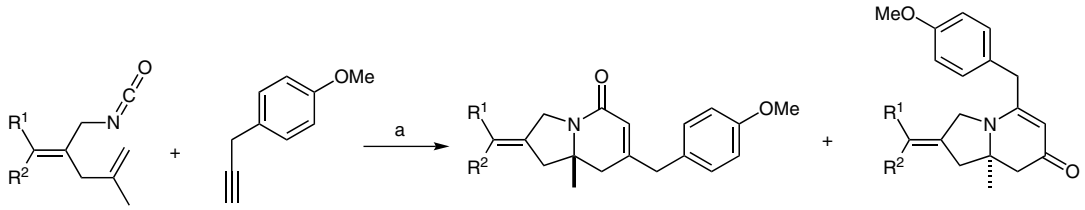
[a] Reaction conditions: (a) $[Rh(C_2H_4)Cl]_2$ (3 mol%), phosphoramidite ligand (6 mol%), **7** (1.3 equiv), toluene (0.04 M), 110 °C, 16 h.
[b] Isolated yield of **11**.
[c] 100% conversion of **9** unless specified in parentheses.
[d] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.
[e] Reaction performed at 140 °C in xylene.

ditions of isocyanate **12a** in the presence of **L1** or **L2** as ligand slightly favor the lactam product with very low enantioselectivities for the desired vinylogous 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-substituted acetylenes to form lactam indolizinones and mainly provides vinylogous 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 butyllithium (2 equiv) 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 into the corresponding allylic bromides **20a**,**b**. Alkylation of ethyl benzoylacetate with the respective allylic bromide **20a** or **20b** (neat, 50 °C) gives keto esters **21a**,**b**, which are not isolated.[12] Addition of tetrahydrofuran, paraformaldehyde, and potassium carbonate triggers a

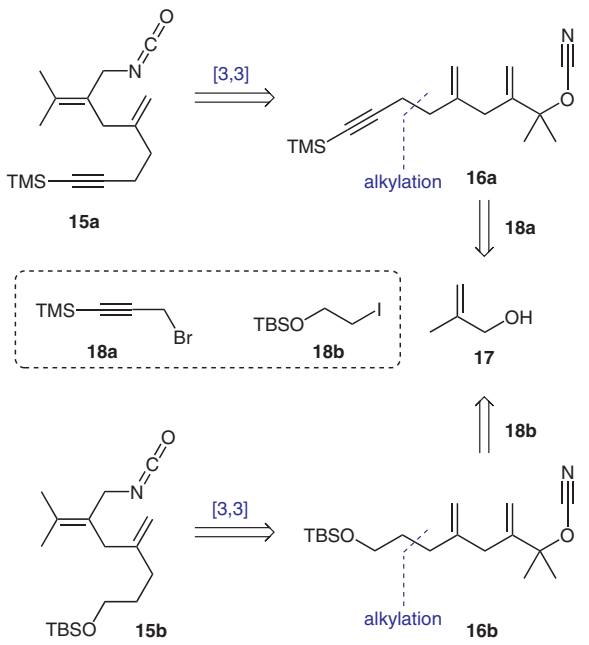
Table 2 Model Study Using Allylic Isocyanates[a]



12a–f **7** **13a–f** **14a–f**

Entry	Isocyanate			Ligand	Ratio (**13**/**14**)	Compound **14**	
	R^1	R^2				Yield[b,c] (%)	ee[d] (%)
1	H	H	**12a**	**L1**	1.3:1	27	5
2				**L2**	1.1:1	31	46
3				**L3**	1:13	57	94
4	Me	Me	**12b**	**L1**	1:1.3	44	89
5				**L2**	1:2	52	71
6				**L3**	1:7.5	85	98
7	Et	Et	**12c**	**L1**	1:1.8	48	92
8				**L2**	1:3	53	79
9				**L3**	1:5.5	80	98
10	Bu	Bu	**12d**	**L1**	1:2	51	92
11				**L2**	1:3.7	67	81
12				**L3**	1:5	64	99
13	$(CH_2)_5$		**12e**	**L1**	1:1.5	51	91
14				**L2**	1:2.5	60	71
15	H	*i*-Pr	**12f**[e]	**L1**	1:1.3	31	54
16				**L2**	1:1.7	35	9
17				**L3**	1:14	66	99

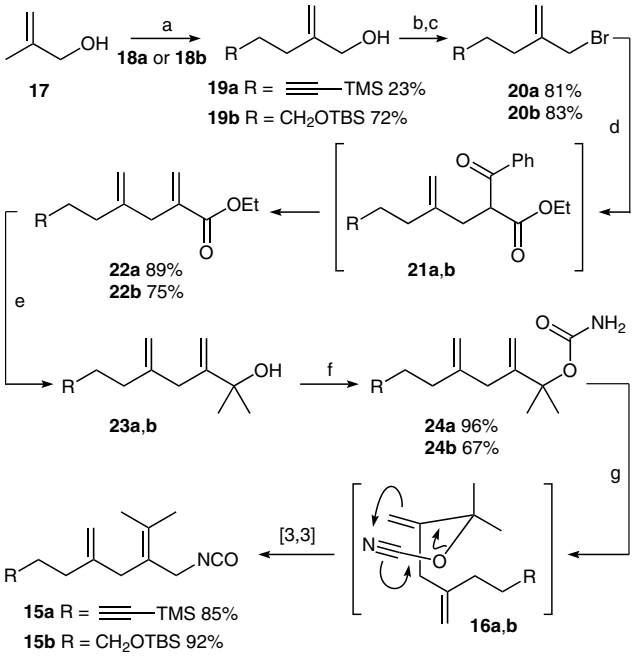
[a] Reaction conditions: (a) $[Rh(C_2H_4)Cl]_2$ (3 mol%), phosphoramidite ligand (6 mol%), **7** (1.3 equiv), toluene (0.04 M), 110 °C, 16 h.
[b] Isolated yield of **14**.
[c] 100% conversion of **12** unless specified in parentheses.
[d] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.
[e] Ratio *E*/*Z* 10:1 (confirmed by NOE).



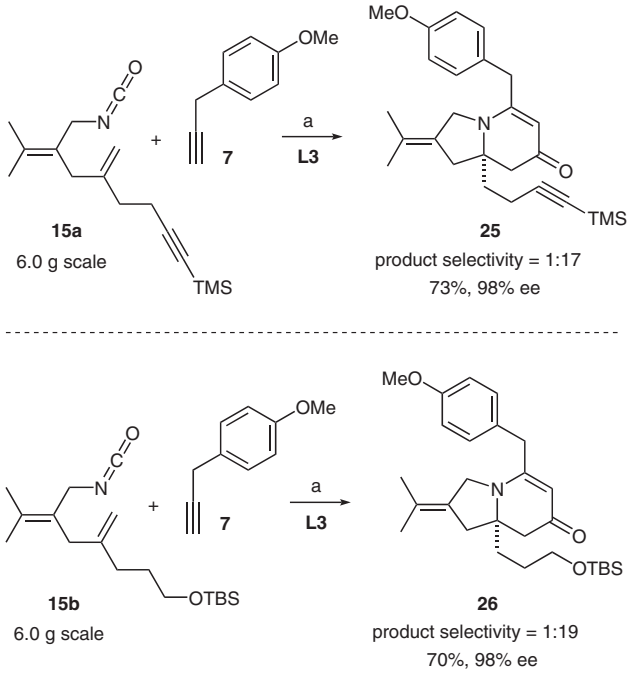
Scheme 3 Retrosynthesis of dienyl isocyanates **15a**,**b**

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**,**b**. Double 1,2-addition of methyllithium on the esters leads to allylic alcohols **23a**,**b**, which are converted into the corresponding carbamates **24a**,**b** using trichloroacetyl isocyanate and a basic workup.[13] Dehydration with trifluoroacetic anhydride[14f] generates cyanates **16a**,**b**, which immediately undergo a [3,3]-sigmatropic rearrangement.[14] This completes the synthesis of dienyl isocyanates **15a**,**b**, 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 rhodium-catalyzed asymmetric [2+2+2] cycloaddition (Scheme 5). In the presence of CKPhos (**L3**), the enantioselective cycloadditions of dienyl isocyanates **15a** and **15b** afford the desired indolizinones **25** and **26**, respectively, with excellent control of product- and enantioselectivities.

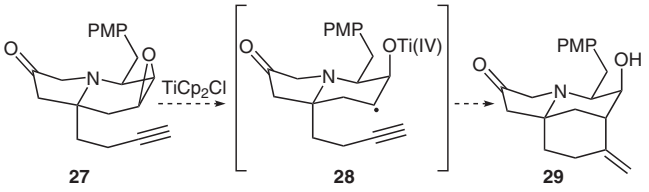


Scheme 4 *Reagents and conditions:* (a) (i) BuLi, TMEDA, Et_2O, –78 °C; (ii) **18a** or **18b**, –78 °C to 23 °C; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) LiBr, THF, 0 °C to 23 °C; (d) (i) ethyl benzoylacetate, K_2CO_3, NaI (cat.), neat, 50 °C; (ii) K_2CO_3, $(CH_2O)_n$, THF, 65 °C; (e) MeLi, $CeCl_3$, Et_2O, 0 °C; (f) (i) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C; (ii) K_2CO_3, MeOH, H_2O, –78 °C to 23 °C; (g) TFAA, Me_2NEt, CH_2Cl_2, 0 °C.



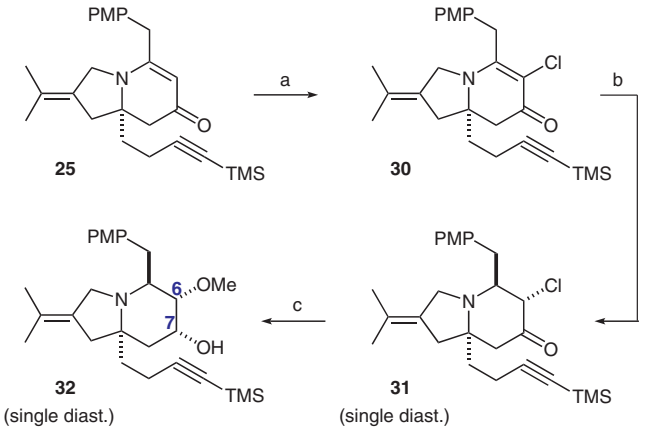
Scheme 5 *Reagents and conditions:* (a) $[Rh(C_2H_4)_2Cl]_2$ (2 mol%), **L3** (4 mol%), toluene (0.08 M), 110 °C, 36–48 h.

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 ($TiCp_2Cl$) 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.



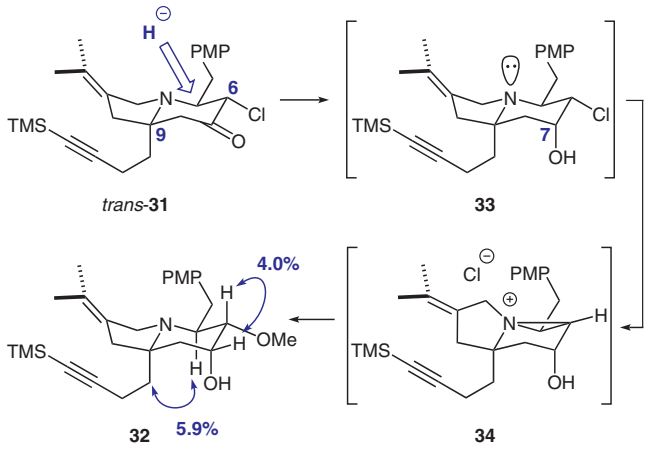
Equation 1

En route to epoxide **27**, we observed something very interesting in one of our approaches (Scheme 6). Chlorination of cycloadduct **25** with *N*-chlorosuccinimide to give **30** followed by a 1,4-reduction mediated by Red-Al affords a single diastereomer of chloro ketone **31**. Treatment of chloro ketone **31** with sodium borohydride in dichloromethane and methanol (1:1) 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 = CH_2).

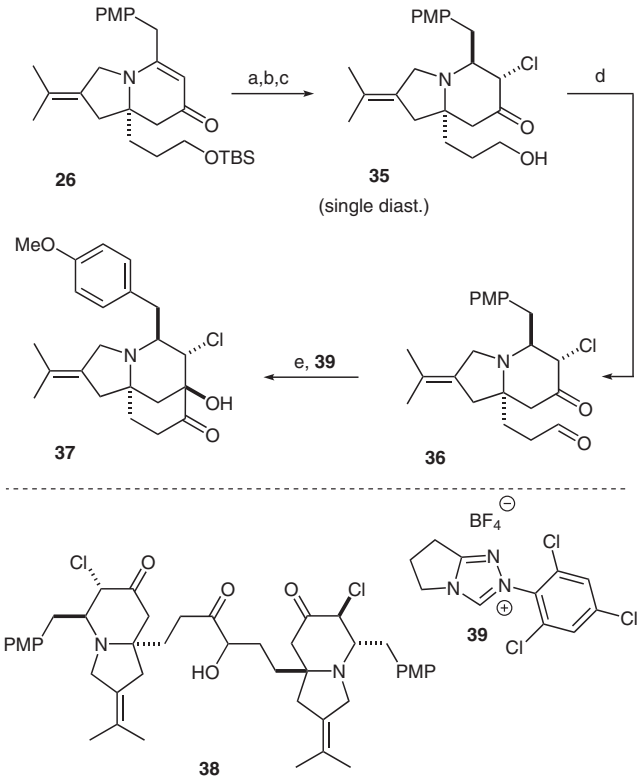


Scheme 6 *Reagents and conditions:* (a) NCS, CH_2Cl_2, –78 °C; (b) Red-Al, THF, –78 °C; (c) $NaBH_4$, MeOH, CH_2Cl_2, –78 °C to 23 °C (77%, 3 steps).

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]



Scheme 7 Rationale for the stereochemistry of **32**



Scheme 8 *Reagents and conditions:* (a) NCS, CH_2Cl_2, –78 °C; (b) Red-Al, THF, –78 °C (85%, 2 steps); (c) 1% HCl–MeOH, 0 °C (90%); (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C; (ii) Et_3N, –78 °C to 23 °C (87%); (e) (i) **39** (50 mol%), KHMDS (45 mol%), toluene; (ii) high vacuum; (iii) **36**, toluene (0.05 M), 70 °C (41%).

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 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 out-perform 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 4-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.

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. THF and CH_2Cl_2 were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Et_3N, DIPEA, and MeOH were distilled from CaH_2. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40–63 μm 60A. ^1H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers at r.t., from $CDCl_3$ or acetone-d_6. ^{13}C NMR spectra were recorded a Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at r.t., from $CDCl_3$ (δ = 77.0). LR-MS and HRMS were recorded on a Fisons VG Autospec spectrometer. HPLC spectra were obtained on an Angilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter.

2-(ω-Silylalkyl)allyl Bromides 20a,b; General Procedure

To a 0.1 M soln of allylic alcohol **19a**,**b** (1.0 equiv) in CH_2Cl_2 at –78 °C were added Et_3N (2.2 equiv) and MsCl (2.0 equiv). The mixture was allowed to warm to 0 °C over a period of 3 h and quenched with sat. aq $NaHCO_3$. CH_2Cl_2 was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 ×) The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. To a 0.2 M soln of the crude mesylate in THF at 0 °C was added LiBr (4.0 equiv). The mixture was stirred at 23 °C for 3–6 h and quenched with brine. The phases were separated and the aqueous phase was extracted with Et_2O (2 ×). The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (pentane).

1-(Bromomethyl)-6-(trimethylsilyl)hex-1-en-5-yne (20a)

Colorless oil; yield: 9.20 g (81%).

^1H NMR (300 MHz, $CDCl_3$): δ = 5.23 (s, 1 H), 5.02 (s, 1 H), 4.0 (s, 2 H), 2.45–2.41 (m, 4 H), 0.14 (s, 9 H).

1-(Bromomethyl)-5-(*tert*-butyldimethylsiloxy)pent-1-ene (20b)
Colorless oil; yield: 13.2 g (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (s, 1 H), 4.98–4.97 (m, 1 H), 3.98 (s, 2 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 2.27 (t, *J* = 7.7 Hz, 2 H), 1.74–1.64 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

Ethyl 2-(2,4-Dimethylenealkyl)acrylates 22a,b; General Procedure
To a mixture of ethyl benzoylacetate (90% from Aldrich, 1.1 equiv) and allylic bromide **20a**,**b** (1.0 equiv) was added K_2CO_3 (1.5 equiv) and NaI (0.15 equiv). The flask was sealed with a septum and the mixture was stirred at 50 °C for 24–48 h (the disappearance of the allylic bromide and the in situ generated allylic iodide were followed by NMR aliquot). THF (0.7 M), K_2CO_3(1.0 equiv), and paraformaldehyde (2.0 equiv) were then added. The mixture was stirred at 65 °C for 24–48 h (the disappearance of the intermediate was followed by TLC). After cooling, the mixture was quenched with H_2O. Et_2O was added, the phases were separated, and the aqueous phase was extracted with Et_2O (2 ×). The organic layers were combined, washed with brine (1 ×), dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane–Et_2O, 20:1).

Ethyl 2,4-Dimethylene-8-(trimethylsilyl)oct-7-ynoate (22a)
Colorless oil; yield: 8.84 g (89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.24 (s, 1 H), 5.57 (s, 1 H), 4.88 (s, 1 H), 4.82 (s, 1 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 3.03 (s, 2 H), 2.37 (t, *J* = 7.7 Hz, 2 H), 2.24 (t, *J* = 7.7 Hz, 2 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 0.13 (s, 9 H).

Ethyl 7-(*tert*-Butyldimethylsiloxy)-2,4-dimethyleneheptanoate (22b)
Colorless oil; yield: 10.5 g (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.22 (s, 1 H), 5.55–5.54 (m, 1 H), 4.84 (s, 1 H), 4.75 (s, 1 H), 4.19 (q, *J* = 7.3 Hz, 2 H), 3.61 (t, *J* = 6.3 Hz, 2 H), 3.02 (s, 2 H), 2.07 (t, *J* = 7.7 Hz, 2 H), 1.71–1.62 (m, 2 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

2-Methyl-3,5-dimethylenealkan-2-ols 23a,b; General Procedure
A flame-dried round bottom flask was charged with anhyd $CeCl_3$ (2.0 equiv) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, THF (0.1 M based on α,β-unsaturated ester) was added and the suspension was stirred for 1 h at 23 °C. After cooling to 0 °C, the α,β-unsaturated ester **22a**,**b** (1.0 equiv) was added and the mixture was stirred 1 h at 0 °C. After cooling to –40 °C, MeLi (1.6 M in Et_2O, 2.0 equiv) was added over 30 min with a syringe pump. The mixture was stirred for 5 min and quenched with H_2O. Et_2O was added, the phases were separated, and the aqueous phase was extracted with Et_2O (2 ×). The organic layers were combined, washed with brine (1 ×), dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product was used without further purification.

2-Methyl-3,5-dimethylene-9-(trimethylsilyl)non-8-yn-2-ol (23a)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18 (s, 1 H), 4.93 (s, 1 H), 4.90 (s, 1 H), 4.82 (s, 1 H), 2.87 (s, 2 H), 2.38 (t, *J* = 7.7 Hz, 2 H), 2.24 (t, *J* = 7.7 Hz, 2 H), 1.36 (s, 6 H), 0.13 (s, 9 H).

8-(*tert*-Butyldimethylsiloxy)-2-methyl-3,5-dimethyleneoctan-2-ol (23b)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (s, 1 H), 4.89–4.88 (m, 1 H), 4.84 (s, 1 H), 4.81 (s, 1 H), 3.61 (t, *J* = 6.2 Hz, 2 H), 2.07 (t, *J* = 7.4 Hz, 2 H), 1.71–1.61 (m, 2 H), 1.35 (s, 6 H), 0.88 (s, 9 H), 0.04 (s, 6 H).

2-Methyl-3,5-dimethylenealkan-2-yl Carbamates 24a,b; General Procedure
To a 0.2 M soln of allylic alcohol **23a**,**b** (1.0 equiv) in CH_2Cl_2 at 0 °C was added trichloroacetyl isocyanate (1.05 equiv) dropwise. The soln was stirred 0 °C for 45 min and the solvent was evaporated under reduced pressure. MeOH–H_2O (2:1, 0.1 M) was then added to the resulting precipitate. The suspension was cooled to 0 °C and CH_2Cl_2 was added until completely soluble. K_2CO_3 (3.0 equiv) was added. The mixture was allowed to warm slowly to 23 °C and stirred for 16 h (for **23a**, the mixture was kept at 0 °C for 8 h to minimize the desilylation reaction). MeOH was evaporated under reduced pressure and the aqueous phase was extracted with CH_2Cl_2 (3 ×). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1).

2-Methyl-3,5-dimethylene-9-(trimethylsilyl)non-8-yn-2-yl Carbamate (24a)
Yellowish oil; yield: 7.94 g (96%, 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10 (s, 1 H), 4.95 (s, 1 H), 4.90 (s, 1 H), 4.89 (s, 1 H), 4.56 (br s, 2 H), 2.83 (s, 2 H), 2.36 (t, *J* = 6.9 Hz, 2 H), 2.22 (t, *J* = 6.9 Hz, 2 H), 1.56 (s, 6 H), 0.13 (s, 9 H).

8-(*tert*-Butyldimethylsiloxy)-2-methyl-3,5-dimethyleneoctan-2-yl Carbamate (24b)
Yellowish oil; yield: 7.72 g (67%, 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.10 (s, 1 H), 4.89 (s, 1 H), 4.88 (s, 1 H), 4.84 (s, 1 H), 4.48 (br s, 2 H), 3.61 (t, *J* = 6.6 Hz, 2 H), 2.82 (s, 2 H), 2.04 (t, *J* = 7.7 Hz, 2 H), 1.71–1.64 (m, 2 H), 1.56 (s, 6 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

2-Isopropylidene-4-methylenealkyl Isocyanate 15a,b; General Procedure
To a cold soln (0 °C) of allyl carbamate **24a**,**b** (1.0 equiv) in CH_2Cl_2 (0.2 M) was added Me_2NEt (2.6 equiv). Then, TFAA (1.2 equiv, freshly distilled over P_2O_5) was added dropwise to the soln at 0 °C. After stirring at 0 °C for 30 min, the mixture was concentrated under reduced pressure. Hexane was then added to the residual oil. The biphasic mixture was stirred for 10 min and allowed to decant. After decantation, the same process was repeated one more time with the residual oil before removing the hexane under reduced pressure. The crude isocyanate was then purified by short path distillation.

2-Isopropylidene-4-methylene-8-(trimethylsilyl)oct-7-ynyl Isocyanate (15a)
Yellowish oil; yield: 6.35 g (85%); bp 100 °C/4 mbar.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (s, 1 H), 4.73 (s, 1 H), 3.82 (s, 2 H), 2.86 (s, 2 H), 2.38 (t, *J* = 7.3 Hz, 2 H), 2.20 (t, *J* = 7.3 Hz, 2 H), 1.80 (s, 3 H), 1.71 (s, 3 H), 0.14 (s, 9 H).

7-(*tert*-Butyldimethylsiloxy)-2-isopropylidene-4-methyleneheptyl Isocyanate (15b)
Yellowish oil; yield: 6.75 g (92%); bp 120 °C/2 mbar.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.79 (s, 1 H), 4.68 (s, 1 H), 3.81 (s, 2 H), 3.62 (t, *J* = 6.6 Hz, 2 H), 2.86 (s, 2 H), 2.02 (t, *J* = 7.8 Hz, 2 H), 1.80 (s, 3 H), 1.71 (s, 3 H), 1.71–1.62 (m, 2 H), 0.90 (s, 9 H), 0.04 (s, 6 H).

Rhodium-Catalyzed Enantioselective [2+2+2] Cycloaddition; General Procedures
Method A (less than 0.4 mmol of isocyanate): A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (3 mol%) and the phosphoramidite ligand (6 mol%), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, a soln of alkyne (1.3 equiv) and isocyanate (1.0 equiv) in toluene was 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 soln was heated to 110 °C in an oil bath for 16–48 h. The mixture was cooled to r.t., concentrated in vacuo, and purified by flash column chromatography (gradient elution typically hexane–EtOAc, 40:60 for the lactam adduct followed by 100% EtOAc or EtOAc–MeOH, 20:1 for the vinylogous amide adduct).

Method B (0.4 to 12 mmol of isocyanate): A flame-dried round bottom flask was charged with $[Rh(C_2H_4)_2Cl]_2$ (2 mol%) and the phosphoramidite ligand (4 mol%), and was fitted with a flame-dried reflux condenser in an inert atmosphere (N_2) glove box. Upon removal from the glove box, toluene was added (90% of the amount needed to reach 0.08 M). A soln of alkyne (1.3 equiv) and isocyanate (1.0 equiv) in toluene was 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 was heated to 110 °C in an oil bath for 24–48 h (the disappearance of the isocyanate is followed by NMR of aliquots).

Method C (more than 12 mmol of isocyanate): A vial was charged with $[Rh(C_2H_4)_2Cl]_2$ (2 mol%) and the phosphoramidite ligand (4 mol%) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, the contents of the vial were 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) was then added using a funnel and the system was evacuated and refilled with argon (2 ×). A soln of alkyne (1.3 equiv) and isocyanate (1.0 equiv) in toluene was 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 soln was heated to 110 °C in an oil bath for 36–48 h (the disappearance of the isocyanate is followed by NMR of aliquots).

(*R*)-2-Isopropylidene-5-(4-methoxybenzyl)-8a-[4-(trimethylsilyl)but-3-ynyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (25)
Following the general procedure, method C; yellow solid; yield: 6.81 g (73%); 98% ee by HPLC (Chiracel ADH, hexane–*i*-PrOH, 90:10, 1 mL/min).

$[\alpha]_D^{20}$ +40.0 (*c* 0.010, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 4.83 (s, 1 H), 3.89 (d, *J* = 14.9 Hz, 1 H), 3.76 (d, *J* = 14.9 Hz, 1 H), 3.66 (s, 3 H), 3.43–3.34 (ABq, 2 H), 2.73 (d, *J* = 15.7 Hz, 1 H), 2.46 (d, *J* = 16.4 Hz, 1 H), 2.36 (d, *J* = 16.4 Hz, 1 H), 2.18 (d, *J* = 15.7 Hz, 1 H), 2.11–2.03 (m, 1 H), 1.89–1.61 (m, 3 H), 1.51 (s, 3 H), 1.42 (s, 3 H), 0.01 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.5, 161.1, 158.7, 129.7, 127.0, 126.0, 125.3, 114.2, 106.0, 98.6, 85.0. 66.3, 55.2, 50.0, 45.7, 41.6, 39.6, 31.5, 20.8, 15.2, 0.0.

MS (EI): *m*/*z* (%) = 422 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{36}NO_2Si$: 422.2510; found: 422.2510.

(*R*)-8a-[3-(*tert*-Butyldimethylsiloxy)propyl)-2-isopropylidene-5-(4-methoxybenzyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (26)
Following the general procedure, method C; yellow oil; yield: 5.89 g (70%); 98% ee by HPLC (Chiracel ADH, hexane–*i*-PrOH, 90:10, 1 mL/min).

$[\alpha]_D^{20}$ +34.4 (*c* 0.010, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 8.6 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 4.96 (s, 1 H), 4.04 (d, *J* = 15.3 Hz, 1 H), 3.87 (d, *J* = 15.3 Hz, 1 H), 3.79 (s, 3 H), 3.58–3.44 (m, 4 H), 2.74 (d, *J* = 15.7 Hz, 1 H), 2.58 (d, *J* = 16.0 Hz, 1 H), 2.51 (d, *J* = 16.0 Hz, 1 H), 2.28 (d, *J* = 15.7 Hz, 1 H), 1.72–1.44 (m, 3 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.26–1.17 (m, 1 H), 0.85 (s, 9 H), 0.01 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 166.4, 164.0, 135.0, 132.6, 131.8, 130.4, 119.6, 103.8, 103.7, 72.3, 68.1, 60.6, 55.3, 51.0, 47.0, 45.0, 33.7, 32.9, 31.2, 26.3, 26.2, 23.6, 0.1. 0.0.

MS (EI): *m*/*z* (%) = 470 (100), 356 (85).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{44}NO_3Si$: 470.3085; found: 470.3083.

(*R*)-6-Chloro-2-isopropylidene-5-(4-methoxybenzyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-ones; General Procedure
To a 0.1 M soln of vinylogous amide cycloadduct **25** or **26** (1.0 equiv) in CH_2Cl_2 at –78 °C was added NCS (recrystallized from benzene, 1.3 equiv) in one portion. The mixture was stirred at –78 °C for 15 min and quenched with sat. aq $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product can be purified by flash column chromatography (hexane–EtOAc, 1:1) but was usually used without further purification for the next step.

(*R*)-6-Chloro-2-isopropylidene-5-(4-methoxybenzyl)-8a-[4-(trimethylsilyl)but-3-ynyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (30)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.13–4.04 (m, 2 H), 3.95 (d, *J* = 16.1 Hz, 1 H), 3.85 (d, *J* = 15.4 Hz, 1 H), 3.80 (s, 3 H), 2.90 (d, *J* = 16.5 Hz, 1 H), 2.72 (s, 2 H), 2.39–2.26 (m, 1 H), 2.24– 2.12 (m, 1 H), 2.00–1.80 (m, 3 H), 1.63 (s, 3 H), 1.54 (s, 3 H), 0.14 (s, 9 H).

(*R*)-8a-[3-(*tert*-Butyldimethylsiloxy)propyl)-6-chloro-2-isopropylidene-5-(4-methoxybenzyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.30 (s, 1 H), 4.15–4.05 (m, 2 H), 3.93 (d, *J* = 13.9 Hz, 1 H), 3.83 (d, *J* = 11.0 Hz, 1 H), 3.79 (s, 3 H), 3.58–3.42 (m, 2 H), 2.77 (s, 1 H), 2.71 (s, 1 H), 2.70 (s, 1 H), 2.34–2.22 (m, 1 H), 1.70–1.43 (m, 3 H), 1.62 (s, 3 H), 1.53 (s, 3 H), 0.84 (s, 9 H), 0.01 (s, 6 H).

(6*S*,8a*R*)-6-Chloro-2-isopropylidene-5-(4-methoxybenzyl)hexahydroindolizin-7(1*H*)-ones; General Procedure
To a 0.08 M soln of chlorinated vinylogous amide cycloadduct (from the previous general procedure) in THF at –78 °C was added Red-Al (65% wt in toluene, 2.0 equiv) dropwise. The mixture was stirred at –78 °C for 6 h and quenched slowly with H_2O. CH_2Cl_2 was added and the biphasic mixture was allowed to warm to 23 °C and stirred for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product can be purified by flash column chromatography (hexane–EtOAc, 4:1) or can be used without further purification for the next step.

(5*S*,6*S*,8a*R*)-6-Chloro-2-isopropylidene-5-(4-methoxybenzyl)-8a-[4-(trimethylsilyl)but-3-ynyl)-hexahydroindolizin-7(1*H*)-one (31)
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 4.52 (d, *J* = 10.2 Hz, 1 H), 3.81–3.74 (m, 1 H), 3.80 (s, 3 H), 3.65– 3.56 (m, 1 H), 3.49–3.29 (m, 2 H), 2.74 (dd, *J* = 14.6, 11.0 Hz, 1 H), 2.56 (d, *J* = 13.4 Hz, 1 H), 2.47–2.40 (m, 1 H), 2.43 (d, *J* = 13.4 Hz, 1 H), 2.12 (dm, *J* = 15.4 Hz, 1 H), 2.01–1.78 (m, 2 H), 1.68–1.52 (m, 2 H), 1.63 (s, 3 H), 1.59 (s, 3 H), 0.13 (s, 9 H).

(5*S*,6*S*,8a*R*)-8a-[3-(*tert*-Butyldimethylsiloxy)propyl)-6-chloro-2-isopropylidene-5-(4-methoxybenzyl)-hexahydroindolizin-7(1*H*)-one
Colorless oil; yield: 1.37 g (85%, 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.50 (d, *J* = 9.9 Hz, 1 H), 3.80–3.70 (m, 1 H), 3.78 (s, 3 H), 3.65–3.60 (m, 1 H), 3.52–3.38 (m, 4 H), 2.77 (dd, *J* = 15.4, 11.4 Hz, 1 H), 2.55 (d, *J* = 13.1 Hz, 1 H), 2.44 (d, *J* = 13.1 Hz, 1 H), 2.41–2.34 (m, 1 H), 2.12 (dm, *J* = 15.0 Hz, 1 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.55–1.33 (m, 4 H), 0.87 (s, 9 H), 0.01 (s, 6 H).

(5*S*,6*S*,7*R*,8a*R*)-2-Isopropylidene-6-methoxy-5-(4-methoxybenzyl)-8a-[4-(trimethylsilyl)but-3-ynyl)-hexahydroindolizin-7-ol (32)
To a 0.1 M soln of α-chloro ketone **31** in CH_2Cl_2–MeOH (1:1) at –78 °C was added $NaBH_4$ (1.8 equiv) in 1 portion. The mixture was stirred at –78 °C to 23 °C for 16 h and quenched with H_2O. CH_2Cl_2

was added and the biphasic mixture was stirred for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane–EtOAc, 3:1) to give alcohol **32** (416 mg, 77%, 3 steps) as a colorless gum.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 4.26–4.23 (m, 1 H), 3.79 (s, 3 H), 3.46 (br s, 2 H), 3.40 (s, 3 H), 3.35–3.21 (m, 2 H), 3.11 (dd, *J* = 14.6, 2.9 Hz, 1 H), 2.54 (dd, *J* = 14.7, 4.4 Hz, 1 H), 2.43 (s, 1 H), 2.22 (dm, *J* = 15.7 Hz, 1 H), 2.15–2.05 (m, 2 H), 2.04–1.94 (m, 3 H), 1.82 (dd, *J* = 15.0, 3.0 Hz, 1 H), 1.56 (s, 6 H), 1.55–1.48 (m, 1 H), 0.13 (s, 9 H).

(5*S*,6*S*,8a*R*)-6-Chloro-8a-[3-hydroxypropyl)-2-isopropylidene-5-(4-methoxybenzyl)-hexahydroindolizin-7(1*H*)-one (35)

A cold soln of 1% HCl in MeOH (0.29 M, 24 mL, 2.5 equiv) was added to (6*S*,8a*R*)-8a-[3-(*tert*-butyldimethylsiloxy)propyl)-6-chloro-2-isopropylidene-5-(4-methoxybenzyl)-hexahydroindolizin-7(1*H*)-one (1.4 g, 2.76 mmol). The mixture was stirred at 0 °C for 15 min and concentrated to dryness. CH_2Cl_2 and sat. aq $NaHCO_3$ were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 ×). The organic layers were combined, dried (anhyd $MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane–EtOAc, 3:2) to give **35** (974 mg, 90%) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 4.52 (d, *J* = 10.6 Hz, 1 H), 3.86–3.78 (m, 2 H), 3.78 (s, 3 H), 3.67–3.61 (m, 1 H), 3.52–3.33 (m, 4 H), 2.77 (dd, *J* = 15.4, 11.4 Hz, 1 H), 2.57 (d, *J* = 13.1 Hz, 1 H), 2.45 (d, *J* = 13.1 Hz, 1 H), 2.46–2.37 (m, 1 H), 2.15 (dm, *J* = 15.0 Hz, 1 H), 1.64 (s, 3 H), 1.61 (s, 3 H), 1.55–1.35 (m, 3 H).

(5*S*,6*S*,8a*R*)-6-Chloro-8a-[3-oxopropyl)-2-isopropylidene-5-(4-methoxybenzyl)-hexahydroindolizin-7(1*H*)-one (36)

To a soln of oxalyl chloride (50 μL, 1.5 equiv) in CH_2Cl_2 (0.7 mL) at –78 °C was added DMSO (46 μL, 1.7 equiv) dropwise. The soln was stirred at –78 °C for 30 min followed by addition of a soln of alcohol **35** (150 mg, 0.382 mmol) in CH_2Cl_2 (0.6 mL). The mixture was stirred for 90 min followed by addition of Et_3N (159 μL, 3.0 equiv). The mixture was stirred at 0 °C for 30 min and at 23 °C for 30 min. Et_2O was then added and the suspension was filtered. Some toluene was added to the filtrate and the soln was evaporated under reduced pressure. The crude product was purified by flash column chromatography (short column, hexane–EtOAc, 7:3) to give ketoaldehyde **36** (130 mg, 87%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 7.09 (d, *J* = 8.6 Hz, 2 H), 6.77 (d, *J* = 8.6 Hz, 2 H), 4.47 (d, *J* = 10.6 Hz, 1 H), 3.76 (d, *J* = 13.3 Hz, 1 H), 3.72 (s, 3 H), 3.56 (d, *J* = 13.3 Hz, 1 H), 3.37 (dd, *J* = 14.5, 2.8 Hz, 1 H), 3.16 (dt, *J* = 10.9, 3.1 Hz, 1 H), 2.66 (dd, *J* = 14.5, 10.9 Hz, 1 H), 2.53 (d, *J* = 13.3 Hz, 1 H), 2.35 (d, *J* = 13.3 Hz, 1 H), 2.22–2.10 (m, 2 H), 2.07–1.94 (m, 2 H), 1.66–1.57 (m, 2 H), 1.59 (s, 3 H), 1.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2, 199.7, 158.2, 130.6, 129.5, 126.2, 125.3, 113.7, 98.4, 66.5, 63.6, 63.5, 55.2, 48.6, 48.4, 40.3, 37.6, 35.8, 25.4, 20.81, 20.80.

(1*R*,6S,7S,8*R*)-7-Chloro-8-hydroxy-3-isopropylidene-6-(4-methoxybenzyl)-5-azatricyclo[6.3.1.0^{1,5}]dodecan-9-one (37); Tricyclic Core of FR90483

In a flame-dried round bottom flask under an argon atmosphere containing the triazolium salt **39** (39 mg, 0.5 equiv) was added toluene (1.0 mL). A soln of KHMDS (18 mg, 0.45 equiv) in toluene (1.0 mL) was added. The mixture was stirred at 23 °C for 20 min and the volatiles were then removed under high vacuum. Toluene (1.0 mL) was added and the mixture was heated to 70 °C. A soln of ketoaldehyde **36** (80 mg, 0.205 mmol) in toluene (2.0 mL) was added and argon was bubbled for 5 min. The mixture was stirred at 70 °C for 6 h and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane–EtOAc, 3:1) to give the aza-tricycle **37** (33 mg, 41%) as a colorless gum.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.6 Hz, 2 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 4.30 (s, OH), 3.85 (d, *J* = 12.9 Hz, 1 H), 3.75 (s, 3 H), 3.69 (d, *J* = 10.2 Hz, 1 H), 3.47–3.41 (m, 1 H), 3.20–3.10 (m, 2 H), 2.80 (dd, *J* = 15.3, 5.5 Hz, 1 H), 2.66 (dd, *J* = 17.6, 8.2 Hz, 1 H), 2.59–2.41 (m, 1 H), 2.29–2.22 (m, 1 H), 2.18 (d, *J* = 14.4 Hz, 1 H), 2.09 (d, *J* = 14.4 Hz, 1 H), 1.97 (d, *J* = 12.9 Hz, 1 H), 1.86 (dd, *J* = 12.9, 3,6 Hz, 1 H), 1.58–1.47 (m, 1 H), 1.54 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.5, 158.3, 130.7, 129.0, 128.1, 123.5, 113.7, 78.2, 65.0, 63.6, 61.7, 55.2, 51.9, 45.1, 43.7, 37.8, 35.5, 29.9, 20.7, 20.6.

MS (EI): *m*/*z* (%) = 470 (100), 356 (85).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{29}ClNO_3$: 390.1830; found: 390.1827.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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