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Diastereoselective synthesis of 3,4-disubstituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones: chirality transfer in the enantioselective synthesis of ethyl (+)-(3*S*,4a*S*,7a*S*)-1-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate

Hassan Acherki, Carlos Alvarez-Ibarra,* Juan F. Collados Luján and María L. Quiroga-Feijóo

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, Ciudad Universitaria, 28040 Madrid, Spain

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Dedicated to Professor Antonio García-Martínez on the occasion of his 65th birthday

Abstract—The base-mediated reaction of enantiomerically pure α-sulfinylketimine (+)-**1** with (*E*)-α,β-disubstituted propenoate esters afforded 3,4-disubstituted-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones **9α**-**13α** and **14** with high or complete diastereoselectivity. A sole diastereomer of the four possible ones, with regard to the nature of ester, was isolated, which revealed the stereocontrol of the chiral sulfinyl group in the Michael reaction and transenolization steps. In addition, the enantioselective synthesis of ethyl (+)-(3*S*,4a*S*,7a*S*)-1-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylates (+)-**17α** is described (five steps; 47% yield; ee ⩾97%). The absolute configuration of stereocentres introduced in (+)-**17α** was assigned on the basis of ^{1}H NMR data.

1. Introduction

Substituted and functionalized 6-oxopipecolic acids are precursors of α-aminoadipic acid derivatives. The α-aminoadipic acid (homoglutamic acid) is a constituent of tripeptide δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine, which serves as a biosynthetic precursor of penicillins and cephalosporins.[1] Furthermore, substituted pipecolic acid derivatives have been used as conformationally constrained amino acids and, for this reason, could serve as building blocks for the synthesis of peptidomimetics,[2] immunosuppressor agents,[3] enzyme inhibitors,[4] and NMDA antagonists.[5] For all these goals, easy and chiral routes for these substances with different substitution on the piperidone and piperidine ring have yet to be proposed.[6]

We have recently reported a highly efficient method for the synthesis of substituted pipecolic acid derivatives **7** and **8**, based on the Michael addition of the α-sulfinyl ketimine (+)-**1** to isopropyl and methyl (*E*)-crotonate and (*E*)-cinnamate **2** (Scheme 1).[7] Diastereomeric lactams **5** and **6** were obtained from a one-pot procedure upon cyclization of the aza-enolates **4**, which are achieved from the transient adducts **3** (Scheme 1). The reaction times and diastereoselectivities were entirely dependent on the nature of the *O*-alkyl group in the ene ester. Thus, isopropyl ene esters required the highest reaction times (⩾2 days) for completion of the cyclization to lactams, whereas methyl ene esters only needed 2–6 h. In addition, we observed that the diastereoselectivity was completely in favour of isomers **5** with isopropyl ene esters, whereas the lowest diastereoselectivities were obtained with methyl ene esters (de = 32–76%). Subsequent transformations of the lactam and oxazolidine moieties of **5** (Scheme 1; R = Me) allowed us to transfer the chirality of the sulfinyl group to the 2-, 4- and 6-positions of the piperidine ring. This represents

* Corresponding author. Tel.: +34 913944223; fax: +34 913944103; e-mail: caibarra@quim.ucm.es

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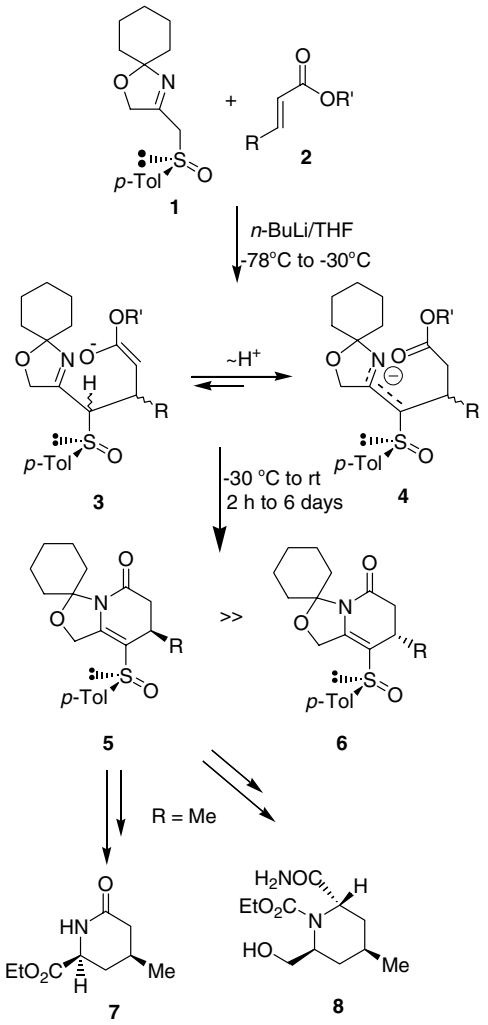
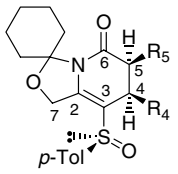
a new approach to the enantioselective synthesis of 4- and 4,6-disubstituted L-pipecolates **7** and **8**, respectively (Scheme 1).[7,8]



Scheme 1.

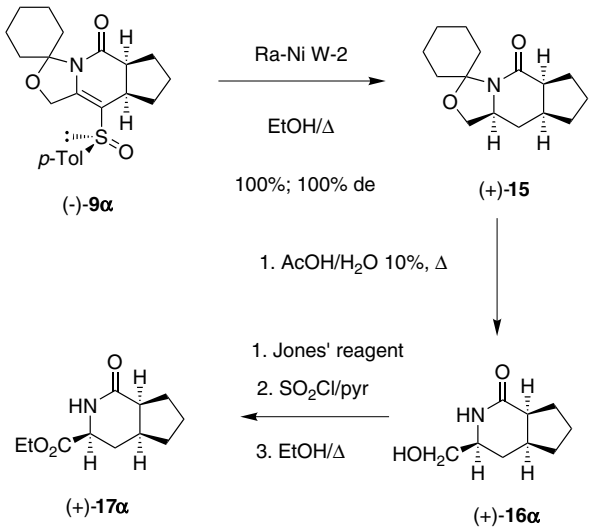
Herein, we report the diastereoselective synthesis of polycyclic lactams **9α** and other structurally related compounds **10**–**14** through the sulfoxide-mediated diastereoselective one-pot procedure (Michael addition-*trans*-enolization-cyclization) from α-sulfinylketimine (+)-**1** and (*E*)-α,β-disubstituted ene esters (Chart 1). Furthermore, we describe an approach to the synthesis of 4,5-disubstituted 6-oxopipecolic esters such as (+)-**17α** through desulfuration and reduction of the piperidinone ring with Ra Ni W2, followed by deprotection of the masked 1,2-amino alcohol functionality and subsequent transformation of the hydroxymethyl group to an ester derivative (+)-**17α** (Scheme 2).

NMR analysis of the reaction mixtures leading to lactams **9**–**13** revealed the formation of a cyclic compound with a *cis*-stereochemistry as a major component (series α), the *trans*-isomer (series β) being present in minor amounts. The analysis of the observed coupling pattern for vicinal hydrogens H4 and H5 allowed us to establish the stereochemistry of the new stereogenic centres C4 and C5. The-



Compound	R_4	R_5
9α	—$(CH_2)_3$—	
10α	—$(CH_2)_4$—	
11α	Ph	Ph
12α	Ph	Me
13α	Me	Me
14	CF_3	H

Chart 1.



Scheme 2.

oretical calculations on the compounds **9α** and **5** (R = Me) are in agreement with the observed vicinal coupling constants for hydrogens H4 and H5. The newly observed stereocontrol in the *trans*-enolization step to create the second stereogenic centre of C5 afforded a high value to this synthetic methodology. A study aimed at extending this to α-heterosubstituted ene esters and other functionalized Michael acceptors is currently in progress.

2. Results and discussion

2.1. Synthesis and structural analysis of (+)-17α

The synthesis of (+)-**17α** was accomplished from (−)-**9α** as outlined in Scheme 2. Compound (−)-**9α** was success-

fully prepared as the sole diastereomer from α-sulfinylketimine (+)-**1** and ethyl cyclopenten-1-carboxylate by following the general procedure reported previously by us.[7] The best results were obtained by the addition of *n*-BuLi (1.2 equiv) to (+)-**1** at −78 °C, and then allowing the temperature to rise to −30 °C before the unsaturated ester was added. Next, the reaction mixture was allowed to reach room temperature and stirred for seven days to drive the cyclization to lactam (−)-**9α** to completion, which was then isolated by flash chromatography in 83% yield. The open chain adducts were detected in the reaction mixture (TLC; silica gel; hexane/EtAcO: 6:1, two spots) but their separation was unsuccessful.

The structure and relative configuration of compound (−)-**9α** were easily established by analysis of its ^{1}H NMR (500 MHz) spectrum. The stereochemistry of the stereogenic centres C4 and C5 of the fused rings was established from the observed vicinal coupling constants $^3J_{H4,H5}$ (8.3 Hz). This value is very close to the gauche constant described by Hua et al.[9] for the *cis*-isomer **18** ($^3J = 9.3$ Hz) and is very different from the reported vicinal coupling constant for the *trans*-isomer **19** ($^3J = 14.0$ Hz) (Fig. 1).

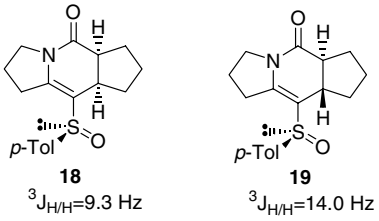


Figure 1. Significant ^{1}H NMR data for compounds **18** and **19**.

The absolute configuration of (−)-**9α** was easily established by taking into account other structurally analogous lactams obtained by the same procedure which have been previously reported by us.[7] The stereochemical pathway proposed for the formation of lactam (−)-**9α** is outlined in Figure 2. Thus, the Michael addition step gives the sole diastereomer **21** (*anti*-adduct) through a *re–re* attack (transition state **20**), which is more favoured than a *si–re* approach (transition state **24**). In any case, the facial selectivity of the *Z*-enolate is always *re* (*anti* to the *p*-tolyl group) while the relative stereodisposition of OEt group of the ene ester and the oxazolidine moiety is *anti* for the *re–re* approach and *syn* for the *si–re* attack. Hence, the former would be sterically more favoured than the second attack. Since lactam (−)-**9α** was isolated as the sole stereoisomer with a *cis*-stereodisposition of the hydrogens at the carbon atoms of the ring fusion, the subsequent *trans*-enolization to aza-enolate **23** must occur with complete stereocontrol. A reactive conformation of the *anti*-adduct such as **21** could be responsible for this reaction pathway, since the metal ion complexation allows that the equilibrium between imine–enamine to be diastereoselective. Thus, the sole *E*-isomer **22** can be formed in the reaction medium and, consequently, an *s-trans* conformation of the sulfinyl group would allow the proton transfer to be *anti* versus the bulkiest *p*-tolyl substituent.

Next, lactam (−)-**9α** was reduced with freshly prepared Ni-Raney W-2[10] (5 equiv) in refluxing ethanol over 30 min to give (+)-**15** in quantitative yield (Scheme 2). The ^{1}H NMR (500 MHz) analysis of **15** revealed the presence of a sole diastereomer. As expected, the configuration of the new stereocentre C2 became *S* taking into account the stereodifferentiation effects developed by the carbons C4 and C5, which induce an *anti*-orientation of the hydrogen H2 with regard to cyclopentane ring. Furthermore, this configuration is in accordance with the observed ^{1}H NMR vicinal coupling constants ($^3J_{H3',H4}$ and $^3J_{H3',H2}$) for methine hydrogens H2 and H4 (Fig. 3). The high observed values of these vicinal coupling constants (12.6 Hz and 11.3 Hz, respectively) fall in

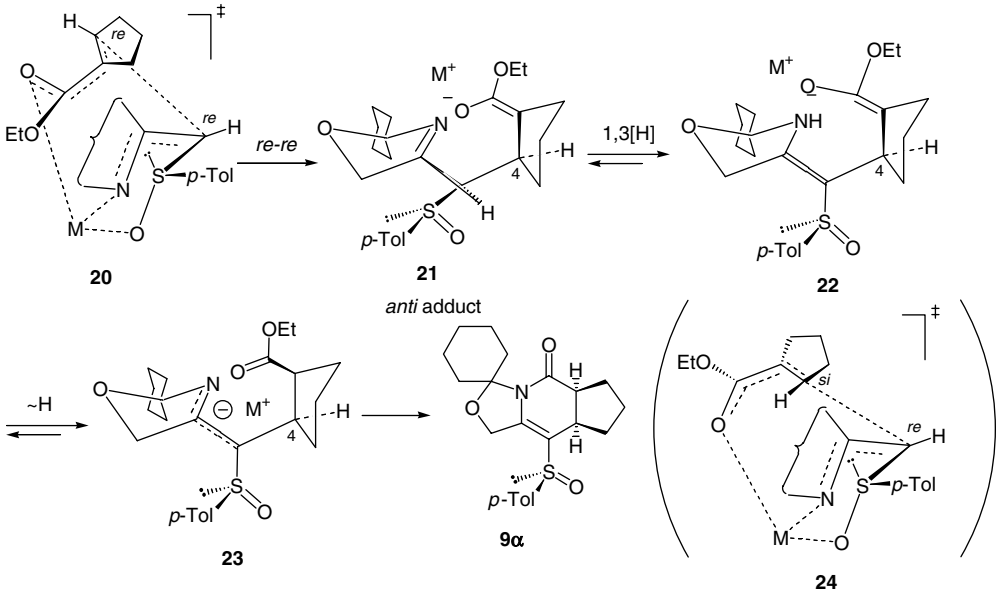
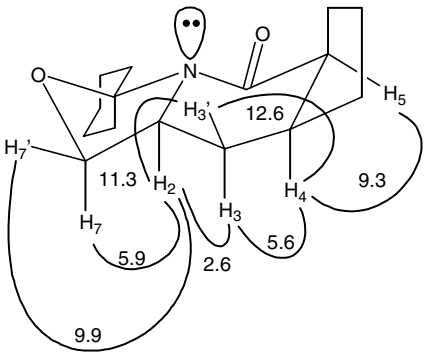


Figure 2. Stereochemical pathway proposed for the formation of lactam **9α** between parenthesis ET$^{\neq}$ leading to *syn*-adduct by a *si–re* approach.



(+)-**15**

Figure 3. Observed ^{1}H NMR vicinal coupling constants (Hz) for (+)-**15**.

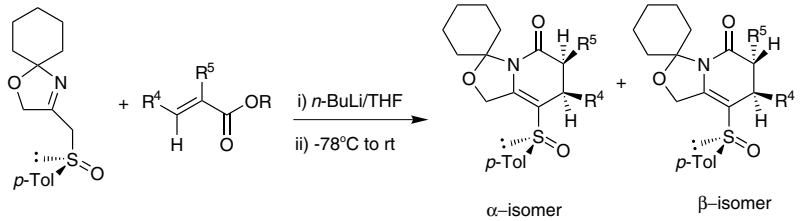
line with a pseudoaxial orientation of the implied hydrogens and, therefore, with a relative *syn*-configuration of the hydrogens H2 and H4. On the other hand, the relative magnitudes of the coupling constants $^3J_{H7',H2} = 9.5$ Hz, $^3J_{H3,H4} = 5.6$ Hz and $^3J_{H4,H5} = 9.3$ Hz are in agreement with the proposed structure. The most averaged values of the coupling constants $^3J_{H7;H2}$ and $^3J_{H7',H2}$ are the result of pseudorotation of the oxazolidine ring.

Next, we accomplished the hydrolysis of the *N*,*O*-ketal moiety in (+)-**15** with an AcOH/H_2O mixture (10:90: v/v) at reflux over 12 h to afford the alcohol **16α** in high yield (98%).[7] The reaction mixture was treated directly with Jones' reagent[11] to give the carboxylic acid, which was used without further purification for the subsequent transformations. Ethyl ester (+)-**17α** was obtained from the acid chloride ($SOCl_2$) and ethanol in 47% yield from (+)-**1** and its specific rotation $\{[\alpha]_D^{23} = +2.1$ (*c* 2.1, $CHCl_3)\}$ was determined on an analytical sample obtained by flash chromatography (EtAcO). ^{1}H NMR chiral shift experiments with (+)-Eu(hfc)$_3$ confirmed that no racemization occurs during the synthesis (ee $\geqslant$97%).

2.2. Synthesis of substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidine-2-ones

Our previous results on the reactivity of α-sulfinyl ketimine (+)-**1** with either methyl, ethyl or isopropyl β-substituted ene esters[7] prompted us to apply this methodology for obtaining chiral non-racemic 3,4-disubstituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones (Table 1). Compounds **5**[7] and **14** (4-substituted examples) have been included for the sake of comparison. In all cases, the procedure was the same as that previously described for the compound (−)-**9α**. The reaction mixtures were monitorized by TLC (silica gel) and, under these conditions, we were able to observe the evolution of the open chain adducts with an increase in reaction time until their disappearance [these intermediate derivatives displayed a higher R_f than the cyclic products in hexane/EtAcO mixtures (6:1 to 3:1) as eluent]. This reaction required between 2 h and 7 days depending on the nature of the ene ester (Table 1). A sole β-monosubstituted ene ester was used to prepare lactam **14** (Table 1; cf. entry 7) and, thus, to compare the observed diastereoselectivity with the result of the reaction with the isopropyl crotonate (Table 1; cf. entry 8). An analogous result was observed to that which provided lactam **5** with the diastereoselectivity controlled by the stereodifferentiation effect of the R-group in the ester

Table 1. Reaction of α-sulfinylketimine (+)-**1** with (*E*) ene esters[a]



Entry	R	R^4	R^5	Product	Reaction time (h)	Yield[b] (%)	Diastereoselectivity[c] α:β
1	Et	–$(CH_2)_3$–		**9**	168	83	100:–
2	Et	–$(CH_2)_4$–		**10**	192	76	100:–
3	Me	Ph	Ph	**11**	120	70	90:10
4	*i*-Pr	Ph	Ph	**11**	194	20	100:–
5	*i*-Pr	Ph	Me	**12**	24	48	88:12
6	Et	Me	Me	**13**	24	77 (16)[d]	87:13 (85:15)[d]
7	*i*-Pr	CF_3	H	**14**	48	75	100:–
8	*i*-Pr	CH_3	H	**5**	24	70	100:–
9	Me	CH_3	H	**5**	24	61 (31)[e]	66 (34)[e]

[a] The *E*-configuration of all the esters was confirmed from the analysis of their ^{1}H NMR data.
[b] Isolated cyclic isomers.
[c] Evaluated from integration of the key signals in the ^{1}H NMR spectra (500 MHz) of the reaction crudes.
[d] Isolated as a mixture of four isomers (**13α**: 71.8%; **13β**: 10.8%; **13γ**: 14.7%; **13δ**: 2.6%), two of them (**13γ/13δ**) display an opposite configuration at the C4 carbon to that of their **13α/13β** isomers.
[e] Isolated as a mixture of two isomers; between parenthesis is the epimer with an opposite configuration in C4 with regard to the isomers titled as α or β.

(Table 1; cf. entries 8 and 9). However, this effect was not significant for β-phenyl α,β-disubstituted ene esters (Table 1; cf. entries 3–5) because the sole cyclic compounds isolated were epimers at the C5 carbon irrespective of the nature of R in the ene ester. An identical result was observed for ethyl cycloalkenyl esters (Table 1; cf. entries 1 and 2). Thus, it can be established that the presence of a second substituent in the α-position of the ene ester amplifies the stereoselectivity of the Michael reaction. Also, this effect could be observed in the reaction of ethyl itaconate (Table 1; cf. entry 6) since the major epimer in C4 was obtained in 82.7% yield versus the minor epimer, whereas the methyl crotonate, a monosubstituted ene ester, displayed a minor diastereoselectivity (66:34) in favour of the same epimer (Table 1; cf. entry 9).

An explanation for this effect can be based on the previously proposed transition states for the formation of lactam (−)-**9α** (Fig. 2). In fact, a *re–si* approach, which determines a relative *syn*-orientation of the R-group and the oxazoline moiety, obviously provides a similar relative arrangement of the groups R_4 and R_5 (Fig. 4; $R_4 = R_5 = Me$) on the basis of an *s-cis* conformation for the acceptor. These interactions strongly destabilize transition state **25** but are not present in the transition state, which would form the *anti*-adduct through a *re–re* approach since the three substituents of the ester (OR, R_4 and R_5) become in *anti* with regard to the oxazolidine ring. Thus, the R_5 group works in the same sense as the groups R_4 and OR to decide the stereoselectivity in favour of the *anti*-adduct.

On the other hand, the formation of the isomer with a α-configuration at the C5 carbon as the major epimer has been generally observed (Table 1; cf. entries 1–6). This result can be rationalized, just like the formation of lactam (−)-**9α** (Table 1; cf. entry 1), through the extensive stereocontrol induced by the sulfinyl group (Fig. 4).

From a mechanistic point of view, it is interesting to take into account the ratio of epimers **13γ/13δ** that are formed as minor products in the reaction of (+)-**1** with ethyl (*E*)-itaconate (Table 1; cf. entry 6). Both compounds are epimers at the C5 carbon and are formed from the (4*S*)-or *syn*-adduct (Fig. 4). The γ-epimer with a relative *trans*-configuration (vide infra) is formed in a higher ratio than the δ-epimer (*cis*-isomer) (**13γ/13δ** = 85:15). This result seems to point out that the stereocontrol in the *trans*-enolization step is originated by the sulfinyl group with independence of the configuration of the most next stereocentre (carbon C4) (Fig. 4).

2.3. Structural analysis of substituted 5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones

The structure and stereochemistry of the major isomers α, isolated by flash chromatography from the reaction crudes were established by analysis of their ^{1}H NMR (500 MHz; $CDCl_3$) spectra. Under these conditions, a good signal separation was observed, which allowed a full assignment (see Table 2). In our hands, compound **13α** became inseparable from its epimer **13β**, but a careful spectroscopic analysis of the fraction containing both isomers allowed the assignment of their signals. Similarly, the fraction containing isomers **13γ** and **13δ** was carefully analyzed to establish the stereochemistry from the key signals of the spectrum. By an analogous analysis of NMR data, the structure and stereochemistry of the minor isomers **11β** and **12β** could be easily established from samples, which were contaminated with the major epimers **11α** and **12α**, respectively, after the isolation of each of them was carried out.

Table 2 summarizes the spectroscopic data of lactams **9**–**14** together with the data of compound **5** (Scheme 1; R = Me), which can be used as a reference to establish the absolute configuration of all the α major stereoisomers. In fact, the absolute configuration of **5** has been established taking into account the different observed chemical shifts for the methyl group attached at carbon C4 ($\delta = 0.418$ ppm for the major isomer and $\delta = 1.210$ ppm for the minor one) and by comparison of these values with the data described by Hua et al.[9] for similar compounds whose absolute configuration was established by X-ray diffraction.

Conversely, it is interesting to note that the observed difference for the chemical shifts of the hydrogens in the CH_2–O group in the epimers **13α** and **13β** was negligible, whereas this difference in the epimers **13γ** and **13δ** was 0.23 and 0.24 ppm, respectively. When the whole series of chemical shifts for the compounds with a configura-

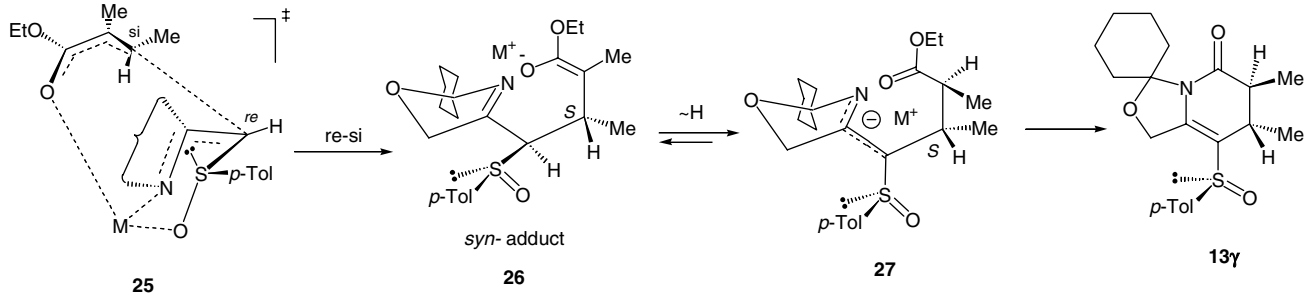


Figure 4. Stereochemical pathway leading to **13γ** from the *syn*-adduct (minor isomer) formed through a *re–si* approach of the reactants. Imine–enamine isomerization of the adduct followed by transenolization to the aza-enolate become *anti* versus the most bulkiest *p*-tolyl group of the actual inductor centre.

Table 2. ^{1}H NMR (500 MHz) Observed chemical shifts (ppm) and coupling constants (Hz) of the compounds **9**–**14** and **5**

Compd.	R^4	R^5	$H4_{ax}$	$H4_{ec}$	$H5_{ax}$	$H5_{ec}$
9α	–$(CH_2)_3$–		2.936 (dt, $^3J = 8.3$, 9.8, 9.8)	—	—	2.881 (dt, $^3J = 2.7$, 8.3, 8.3)
10α	–$(CH_2)_4$–		2.703 (dt, $^3J = 3.5$, 6.3, 6.3)	—	—	2.684 (dt, $^3J = 2.7$, 6.3, 6.3)
11α	Ph	Ph	3.998 (d, $^3J = 1.4$)	—	—	3.635 (d, $^3J = 1.4$)
11β	Ph	Ph	4.169 (d, $^3J = 7.1$)	—	3.800 (d, $^3J = 7.1$)	—
12α	Ph	Me	3.405 (d, $^3J = 1.7$)	—	—	2.479 (qd, $^3J = 7.3$, 1.7)
12β	Ph	Me	3.643 (d, $^3J = 7.3$)	—	2.937 (quint., $^3J = 7.3$)	—
13α	Me	Me	2.432 (qd, $^3J = 1.7$, 7.2)	—	—	2.287 (qd, $^3J = 1.7$, 7.0)
13β	Me	Me	2.705 (qd, $^3J = 5.5$, 6.6)	—	2.681 (cd, $^3J = 5.5$, 7.0)	—
13γ	Me	Me	—	2.310 (quint., $^3J = 6.8$)	—	2.269 (quint., $^3J = 6.8$)
13δ	Me	Me	—	2.34–2.20 (m)	2.139 (ABX_3 system, $^3J = 7.3$, 1.8)	—
14	CF_3	H	2.940 (ddq, $^3J = 7.3$, 1.7, $^3J_{H,F}$=8.4)	—	—	2.21–2.50 (m)
5	Me	H	2.860 (qd, $^3J = 6.9$, 6.9, 2.3)	—	2.380 (dd, $^2J = 15.9$; $^3J = 6.9$)	21.30 (dd, $^2J = 15.9$; $^3J = 2.3$)

tion α or β are compared (Table 2), it becomes clear that there is a minimum difference ($\Delta\delta = 0.088$ ppm) between these values. Hence, this behaviour in the series of studied compounds can also be related with the configuration of the C4 carbon.

In addition, the relative configurations of α/β and γ/δ can be established by taking into account the coupling pattern of the hydrogens bonded at carbons C4 and C5. Thus, compounds **9α** and **10α** display typical values for *cis*-coupling (axial–equatorial; $^3J = 8.3$ Hz and 6.3 Hz, respectively) that can be successfully contrasted with the published data by Hua et al.[9] for the compounds **18** and **19** (Fig. 1) and, thus, the *cis*-fusion is unequivocally established.

Compounds **11α**, **12α**, **13α**, **14** and **5** display a small coupling (1.4–1.8 Hz) between hydrogens H4 and H5 whereas this coupling was significantly highest in the epimeric compounds **11β**, **12β** and **13β** (5.5–7.3 Hz). This was also observed in the derivatives **14** and **5**. In any case, this finding represents a generalized behaviour, which could be in agreement with a relative *cis*-configuration for the series **α** and a *trans*-configuration for the series **β**. Since it is related to the relative magnitude of the dihedral angles between the vicinal hydrogens in the carbon atoms C4 and C5, a computational study was carried out (in vacuum) by means of semi-empirical and DFT calculations. The semi-empirical calculations were carried out using the PM3 model Hamiltonian[12] as it is implemented in Hyperchem.[13] The DFT[14] calculations have been carried out with Gaussian 03[15] using the B3LYP functional[16] and the 6-31G(d) split valence-shell basis set.[17] Vibrational frequencies were calculated for all the structures at the B3LYP/6-31G(d) level to confirm the absence of imaginary frequencies.

As a preliminary step, a conformational analysis around the dihedral angle H5–C5–C4–H4 of compound **5** was performed by means of a conformational search as implemented in Hyperchem.[13] Three conformations were selected and optimized by PM3 semi-empirical calculation and these structures were used as the starting point for complete geometry optimizations at the DFT level with the 6-31G(d) basis set. According to the results, a unique conformer was unequivocally selected and calculated; dihedral angles H4–C4–C5–H5′ and H4–C4–C5–H5 were −73.6° and 45.5°, respectively. These values were introduced in the Altona equation[18] to calculate the vicinal coupling constants $^3J_{H4,H5}$ and $^3J_{H4,H5'}$ (Table 3). The excellent agreement between the calculated and observed results supports the proposed relative stereochemistry for hydrogens H4, H5 and H5′ in **5** and by extension in the related compounds **11α**, **12α**, **13α** and **11β**, **12β**, **13β**.

In order to rationalize the observed vicinal coupling constants in compound **9α**, a complete geometry optimization of the initial structure was carried out using the same procedure. The calculated dihedral angle H4–C4–C5–H5′ (−38.0°) was introduced in the Altona equation[18] to calculate a value of 6.7 Hz for the

Table 3. Theoretical and observed values of coupling constants $^3J_{H4/H5}$ and $^3J_{H4/H5'}$ in lactams **5** and **9α** and dihedral angles calculated with the B3LYP/6-31G(d) chemistry model

Compound	Dihedral angle H4–C4–C5–H5	Dihedral angle H4–C4–C5–H5′	$^3J_{calc}$ H4/H5 (Hz)	$^3J_{obs}$ H4/H5 (Hz)	$^3J_{calc}$ H4/H5′ (Hz)	$^3J_{obs}$ H4/H5′ (Hz)
5[a]	−73.6	45.5	1.7	2.3	5.6	6.9
9α	−38.0	—	6.7	8.3	—	—

[a] See Scheme 1 (R = Me).

$^3J_{H4,H5}$ coupling constant, which is in excellent agreement with the observed value (Table 3). This result reproduces fairly the observed difference for the coupling constant of this isomer and for its analogous compound **10α**.

3. Conclusion

The base-mediated reaction of enantiomerically pure α-sulfinylketimine (+)-**1** with (*E*)-ene esters is a useful method for the diastereoselective synthesis of enantiomerically pure 3,4-disubstituted-5-(*p*-tolylsulfinyl)-5,6-dehydropiperidin-2-ones. The presence of a second substituent at the α-position of the unsaturated ester strengthens the *anti*-selectivity observed with β-substituted ene esters. A double chirality transfer from the sulfinyl group can be proposed to justify the high observed distereoselectivity in these reactions. The application of this methodology has allowed us to achieve an enantioselective synthesis of ethyl (−)-(3*S*,4a*S*,7a*S*)-1-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate (+)-**17α** (five steps; 47% yield; ee ⩾97%) through a simple transformation of lactam (−)-**9α**.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded at 200 or 500 MHz and 50 or 125 MHz, in a Bruker AC-200 or Bruker AM-500 spectrometer, respectively, using $CDCl_3$. The chemical shifts (δ) refer to TMS (^1H) or deuterated chloroform (^{13}C) signals. Coupling constants (J) are reported in hertz. Multiplicities in the proton spectra are indicated as s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintuplet) and m (multiplet). Elemental analyses were performed with a Perkin–Elmer 2400 C, H, N analyzer. Optical rotations were measured at room temperature (20–23 °C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). Infrared spectra were recorded on a Perkin–Elmer 781 IR spectrophotometer.

All reactions in non-aqueous media were carried out in flame-dried glassware under an argon atmosphere. Reagents and solvents were handled by using standard cannule or syringe techniques. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone, dichloromethane from P_2O_5 and isopropanol from CaH_2. In all other cases, commercially available reagent-grade solvents were employed without purification. Analytical TLC was routinely used to monitor reactions. Plates precoated with Merck silica gel 60 F_{254} of 0.25 mm thickness were used, and visualized with UV light, with either anisaldehyde/sulfuric acid/ethanol (2:1:100) or phosphomolibdic acid solution (PMA, 10% in ethanol) as developing agents. Merck silica gel 60 (230-400 ASTM mesh) was employed for flash column chromatography. Chromatography using deactivated silica gel was performed by eluting with a 2% aqueous solution of $NaHCO_3$/MeOH (5:95, v/v) until pH of the eluent was basic, and then passing dry acetone through it. Chemicals for reactions were used as purchased from the Aldrich Chemical Co. The synthesis of starting compound (+)-**1** has been previously described.[7] Isopropyl 3- and 2,3-substituted propenoate esters **2** were obtained from commercially available acids following standard procedures. 4-Methyl-2,2-pentamethylene-2,5-dihydrooxazol[7,19] and (−)-menthyl *p*-toluenesulfinate[20] were accomplished following the reported procedures.

4.2. Synthesis of 5-(*p*-tolylsulfinyl)-5,6-dehydro-piperidin-2-ones 9–14. Typical procedures

Method A: To a cold (−78 °C) solution of sulfinyl ketimine (+)-**1** (524.5 mg, 1.8 mmol) in dry THF (40 mL) under an argon atmosphere was added a solution of *n*-BuLi (1.6 M in hexane, 1.25 mL, 2 mmol). The solution was stirred at −78 °C for 0.5 h, the temperature raised to −30 °C and the ene ester (3.6 mmol, 0.15 M solution in THF) added. The reaction mixture was kept to rt and stirred until disappearance of the open adducts was complete (TLC analysis; 12 h to 7 days). Then, the mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (20 mL) and extracted with EtAcO (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and chromatographed.

Method B: To a cold (−78 °C) solution of sulfinyl ketimine (+)-**1** (524.5 mg, 1.8 mmol) in dry THF (12 mL) under an argon atmosphere, a cold (−25 °C) solution of LDA[9] (2.25 mmol) in dry THF (4 mL) was added through a cannular. Afterwards, the brown solution was stirred at −78 °C for 1 h and the ene ester (2.2 mmol) was added through a syringe. The solution was stirred at −78 °C for 15 min, and at rt for 2 h. The reaction mixture was poured into 40 mL of H_2O, and extracted with DCM (3 × 20 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated under reduced pressure and chromatographed.

Diastereomeric ratios and conversions were determined by analysis of ^1H NMR spectra of the reaction crudes prior to their isolation. Yields are quoted as isolated products (Table 1).

4.2.1. (−)-(*S*$_S$,5a′*S*,8a′*R*)-9′-[(4-Methylphenyl)sulfinyl]-1′,5a′,6′,7′,8′,8a′-hexahydro-5′*H*-spiro[cyclohexane-1,3′-cyclopenta[*d*][1,3]oxazolo[3,4-*a*]pyridin]-5′-one (−)-9α. *Method A*: $R_f = 0.20$ (hexane/EtAcO: 1:1; v/v). Yellow solid. Mp 111–114°C. $[\alpha]_D^{25} = -45.7$ (*c* 1.7, $CHCl_3$). IR (KBr) 2935, 1682, 1375 cm^{-1}. ^1H NMR (500 MHz) δ 1.430 (dddt, 1H, $^2J = 12.4$, $^3J = 12.4$, 6.3, 3.3, cyclopentyl), 1.55–1.75 (m, 11H, cyclohexyl, cyclopentyl), 1.830 (dddd, 1H, $^2J = 13.7$, $^3J = 10.0$, 8.3, 6.0, cyclopentyl), 2.250 (dddd, 1H, $^2J = 13.7$, $^3J = 8.4$, 5.0, 2., cyclopentyl), 2.36–2.38 (m, 2H, cyclopentyl), 2.422 (s, 3H, CH_3-Ar), 2.881 (dt, 1H, $^3J = 8.3$, 8.3, 2.7, $H5_{ec}$), 2.936 (dt, 1H, $^3J = 9.8$, 9.8, 8.3, $H4_{ax}$), 4.875 (AB system, 1H, $^2J = 13.7$, H7), 4.963 (AB system, 1H, $^2J = 13.7$, H7′), 7.311 (AA′XX′ system, 2H, $^3J = 8.0$, H_{ortho}-CH_3),

7.473 (AA′XX′, 2H, $^3J = 13.7$, H_{ortho}-SO). ^{13}C NMR (125 MHz) δ 21.39, 22.84, 22.91, 23.24, 24.39, 27.19, 31.23, 31.94, 33.57, 34.38, 46.83, 65.02, 99.70, 113.31, 124.37, 129.86, 141.21, 141.96, 146.12, 164.24. Anal. Calcd for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.32; H, 7.01; N, 3.54.

4.2.2. (−)-(S_S,5a′*S*,9a′*R*)-10′-[(4-Methylphenyl) sulfinyl]-5a′,6′,7′,8′,9′,9a′-hexahydrospiro[cyclohexane-1,3′-[1,3]-oxazolo[3,4-*b*]isoquinolin]-5′(1′*H*)-one (−)-10α. *Method A*: $R_f = 0.32$ (hexane/EtAcO: 1:2; v/v). Colourless oil. $[\alpha]_D^{25} = -70.3$ (*c* 0.7, $CHCl_3$). IR (CCl_4) 2940, 1675, 1390 cm^{-1}. ^{1}H NMR (500 MHz) δ 0.850 (qd, 1H, $^2J = 12.6$, $^3J = 12.6$, 12.6, 3.2, cyclohexyl), 0.980 (qt, 1H, $^2J = 12.9$, $^3J = 12.9$, 12.9, 3.4, 3.4, cyclohexyl), 1.200 (qt, 1H, $^2J = 13.1$, $^3J = 13.1$, 3.4, 3.4, cyclohexyl), 1.270 (qt, 1H, $^2J = 12.2$, $^3J = 12.2$, 12.2, 3.5, cyclohexyl), 1.390 (qt, 1H, $^2J = 13.4$, $^3J = 13.4$, 13.4, 4.1, 4.1, cyclohexyl), 1.58–1.74 (m, 9H, cyclohexyl), 2.33–2.46 (m, 4H, cyclohexyl), 2.422 (s, 3H, CH_3-Ar), 2.684 (td, 1H, $^3J = 6.3$, 6.3, 2.7, $H5_{ec}$), 2.703 (dt, 1H, $^3J = 6.3$, 6.3, 3.5, $H4_{ax}$), 4.953 (AB system, 1H, $^2J = 13.7$, H7), 4.987 (AB system, 1H, $^2J = 13.7$, H7′), 7.304 (AA′XX′ system, 2H, $^3J = 8.0$, H_{ortho}-CH_3), 7.507 (AA′XX′ system, 2H, $^3J = 8.0$, H_{ortho}-SO). ^{13}C NMR (125 MHz) δ 21.41, 21.84, 22.81, 22.93, 24.42, 25.77, 27.78, 30.88, 31.25, 34.15, 43.52, 99.13, 114.75, 124.41, 129.84, 138.88, 141.41, 142.61, 168.98. Anal. Calcd for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51. Found: C, 69.00; H, 7.21; N, 3.42.

4.2.3. (+)-(S_S,6′*R*,7′*S*)-6′,7′-8′-[(4-methylphenyl) sulfinyl]-6′,7′-diphenyl-6′,7′dihydrospiro[cyclohexane-1,3′-[1,3]-oxazolo[3,4-*a*]pyridin]-5′(1*H*)-one, 11α, and (+)-(S_S,6′*S*,7′*S*)-8′-[(4-methylphenyl) sulfinyl]-6′,7′-diphenyl-6′,7′-dihydrospiro[cyclohexane-1,3′-[1,3]oxazolo[3,4-*a*]pyridin]-5′(1*H*)-one 11β. *Method A*: From methyl (*E*)-α-phenylcinnamate. The ene ester was obtained from α-phenylcinnamic and methanol following the standard Fischer procedure in 89% yield. After the ene ester was added, the reaction mixture was stirred at rt for 20 h. The crude product was chromatographed on silica gel using gradient mixtures of hexane and ethyl acetate as eluent to give 89 mg (63% yield) of (+)-**11α** and 10 mg (7% yield) of (+)-**11β**.

Compound **11α**: $R_f = 0.48$ (hexane/EtAcO: 1:1; v/v). $[\alpha]_D^{25} = +314.05$ (*c* 0.42, $CHCl_3$). Yellow oil. IR (CCl_4) 3373, 3063, 2935, 1693, 1599, 1371 cm^{-1}. ^{1}H NMR 200 MHz δ 1.40–1.80 (m, 8H, cyclohexyl), 2.130 (s, 3H, CH_3-Ar), 2.20–2.37 (m, 2H, cyclohexyl), 3.635 (d, 1H, $^3J = 1.4$, $H5_{ec}$), 3.998 (d, 1H, $^3J = 1.4$, $H4_{ax}$), 5.061 (AB system, 1H, $^2J = 14.2$, H7), 5.141 (AB system, 1H, $^2J = 14.2$, H7′), 6.66–7.33 (m, 14H, Ar). ^{13}C NMR (50 MHz) δ 21.12, 22.75, 22.79, 24.30, 31.27, 33.54, 41.65, 56.27, 64.92, 99.40, 111.50, 124.47, 126.53, 126.60, 126.92, 127.64, 128.61, 128.85, 129.18, 137.33, 140.91, 141.05, 143.04, 166.46 Anal. Calcd for $C_{31}H_{31}NO_3S$: C, 74.82; H, 6.28; N, 2.81. Found: C, 74.90; H, 6.32, N, 2.65.

Compound **11β**: $R_f = 0.17$ (hexane/EtAcO: 1:1; v/v). $[\alpha]_D^{25} = +154.05$ (*c* 0.6, $CHCl_3$). Yellow oil. IR (CCl_4) 3063, 3030, 2934, 1701, 1668, 1373 cm^{-1}. ^{1}H NMR (200 MHz) δ 1.40–1.90 (m, 8H, cyclohexyl), 2.046 (s, 3H, CH_3-Ar), 2.20–2.40 (m, 2H, cyclohexyl), 3.800 (d, 1H, $^3J = 7.1$, $H5_{ax}$), 4.169 (d, 1H, $^3J = 7.1$, $H4_{ax}$), 5.165, (s, 2H, H7, H7′), 6.15–6.20 (m, 2H, Ar), 6.46–6.51 (m, 2H, Ar), 6.65–6.72 (m, 2H, Ar), 6.81–6.86 (m, 4H, Ar), 6.95–7.00 (m, 4H, Ar). ^{13}C NMR (50 MHz) δ 21.04, 22.94, 24.45, 29.68, 31.27, 33.99, 42.12, 55.96, 65.27, 100.14, 115.12, 124.36, 126.42, 127.07, 127.44, 127.60, 128.09, 128.96, 130.39, 134.07, 135.99, 137.11, 140.82, 144.84, 166.70. Anal. Calcd for $C_{31}H_{31}NO_3S$: C, 74.82; H, 6.28; N, 2.81. Found: C, 74.69; H, 6.21, N, 2.90.

4.2.4. (+)-(S_S,6′*S*,7′*S*)-6′-Methyl-8′-[(4-methylphenyl) sulfinyl]-7′-phenyl-6′,7′-dihydrospiro[cyclohexane-1,3′-[1,3]-oxazolo[3,4-*a*]pyridin]-5′(1′*H*)-one, 12α, and (+)-(S_S,6′*R*,7′*S*)-6′-methyl-8′-[(4-methylphenyl)sulfinyl]-7′-phenyl-6′,7′-dihydrospiro[cyclohexane-1,3′-[1,3]oxazolo[3,4-*a*]pyridin]-5′(1′*H*)-one, 12β. *Method A*: From methyl and isopropyl (*E*)-α-methylcinnamate. The last ene ester was obtained from the α-methylcinnamic acid and isopropyl alcohol following the standard Fischer procedure. The crude ester was distilled at 150 °C (0.1 Torr) (70% yield). After addition of ene ester, the reaction mixtures were stirred at rt for 16 h. The crude products were chromatographed on silica gel using gradient mixtures of hexane and ethyl acetate (1:1 to 3:2) as eluent to give 79 mg of **12α** and 11 mg of **12β**. Yield: 48%.

Compound **12α**: $R_f = 0.21$ (hexane/EtAcO: 1:1; v/v). $[\alpha]_D^{25} = +90.1$ (*c* 0.74, $CHCl_3$). Yellow oil. IR (film) 2962, 2928, 1697, 1261 cm^{-1}. ^{1}H NMR (200 MHz) δ 1.188 (d, 3H, $^3J = 7.3$, CH_3-C5), 1.52–1.68 (m, 8H, cyclochexyl), 2.116 (s, 3H, CH_3-Ar), 2.27–2.32 (m, 2H, cyclohexyl), 2.479 (qd, 1H, $^3J = 7.3$, 1.7, $H5_{ec}$), 3.405 (d, 1H, $^3J = 1.7$, $H4_{ax}$), 5.077 (AB system, 1H, $^2J = 13.9$, H7), 5.116 (AB system, 1H, $^2J = 13.9$, H7′), 6.545 (AA′XX′ system, 2H, $^3J = 7.8$, H_{ortho} Ar-C4), 6.868 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho} Ar-C4), 6.77–6.92 (m, 3H, Ar), 7.098 (AA′XX′ system, 2H, $^3J = 8.3$, Ar). ^{13}C NMR (50 MHz) δ 12.11, 17.64, 21.08, 22.77, 22.882, 24.30, 31.22, 33.75, 46.48, 64.95, 99.27, 111.43, 124.42, 126.31, 129.07, 137.16, 140.91, 140.93, 143.20, 169.72. Anal. Calcd for $C_{26}H_{29}NO_3S$: C, 71.69; H, 6.71; N, 3.22. Found: C, 71.82; H, 6.57, N, 3.40.

Compound **12β**: $R_f = 0.15$ (hexane/EtAcO: 1:1; v/v). Yellow oil. IR film 2971, 2935, 1698, 1252 cm^{-1}. ^{1}H NMR (200 MHz) δ 0.792 (d, 3H, $^3J = 7.3$, CH_3-C5), 1.40–1.83 (m, 8H, cyclohexyl), 2.112 (s, 3H, CH_3-Ar), 2.24–2.41 (m, 2H, cyclohexyl), 2.937 (quint., 1H, $^3J = 7.3$, $H5_{ax}$), 3.643 (d, 1H, $^3J = 7.3$, $H4_{ax}$), 5.062 (AB system, 1H, $^2J = 13.9$, H7), 5.088 (AB system, 1H, $^2J = 13.9$, H7′), 6.461 (AA′XX′ system, 2H, $^3J = 8.2$, Ar), 6.780 (AA′XX′ system, 2H, $^3J = 8.3$, Ar), 6.67–6.99 (m, 3H, Ar), 7.033 (AA′XX′ system, 2H, $^3J = 8.3$, Ar). ^{13}C NMR (50 MHz) δ 11.56, 21.05, 22.89, 24.38, 24.95, 31.44, 39.81, 41.93, 42.98, 65.16, 99.62, 114.69, 124.37, 126.30, 127.96, 128.97, 136.29, 137.89, 139.97, 140.68, 144.94, 166.90. Anal. Calcd for $C_{26}H_{29}NO_3S$: C, 71.69; H, 6.71; N, 3.22. Found: C, 71.49; H, 6.63; N, 3.30.

4.2.5. (S_S,6′*S*/*R*,7′*R*/*S*)-6′,7′-Dimethyl-8′-[(4-methylphenyl)sulfinyl]-6′,7′-dihydrospiro[cyclohexane-1,3′-[1,3]oxazolo[3,4-*a*]pyridin]-5′(1′*H*)-one, 13α/13β and 13γ/13δ. *Method A*: From ethyl (*E*)-α-methylcrotonate. After the ene ester was added, the reaction mixture was stirred at rt for 16 h. The crude product was chromatographed on silica gel (hexane/EtAcO: 3:2; v/v) to obtain two fractions of $R_f = 0.28$ (86 mg; 77% yield) and $R_f = 0.15$ (18 mg, 16% yield), which were identified as a mixture of two isomers.

First fraction: **13α/13β**. $R_f = 0.16$ (hexane/EtAcO: 3:2; v/v). Colourless oil. ^{1}H NMR (500 MHz) δ **13α**: 0.433 (d, 3H, $^3J = 7.2$, CH_3-C4), 1.050 (d, 3H, $^3J = 7.0$, CH_3-C5), 1.51–1.72 (m, 8H, cyclohexyl), 2.30–2.38 (m, 2H, cyclohexyl), 2.395 (s, 3H, CH_3-Ar), 2.287 (qd, 1H, $^3J = 7.2$, 1.7, $H5_{ec}$), 2.432 (qd, 1H, $^3J = 7.2$, 1.7, $H4_{ax}$), 4.988 (s, 2H, H7, H7′), 7.292 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho}-CH_3), 7.495 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho}-SO). **13β**: 0.266 (d, 3H, $^3J = 7.0$, CH_3-C4), 1.090 (d, 3H, $^3J = 6.6$, CH_3-C5), 1.51–1.72 (m, 8H, cyclohexyl), 2.30–2.38 (m, 2H, cyclohexyl), 2.408 (s, 3H, CH_3-Ar), 2.681 (qd, 1H, $^3J = 7.0$, 5.5, $H5_{ax}$), 2.705 (qd, 1H, $^3J = 6.6$, 5.5, $H4_{ax}$), 4.966 (s, 2H, H7, H7′), 7.302 (AA′XX′ system, 2H, $^3J = 8.5$, H_{ortho}-Me), 7.505 (AA′X′ system, 2H, ^3J=8.5, H_{ortho}-SO). ^{13}C NMR (125 MHz) δ **13α**: 15.89, 18.99, 21.34, 22.72, 22.80, 24.27, 30.69, 30.89, 33.88, 45.17, 64.70, 98.85, 113.50, 124.43, 129.77, 138.91, 141.00, 141.40, 170.59. **13β**: 11.09, 12.32, 20.97, 22.80, 22.96, 24.35, 28.53, 31.04, 33.98, 42.54, 64.76, 98.97, 116.26, 128.47, 129.85, 138.48, 141.44, 142.69, 169.77. Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.47; H, 7.38, N, 3.60.

Second fraction: **13γ/13δ**. $R_f = 0.31$ (hexane/EtAcO: 3:2; v/v). Yellow oil. ^{1}H NMR (500 MHz) δ **13γ**: 0.974 (d, 3H, $^3J = 6.8$, CH_3-C4), 1.014 (d, 3H, $^3J = 6.8$, CH_3-C5), 1.30–1.82 (m, 8H, cyclohexyl), 2.20–2.34 (m, 2H, cyclohexyl), 2.269 (quint., 1H, $^3J = 6.8$, $H5_{ec}$), 2.310 (quint, 1H, $^3J = 6.8$, $H4_{ec}$), 2.353 (s, 3H, CH_3-Ar), 4.778 (AB system, 1H, $^2J = 13.6$, H7), 5.019 (AB system, 1H, $^2J = 13.6$, H7′) 7.249 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho}-CH_3), 7.370 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho}-SO). **13δ**: 0.511 (d, 3H, $^3J = 7.3$, CH_3-C5), 1.134 (d, 3H, $^3J = 7.0$, CH_3-C4), 1.30–1.82 (m, 8H, cyclohexyl), 2.139 (ABX_3 system, 1H, $^3J = 7.3$, 1.8, $H5_{ax}$), 2.20–2.34 (m, 3H, cyclohexyl, $H4_{ec}$), 2.247 (s, 3H, CH_3-Ar), 4.809 (AB system, 1H, $^2J = 13.6$, H7), 5.033 (AB system, 1H, $^2J = 13.6$, H7′), 7.308 (AA′XX′ system, 2H, $^3J = 8.3$, H_{ortho}-Me), 7.355 (AA′X′ system, 2H, $^3J = 8.3$, H_{ortho}-SO). ^{13}C NMR (125 MHz) δ **13γ**: 11.10, 14.86, 21.35, 22.78, 22.90, 24.39, 31.41, 31.57, 33.82, 42.30, 64.74, 99.08, 115.40, 124.18, 129.97, 140.03, 140.91, 142.73, 169.16. **13δ**: 16.3, 21.03, 21.86, 22.82, 23.01, 27.00, 33.06, 31.22, 36.03, 44.98, 72.43, 95.51, 113.36 124.07, 129.97, 139.62, 140.79, 141.00, 170.01. Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.68; H, 7.32, N, 3.67.

4.2.6. (S_S,7′*S*)-8′-[(4-Methylphenyl)sulfinyl]-7′-(trifluoromethyl)-6′,7′-dihydrospiro[cyclohexane-1,3′-[1,3] oxazolo-[3,4-*a*]pyridin]-5′(1′*H*)-one, 14. *Method B*: From isopropyl (*E*)-4,4,4-trifluoromethyl propenoate. After the ene ester was added, the reaction mixture was stirred for 12 h at rt. The crude was flash chromatographed on silica gel (hexane/EtAcO: 2:1; v/v). Obtained 138 mg (75% yield) as a sole isomer.

Compound **14**: $R_f = 0.22$ (hexane/EtAcO: 2:1; v/v). $[\alpha]_D^{25} = +50.4$ (*c* 0.46, $CHCl_3$). Colourless solid. Mp 151–153 °C. IR (KBr) 3924, 1709, 1662, 1375 cm^{-1}. ^{1}H NMR (500 MHz) δ 1.47–1.67 (m, 8H, cyclohexyl), 2.21–2.50 (m, 3H, cyclohexyl, $H5_{ec}$), 2.352 (s, 3H, CH_3-Ar), 2.750 (dd, 1H, $^2J = 17.1$, $^3J = 1.7$, $H5_{ec}$), 2.940 (ddq, 1H, $^3J_{H,F} = {}^3J = 8.3$, $^3J = 1.7$, $H4_{ax}$), 5.014 (AB system, 1H, $^2J = 14.6$, H7), 5.033 (AB system, 1H, $^2J = 14.6$, H7′), 7.259 (AA′XX′ system, 2H, $^3J = 8.0$, H_{ortho}-CH_3), 7.429 (AA′XX′ system, 2H, $^3J = 8.0$, H_{ortho}-SO). ^{13}C NMR (125 MHz) δ 21.34, 22.59, 22.83, 24.18, 31.39, 33.30, 33.33, 35.42 (d, $^3J_{C,F} = 31.3$), 65.43, 100.27, 105.07, 127.01 (q, $^1J_{C,F} = 133.1$),124.14, 130.31, 138.96, 141.61, 19.38, 163.59. Anal. Calcd for $C_{20}H_{22}F_3NO_3S$: C, 58.10; H, 5.36; N, 3.39. Found: C, 58.23; H, 5.27; N, 3.53.

4.3. Synthesis of (+)-(5a*S*,8a*S*,9a*S*)-octahydro-5′*H*-spiro[cyclohexane-1,3′-cyclopenta[*d*][1,3]oxazolo[3,4-*a*]-pyridin]-5′-one, (+)-15

To a stirred solution of (−)-**9α** (460 mg, 1.19 mmol) in absolute EtOH (20 mL) was added Raney Nickel W-2[14] (2.3 g) and the reaction mixture refluxed for 20 min. Then, it was cooled until rt, filtered on a thin pad of Celite and the metallic salts washed with ether (5 × 10 mL). The combined organic extracts were evaporated at reduced pressure to give a colourless solid that was purified by flash chromatography (silica gel; hexane/EtAcO: 1:1; v/v). Obtained: 289 mg 97% yield. $R_f = 0.41$ (hexane/EtAcO: 1:1; v/v). Colourless solid. Mp 78–80 °C. $[\alpha]_D^{25} = +42.0$ (*c* 0.7, $CHCl_3$). IR (KBr) 2935, 2852, 1630, 1448 cm^{-1}. ^{1}H NMR (500 MHz) δ 1.040 (dt, 1H, $^2J = {}^3J = 12.6$, $^3J = 11.3$, H5′), 1.24–1.32 (m, 1H, H15′), 1.370 (dt, 1H, $^2J = 12.7$, $^3J = 7.5$, 7.5, 5.6, H14′), 1.43–1.57 (m, 9H, cyclohexyl), 1.840 (dddt, 1H, $^2J = {}^3J = 13.1$, $^3J = 9.3$, 9.3, 7.7, H16′), 1.950 (ddt, 1H, $^2J = 12.7$, $^3J = 7.6$, 7.6, 5.1, H14), 1.980 (ddd, 1H, $^2J = 12.6$, $^3J = 5.6$, 2.6, H5), 2.090 (dddd, 1H, $^2J = 12.7$, $^3J = 9.3$, 7.9, 4.3, H16), 2.370 (dddt, 1H, $^3J = 12.6$, 9.2, 7.6, 5.6, 5.6, H4), 2.500 (dt, 1H, $^2J = {}^3J = 13.3$, $^3J = 4.6$, $H9_{ax}$), 2.559 (dt, 1H, $^2J = {}^3J = 14.0$, $^3J = 4.3$, $H13_{ax}$), 2.680 (q, 1H, $^3J = 9.3$, H3), 3.450 (dd, 1H, $^2J = 8.6$, $^3J = 9.9$, H7), 3.690 (dddd, 1H, $^3J = 11.3$, 9.9, 5.9, 2.6, H6), 4.080 (dd, 1H, $^2J = 8.6$, $^3J = 5.9$, H7′). ^{13}C NMR (125 MHz) δ 23.01, 23.07, 24.55, 29.80, 30.97, 32.67, 33.40, 33.87, 37.26, 46.02, 57.01, 68.86, 95.62, 170.15. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.17; H, 9.3; N, 5.40.

4.4. Synthesis of (+)-(3*S*,4a*S*,7a*S*)-3-(hydroxymethyl) octahydro-1*H*-cyclopenta[*c*]pyridin-1-one, (+)-16α

A stirred solution of (+)-**15** (147 mg, 0.59 mmol) in AcOH (10% v/v in H_2O, 20 mL) was refluxed for 12 h. Next, the reaction mixture was kept at rt for 12 hours

then the temperature was reduced to 0 °C and an aqueous saturated solution of $NaHCO_3$ carefully added until pH 7. The reaction mixture was then extracted with $CHCl_3$/*i*-PrOH (8×15 mL; 80/20; v/v). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure at rt. The crude product (98 mg; yield: 98%) was directly transformed in the carboxylic acid. $R_f = 0.1$ (EtAcO/EtOH: 3:1; v/v). $[\alpha]_D^{25} = +16.8$ (*c* 0.1, $CHCl_3$). Colourless solid. Mp 89–92 °C. IR (KBr) 3265, 2926, 1622 cm^{-1}. ^1H NMR (200 MHz) δ 1.10 (dt, 1H, $^2J = 12.9$, $^3J = 11.2$, cyclopentyl), 1.45–1.77 (m, 5H, cyclopentyl), 1.90–2.23 (m, 2H, cyclopentyl, $H3_{ec}$), 2.31–2.43 (m, 1H, H4), 2.63 (q, 1H, $^3J = 8.8$, H5), 3.33–3.72 (m, 3H, H7, H7′, H2), 4.63 (br s, 1H, OH), 7.64 (br s, 1H, NH). ^{13}C NMR (50 MHz) δ 23.55, 29.65, 30.10, 32.80, 35.91, 44.39, 54.94, 65.74, 176.75.

4.5. Synthesis of ethyl (+)-(3*S*,4a*S*,7a*S*)-1-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate,(+)-17α

To a stirred solution of (+)-**16α** (93 mg, 0.55 mmol) in dry acetone (4.5 mL) was added Jones' reagent (1.5 equiv) at 0 °C over 4 h and the reaction mixture kept to rt and stirred for 12 h. Next, *i*-PrOH (0.3 mL) was added and the mixture stirred at rt for 30 min. Subsequently, water (5 mL) was added and the mixture extracted with EtAcO (5×2 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure at rt. The crude product (61 mg; yellow oil; 60% yield) was directly transformed at the ethyl ester.

A solution of crude carboxylic acid (61 mg, 0.33 mmol) in dry ethanol (2.5 mL) was cooled at 0 °C and $SOCl_2$ (0.55 mL, 0.68 mmol) slowly added. Next, the temperature was raised to rt and the mixture stirred overnight at rt. Then, saturated aqueous $NaHCO_3$ was added and the reaction mixture was extracted with EtAcO (3×5 mL) and the combined organic layer was washed with brine, water and dried on Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by chromatography (silica gel; EtAcO) to give 68 mg of a colourless solid that was identified as ethyl ester (+)-**17α**. Yield: 98%. $R_f = 0.24$ (EtAcO). Colourless solid. Mp 42–45 °C. $[\alpha]_D^{25} = +2.1$ (*c* 2.1, $CHCl_3$). IR (KBr) 3219, 3082, 2960, 1738, 1662 cm^{-1}. ^1H NMR (500 MHz) δ 1.32 (t, 3H, $^3J = 7.1$, CH_3 of ethyl ester), 1.390 (dt, 1H, $^2J = 12.8$, $^3J = 12.8$, 11.8, $H5'_{ax}$), 1.440 (dddd, 1H, $^2J = 13.2$, $^3J = 7.8$, 7.2, 4.4, H8′), 1.570 (ddddd, 1H, $^2J = 12.6$, $^3J = 8.6$, 8.1, 7.6, 7.2, H9′), 1.710 (ddddd, 1H, $^2J = 12.6$, $^3J = 8.3$, 7.8, 5.8, 4.4, H9), 1.830 (dddd, 1H, $^2J = 13.1$, ^3J=8.9, 8.6, 8.3, H10′), 1.960 (tdd, 1H, $^2J = 13.2$, ^3J=8.1, 8.1, 5.8, H8), 2.150 (dddd, 1H, $^2J = 13.1$, $^3J = 9.1$, 7.6, 4.4, H10), 2.25 (ddd, 1H, $^2J = 12.8$, $^3J = 5.0$, 3.7, $H5_{ec}$), 2.440 (ddddd, 1H, $^3J = 12.5$, 9.0, 8.0, 5.0, 4.4, $H4_{ax}$), 2.690 (q, 1H, $^3J = 9.0$, H3), 4.03 (dd, 1H, $^3J = 11.8$, 3.7, $H6_{ax}$), 4.24 (q, 2H, $^3J = 7.1$, CH_2 of ethyl ester), 6.30 (br s, 1H, NH). ^{13}C NMR (75 MHz) δ 14.07, 23.92, 29.43, 31.67, 32.84, 36.51, 44.13, 54.34, 61.87, 170.56, 174.40. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.61; H, 8.00; N, 6.71.

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References

1. Fawcett, P. A.; Usher, J. J.; Huddleston, J. A.; Blaney, R. C.; Nisbet, J. J.; Abraham, E. P. *Biochem. J.* **1976**, *157*, 651–660.
2. (a) *Peptide Secondary Structure Mimetics; Tetrahedron*; Khan, M., Ed., 1993; 49, pp 3433–3689 (Symposia-in-print 50); (b) Giannins, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244–1267.
3. Dragovich, P. S.; Barker, J. E.; French, J.; Imbacuan, M.; Kalish, V. J.; Kissinger, C. R.; Knighton, D. R.; Lewis, C. T.; Moomaw, E. W.; Parge, H. E.; Pelltier, L. A. K.; Prins, J. J.; Showalter, R. E.; Tatlock, J. H.; Tucker, K. D.; Villafranca, J. E. *J. Med. Chem.* **1996**, *39*, 1872–1874.
4. Guillard, J.; Abraham, A.; Anderson, P. C.; Beaulieu, P. L.; Bogri, T.; Bousquet, Y.; Grenier, L.; Guse, I.; Lavallée, P. *J. Org. Chem.* **1996**, *61*, 2226–2231.
5. Skiles, J. W.; Giannousis, P. P.; Fales, K. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 963–966.
6. (a) Brewster, A. G.; Broady, S.; Hughes, M.; Moloney, M. G.; Woods, G. A. *Org. Biomol. Chem.* **2004**, *2*, 1800–1810; (b) Brewster, A. G.; Broady, S.; Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Hughes, M.; Moloney, M. G.; Woods, G. A. *Org. Biomol. Chem.* **2004**, *2*, 1031–1043; (c) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870–880; (d) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158; (e) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843–9873; (f) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394.
7. Acherki, H.; Alvarez-Ibarra, C.; de Dios, A.; Gutiérrez, M.; Quiroga Feijóo, M. L. *Tetrahedron: Asymmetry* **2001**, *12*, 3173–3183.
8. Acherki, H.; Alvarez-Ibarra, C.; Guzmán-Fernández, S.; Quiroga Feijóo, M. L. *Tetrahedron: Asymmetry* **2004**, *15*, 693–697.
9. Hua, D. H.; Bharathy, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6698–6707.
10. Mozingo, R. *Org. Synthesis* **1955**, *Collective Vol. 3*, 181.
11. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45.
12. The PM3 calculations were done using Hyperchem version 5.0 for Windows (a) Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209–220; (b) Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 221–264.
13. Hyperchem Release 5.0 for Windows; Hypercube; Waterloo, Ontario (Canada).
14. (a) Sosa, C.; Lee, C. *J. Chem. Phys.* **1993**, *98*, 8004–8011; (b) Perdew, J. P.; Wang, Y. *Phys. Rev.* **1992**, *B45*, 13244–13249; (c) Perdew, J. P.; Cheway, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. *Phys. Rev.* **1992**, *B46*, 6671–6687; (d) Andzelm, J.; Wimmer, E. *J. Chem. Phys.* **1992**, *96*, 1280–1303; (e) Scuseria, G. E. *J. Chem. Phys.* **1992**, *97*, 7528–7530; (f) Becke, A. D. *J. Chem. Phys.* **1992**, *97*, 9173–9177; (g) Becke, A. D. *J. Chem. Phys.* **1992**, *96*, 2155–2160; (h) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1992**, *197*, 499–505; (i) *Density Functional Methods in Chemistry*; Labanowski, J. K., Andzelm,

J. W., Eds.; Springer: New York; (j) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133–A1138; (k) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864–B871.

15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Peterson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratman, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Slavador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malich, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Ciolowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskerz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, J.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, P.A. Gaussian 03, revision B.04; Gaussian, Inc., Pittsburgh PA, **2003**.
16. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
17. (a) Dill, J. D.; Pople, J. A. *J. Chem. Phys.* **1975**, *62*, 2921–2923; (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222; (c) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261; (d) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728.
18. Haasnoot, C. A. G.; de Leeuw, F. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.
19. Khiar, N.; Fernández, I.; Alcudia, F.; Hua, D. H. *Tetrahedron Lett.* **1993**, *34*, 699–702.
20. Hulce, M.; Mallamo, J. P.; Frye, L. L.; Kogen, T. P.; Posner, G. H. *Org. Synth.* **1984**, *64*, 196–206.