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Asymmetric synthesis of fluorinated monoterpenic alkaloid derivatives from chiral fluoroalkyl aldimines via the Pauson-Khand reaction

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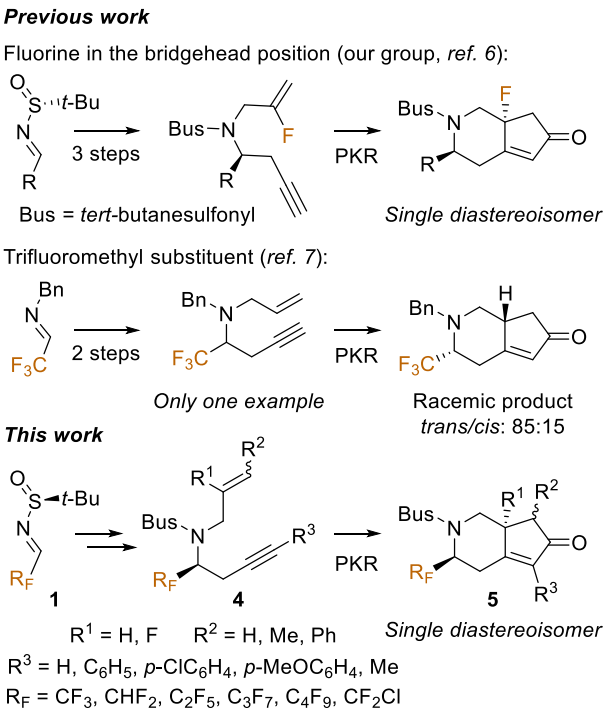
Abstract. Enantioenriched fluorinated monoterpenic alkaloid analogues were synthesised, employing a strategy based on the previously undescribed diastereoselective propargylation of fluorinated *tert*-butanesulfinyl imines, and subsequent Pauson-Khand reaction of resulting enyne derivatives, carried out both stoichiometrically and catalytically. The Pauson-Khand reaction tolerated both substituted alkenes and alkynes, and took place in good yields and diastereoselectivities, even when applied to a gram-scale synthesis.

Keywords: *N-tert*-butanesulfinyl imine; propargylation; Pauson-Khand; organofluorine chemistry; asymmetric synthesis

Monoterpenic alkaloids possessing a piperidine heterocycle fused with a five-membered carbocyclic ring are of utmost interest since they present important biological activities.[1] Tecomanine and incarvilline, exhibiting hypoglucemic and analgesic activity respectively, are representative examples of this group of alkaloids. The intramolecular Pauson-Khand reaction (PKR) has been widely applied to the synthesis of natural products, both stoichiometrically and catalytically,[2] and has also proved to be a feasible method for the preparation of the cyclopentane[*c*]piperidine core present in this class of monoterpenic alkaloids.[3] Recent reports from several groups illustrate the preparation, in some cases stereocontrolled, of similar structures such as the marine alkaloid nakadomarin A,[3a] or those belonging to the kinabalurine, incarvilline and skytanthine families.[3c] In contrast, access to the tecomanine skeleton through the Pauson-Khand cycloaddition of chiral *N*-tethered 1,7-enynes has been more scarcely explored.[4,5]

In terms of fluorinated derivatives, our group recently reported the synthesis of similar bicyclic structures via fluoro-Pauson-Khand reaction, resulting in a stereogenic bridgehead C—F bond (Scheme 1).[6] In addition, Bonnet-Delpon and co-workers briefly explored the synthesis of racemic trifluoromethylated derivatives of the same heterobicylic skeleton (Scheme 1).[7] This, incidentally, is the only documented example of the propargylation of fluorinated imines, to the best of our knowledge. The introduction of fluorine into organic molecules has become a common strategy to fine-tune their biological and pharmacological activities.[8] In this way, the potentially positive effects derived from the introduction of fluoroalkyl groups in heterocyclic structures, in particular nitrogen containing heterocycles, has been extensively demonstrated.[9] Currently, there are several generalised methods for the introduction of fluorine in organic molecules, one of which is the use of fluorinated building blocks.[10] Imines bearing fluorinated groupings represent an interesting class of building blocks, given that they can be used as electrophiles in many transformations, giving rise to amines bearing proximal fluorinated groups that have the potential to modify the basicity of the amine as necessary.



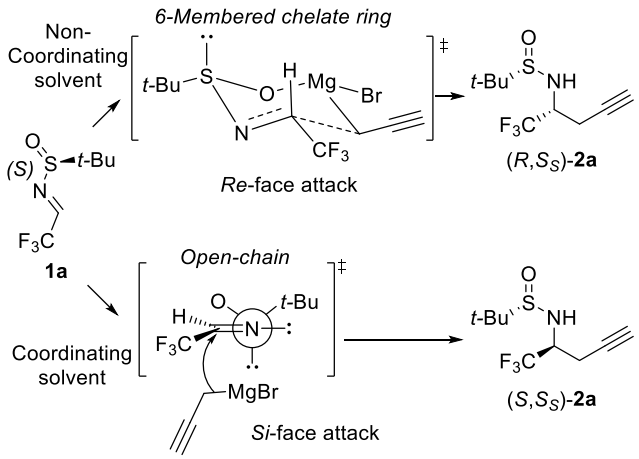
Scheme 1. Previous work relevant to this report.

Specifically, fluorinated *tert*-butane sulfinyl imines can be used to produce optically pure fluorinated amines that could be valuable to medicinal and pharmaceutical research,[11] although their full potential in organic synthesis is only recently coming to light.[12]

Therefore, continuing our interest in this class of fluorinated molecules, in this update we describe the asymmetric synthesis of tecomanine analogues through Pauson-Khand cyclisation of *N*-tethered 1,7-enynes **4** bearing a series of fluorinated substituents in a different position to those disclosed previously, originating from chiral fluorinated imines **1** (Scheme 1). Herein, we also report a wider reaction scope of the Pauson-Khand reaction, including an efficient catalytic version, and new substrates bearing substitutions at both the alkyne and alkene groups.

With the starting imines **1** in hand, we envisioned a synthetic route with diastereoselective propargylation of imines **1** as the key step in order to introduce the chiral information necessary for the rest of the sequence. To our surprise, we found that the asymmetric propargylation of this class of fluorinated imines remained undescribed in the scientific literature, despite similar non-fluorinated substrates being widely employed as electrophiles in diastereoselective addition reactions.[13]

We first assayed the addition of propargyl magnesium bromide to sulfinimine **1a** in CH_2Cl_2 using the conditions described by Zhang *et al*. for several non-fluorinated imines,[13a] however, the resulting homopropargyl amine **2a** was obtained with only slight diastereoselectivity (44:56). We therefore changed the solvent to THF and found that not only the diastereoselectivity was vastly improved (96:4), but the major diastereoisomer was actually the opposite of that observed in CH_2Cl_2.[14]



Scheme 2. Rationale behind the solvent effects observed.

The dramatic effect of the solvent in this kind of transformation is well documented, and is attributed to differing transition states according to the nature of the solvent (Scheme 2).[12d,13b,15] Nonetheless, it is clear that in our case the substrate also plays a role.

We suspect that the fluorinated group, given its strong electron-withdrawing character, increases the reactivity of the imine and decreases the difference in energy between the two transition states in non-coordinating solvents such as CH_2Cl_2. In coordinating solvents such as THF, the six-membered transition state is less favoured and therefore the reaction takes place *via* the open-chain transition state, resulting in much higher diastereoselectivity.

Accordingly, the propargylation reaction was carried out at -78 °C in THF affording the corresponding homopropargyl sulfinamides **2a** and **2e-i** in moderate to good yields (60-87%) and excellent diastereomeric ratios (dr >20:1) (Table 1).

Allylation of the homopropargyl sulfinamides **2** to achieve the desired enynes proved problematic, and resulted in unsatisfactory yields (<30%). Fortunately, we found that after oxidation of the sulfinyl group with *m*-CPBA in CH_2Cl_2 at 0 °C,[16] the corresponding homopropargyl sulfonamides **3a** and **3e-i** successfully underwent allylation through reaction with the corresponding bromide in basic conditions at room temperature to give **4a-i** with good yields in general (Table 1).

With the goal of exploring the scope and limitations of the final Pauson-Khand reaction, we next synthesised *N*-tethered 1,7-enynes bearing an internal triple bond. To this end, we first attempted the preparation of phenyl-substituted **2j** through the addition of phenyl propargyl magnesium bromide to sulfinimine **1a**. However, in this case an inseparable mixture of the corresponding homopropargyl and allenyl products, **2j** and **2j'** respectively, was observed (Table 2). This has been described in several reports owing to the alkyne/allene equilibrium of the organometallic reagent in solution.[17] We found that this setback could be overcome to a certain degree modifying the reaction temperature; at higher temperatures, the desired propargylation reaction product **2j** was favoured by up to 11:1 (Table 2).

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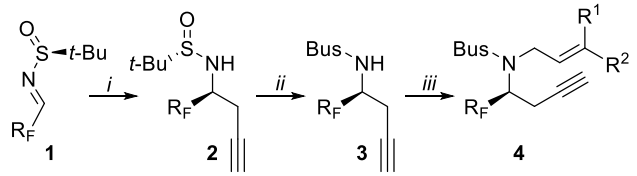
Table 1. Asymmetric synthesis of enynes **4a-g**.[a), b)]

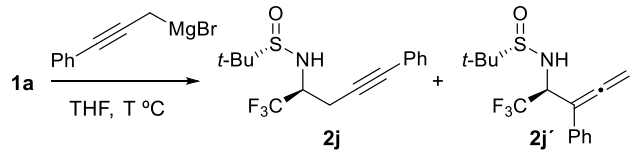


R_F	**2** (%) (dr)[c)]	**3** (%)	R^1	R^2	**4** (%)
CF_3	**a** (87) (96:4)	**a** (82)	H	H	**a** (92)
CF_3 [d)]	**a**	**a**	H	Me	**b** (93)
CF_3	**a**	**a**	H	Ph	**c** (84)
CF_3	**a**	**a**	Me	Me	**d** (93)
CHF_2	**e** (60) (95:5)	**e** (63)	H	H	**e** (53)
C_2F_5	**f** (65) (98:2)	**f** (81)	H	H	**f** (70)
C_3F_7	**g** (60) (97:3)	**g** (82)	H	H	**g** (55)
C_4F_9	**h** (60) (99:1)	**h** (83)	H	H	**h** (82)
CF_2Cl	**i** (74) (96:4)	**i** (84)	H	H	**i** (77)

Reaction conditions: *i*. Magnesium propargyl bromide (1.5 equiv), THF [0.1 M], -78 °C, 2-3 h. *ii*. *m*-CPBA (1.2 equiv), CH_2Cl_2 [0.1 M], 0 °C – r.t., 1-2 h. *iii*. Corresponding allyl bromide (2 equiv), K_2CO_3 (3 equiv), DMF [0.1 M], 0 °C – r.t., 5-12 h. [a)] Yields refer to isolated yields in all cases. [b)] Bus = *tert*-butanesulfonyl. [c)] Diastereomeric ratios were determined by ^1H and ^{19}F NMR (see Supporting Information). [d)] A 4:1 mixture of *E*/*Z*-crotyl bromide was used. We were unable to separate the resulting two isomers of **4b** by column chromatography, and as such continued with the isomeric mixture.

Despite this partial solution, in the end we decided to follow a different strategy and introduce an aryl group at the triple bond *via* Sonogashira reaction with **3a**, thereby eliminating completely allenyl derivative **2j'** from the resulting product. In this way, the corresponding homopropargyl sulfinamides were obtained in moderate to good yields. These derivatives were then subjected to the same

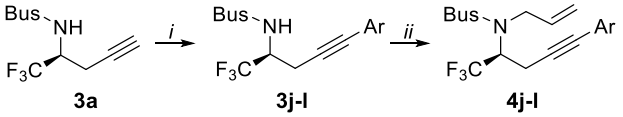
Table 2. Effect of temperature on alkyne vs allene selectivity.[a)]



Entry	T (°C)	**2j**	:	**2j'**
1	-78	29	:	71
2	0	80	:	20
3	50	90	:	10
4	75	92	:	8

[a)] Selectivity was measured by ^{19}F NMR (see Supporting Information).

Table 3. Synthesis of enynes **4j-l**.[a), b)]



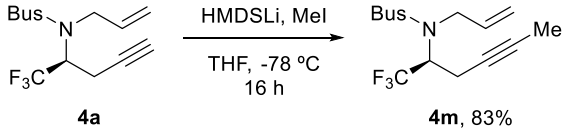
Entry	Ar	**3** (%)	**4** (%)
1	Ph	**3j** (87)	**4j** (81)
2	*p*-$MeOC_6H_4$	**3k** (40)	**4k** (99)
3	*p*-ClC_6H_4	**3l** (65)	**4l** (97)

Reaction conditions: *i*. Ar-I (1.2 equiv), $Pd(Ph_3)_2Cl_2$ (4 mol%), CuI (8 mol%), (*i*-Pr)$_2$NH [0.06 M], 50 °C, 2-3 h. *ii*. Allyl bromide (2 equiv), K_2CO_3 (3 equiv), DMF [0.1 M], 0 °C – r.t., 5-12 h. [a)] Yields refer to isolated yields in all cases. [b)] Bus = *tert*-butanesulfonyl.

oxidation/allylation sequence mentioned previously to prepare the target 4-aza-8-aryl-1,7-enynes **4j-l** (Table 3). Similarly, we attempted the synthesis of **4m** bearing a methyl substituent at the triple bond, firstly *via* propargylation analogous to that previously discussed. However, this resulted in poor yield and diastereoselectivity. We therefore opted to directly methylate the triple bond in **4a** using HMDSLi and methyl iodide, following a previously described procedure (Scheme 3).[18]

With a variety of chiral 1,7-enynes **4** in hand, we then explored their Pauson-Khand cyclisation to obtain adducts bearing stereodefined substitutions in various positions. Treatment of **4a-m** with 1.2 equivalents of $Co_2(CO)_8$ resulted in their full conversion to the corresponding cobalt complexes after 2 hours in CH_2Cl_2 that, upon treatment with 10 equivalents of *N*-methylmorpholine-*N*-oxide (NMO) overnight at room temperature, underwent an efficient intramolecular PKR to afford the corresponding bicyclic derivatives **5a-m** as single diastereomers (Table 4).

The yields were moderate to good, and high diastereoselectivity was observed in almost all cases. In general, substrates with substituted olefin components (**4b-c**) or longer fluoroalkyl chains (**4f-h**) resulted in lower yields and higher diastereoselectivities (**5b-c** and **5f-h**, Table 4). Fortunately, when we carried out the PKR with the isomeric mixture of *E*/*Z*-**4b** we obtained only two diastereoisomers, indicating that the reaction took place stereospecifically. Furthermore, **5b** and **5b'** were separable by column chromatography, and their stereochemistry was determined according to NOESY experiments as well as previous literature reports involving similar substrates.[4] Enyne **4h** bearing the CF_2Cl substituent resulted in a higher yield but a low diastereoselectivity (**5i**, Table 4),



Scheme 3. Synthesis of 1,7-enyne **4m**.

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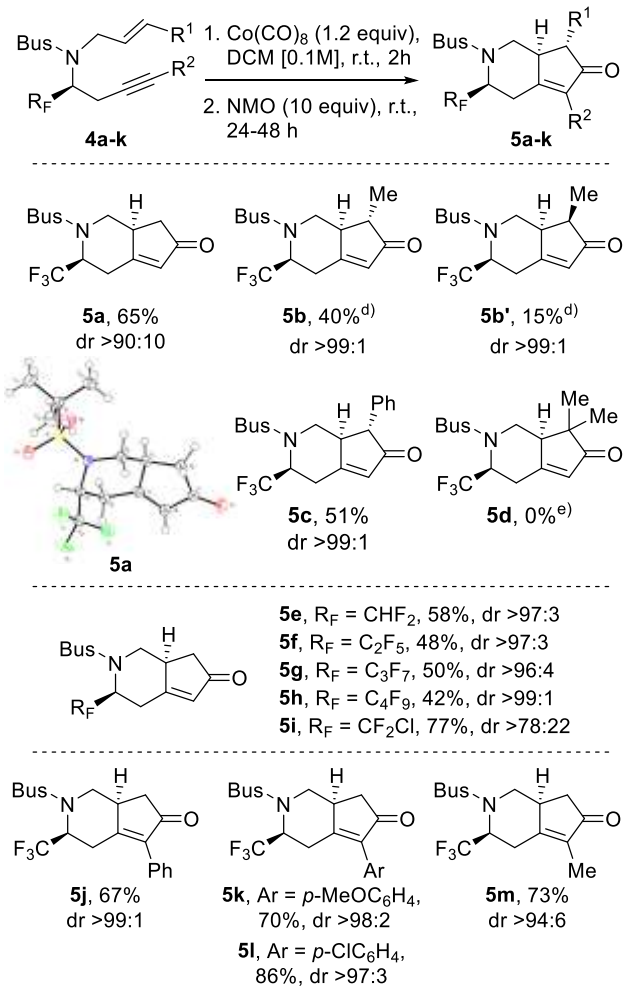
Table 4. Pauson-Khand cyclisation of enynes **4a-m**. [a), b), c)]

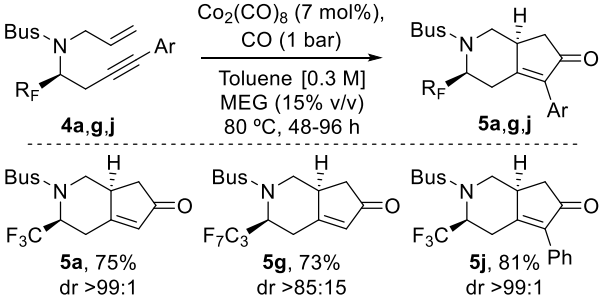


[a)] Yields refer to isolated yields in all cases. [b)] Diastereomeric ratios were determined by ^{1}H and ^{19}F NMR (see Supporting Information). [c)] Bus = *tert*-butanesulfonyl. [d)] Compounds **5b** and **5b'** were isolated from the same reaction mixture using the isomeric *E*/*Z* mixture of **4b** mentioned earlier, thus the global yield for this reaction was 55%. [e)] After addition of NMO, the cobalt complex reverted back to starting enyne **4d** (see text for details).

whereas enynes containing an internal alkyne group gave both higher yields and diastereoselectivities (**5j-m**, Table 4). An exception to this was enyne **4d**, bearing a trisubstituted olefin. As could be expected, due to the poor coordination ability of the trisubstituted alkene, treatment with NMO lead to the decomposition of the cobalt complex affording the initial alkyne **4d**. In fact, several precedents can be found in the literature showing that trisubstituted alkenes are very unreactive substrates in the Pauson-Khand reaction.[19]

The stereochemistry of the newly formed stereogenic centre in the bridgehead position was confirmed by X-ray crystallography of PK adduct **5a**.[20] In addition, **5a** was prepared starting from 1.2 grams of imine **1a** with no significant loss of yield or

Table 5. Catalytic Pauson-Khand cyclisation of selected enynes **4**.[a), b)]



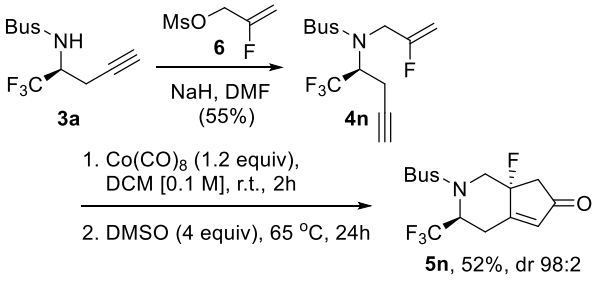
[a)] Yields refer to isolated yields in all cases. [b)] Bus = *tert*-butanesulfonyl.

diastereoselectivity (global yield 36%, see Supporting Information for details).

We also explored the use of 1,7-enynes **4** in a catalytic version of the PKR, for which we selected a new synthetic protocol recently reported by Riera and co-workers.[21] This procedure is based on a biphasic system of ethylene glycol/toluene, and usually results in an enhancement of yield and selectivity for the PK adducts, as well as simplifying purification of the products. By applying these reaction conditions (7 mol% catalyst, low CO pressure, and 15% v/v of ethylene glycol in toluene) to enynes **4a**, **4g**, and **4j**, the corresponding bicyclic derivatives **5** were obtained (Table 5).

For adducts **5a** and **5j**, the yields and diastereoselectivities were clearly improved with respect to the stoichiometric version. However, **5g** was obtained with a higher yield but reduced diastereoselectivity. We suspect the higher yields were due to the simpler purification arising from the reaction mixture containing only small amounts of cobalt compared with the stoichiometric version.

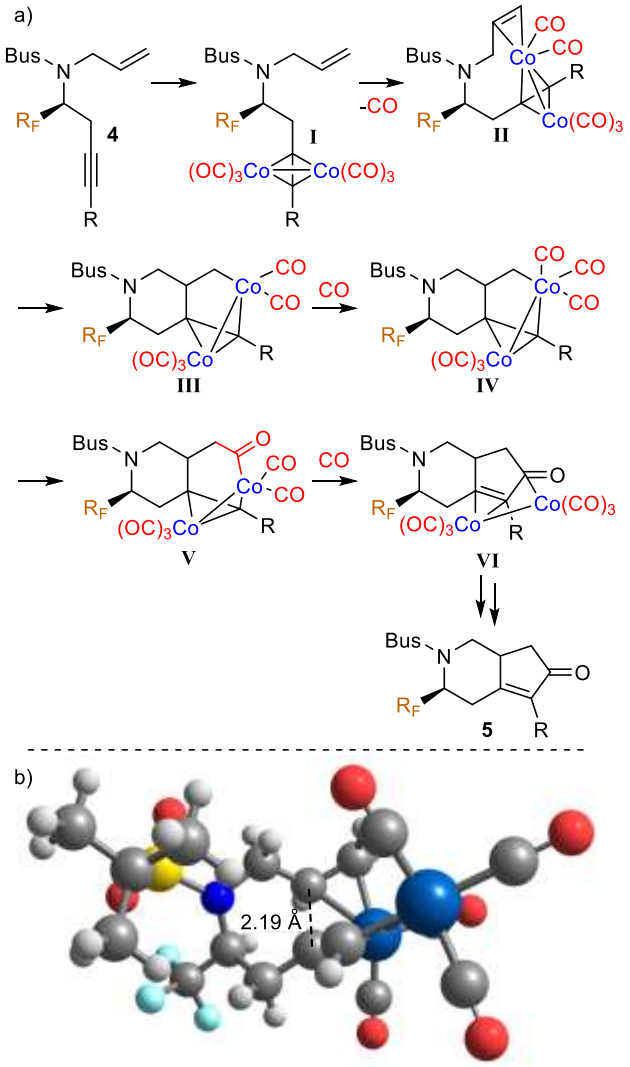
Furthermore, we tested the influence of the introduction a vinyl fluoride moiety on the Pauson-Khand cyclisation. To this end, the allylation reaction of the homopropargyl sulfonamine **3a** was carried out with 2-fluoroallyl mesylate **6** to afford enyne **4n** (Scheme 4).[22] For the cyclisation of this enyne derivative, we followed the reaction conditions previously applied by our group in analogous fluoro-



Scheme 4. Use of fluorinated mesylate **6** in the synthesis of PKR adducts bearing a stereodefined C—F bond at the bridgehead position. Bus = *tert*-butanesulfonyl.

Pauson-Khand reactions, in which DMSO is used as the promoter instead of NMO.[6, 23] It is worth noting that this transformation involves the asymmetric construction of a carbon-fluorine quaternary stereogenic centre, a goal that constitutes remarkable interest in organic synthesis.[24] Unfortunately, after several attempts, the catalytic version of the Pauson-Khand could not be applied to the synthesis of this class of previously reported quaternary C—F containing bicycles, such as **5n** (Scheme 4).[6, 23]

The mechanism of the Pauson-Khand reaction catalyzed by $Co_2(CO)_8$ was initially proposed by Magnus in 1985,[25] and the same mechanism has since been supported by theoretical studies.[26] In our case, 1,7-enyne **4** reacts with $Co_2(CO)_8$ through a ligand exchange reaction to form the alkyne-coordinated $Co_2(CO)_6$ complex **I** upon release of two molecules of CO (Scheme 5). In the next step, the addition of NMO facilitates the liberation of a molecule of CO from the cobalt centre, leaving a vacant site for alkene coordination.



Scheme 5. a) Plausible mechanism of our Pauson-Khand reaction. b) Most favourable transition state between complexes **II** and **III**, determining the configuration of the newly formed stereogenic centre (see Supporting Information).

The alkene group then coordinates to the electronically unsaturated cobalt centre, yielding complex **II** and releasing another molecule of CO. From here, the alkene is inserted into the Co—C bond, generating a new C—C bond in the six-membered cobaltacycle intermediate **III**. This cyclisation step occurs with high diastereoselectivity due to the energy difference between the two possible transition states shown by density functional theory (DFT) calculations (see Supporting Information for details), reinforcing the experimental results observed. The coordination of a CO molecule to the cobalt centre then generates complex **IV**, and subsequent CO insertion into the Co—C bond yields complex **V**. A second molecule of CO then coordinates to the unsaturated cobalt centre in **V** to form complex **VI**, and a final reductive elimination releases the corresponding cyclopentenone product **5**.

In conclusion, the Pauson-Khand cycloaddition of fluoroalkyl substituted chiral 4-aza-1,7-enynes allows the synthesis of fluorinated derivatives of the 6*H*-cyclopenta[*c*]pyridine-6-one skeleton that is present in several classes of monoterpene alkaloids. The key step to access the enyne precursors is the diastereoselective propargylation of fluorinated *tert*-butanesulfinyl imines, which was explored here for the first time and took place in good yields and high diastereoselectivities, despite performing differently to their non-fluorinated counterparts. Substitution of both the reacting alkene and alkyne groups has been shown to be compatible with the Pauson-Khand reaction, allowing further functionalisation of the heterobicyclic core. This synthetic route was also carried out at gram scale maintaining high yields and diastereoselectivities throughout. A catalytic version of the Pauson-Khand reaction could also be used to produce the desired adducts, generally offering improved yields and diastereoselectivities. The process was also applied to the synthesis of a derivative bearing a fluorine atom at a fully substituted bridgehead carbon stereogenic center, an interesting feature given the difficulty in obtaining similar structures by alternative methods.

Experimental Section

General procedure for the stoichiometric Pauson-Khand reaction

Sulfonamides **4** (1 equiv) were dissolved in DCM [0.1 M] at room temperature in a round-bottomed flask. Octacarbonyl dicobalt complex (1.2 equiv) was then added and the mixture was stirred until the starting sulfonamide had been consumed (TLC analysis, typically 2 hours). At this time, *N*-methylmorpholine *N*-oxide (10 equiv) was added and the reaction was stirred overnight at room temperature. Once the reaction had finished, the solvent was removed under reduced pressure and products **5** were purified by flash column chromatography (*n*-hexane:ethyl acetate).

General procedure for the catalytic Pauson-Khand reaction

Sulfonamides **4** (1 equiv) were dissolved in anhydrous toluene [0.3 M] at room temperature in a flame-dried pressure tube containing a magnetic stirrer. Octacarbonyl dicobalt complex (7 mol%) was then added, followed by ethylene glycol (15% v/v). The vessel was sealed and purged with N_2, and then three times with CO, before finally being charged with CO (1 bar) and heated to 80 °C for 2 days (TLC analysis, typically 2 hours). The vessel was then degassed, filtered through a plug of Celite and the crude reaction mixture was concentrated under reduced pressure. Products **5** were purified by flash column chromatography (*n*-hexane:ethyl acetate).

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UPDATE

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