Preparation of Intermediates for the Synthesis of Polycyclic Alkaloids: A New Access to the Azabicyclic Core of the *Stemona* Alkaloids

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Dedicated to the memory of Dr. Juan Carlos del Amo[‡]

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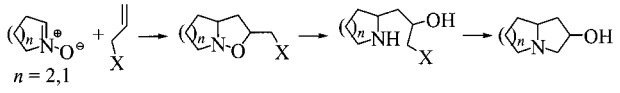
Several isoxazolidines, derived from the 1,3-dipolar cycloaddition of α,β-hexenolides to cyclic nitrones, were converted into the corresponding piperidine- and pyrrolidine-oxepinones by reduction of the nitrogen–oxygen bond. The potential of the resulting amino alcohols as synthetic precursors of polycyclic alkaloids was explored. These intermediates provide a new access to the 1-azabicyclo[5.3.0]decane core of the *Stemona* alkaloids.

Introduction

The 1,3-dipolar cycloaddition reaction of nitrones to olefins is an effective procedure for the preparation of chiral isoxazolidines.[1] These compounds have been used as intermediates in the synthesis of many nitrogen containing target molecules. In particular, the cycloaddition of five and six membered cyclic nitrones to olefins has been successfully employed as a key step in the preparation of various indolizidine and pyrrolizidine alkaloids[2] by the general strategy shown in Scheme 1, developed by Tufariello in the mid-nineteen seventies. In this approach, after the cycloaddition reaction, the formation of the pyrrolidine ring is accomplished by reduction of the isoxazolidine nitrogen−oxygen bond, followed by intramolecular nucleophilic displacement of a leaving group previously introduced at the appropriate position in the starting olefin. In connection with a program of polycyclic alkaloid synthesis, we have studied in detail the stereoselectivity of the 1,3-dipolar cycloaddition of nitrones to (*E*)-α,β-unsaturated esters[3] and also to five, six and seven membered α,β-unsaturated lactones[3c,4] with a variety of substitution patterns. As a result of these studies, we prepared a series of piperidine and pyrrolidine fused isoxazolidines, some of which were further elaborated yielding useful synthetic intermediates.

One of the purposes of this work was to investigate if the procedure outlined in Scheme 1, which is already firmly established for the construction of the indolizidine and pyrrolizidine frameworks, could be extended to the formation of the 1-azabicyclo[5.3.0]decane core common to most alkaloids of the *Stemona* class (Scheme 2).[5]

In a previous paper, we described the reduction of several piperidineisoxazolidines derived from ester type dipolarophiles.[6] Herein we present the study of the reduction of several tricyclic adducts derived from α,β-hexenolides and further elaboration of the products towards the 1-azabicyclo[5.3.0]decane system.



Scheme 1. The "cyclic nitrone approach" to indolizidine and pyrrolizidine alkaloids.

Results and Discussion

Reduction of the N−O Bond

The reductive cleavage of nitrogen−oxygen bonds has been performed using a variety of procedures and reagents including catalytic hydrogenation, various metals in different solvents, hydrides, and metal complexes.[1c] The procedure of choice depends on what other functional groups are present in the substrate and also on its particular struc-

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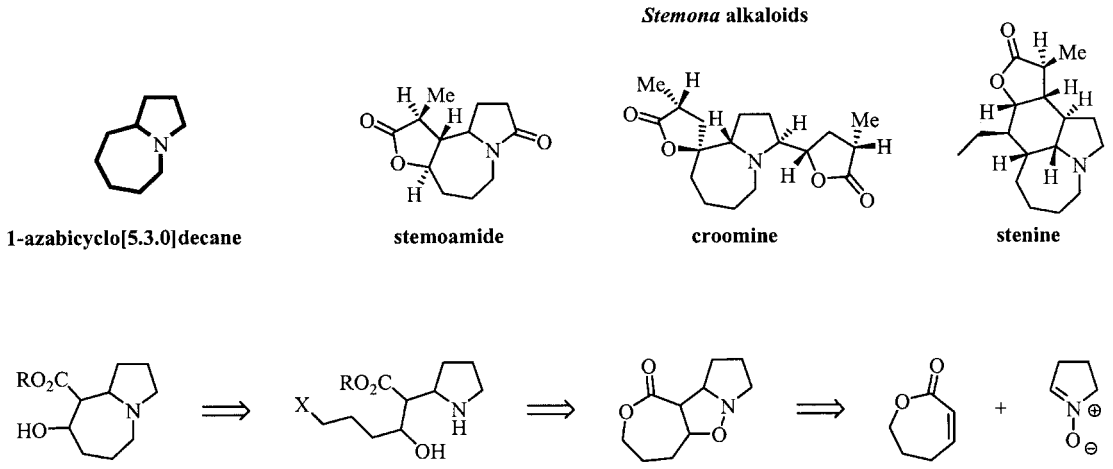
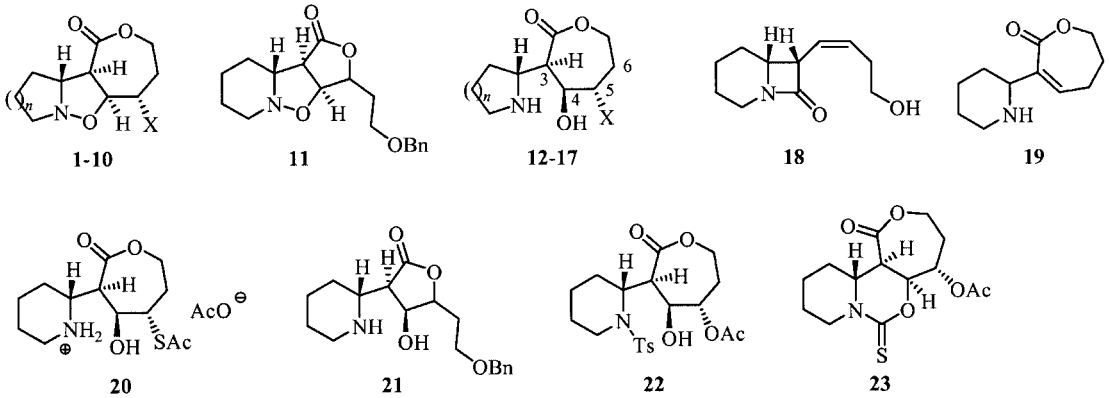


Scheme 2. The designed "cyclic nitrone approach" to *Stemona* alkaloids.

tural features. Figure 1 shows the piperidine and pyrrolidine fused isoxazolidines **1**−**11**,[4] which were the subject of our investigation.

Some preliminary attempts at catalytic hydrogenation in the presence of Pd[2a−2e,7] or molybdenum hexacarbonyl[8] rendered either unchanged starting material or unidentified products, while the reduction with zinc in acidic media[2e,9] emerged as the most appropriate method for our substrates. After extensive experimentation with variable molar proportions of activated zinc, either in acetic or hydrochloric acid over a range of concentrations, we found that the best conditions for the reduction are obtained by using 10 equivalents of zinc powder in 10% aqueous HCl under sonication at room temperature. Absence of sonication gave slightly slower substrate conversions and significantly lower yields. Products and yields are shown in Table 1. The reductive cleavage of the nitrogen−oxygen bond furnished the expected amino alcohols for seven of the eleven studied isoxazolidines. The substrates **5** and **9** bearing the phenylthio substituent gave the best yield in both the piperidine and pyrrolidine series. The amino alcohols **12**−**17** were fully characterized according to their spectroscopic data. All the signals in their ^{1}H NMR spectra were assigned with the help of bidimensional experiments. Subsequently, the coupling constant values were examined to deduce the preferred conformation of these compounds in solution and in order to confirm their relative configuration. For instance, in the ^{1}H NMR spectrum of compound **15**, the signal of the α-carbonyl proton (3-H) appears at $\delta = 3.12$ as a broad singlet, while 5-H displays a false quadruplet at $\delta = 3.75$ ($J \approx$



	1	2	3	4	5	6	7	8	9	10	12	13	14	15	16	17
n	2	2	2	2	2	2	1	1	1	1	2	2	2	2	1	1
X	H	Br	OTs	OAc	SPh	SAc	H	OAc	SPh	SAc	H	OTs	OAc	SPh	OAc	SPh

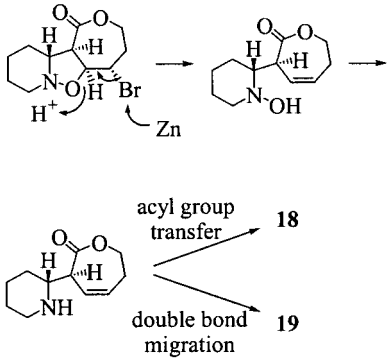
Figure 1. The isoxazolidine substrates studied, products of the N−O bond reduction, and related derivatives.

Table 1. Reduction of isoxazolidines **1**−**11** with Zn in 10% aqueous HCl.

Substrate	Products (yield)
1	**12** (51%)
2	**18** (59%), **19** (6%)
3	**13** (50%)
4	**14** (75%)
5	**15** (80%)
6[a]	**20** (51%)
7	none
8	**16** (60%)
9	**17** (83%)
10	none
11	**21** (77%)

[a] Reduction performed in AcOH/H_2O, 1:1.

3.1 Hz, due to its coupling with 4-H and the two protons at C-6) denoting its equatorial orientation. These data are in agreement with a chair conformation of the oxepinone with the piperidine substituent equatorial and the hydroxyl and phenylthio groups axial, favouring the formation of an intramolecular hydrogen bond. In such a conformation, the protons at C-3 and C-4 are near orthogonal and hence present a coupling constant close to zero. These considerations can be extended to the other related amino alcohols. The reduction of the bromo derivative **2** led to the isolation of the β-lactam **18** as the major product, along with a minor quantity of the α,β-hexenolide **19**. Decisive spectroscopic data for the identification of **18** are given by the olefin proton signals at $\delta = 5.33$ and 5.82 ppm with a vicinal coupling of 10.8 Hz in the ^{1}H NMR spectrum, and the lactam absorption at 1780 cm^{-1} in the IR spectrum. The formation of **18** and **19** can be explained using the mechanistic pathway depicted in Scheme 3. A metal-induced reductive debromination[10] with a concomitant opening of the isoxazolidine ring is followed by cleavage of the nitrogen−oxygen bond to give a piperidine. This piperidine can then evolve either by intramolecular acyl group transfer to the lactam **18**, or by double bond migration to the conjugate lactone **19**.



Scheme 3. Proposed mechanism for the formation of **18** and **19** from **2** by treatment with Zn/aqueous HCl.

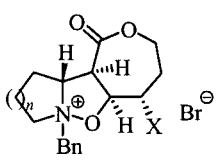
Instead of the expected amino alcohols, the parent pyrrolidineisoxazolidine **7** and the thioesters **6** and **10** only gave complex mixtures of unidentified products when they were subjected to the same reduction conditions. For substrate **6**, the N−O reduction was accomplished in AcOH/H_2O (1:1) as solvent and, avoiding basic workup conditions, the piperidinium acetate **20** could be isolated in 51% yield, although the corresponding free amine decomposed rapidly. Analogous reaction conditions failed when applied to pyrrolidines **7** and **10**.

Since we intended to explore the potential of the amino alcohols **12**−**17** as synthetic intermediates for polycyclic alkaloids, we thought that the presence of a free secondary amine could be problematic for further transformations especially in reactions involving the hydroxyl group. This presumption was soon confirmed when the deoxygenation of compound **14** was attempted by passing either through a sulfonate or a thiocarbonate. Thus, treatment of **14** with tosyl chloride in pyridine furnished the sulfonamide **22** in 86% yield, while the reaction of **14** with thiocarbonyldiimidazole delivered the thiocarbamate **23** in 60% yield. The necessity for protection of the nitrogen atom led us to consider the possibility of improving the yields of the N−O reduction by initial *N*-benzylation of the substrates, as has been reported previously.[11]

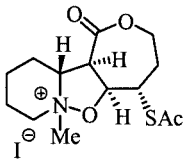
N-Benzylation and Further Reactions

Accordingly, the benzylisoxazolidinium bromides **24**−**31** (Figure 2) were prepared in quantitative yields by reaction of the corresponding isoxazolidines **1** and **4**−**10** with benzyl bromide in THF at room temperature. Although the *N*-benzylation generates a new stereogenic centre at the nitrogen atom, a unique diastereoisomer was obtained in all cases. We know from previous studies that the tricyclic pyrrolidine substrates such as **7** exist in solution as a unique *cis*-fused invertomer, while the piperidine derivatives of type **1** present a conformational equilibrium with a clear predominance of the *trans*-fused invertomer, and so we were intrigued by the stereochemistry of the isoxazolidinium bromides **24**−**31**.

A detailed ^{1}H NMR study revealed that all these compounds are *cis*-fused. Most spectra were obtained from $CDCl_3$ solutions, but the salts **29** and **31** have low solubility in most common organic solvents and their spectra had to be measured in [D_6]DMSO. The signals were assigned with the assistance of homo- and hetero-nuclear bidimensional experiments. Table 2 and Table 3 show the most significant data. It is noticeable that the signal of the proton at the α-carbonyl position (H_{11b} or H_{10b} for the piperidine or pyrrolidine series, respectively) appears more downfield shifted (cfr. last columns of Table 2−3) than any of the others on going from the original isoxazolidine to the corresponding *N*-benzylisoxazolidinium cation. A possible anisotropic effect caused by its proximity to the aromatic residue was discarded, since the *N*-methylisoxazolidinium iodide **32**, prepared by reaction of **10** with methyl iodide, exhibits a δ for H_{11b} (see Figure 3 for numbering) similar to that of its analogue **27**. Therefore, the deshielding of H_{11b} must orig-



24-31



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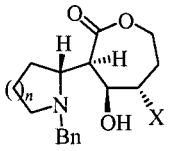

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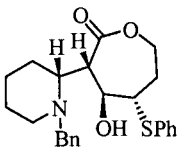

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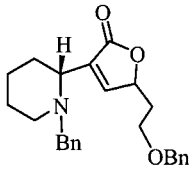

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	24	25	26	27	28	29	30	31	33	34	35	36	37	38	39
n	2	2	2	2	1	1	1	1	2	2	2	1	1	1	1
X	H	OAc	SPh	SAc	H	OAc	SPh	SAc	H	OAc	SPh	H	OAc	SPh	SAc

Figure 2. Prepared isoxazolidinium salts and products of their N−O bond reduction.

Table 2. Chemical shifts of important resonances in the ^{1}H NMR spectra ($CDCl_3$) of **24**−**27** and **32**.

Compound	δ $H_{3\alpha}$	δ $H_{3\beta}$	δ H_5	δ H_{5a}	δ $H_{8\alpha}$	δ $H_{8\beta}$	δ H_{11a}	δ H_{11b}	[δ H_{11b}, *c* and *t*][a]
24	5.00	4.25		5.58	4.92	3.37	4.21	5.44	3.88 *c*, 3.46 *t* (**1**)
25	5.15	4.25	5.10	5.55	4.77	3.40	4.30	5.71	3.97 *c*, 3.59 *t* (**4**)
26	5.12	4.21	3.29	5.50	4.95	3.39	4.21	5.71	3.95 *c*, 3.50 *t* (**5**)
27	5.17	4.27	3.80	5.53	4.80	3.28	4.41	5.69	3.63 *t* (**6**)
32	5.18	4.32	3.82	5.48	5.03	3.46	4.35	5.55	3.63 *t* (**6**)

[a] Chemical shift for the *cis* (*c*) and *trans* (*t*) invertomer of the corresponding precursors (indicated in parenthesis).

Table 3. Chemical shifts of important resonances in the ^{1}H NMR spectra of **28**−**31**.

Compound	Solvent	δ $H_{3\alpha}$	δ $H_{3\beta}$	δ H_5	δ H_{5a}	δ H_8	δ H_{10a}	δ H_{10b}	[δ H_{10b}][a]
28	$CDCl_3$	5.02	4.31		5.52	3.65, 4.38	5.52	5.52	3.39 (**7**)
28	[D_6]DMSO	4.44	4.33		5.11	3.65, 4.06	5.23	4.63	
29	[D_6]DMSO	4.52	4.41	4.95	5.35	4.06, 3.68	5.32	4.80	3.50 (**8**)[b]
30	$CDCl_3$	5.08	4.32	3.72	5.32	4.18, 3.16	5.49	5.86	3.49 (**9**)
30	[D_6]DMSO	4.44	4.32	3.35	5.07	4.07, 3.66	5.29	4.75	
31	[D_6]DMSO	4.53	4.39	3.60	5.23	4.07, 3.60	5.33	4.77	3.53 (**10**)[b]

[a] Chemical shift for the corresponding precursors (indicated in parenthesis). [b] In $CDCl_3$ solution.

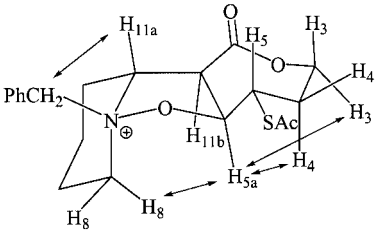


Figure 3. NOE correlations for compound **27**.

inate in the polarization of the C−H_{11b} bond, as a consequence of the electric field induced by the positive charge on the nitrogen atom.[12] Once all proton signals were assigned, the *cis* stereochemistry was determined by a NOESY experiment performed on **27** (Figure 3), where crossed signals between H_{5a} and $H_{8\alpha}$ and between H_{11a} and one of the benzylic protons were observed.

Considering the strong similarities in their NMR spectra, we assume that all the salts **24**−**31** present a *cis* fusion between the isoxazolidine and the piperidine (or pyrrolidine) rings, despite the fact that the piperidine precursors exist in solution mainly or exclusively as their *trans* invertomers.

When the isoxazolidinium salts **24**−**31** were treated with activated zinc powder in 10% aqueous HCl under the standard conditions established for their amine precursors, the parent oxepinones (**24** and **28**) and the acetoxyoxepinones (**25** and **29**) rendered the expected *N*-benzylamino alcohols in excellent yields (Table 4). The sulfides **26** and **30** furnished the N−O reduction products in moderate yields, in contrast with the previous results (see Table 3, substrates **5** and **9**). From the reduction of **26**, besides the expected amino alcohol **35**, we also isolated a minor amount of its epimer at the α-carbonyl centre, **40**. The reduction of the acetylthiolates **27** and **31** furnished unstable products and, although the formation of the amino alcohol **39** was observed by NMR analysis of the crude reaction mixture, all attempts to purify this compound led to decomposition. We also studied the N−O reduction of the *N*-benzyl derivative of the tricyclic furanone **11**, but the only identifiable prod-

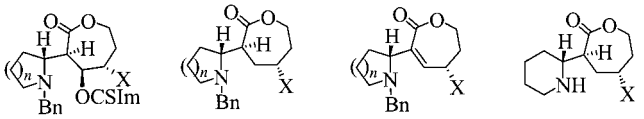
Table 4. Reduction of isoxazolidinium bromides **24**−**31** with Zn in 10% aqueous HCl.

Substrate	Product (yield)
24	**33** (100%)
25	**34** (100%)
26	**35** (50%), **40** (14%)
27	**none**
28	**36** (99%)
29	**37** (97%)
30	**38** (51%)
31	**39** (85%)[a]

[a] Yield refers to crude material; compound **39** decomposes rapidly.

uct that could be isolated from this reaction was the dehydrated compound **41** (22% yield).

To examine the effectiveness of the benzylic protection, we then studied the deoxygenation of the *N*-benzylamino alcohols. Compounds **33**, **34**, **36** and **37** were selected as substrates and the Barton−McCombie procedure[13] as the methodology. Treatment of **33** with TCDIm in refluxing THF furnished the expected thiocarbamate **42** (Figure 4), but attempted chromatographic purification over silica gel led to the elimination product **49** (60% yield). Fortunately, the thiocarbamate **42** could be purified and isolated in 83% yield by crystallization from acetone/hexane.The thiocarbamate **43** was prepared analogously in 73% yield from the corresponding precursor **34**. Reaction of **42** with Bu_3SnH, in the presence of AIBN in refluxing toluene, gave the reduction product **46** in 70% yield together with a small quantity of the α,β-unsaturated lactone **49**. The same procedure applied to the thiocarbamate **43** rendered the corresponding reduction product **47** in 76% yield. The reaction of the pyrrolidine substrates **36** and **37** with TCDIm provided the thiocarbamates **44** and **45**, respectively, as revealed by NMR analyses of the crude reaction products, but all attempts to purify these compounds were unsuccessful. Therefore, the crude materials were used in the following step. Treatment of **44** with Bu_3SnH delivered the elimination product **50** (49% yield), while the same reaction conditions applied to **45** gave a poor yield of the deoxygenation product **48** (9%), along with the olefin **51** (19%) and the alcohol **37** (20%). Thus, it became clear that the size of the nitrogen ring has a decisive influence on the stability of the thiocarbamates



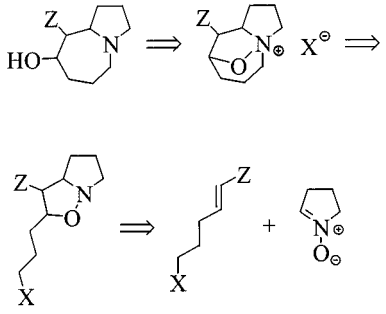
	42	43	44	45	46	47	48	49	50	51	52	53
n	2	2	1	1	2	2	1	2	1	1		
X	H	OAc	H	OAc	H	OAc	OAc	H	H	OAc	H	OAc

Figure 4. Prepared thiocarbamates and products of their reaction with Bu_3SnH and subsequent debenzylation

and also on their evolution pathway under the reduction conditions. Hydrogenolysis of the *N*-benzylamines **46** and **47** was accomplished using $Pd(OH)_2$ as catalyst in methanol with the secondary amines **52** and **53** being isolated in 93% and 96% yield, respectively.

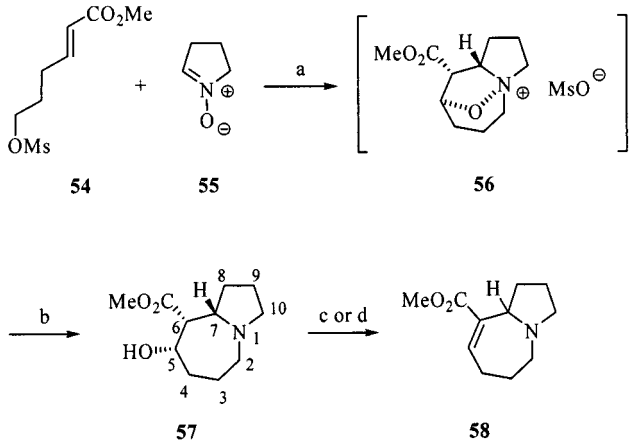
Construction of the 1-Azabicyclo[5.3.0]decane Skeleton

The results obtained hitherto indicate that the reductive cleavage of the nitrogen−oxygen bond of the oxepinoisoxazolopiperidine framework is a convenient entrance to a variety of piperidine-oxepinones with different substitution patterns, but that their pyrrolidine analogues are very sensitive to minor structural changes and chemical manipulation often ends in their decomposition. We were then confronted with the problem of avoiding these unstable intermediates during construction of the 1-azabicyclo[5.3.0]decane system (Scheme 2) . Since the isoxazolium salts proved in most cases better substrates than their amine precursors towards the N−O reduction, we thought that it would be advantageous to firstly construct the azepine ring by intramolecular *N*-alkylation and then proceed with the N−O cleavage (Scheme 4). The analogous approach for the construction of the indolizidine skeleton using the appropriate homoallyl derivatives is well documented.[14]



Scheme 4. The "cyclic nitrone approach" to the 1-azabicyclo[5.3.0]-decane system.

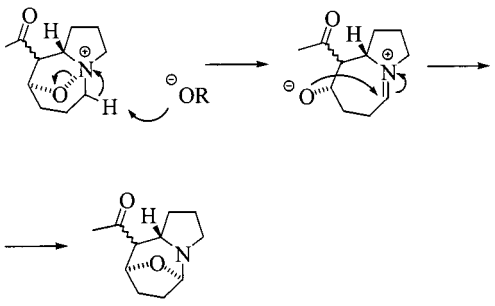
To this end, the olefins **54** (Scheme 5) and **59** (Scheme 6) were considered the most suitable dipolarophiles and so their cycloadditions to nitrone **55**[4b,15] were investigated. The reaction between the unsaturated ester **54**, prepared by mesylation of methyl (*E*)-6-hydroxyhex-2-enoate,[16] and nitrone **55** in refluxing chloroform furnished directly the tricyclic isoxazolidinium mesylate **56**, whose stereochemistry was assigned assuming that the primary adduct must derive from an *endo* (CO_2Me) transition state.[3] Treatment of **56** with zinc in 10% aqueous HCl effected clean N−O reduction to give the azabicycle **57** in 83% overall yield. These findings demonstrate that Tufariello's "cyclic nitrone approach" to indolizidine and pyrrolizidine systems is equally efficient for the construction of the 1-azabicyclo[5.3.0]-decane core present in most *Stemona* alkaloids, opening a new pathway to these natural products. When reductive deoxygenation of **57** was attempted by consecutive treatment with TCDIm and Bu_3SnH, traces of the olefin **58** were de-



Scheme 5. (a) $CHCl_3$, reflux, 24 h; (b) Zn/10% aqueous HCl, sonication, room temp., 40 min, 83% (two steps); (c) (i) TCDIm; (ii) Bu_3SnH/AIBN, toluene, 100 °C; (d) (i) MsCl, CH_2Cl_2, 0 °C to room temp., 5 h, 84%; (ii) K*t*BuO, CH_2Cl_2, reflux, 3 h, 75%.

tected exclusively. For characterization purposes, this olefin was independently synthesized in 75% yield by mesylation of **57**, followed by reaction with potassium *tert*-butoxide.

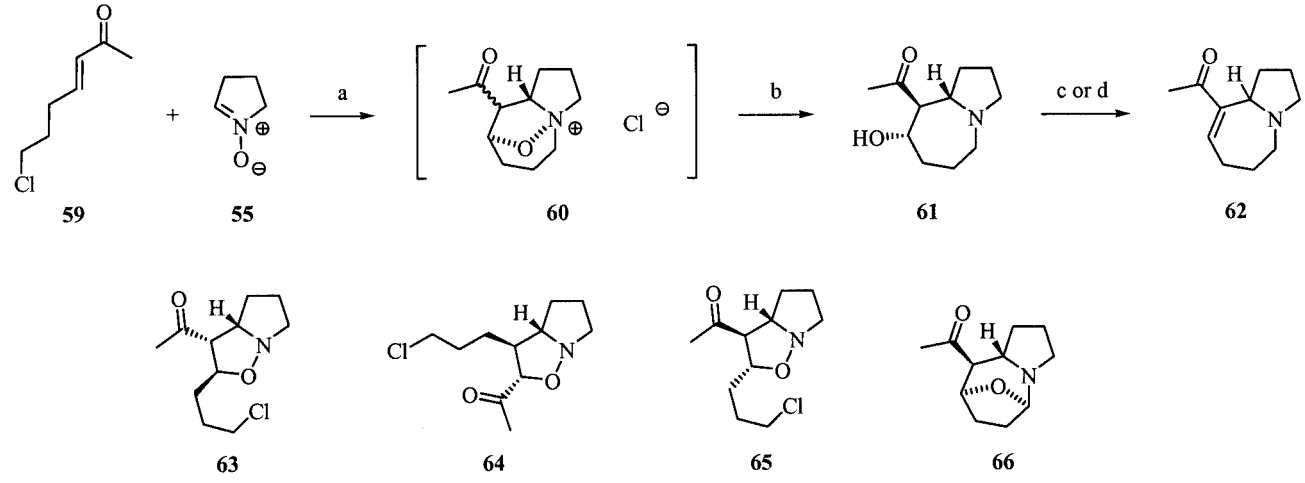
Ketone **59**[17] was prepared from 4-chlorobutanol, by PCC oxidation followed by Wittig olefination, in 58% yield. Its cycloaddition to nitrone **55** in refluxing chloroform turned out to be quite complicated. The resulting mixture of products was partitioned between ether and water. The water soluble fraction contained the isoxazolidinium chloride **60**, as a mixture of epimers at the α-carbonyl centre. From the organic fraction we isolated the primary regioisomeric adduct **64** (5% yield), the *exo* isomer **65** (4% yield) and some unchanged **59** (17% recovery). When performing the same reaction in refluxing toluene, the primary *endo* cycloadduct **63** could be isolated (50% yield), but the regio- and stereo-selectivity of the cycloaddition was diminished (21% of **64** and 9% of **65**). Moreover, the cycloadduct **63** cyclizes on standing and the resulting tricyclic product epimerizes rapidly. When the salt **60** was subjected to Zn/aqueous HCl reduction followed by treatment with NaOMe in refluxing methanol, the azabicycle **61** was isolated in 53% overall yield (cycloaddition-reduction-epimerization) as a single isomer, along with another compound identified as **66** (4% yield). The incomplete reduction of the isoxazolidinium salt **60** may account for the formation of this unexpected compound, with an intermediate iminium alkoxide being generated under basic conditions (Scheme 7).



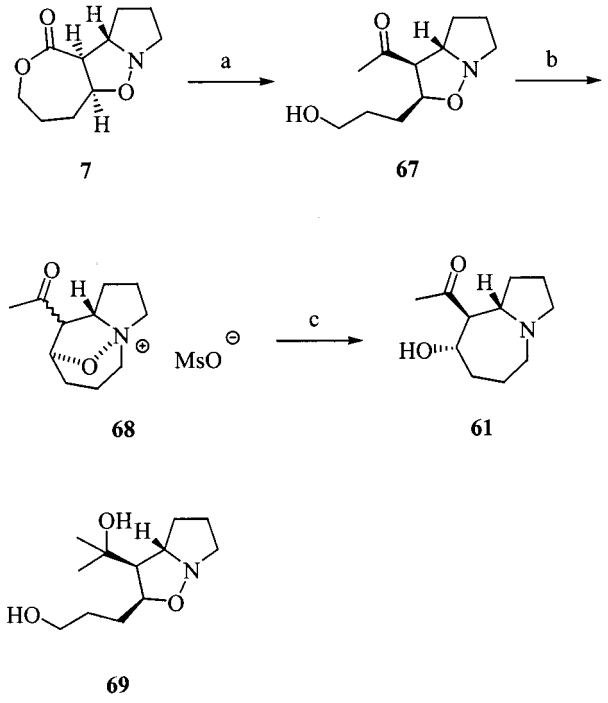
Scheme 7. Proposed mechanism for the formation of **66**.

The bicyclic ketone **61** was also prepared from oxepinone **7**, the *exo* adduct derived from nitrone **55** and α,β-hexenolide, by treatment with MeLi, followed by mesylation and N−O reduction in 53% overall yield (Scheme 8). Despite extensive experimentation, the competitive formation of the alcohol **69** during the nucleophilic addition of the organometallic reagent could not be completely avoided. When subjected to the usual deoxygenation protocol, ketone **61** showed a similar behavior to the analogous ester **57** so that only the elimination product **62** was detected in this experiment. Enone **62** proved to be highly unstable although it could be prepared independently from **61** by consecutive mesylation and basic treatment as above (79% yield).

In view that any structural modification of our substrates could critically affect their evolution towards a specific reagent, we decided to prepare the ester **72** (epimer of **57** at

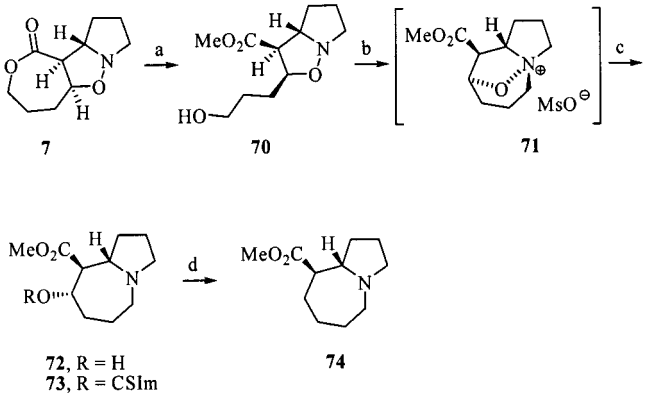


Scheme 6. (a) $CHCl_3$, reflux, 48 h; (b) (i) Zn/10% aqueous HCl, sonication, room temp., 45 min; (ii) NaMeO/MeOH, reflux, 2.5 h, 53% (three steps); (c) (i) TCDIm; (ii) Bu_3SnH/AIBN, toluene, 100 °C; (d) (i) MsCl, CH_2Cl_2, 0 °C to room temp., 5 h, 84%; (ii) K*t*BuO, CH_2Cl_2, reflux, 3 h, 79%.



Scheme 8. (a) MeLi, THF, −100 °C, 2 h, 57%; (b) MsCl, pyridine, CH_2Cl_2, 0 °C to room temp., 6 h; (c) Zn/10% aqueous HCl, sonication, room temp., 45 min, 93% (two steps).

the α-carbonyl position) and attempt the Barton-McCombie deoxygenation of this isomer (Scheme 9). To this end, oxepinone **7** was subjected to methanolysis, followed by mesylation of the resulting hydroxy ester **70**, with concomitant cyclization, and then reductive cleavage of the isoxazolidinium salt **71**, with an overall yield of 78%. The amino alcohol **72** was converted into the corresponding thiocarbamate **73**, which upon treatment with Bu_3SnH furnished the deoxygenation product **74**, isolated in 67% yield over the two steps. This result confirms the relevance of the relative stereochemistry of the substituted 1-azabicyclo[5.3.0]decane



Scheme 9. (a) MeOH, TsOH, reflux, 6 h, 91%; (b) MsCl, pyridine, CH_2Cl_2, 0 °C to room temp., 6 h; (c) Zn/10% aqueous HCl, sonication, room temp., 30 min, 86% (two steps); (d) (i) TCDIm, THF, room temp., overnight; (ii) Bu_3SnH/AIBN, toluene, 100 °C 30 min, 67% (two steps).

derivatives for further elaboration of their functional groups. This point is of major importance for synthetic routes to the *Stemona* alkaloids following the present approach. In **57**, an elimination pathway may be favored by the *trans* relationship between the leaving oxygen residue and the α-carbonyl proton, facilitating an antiperiplanar arrangement, consistent with an E2 type mechanism, which is poorly accessible by the diastereomer **72**. The feasibility of following the elimination pathway observed for the methyl ketone **61**, which has a relative stereochemistry identical to **72**, may be explained by operation of an E1cb type mechanism, caused by the stronger acidity of its α-carbonyl proton.

Conclusion

In summary, the reduction of the nitrogen−oxygen bond of a series of tricyclic isoxazolidines bearing a variety of additional functionalities was performed effectively by treatment with Zn in 10% aqueous HCl under sonication. In most cases, the formation of the *N*-benzylisoxazolidinium salts prior to the reduction improves notably the yield of amino alcohol and ends with an *N*-protected derivative, which is more suitable for further synthetic elaboration. According to our results, the reductive cleavage of the nitrogen−oxygen bond of the oxepinoisoxazolopiperidine framework is a convenient entrance to a variety of piperidine-oxepinones, although their pyrrolidine analogues are very sensitive to minor structural changes and often of low stability. We have also shown that "the cyclic nitrone strategy", previously developed for indolizidine and pyrrolizidine alkaloids,[2] can be successfully applied to the synthesis of intermediates containing the 1-azabicyclo[5.3.0]decane core of the *Stemona* alkaloids, with the relative stereochemistry of these bicyclic polysubstituted derivatives being of crucial importance in successive synthetic transformations.

Experimental Section

General Remarks: Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous magnesium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5−10 Torr. Tlc was performed on Alugram Sil G/UV254 plates of 0.25 mm thickness (purchased from Macherey−Nagel). Flash chromatography was performed using Merck silica gel (230−400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^1H and ^{13}C NMR spectra were recorded by *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona*, on Bruker AC-250-WB or AM-400-WB instruments at 250 or 400 MHz and 62.5 or 100 MHz, respectively, in $CDCl_3$ solutions (unless otherwise stated). Tetramethylsilane ($\delta = 0.00$) or $CHCl_3$ ($\delta = 7.27$ for ^1H and 77.2 for ^{13}C) were used as internal standards for ^1H and ^{13}C NMR spectra. The assignment of the signals was assisted by DEPT, COSY and ^1H-^{13}C correlation experiments. Mass spectra were performed on a Hewlett−Packard 5985B instrument at 70 eV; only peaks of intensity greater than 20% are reported, unless they were molecular ions or significant fragments. MS and Microanalyses were performed by Servei d'Anàlisi

Química de la Universitat Autònoma de Barcelona. HRMS were performed by Servei de Masses del Centre d'Investigació i Desenvolupament de Barcelona CSIC, using a VG AutoSpec-Q instrument. Compounds **1**−**11** were prepared as described previously: see ref.[4c] for **1**, **2**, **4**, **6**, ref.[4d] for **3**, **5**, **8**, **9**, **10**, ref.[4b] for **7**, and ref.[4a] for **11**. The elemental analysis data for isoxazolium bromides **26**−**29**, **31**, amines **35**, **52**, **53**, **58**, **72**, **74** and isoxazolidines **67**, **70** were erratic.

(3*RS*,4*RS*)-4-Hydroxy-3-[(2*RS*)-2-piperidyl]oxepan-2-one (12). General Reduction Procedure Using Activated Zn in 10% Aqueous HCl: Activated zinc powder (4.69 g, 71.7 mmol) was added to a solution of **1** (210 mg, 1.00 mmol) in 10% aqueous HCl (20 mL). The mixture was immersed in an ultrasound bath and reaction progress was monitored by TLC analysis (eluent: CH_2Cl_2/MeOH/NH_3 saturated solution in MeOH, 10:1/0.1). When the starting material had been consumed (25 min), the mixture was filtered and the solid washed with 10% aqueous HCl and water. The solution was brought to pH 9−10 by addition of 30% aqueous NH_3. A white solid appeared which was filtered under vacuum. The solution was then extracted with $CHCl_3$ (4 × 50 mL), the combined organic extracts were dried and the solution was concentrated to furnish a white solid residue identified as **12** (108 mg, 0.51 mmol, 51% yield). M.p. 152−154 °C (from $CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3325, 3170, 2931, 2854, 2812, 1715, 1166 cm^{-1}. ^1H NMR (400 MHz): δ = 1.30−1.82 (m, 8 H, 5,5,3′,3′,4′,4′,5′,5′-H), 2.15 (m, 2 H, 6,6-H), 2.64 (ddd, $J_{6'ax,6'eq} \approx J_{6'ax,5'ax} \approx$ 11.9, $J_{6'ax,5'eq}$ = 2.7 Hz, 1 H, 6′ax-H), 2.65 (br. s, 1 H, 3-H), 3.08 (m, $J_{6'eq,6'ax} \approx$ 11.6 Hz, 1 H, 6′eq-H), 3.21 (ddd, $J_{2',3'ax} \approx$ 11.3, $J_{2',3'eq} \approx J_{2',3} \approx$ 2.1 Hz, 1 H, 2′-H), 4.16 (dd, $J_{7\alpha,7\beta}$ = 12.5, $J_{7\alpha,6\beta}$ = 11.0 Hz, 1 H, 7α-H), 4.31 (ddt, $J_{7\beta,7\alpha} \approx$ 12.4, $J_{7\beta,6\alpha} \approx$ 4.7, $J_{7\beta,6\beta} \approx J_{7\beta,5} \approx$ 1.8 Hz, 1 H, 7β-H), 4.45 (t, $J_{4,3} \approx J_{4,5} \approx$ 3.5 Hz, 1 H, 4-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.9 (C-6), 24.4 (C-4′), 25.2 (C-5′), 29.6 (C-3′), 35.0 (C-5), 46.5 (C-6′), 52.1 (C-3), 56.8 (C-2′), 64.3 (C-4), 68.7 (C-7), 175.0 (C-2) ppm. EIMS: *m*/*z* = 213 (1) $[M]^+$, 170 (6), 152 (8), 84 (100). $C_{11}H_{19}NO_3$ (213.27) calcd. C 61.93, H 8.98, N 6.57; found C 61.85, H 8.97, N 6.55.

(3*RS*,4*SR*,5*SR*)-4-Hydroxy-3-[(2*RS*)-2-piperidyl]-5-(tosyloxy)-oxepan-2-one (13): Following the general procedure described for **12**, reduction of **3** (54 mg, 0.14 mmol) rendered the unstable compound **13** (27 mg), contaminated by other products. Attempted crystallisation or column chromatography resulted in total decomposition of **13**. ^1H NMR (250 MHz): δ = 1.20−1.48 (m, 4 H), 1.58 (m, 1 H), 1.76 (m, 1 H), 1.88 (dt, $J_{6\alpha,6\beta}$ = 16.1, $J_{6\alpha,7\beta} \approx J_{6\alpha,5} \approx$ 4.0 Hz, 1 H, 6α-H), 2.28 (m, 1 H, 6β-H), 2.44 (s, 3 H, CH_3), 2.64 (m, 1 H, 6′-H), 2.97 (s, 1 H, 3-H), 3.04 (br. d, $J_{6',6'} \approx$ 11.7 Hz, 1 H, 6′-H), 3.19 (br. d, $J_{2',3} \approx$ 8.8 Hz, 1 H, 2′-H), 4.07 (br. dd, $J_{7\beta,7\alpha}$ = 13.2, $J_{7\beta,6\beta}$ = 2.2 Hz, 1 H, 7β-H), 4.21 (d, $J_{4,5} \approx$ 4.4 Hz, 1 H, 4-H), 4.45 (t, $J_{7\alpha,7\beta} \approx J_{7\alpha,6\beta} \approx$ 12.4 Hz, 1 H, 7α-H), 4.66 (m, 1 H, 5-H), 7.36 (d, $J_{m,o}$ = 8.4 Hz, 2 H, *m*-Ph-H), 7.77 (d, $J_{o,m}$ = 8.4 Hz, 2 H, *o*-Ph-H) ppm.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-4-hydroxy-3-[(2*RS*)-2-piperidyl]oxepan-2-one (14): Following the general procedure described for **12**, reduction of **4** (200 mg, 0.74 mmol) rendered **14** (150 mg, 55.3 mmol, 75% yield) as a white solid (crystallized from acetone) decomp. 145−155 °C. IR (KBr): $\tilde{\nu}$ = 3318, 3100, 2983, 1740, 1720, 1372, 1273, 1226, 1218, 1174, 1155, 1083 cm^{-1}. ^1H NMR (400 MHz): δ = 1.33 (m, 4 H, 3′ax,3′eq,4′ax,5′ax-H), 1.54 (m, 1 H, 5′eq-H), 1.75 (m, 1 H, 4′eq-H), 1.89 (dt, $J_{6\alpha,6\beta}$ = 16.3, $J_{6\alpha,7\alpha} \approx J_{6\alpha,7\beta} \approx$ 4.2 Hz, 1 H, 6α-H), 2.03 (s, 3 H, CH_3), 2.34 (ddt, $J_{6\beta,6\alpha}$ = 16.3, $J_{6\beta,7\alpha}$ = 11.7, $J_{6\beta,7\beta} = J_{6\beta,5}$ = 2.3 Hz, 1 H, 6β-H), 2.60 (td, $J_{6'ax,6'eq} = J_{6'ax,5'ax}$ = 11.6, $J_{6'ax,5'eq}$ = 2.5 Hz, 1 H, 6′ax-H), 2.90 (d, $J_{3,2'}$ = 1.3 Hz, 1 H, 3-H), 2.99 (br. d, $J_{6'eq,6'ax} \approx$ 11.0 Hz, 1 H, 6′eq-H), 3.14 (br. d, $J_{2',3'ax} \approx$ 10.0 Hz, 1 H, 2′-H), 4.07 (dddd, $J_{7\beta,7\alpha}$ = 13.0, $J_{7\beta,6\alpha} \approx$ 4.6, $J_{7\beta,6\beta}$ = 2.3, $J_{7\beta,5}$ = 0.6 Hz, 1 H, 7β-H), 4.22 (d, $J_{4,5}$ = 4.4 Hz, 1 H, 4-H), 4.41 (dd, $J_{7\alpha,7\beta}$ = 13.0, $J_{7\alpha,6\beta}$ = 11.7 Hz, 1 H, 7α-H), 5.03 (m, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz): δ = 21.0 (CH_3), 24.4 (C-4′), 25.0 (C-5′), 28.4 (C-6), 29.3 (C-3′), 46.7 (C-6′), 47.4 (C-3), 56.8 (C-2′), 62.6 (C-7), 65.5 (C-4), 70.8 (C-5), 169.2 (CH_3CO), 174.5 (C-2) ppm. EIMS: *m*/*z* = 272 (1) $[M+1]^+$, 228 (2), 211 (1), 171 (1), 124 (10), 84 (100), 43 (15). $C_{13}H_{21}NO_5$ (271.31) calcd. C 57.55, H 7.80, N 5.16; found C 57.57, H 7.66, N 5.06.

(3*RS*,4*SR*,5*SR*)-4-Hydroxy-5-phenylthio-3-[(2*RS*)-2-piperidyl]-oxepan-2-one (15): Following the general procedure described for **12**, reduction of **5** (200 mg, 0.63 mmol) rendered **15** (160 mg, 0.50 mmol, 80% yield) as a white solid. M.p. 156−158 °C ($CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3600−2500 (br), 3311, 3065, 2924, 2854, 1729, 1152, 1054 cm^{-1}. ^1H NMR (400 MHz): δ = 1.29 (m, 4 H, 3′,3′,4′, 5′-H), 1.53 (m, 1 H, 5′-H), 1.72 (m, 1 H, 4′-H), 1.92 (ddd, $J_{6\alpha,6\beta}$ = 15.9, $J_{6\alpha,7\beta}$ = 4.9, $J_{6\alpha,5}$ = 2.7 Hz, 1 H, 6α-H), 2.53 (dddd, $J_{6\beta,6\alpha} \approx$ 15.5, $J_{6\beta,7\alpha}$ = 11.6, $J_{6\beta,7\beta}$ = 4.3, $J_{6\beta,5}$ = 1.5 Hz, 1 H, 6β-H), 2.61 (td, $J_{6'ax,6'eq} \approx J_{6'ax,5'ax} \approx$ 11.9, $J_{6'ax,5'eq} \approx$ 2.7 Hz, 1 H, 6′ax-H), 2.97 (br. d, $J_{6'eq,6'ax}$ = 11.6 Hz, 1 H, 6′eq-H), 3.12 (br. s, 1 H, 3-H), 3.22 (br. d, $J_{2',3'ax} \approx$ 11.6 Hz, 1 H, 2′-H), 3.75 (q, $J_{5,4} \approx J_{5,6\alpha} \approx J_{5,6\beta} \approx$ 3.1 Hz, 1 H, 5-H), 4.12 (br. dd, $J_{7\beta,7\alpha}$ = 12.8, $J_{7\beta,6\alpha}$ = 4.3 Hz, 1 H, 7β-H), 4.33 (d, $J_{4,5}$ = 3.7 Hz, 1 H, 4-H), 4.56 (dd, $J_{7\alpha,7\beta}$ = 12.8, $J_{7\alpha,6\beta}$ = 11.0 Hz, 1 H, 7α-H), 7.29 (m, 3 H, Ar-H), 7.39 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.5 MHz): δ = 24.4 (C-4′), 25.1 (C-5′), 28.2 (C-6), 29.5 (C-3′), 46.7 (C-6′), 47.8 (C-3), 50.2 (C-5), 56.9 (C-2′), 63.5 (C-7), 67.1 (C-4), 127.5/129.2/131.6/132.9 (C-Ar), 174.8 (C-2) ppm. EIMS: *m*/*z* = 321 (1) $[M]^+$, 293 (2), 212 (1), 84 (100). $C_{17}H_{23}NO_3S$ (321.43) calcd. C 63.52, H 7.22, N 4.36, S 9.96; found C 63.48, H 7.24, N 4.36, S 9.84.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-4-hydroxy-3-[(2*RS*)-2-pyrrolidyl]oxepan-2-one (16): Following the general procedure described for **12**, reduction of **8** (206 mg, 0.81 mmol) rendered **16** (125 mg, 0.49 mmol, 60% yield) as a white solid. M.p. 138−140 °C (acetone/hexane). IR (KBr): $\tilde{\nu}$ = 3600−2500 (br), 3276, 3002, 2952, 2924, 1743, 1244, 1068 cm^{-1}. ^1H NMR (400 MHz): δ = 1.41 (m, 1 H, 3′-H), 1.77 (m, 2 H, 4′,4′-H), 1.94 (m, 2 H, 3′,6α-H), 2.08 (s, 3 H, CH_3), 2.35 (ddt, $J_{6\beta,6\alpha} \approx$ 16.2, $J_{6\beta,7\alpha} \approx$ 11.3, $J_{6\beta,7\beta} \approx J_{6\beta,5} \approx$ 2.4 Hz, 1 H, 6β-H), 2.91 (m, 2 H, 5′,5′-H), 3.08 (br. s, 1 H, 3-H), 3.88 (t, $J_{2',3'} \approx$ 8.2 Hz, 1 H, 2′-H), 4.02 (d, $J_{4,5}$ = 4.3 Hz, 1 H, 4-H), 4.10 (ddd, $J_{7\beta,7\alpha} \approx$ 12.8, $J_{7\beta,6} \approx$ 4.6, 1.5 Hz, 1 H, 7β-H), 4.43 (dd, $J_{7\alpha,7\beta}$ = 12.8, $J_{7\alpha,6\beta}$ = 11.6 Hz, 1 H, 7α-H), 5.18 (q, $J_{5,4} \approx J_{5,6\alpha} \approx J_{5,6\beta} \approx$ 3.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 21.1 (CH_3), 25.9 (C-4′), 28.6/28.7 (C-3′/C-6), 46.5/46.8 (C-3/C-5′), 57.8 (C-2′), 62.4 (C-7), 66.7 (C-4), 70.5 (C-5), 169.3 (CH_3CO), 174.7 (C-2) ppm. EIMS: *m*/*z* = 258 (1) $[M+1]^+$, 214 (2), 198 (1), 197 (1), 186 (2), 70 (100), 43 (34). $C_{12}H_{19}NO_5$ (257.28) calcd. C 56.00, H 7.45, N 5.45; found C 56.01, H 7.41, N 5.39.

(3*RS*,4*SR*,5*SR*)-4-Hydroxy-5-phenylthio-3-[(2*RS*)-2-pyrrolidyl]-oxepan-2-one (17): Following the general procedure described for **12**, reduction of **9** (201 mg, 0.66 mmol) rendered **17** (168 mg, 0.55 mmol, 83% yield) as a white solid. M.p. 99−101 °C ($CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3600−2800 (br), 3344, 2976, 2960, 2944, 2928, 2880, 2816, 1728, 1408, 1152 cm^{-1}. ^1H NMR (400 MHz): δ = 1.36 (m, 1 H, 3′-H), 1.61 (m, 1 H, 4′-H), 1.68 (m, 1 H, 4′-H), 1.86 (m, 1 H, 3′-H), 1.92 (ddd, $J_{6\alpha,6\beta}$ = 15.9, $J_{6\alpha,7\beta}$ = 5.5, $J_{6\alpha,5}$ = 3.0 Hz, 1 H, 6α-H), 2.57 (dddd, $J_{6\beta,6\alpha} \approx$ 16.2, $J_{6\beta,7\alpha}$ = 11.3, $J_{6\beta,5} \approx$ 4.0, $J_{6\beta,7\beta} \approx$ 1.7 Hz, 1 H, 6β-H), 2.85 (m, 2 H, 5′,5′-H), 3.29 (br. s, 1 H, 3-H), 3.77 (q, $J_{5,4} \approx J_{5,6\alpha} \approx J_{5,6\beta} \approx$ 3.2 Hz, 1 H, 5-H), 3.87 (td, $J_{2',3'} \approx$ 8.7, $J_{2',3} \approx$ 0.9 Hz, 1 H, 2′-H), 4.07 (d, $J_{4,5} \approx$ 3.4 Hz, 1 H, 4-H), 4.12 (ddt, $J_{7\beta,7\alpha}$ = 13.1, $J_{7\beta,6\alpha}$ = 4.9, $J_{7\beta,6\beta} \approx J_{7\beta,5} \approx$ 1.4 Hz, 1 H, 7β-H), 4.56 (dd, $J_{7\alpha,7\beta}$ = 13.1, $J_{7\alpha,6\beta}$ = 11.3 Hz, 1 H,

7α-H), 7.28 (m, 3 H, Ar-H), 7.39 (m, 2 H, Ar-H) ppm. ^{13}C NMR (62.5 MHz): δ = 25.8 (C-4′), 28.4 (C-6 + C-3′), 46.4/47.0 (C-3/C-5′), 49.2 (C-5), 57.8 (C-2′), 63.3 (C-7), 67.8 (C-4), 127.4/129.2/131.4/132.9 (C-Ar), 174.8 (C-2). EIMS: *m*/*z* = 307 (2) $[M]^+$, 279 (3), 238 (1), 110 (15), 70 (100) ppm. $C_{16}H_{21}NO_3S$ (307.41) calcd. C 62.52, H 6.89, N 4.56, S 10.41; found C 62.48, H 6.84, N 4.45, S 10.34.

Reduction of 2: Activated zinc powder (542 mg, 8.28 mmol) was added to a solution of **2** (290 mg, 0.69 mmol) in a 1:1 mixture of AcOH and H_2O (32 mL). The mixture was stirred at room temperature and reaction progress was monitored by TLC analysis (eluent: CH_2Cl_2/diethyl ether/MeOH/NH_3 saturated solution in MeOH, 10:1/1:0.1). When the starting material had been consumed (3 h), the mixture was filtered and the solid washed with AcOH/H_2O (1:1). The solution was brought to pH 8−9 by addition of 30% aqueous NH_3 and then it was extracted with $CHCl_3$ (6 × 40 mL). The combined organic extracts were dried and the solution was concentrated to furnish an oily residue. Purification by flash column chromatography (same eluent as TLC) gave the following fractions: **2** (97 mg, 33% recovery), (1*RS*,7a*SR*)-1-[(*Z*)-4-hydroxybutenyl]azetidino[1,2-*a*]piperidin-2-one (**18**) (80 mg, 0.40 mmol, 59% yield, 88% considering unrecovered **2**) and 6,7-dihydro-3-(piperidin-2-yl)-2(5*H*)-oxepinone (**19**) (8 mg, 0.04 mmol, 6% yield, 9% over unrecovered **2**).

18: IR (KBr): $\tilde{\nu}$ = 3416 (br), 2942, 2858, 1779, 1161, 1124, 1055 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.32 (m, 1 H, 6ax-H), 1.53 (m, 2 H, 6eq,7ax-H), 1.62 (m, 3 H, 5ax,5eq,7eq-H), 2.31 (m, 2 H, 3′,3′-H), 2.68 (ddd, $J_{4ax,5ax}$ = 11.8, $J_{4ax,4eq}$ = 8.7, $J_{4ax,5eq}$ = 3.0 Hz, 1 H, 4ax-H), 2.79 (ddd, $J_{7a,1}$ = 12.5, $J_{7a,7ax}$ = 11.1, $J_{7a,7eq}$ = 2.3 Hz, 1 H, 7a-H), 3.49 (m, 1 H, 4eq-H), 3.55 (m, 2 H, 4′,4′-H), 3.67 (ddd, $J_{1,7a}$ = 12.5, $J_{1,1'}$ = 9.3, $J_{1,2'}$ = 1.0 Hz, 1 H, 1-H), 3.94 (t, $J_{OH,4'}$ = 5.4 Hz, 1 H, O-H), 5.33 (ddt, $J_{1',2'}$ = 10.8, $J_{1',1}$ = 9.3, $J_{1',3}$ = 1.6 Hz, 1 H, 1′-H), 5.82 (dtd, $J_{2',1'}$ = 10.8, $J_{2',3'}$ = 7.5, $J_{2',1}$ = 1.0 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 23.7 (C-6), 25.4 (C-5), 28.5 (C-7), 32.1 (C-3′), 47.3 (C-1), 55.9 (C-4), 61.7 (C-4′), 74.2 (C-7a), 123.1 (C-1′), 134.3 (C-2′), 174.7 (C-2) ppm. CIMS (NH_3): *m*/*z* = 229 (26) $[M + 34]^+$, 212 (100) $[M + 17]^+$. $C_{11}H_{17}NO_2$ (195.26) calcd. C 67.66, H 8.78, N 7.17; found C 67.78, H 8.51, N 7.07.

19: IR (KBr): $\tilde{\nu}$ = 3325, 2931, 2854, 1715, 1469, 1441, 1398, 1349, 1286, 1230, 1180, 1152, 1110 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]acetone): δ = 1.30−2.10 (m, 8 H, 6,6,3′,3′,4′,4′,5′,5′-H), 2.30 (q, *J* ≈ 7.1 Hz, 2 H, 5,5-H), 2.68 (td, $J_{6'ax,6'eq}$ = $J_{6'ax,5'ax}$ = 11.8, $J_{6'ax,5'eq}$ = 2.9 Hz, 1 H, 6′ax-H), 3.09 (m, 1 H, 6′eq-H), 3.44 (br. d, $J_{2',3'}$ = 10.6 Hz, 1 H, 2′-H), 4.19 (m, 2 H, 7,7-H), 6.33 (td, $J_{4,5}$ = 6.7, $J_{4,2'}$ = 1.3 Hz, 1 H, 4-H) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]acetone): δ = 23.1/24.6/25.8/26.1/31.9 (C-6/C-3′/C-4′/ C-5′/C-5), 47.1 (C-6′), 58.1 (C-2′), 65.9 (C-7), 131.8 (C-3), 138.6 (C-4), 171.7 (C-2) ppm. EIMS: *m*/*z* = 195 (4) $[M]^+$, 167 (91), 152 (50), 84 (100), 56 (42), 42 (39), 41 (60).

Reduction of 6: Activated zinc powder (562 mg, 8.59 mmol) was added to a solution of **6** (102 mg, 0.36 mmol) in a 1:1 mixture of AcOH and H_2O (16 mL). The mixture was stirred at room temperature and reaction progress was monitored by TLC analysis (eluent: CH_2Cl_2/MeOH/NH_3 saturated solution in MeOH, 10:1/0.1). When the starting material had been consumed (24 h), the mixture was filtered, the solid washed with AcOH/H_2O (1:1) The solution was brought to pH 7−8 by addition of 30% aqueous NH_3 and then it was extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried and the solution was concentrated to furnish a yellowish solid (64 mg, 0.18 mmol, 51% yield) identified as 2(*RS*)-2-[(3*RS*,4*SR*,5*SR*)-5-acetylthio-4-hydroxy-2-oxooxepin-3-yl]piperidinium acetate (**20**): ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 1.60−1.83 (m, 5 H, 3′,3′,4′,4′,5′-H), 1.86 (m, 1 H, 6α-H), 1.87 (s, 3 H, $CH_3CO_2^-$), 2.07 (m, 1 H, 5′-H), 2.35 (s, 3 H, CH_3COS), 2.63 (dddd, $J_{6\beta,6\alpha}$ ≈ 15.6, $J_{6\beta,7\alpha}$ ≈ 11.5, $J_{6\beta,5}$ ≈ 3.8, $J_{6\beta,7\beta}$ ≈ 1.9 Hz, 1 H, 6β-H), 2.92 (td, $J_{6'ax,6'eq}$ ≈ $J_{6'ax,5'ax}$ ≈ 12.8, $J_{6'ax,5'eq}$ ≈ 3.1 Hz, 1 H, 6′ax-H), 3.23 (d, $J_{3,2'}$ = 1.7 Hz, 1 H, 3-H), 3.43 (dt, $J_{2',3'ax}$ ≈ 12.5, $J_{2',3'eq}$ ≈ $J_{2',3}$ ≈ 2.1 Hz, 1 H, 2′-H), 3.47 (ddt, $J_{6'eq,6'ax}$ ≈ 13.0, $J_{6'eq,5'ax}$ ≈ 4.1, $J_{6'eq,5'eq}$ ≈ $J_{6'eq,4'}$ ≈ 2.2 Hz, 1 H, 6′eq-H), 3.80 (q, $J_{5,4}$ ≈ $J_{5,6\alpha}$ ≈ $J_{5,6\beta}$ ≈ 3.5 Hz, 1 H, 5-H), 4.18 (dddd, $J_{7\beta,7\alpha}$ ≈ 13.5, $J_{7\beta,6\alpha}$ ≈ 5.1, $J_{7\beta,6\beta}$ ≈ 2.0, $J_{7\beta,5}$ ≈ 1.2 Hz, 1 H, 7β-H), 4.37 (d, $J_{4,5}$ = 4.2 Hz, 1 H, 4-H), 4.39 (dd, $J_{7\alpha,7\beta}$ ≈ 13.5, $J_{7\alpha,6\beta}$ ≈ 11.5 Hz, 1 H, 7α-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 22.5 (C-4′), 22.9 ($CH_3CO_2^-$), 24.0 (C-5′), 27.7 (C-3′), 29.7 (C-6), 31.1 (CH_3COS), 47.3 (C-6′), 48.1 (C-5), 49.1 (C-3), 59.8 (C-2′), 66.0/66.1 (C-4/C-7), 175.8/176.3 ($CH_3CO_2^-$/C-2), 194.3 (CH_3COS) ppm. Compound **20** decomposes on standing.

(3*RS*,4*SR*,5*RS*)- and (3*RS*,4*SR*,5*SR*)-5-(2-Benzyloxy)ethyl-4-hydroxy-3-[(2*RS*)-piperidin-2-yl]-3,4-dihydro-2(5*H*)-furanone (21): Following the general procedure described for **12**, reduction of **11** (300 mg, 0.95 mmol) rendered **21** (232 mg, 0.73 mmol, 77% yield) as a mixture of two diastereomers, which could not be separated by crystallisation or flash chromatography.

21: IR (KBr): $\tilde{\nu}$ = 3283, 3200−2600 (br), 3093, 3072, 3044, 2980, 2938, 2854, 2798, 2755, 2699, 1764, 1363, 1173, 1124, 1103, 1075, 1026 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.30−1.50 (m), 1.53−1.97 (m), 2.08 (m), 2.53 (td, *J* = 12.2, 2.4 Hz), 2.59 (m), 2.88 (m), 3.03 (m), 3.36 (dt, *J* = 11.6, 3.0 Hz), 3.62 (m), 4.07 (t, *J* = 7.6 Hz) and 4.09 (dd, *J* = 7.8, 4.6 Hz) (4-H), 4.46 (d, *J* = 6.0 Hz) and 4.59 (dd, *J* = 8.5, 4.9 Hz) (5-H), 4.47 (d, *J* = 11.6 Hz) 4.50 (d, *J* = 11.6 Hz) and 4.53 (s) (OCH_2Ph), 7.32 (m, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 24.4, 25.0, 25.9, 29.2, 29.5, 32.3, 33.2, 46.3, 46.8, 47.4, 52.6, 53.7, 56.0, 65.9, 66.5, 73.2, 73.5, 74.3, 82.0, 85.7, 127.56, 127.61, 127.8, 128.0, 128.3, 128.5, 137.2, 137.9, 174.6, 176.0. EIMS: *m*/*z* = 301 (2) $[M - H_2O]^+$, 256 (1), 228 (2), 210 (6), 180 (14), 167 (12), 91 (87), 84 (100) ppm. $C_{18}H_{25}NO_4$ (319.40) calcd. C 67.67, H 7.89, N 4.39; found C 67.65, H 7.89, N 4.50.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-4-hydroxy-3-[(2*RS*)-*N*-tosylpiperidin-2-yl]oxepan-2-one (22): Tosyl chloride (194 mg, 1.02 mmol) was added to a stirred solution of **14** (55 mg, 0.20 mmol) in anhydrous pyridine (2.5 mL). The mixture was heated at 60 °C and reaction progress was monitored by TLC analysis (eluents: CH_2Cl_2/MeOH/NH_3 saturated solution in MeOH, 10:1/0.1, and hexane/EtOAc, 1:1). After all the starting material had been consumed (60 h), the cold reaction mixture was concentrated under vacuum and the residue (577 mg) was purified by flash column chromatography (hexane/EtOAc, 1:1), furnishing **22** (74 mg, 0.17 mmol, 86% yield) as a yellowish solid. M.p. 135−137 °C ($CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3472 (br), 2960, 2880, 1744, 1728, 1344, 1240, 1216, 1184, 1152, 1064 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.11 (m, 2 H, 3′,5′-H), 1.29 (m, 1 H, 4′-H), 1.46 (m, 3 H, 3′,4′,5′-H), 2.04 (dt, $J_{6\alpha,6\beta}$ = 16.4, $J_{6\alpha,7\beta}$ ≈ $J_{6\alpha,5}$ ≈ 4.3 Hz, 1 H, 6α-H), 2.09 (s, 3 H, CH_3CO_2), 2.32 (ddt, $J_{6\beta,6\alpha}$ = 16.4, $J_{6\beta,7\alpha}$ = 11.5, $J_{6\beta,7\beta}$ ≈ $J_{6\beta,5}$ ≈ 2.2 Hz, 1 H, 6β-H), 2.41 (s, 3 H, C*H*$_3$-Ar), 2.67 (td, $J_{6'ax,6'eq}$ ≈ $J_{6'ax,5'ax}$ ≈ 14.1, $J_{6'ax,5'eq}$ ≈ 2.6 Hz, 1 H, 6′ax-H), 3.47 (d, $J_{3,2'}$ = 11.0 Hz, 1 H, 3-H), 3.49 (d, $J_{OH,4}$ ≈ 6.7 Hz, 1 H, OH), 4.05 (br. dd, $J_{6'eq,6'ax}$ ≈ 13.9, $J_{6'eq,5'eq}$ ≈ 2.1 Hz, 1 H, 6′eq-H), 4.10 (ddd, $J_{7\beta,7\alpha}$ = 13.1, $J_{7\beta,6\alpha}$ = 4.8, $J_{7\beta,6\beta}$ = 1.3 Hz, 1 H, 7β-H), 4.18 (t, $J_{4,5}$ ≈ $J_{4,OH}$ ≈ 4.9 Hz, 1 H, 4-H), 4.47 (dd, $J_{7\alpha,7\beta}$ ≈ 13.0, $J_{7\alpha,6\beta}$ ≈ 11.7 Hz, 1 H, 7α-H), 4.50 (dd, $J_{2',3}$ ≈ 10.6, $J_{2',3'}$ ≈ 7.1 Hz, 1 H, 2′-H), 5.20 (q, $J_{5,4}$ ≈ $J_{5,6\beta}$ ≈ $J_{5,6\alpha}$ ≈ 3.4 Hz, 1 H, 5-H), 7.30 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.74 (d, *J* = 8.0 Hz, 2 H, Ar-H) ppm. ^{13}C NMR

(62.5 MHz): δ = 18.7 (C-3′), 21.2 (CH_3CO_2), 21.5 (CH_3-Ar), 23.9 (C-4′), 25.8 (C-5′), 28.3 (C-6), 41.9 (C-6′), 42.1 (C-3), 50.5 (C-2′), 61.9 (C-7), 65.8 (C-4), 70.8 (C-5), 126.6/130.0/138.0/143.6 (Ar), 168.8 (CH_3CO), 171.4 (C-2) ppm. EIMS: *m*/*z* = 316 (8) [M − H_2O − $CH_3C_6H_4$]$^+$, 270 (24), 238 (46), 179 (30), 155 (31), 135 (66), 91 (47), 57 (33), 55 (43), 43 (100). $C_{20}H_{27}NO_7S$ (425.50) calcd. C 56.46, H 6.40, N 3.29, S 7.53; found C 56.44, H 6.40, N 3.11, S 7.25.

(5*RS*,5a*RS*,12a*SR*,12b*SR*)-5-Acetoxy-7-thioxo-decahydro-1*H*,7*H*-oxepino[3,4-*e*]pyrido[1,2-*c*][1,3]oxazin-1-one (23): A solution of TCDI (50 mg, 0.28 mmol) in THF (2 mL) was added dropwise to a stirred solution of **14** (38 mg, 0.14 mmol) in anhydrous THF (10 mL) under nitrogen, and heated at reflux. Reaction progress was monitored by TLC analysis (eluent: CH_2Cl_2/MeOH/NH_3 saturated solution in MeOH, 10:1/0.1). After all the starting material had been consumed (2 h), the cooled reaction mixture was concentrated under vacuum. The oily residue was dissolved in CH_2Cl_2 (25 mL) and the solution washed with water (2 × 25 mL). The organic extracts were dried and the solvent evaporated, furnishing a brown solid (65 mg). Purification by flash chromatography (hexane/EtOAc, 1:3) gave **23** (21 mg, 0.07 mmol, 60% yield) as a white solid. M.p. 181−183 °C. IR (KBr): $\tilde{\nu}$ = 3009, 2952, 2931, 2861, 1736, 1497, 1237, 1173 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.64 (m, 4 H, 10,10,11,12-H), 1.82 (m, 1 H, 12-H), 1.97 (m, 1 H, 11-H), 2.11 (s, 3 H, CH_3CO_2), 2.12 (dt, $J_{4\alpha,4\beta} \approx 17.1$, $J_{4\alpha,3\beta} \approx J_{4\alpha,5} \approx 4.9$ Hz, 1 H, 4α-H), 2.33 (ddt, $J_{4\beta,4\alpha} = 16.5$, $J_{4\beta,3\alpha} = 11.0$, $J_{4\beta,3\beta} \approx J_{4\beta,5} \approx 1.8$ Hz, 1 H, 4β-H), 3.13 (td, $J_{9ax,9eq} \approx J_{9ax,10ax} \approx 12.8$, $J_{9ax,10eq} \approx 2.7$ Hz, 1 H, 9ax-H), 3.21 (br. s, 1 H, 12b-H), 4.04 (dd, $J_{12a,12} \approx 11.9$, 2.7 Hz, 1 H, 12a-H), 4.19 (br. dd, $J_{3\beta,3\alpha} \approx 12.8$, $J_{3\beta,4\alpha} \approx 4.9$ Hz, 1 H, 3β-H), 4.32 (br. d, $J_{5a,5} = 3.7$ Hz, 1 H, 5a-H), 4.49 (dd, $J_{3\alpha,3\beta} = 13.4$, $J_{3\alpha,4\beta} = 10.4$ Hz, 1 H, 3α-H), 5.09 (dt, $J_{9eq,9ax} = 13.4$, $J_{9eq,10ax} \approx J_{9eq,10eq} \approx 1.8$ Hz, 1 H, 9eq-H), 5.46 (q, $J_{5,4\alpha} \approx J_{5,4\beta} \approx J_{5,5a} \approx 3.1$ Hz, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 20.9 (CH_3CO_2), 24.0 (C-11), 25.4 (C-12), 29.1 (C-4), 31.7 (C-10), 43.6 (C-12b), 53.2 (C-9), 60.0 (C-12a), 61.9 (C-3), 68.4 (C-5), 72.1 (C-5a), 168.7 (CH_3CO), 169.2 (C-1), 185.5 (C-7) ppm. EIMS: *m*/*z* = 313 (80) [M]$^+$, 280 (11), 238 (11), 220 (38), 210 (15), 194 (36), 83 (87), 82 (100), 55 (55), 43 (95). $C_{14}H_{19}NO_5S$ (313.37) calcd. C 53.66, H 6.12, N 4.47, S 10.21; found C 53.38, H 6.12, N 4.33, S 9.96.

(5a*RS*,7*RS*,11a*SR*,11b*SR*)-*N*-Benzyl-1-oxo-decahydro-1*H*-oxepino-[3′,4′:4,5]isoxazolo[2,3-*a*]pyridinium Bromide (24). General Procedure for the Benzylation of Isoxazolidines: Benzyl bromide (72 μL, 0.60 mmol) was added dropwise to a stirred solution of **1** (127 mg, 0.60 mmol) in anhydrous THF (25 mL) at room temperature. Reaction progress was monitored by ^{1}H NMR analysis of aliquot samples. When all the starting material had been consumed (3 days), the solvent was removed furnishing **24** (228 mg, 0.60 mmol, 99% yield) as a yellowish solid (crystallized from acetone/hexane) decomp. 197−204 °C. IR (KBr): $\tilde{\nu}$ = 2976, 2949, 2880, 1733, 1187 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.56 (m, 1 H), 1.78 (m, 1 H), 1.90 (m, 2 H), 2.05 (m, 1 H), 2.12 (m, 1 H), 2.20 (m, 1 H), 2.27 (m, 2 H), 2.47 (m, 1 H), 3.37 (br. d, $J_{8eq,8ax} = 11.6$ Hz, 1 H, 8eq-H), 4.21 (dd, $J_{11a,11b} = 10.4$, $J_{11a,11} = 2.4$ Hz, 1 H, 11a-H), 4.25 (dd, $J_{3\beta,3\alpha} = 13.4$, $J_{3\beta,4} = 6.4$ Hz, 1 H, 3β-H), 4.74 (d, $J = 13.4$ Hz, 1 H, CH_2Ph), 4.89 (d, $J = 13.4$ Hz, 1 H, CH_2Ph), 4.92 (td, $J_{8ax,8eq} \approx J_{8ax,9ax} \approx 13.1$, $J_{8ax,9eq} = 3.1$ Hz, 1 H, 8ax-H), 5.00 (td, $J_{3\alpha,3\beta} \approx J_{3\alpha,4} \approx 13.4$, $J_{3\alpha,4} = 3.7$ Hz, 1 H, 3α-H), 5.44 (t, $J_{11b,11a} \approx J_{11b,5a} \approx 10.0$ Hz, 1 H, 11b-H), 5.58 (ddd, $J_{5a,5} = 12.2$, $J_{5a,11b} = 9.8$, $J_{5a,5} = 2.7$ Hz, 1 H, 5a-H), 7.46 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 15.2 (C-9), 21.8/23.2/24.6 (C-4/C-5/C-10/C-11), 49.0 (C-11b), 57.4 (C-8), 65.3 (C-3), 65.6 (CH_2Ph), 71.5 (C-11a), 77.5 (C-5a), 125.8/128.7/130.6/132.0 (Ph), 169.5 (C-1) ppm. EIMS: *m*/*z* = 211 (6) [M − BnBr]$^+$, 174 (20), 91 (100). $C_{18}H_{24}BrNO_3$ (382.29) calcd. C 56.68, H 6.35, Br 20.71, N 3.67; found C 56.53, H 6.31, Br 20.68, N 3.68.

(5*RS*,5a*RS*,7*RS*,11a*SR*,11b*SR*)-5-Acetoxy-*N*-benzyl-1-oxo-decahydro-1*H*-oxepino[3′,4′:4,5]isoxazolo[2,3-*a*]pyridinium Bromide (25): Following the general procedure described for **24**, treatment of **4** (103 mg, 0.38 mmol) with benzyl bromide (46 μL, 0.38 mmol) rendered **25** (169 mg, 0.38 mmol, 100% yield) as a yellowish solid (crystallized from acetone/hexane) decomp. 169−177 °C. IR (KBr): $\tilde{\nu}$ = 2976, 2952, 2880, 1746, 1733, 1238, 1218, 1054 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.80 (m, 2 H), 1.83 (m, 1 H), 1.98 (m, 1 H), 2.10 (s, 3 H, CH_3CO_2), 2.14 (m, 1 H), 2.30 (m, 1 H), 2.40 (m, 1 H), 2.50 (m, 1 H), 3.40 (br. d, $J_{8eq,8ax} = 12.8$ Hz, 1 H, 8eq-H), 4.25 (dd, $J_{3\beta,3\alpha} = 14.0$, $J_{3\beta,4} = 6.7$ Hz, 1 H, 3β-H), 4.30 (br. d, $J_{11a,11b} = 10.4$ Hz, 1 H, 11a-H), 4.72 (d, $J = 13.4$ Hz, 1 H, CH_2Ph), 4.77 (td, $J_{8ax,8eq} \approx J_{8ax,9ax} \approx 12.9$, $J_{8ax,9eq} \approx 2.5$ Hz, 1 H, 8ax-H), 5.00 (d, $J = 13.4$ Hz, 1 H, CH_2Ph), 5.10 (q, $J_{5,5a} \approx J_{5,4} \approx 9.1$ Hz, 1 H, 5-H), 5.15 (td, $J_{3\alpha,3\beta} \approx J_{3\alpha,4} \approx 13.4$, $J_{3\alpha,4} = 3.1$ Hz, 1 H, 3α-H), 5.55 (t, $J \approx 10.4$ Hz, 1 H, 5a/11b-H), 5.71 (t, $J \approx 10.4$ Hz, 1 H, 5a/11b-H), 7.34 (d, $J = 7.3$ Hz, 2 H, Ar), 7.41 (t, $J = 7.3$ Hz, 2 H, Ar), 7.50 (t, $J = 7.3$ Hz, 1 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 15.6 (C-9), 20.8 (CH_3CO_2), 22.6/24.0 (C-10/C-11), 29.7 (C-4), 47.6 (C-11b), 57.8 (C-8), 64.1 (C-3), 66.1 (CH_2Ph), 68.6 (C-5), 73.2 (C-11a), 78.6 (C-5a), 125.4/129.4/131.5/132.1 (Ph), 168.9/169.4 (C-1/CH_3CO_2) ppm. EIMS: *m*/*z* = 269 (3) [M − BnBr]$^+$, 226 (1), 172 (6), 170 (6), 124 (20), 91 (100), 43 (22). $C_{20}H_{26}BrNO_5$ (440.33) calcd. C 54.66, H 5.97, Br 17.97, N 3.19; found C 54.49, H 5.94, Br 17.84, N 3.17.

(5*RS*,5a*RS*,7*RS*,11a*SR*,11b*SR*)-*N*-Benzyl-1-oxo-5-phenylthio-decahydro-1*H*-oxepino[3′,4′:4,5]isoxazolo[2,3-*a*]pyridinium Bromide (26): Following the general procedure described for **24**, treatment of **5** (501 mg, 1.57 mmol) with benzyl bromide (187 μL, 1.57 mmol) rendered **26** (770 mg, 1.57 mmol, 100% yield) as a yellowish solid (crystallized from $CHCl_3$/hexane) decomp. 144−152 °C. IR (KBr): $\tilde{\nu}$ = 2938, 2868, 1729, 1173 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.77 (m, 1 H), 1.89 (m, 2 H), 2.23 (m, 3 H), 2.37 (m, 1 H), 2.55 (m, 1 H), 3.29 (td, $J_{5,5a} = J_{5,4} = 11.0$, $J_{5,4} = 6.1$ Hz, 1 H, 5-H), 3.39 (br. d, $J_{8eq,8ax} \approx 12.2$ Hz, 1 H, 8eq-H), 4.21 (m, 2 H, 3β,11a-H), 4.64 (d, $J = 13.7$ Hz, 1 H, CH_2Ph), 4.84 (d, $J = 13.7$ Hz, 1 H, CH_2Ph), 4.95 (br. t, $J_{8ax,8eq} \approx J_{8ax,9ax} \approx 11.9$ Hz, 1 H, 8ax-H), 5.12 (td, $J_{3\alpha,3\beta} = J_{3\alpha,4} = 13.4$, $J_{3\alpha,4} = 3.7$ Hz, 1 H, 3α-H), 5.50 (t, $J_{5a,5} \approx J_{5a,11b} \approx 11.0$ Hz, 1 H, 5a-H), 5.71 (t, $J_{11b,11a} \approx J_{11b,5a} \approx 10.4$ Hz, 1 H, 11b-H), 7.25−7.51 (m, 10 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 15.5 (C-9), 22.7/24.0 (C-10/C-11), 31.5 (C-4), 44.3 (C-5), 49.4 (C-11b), 58.1 (C-8), 65.1 (C-3), 66.0 (CH_2Ph), 72.2 (C-11a), 79.9 (C-5a), 125.5/128.5/129.4/131.4/132.1/133.1 (Ph), 169.5 (C-1) ppm.

(5*RS*,5a*RS*,7*RS*,11a*SR*,11b*SR*)-5-Acetylthio-*N*-benzyl-1-oxo-decahydro-1*H*-oxepino[3′,4′:4,5]isoxazolo[2,3-*a*]pyridinium Bromide (27): Following the general procedure described for **24**, treatment of **6** (100 mg, 0.35 mmol) with benzyl bromide (42 μL, 0.35 mmol) rendered **27** (163 mg, 0.35 mmol, 100% yield) as a yellowish solid (crystallized from acetone/hexane) decomp. 142−150 °C. IR (KBr): $\tilde{\nu}$ = 3021, 2962, 2944, 2920, 2880, 1750, 1715, 1272, 1181, 1072 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.80 (m, 1 H, 9-H), 1.93 (td, $J_{4\alpha,4\beta} = J_{4\alpha,5} = 13.4$, $J_{4\alpha,3\alpha} \approx 3.1$ Hz, 1 H, 4α-H), 2.16 (m, 1 H, 9-H), 2.28 (m, 1 H, 11-H), 2.32−2.50 (m, 4 H, 4β,10,10,11-H), 2.42 (s, 3 H, CH_3COS), 3.28 (br. d, $J_{8eq,8ax} = 12.2$ Hz, 1 H, 8eq-H), 3.80 (td, $J_{5,5a} = J_{5,4\alpha} = 11.6$, $J_{5,4\beta} \approx 6.7$ Hz, 1 H, 5-H), 4.27 (dd, $J_{3\beta,3\alpha} = 13.4$, $J_{3\beta,4\beta} = 6.1$ Hz, 1 H, 3β-H), 4.41 (dd, $J_{11a,11b} = 10.4$, $J_{11a,11} = 4.9$ Hz, 1 H, 11a-H), 4.62 (d, $J = 13.7$ Hz, 1 H, CH_2Ph), 4.80 (br. t, $J_{8ax,8eq} \approx J_{8ax,9ax} \approx 12.8$ Hz, 1 H, 8ax-H), 4.90 (d, J =

13.7 Hz, 1 H, CH_2Ph), 5.17 (td, $J_{3\alpha,3\beta} = J_{3\alpha,4\beta} = 13.4$, $J_{3\alpha,4\alpha} \approx 3.7$ Hz, 1 H, 3α-H), 5.53 (t, $J_{5a,5} \approx J_{5a,11b} \approx 10.7$ Hz, 1 H, 5a-H), 5.69 (t, $J_{11b,11a} = J_{11b,5a} = 10.4$ Hz, 1 H, 11b-H), 7.30 (d, $J \approx 7.6$ Hz, 2 H, Ar), 7.43 (t, $J \approx 7.6$ Hz, 2 H, Ar), 7.52 (t, $J \approx 7.6$ Hz, 1 H, Ar) ppm. ^{13}C NMR (62.5 MHz): $\delta = 15.5$ (C-9), 22.2/23.9 (C-10/C-11), 30.2 (C-4), 30.4 (*C*H_3COS), 39.4 (C-5), 49.3 (C-11b), 56.9 (C-8), 64.8 (C-3), 66.1 (*C*H_2Ph), 73.5 (C-11a), 78.4 (C-5a), 125.8/129.2/131.1/131.9 (Ph), 169.1 (C-1), 193.1 (CH$_3$*C*OS) ppm.

(5*RS*,5a*RS*,7*RS*,11a*SR*,11b*SR*)-5-Acetylthio-*N*-methyl-1-oxodecahydro-1*H*-oxepino[3′,4′:4,5]isoxazolo[2,3-*a*]pyridinium Iodide (32): Methyl iodide (700 μL, 11.2 mmol) was added dropwise to a stirred solution of **6** (105 mg, 0.37 mmol) in anhydrous THF (5 mL) at room temperature. Reaction progress was monitored by ^{1}H NMR analysis of aliquot samples. When all the starting material had been consumed (3 days), the solution was concentrated furnishing **32** (157 mg, 0.37 mmol, 100% yield) as a yellowish solid (crystallized from $CHCl_3$/hexane) decomp. 185−201 °C. IR (KBr): $\tilde{\nu}$ = 3008, 2984, 2956, 2933, 2900, 2873, 1736, 1688, 1280, 1176, 1108 cm^{-1}. ^{1}H NMR (400 MHz): $\delta = 1.75$ (m, 2 H, 9,10-H), 1.93 (ddd, $J_{4\alpha,4\beta} = 14.6$, $J_{4\alpha,5} = 11.6$, $J_{4\alpha,3\alpha} = 3.1$ Hz, 1 H, 4α-H), 2.13 (m, 1 H, 9/11-H), 2.23−2.51 (m, 4 H, 4β,10,11,9/11-H), 2.34 (s, 3 H, CH$_3$COS), 3.46 (m, 1 H, 8eq-H), 3.47 (s, 3 H, CH$_3$-N), 3.82 (td, $J_{5,5a} = J_{5,4} = 11.6$, $J_{5,4} = 6.7$ Hz, 1 H, 5-H), 4.32 (dd, $J_{3\beta,3\alpha} \approx 13.4$, $J_{3\beta,4\beta} \approx 6.1$ Hz, 1 H, 3β-H), 4.35 (dd, $J_{11a,11b} \approx 10.4$, $J_{11a,11} \approx 5.5$ Hz, 1 H, 11a-H), 5.03 (td, $J_{8ax,8eq} \approx J_{8ax,9ax} \approx 13.7$, $J_{8ax,9eq} \approx 3.4$ Hz, 1 H, 8ax-H), 5.18 (td, $J_{3\alpha,3\beta} = J_{3\alpha,4\alpha} = 13.4$, $J_{3\alpha,4\beta} = 3.7$ Hz, 1 H, 3α-H), 5.48 (t, $J_{5a,5} \approx J_{5a,11b} \approx 10.7$ Hz, 1 H, 5a-H), 5.55 (t, $J_{11b,11a} \approx J_{11b,5a} \approx 10.1$ Hz, 1 H, 11b-H) ppm. ^{13}C NMR (62.5 MHz): $\delta = 15.5$ (C-9), 22.8/23.9 (C-10/C-11), 29.7 (C-4), 30.4 (*C*H$_3$COS), 39.3 (C-5), 49.7 (C-11b), 51.9 (CH$_3$-N), 62.4 (C-8), 65.0 (C-3), 74.7 (C-11a), 78.6 (C-5a), 168.6 (C-1), 193.1 (CH$_3$*C*OS) ppm. $C_{14}H_{22}INO_4S$ (427.30) calcd. C 39.34, H 5.19, N 3.28, S 7.49; found C 39.47, H 5.28, N 3.19, S 7.40.

(5a*RS*,7*SR*,10a*RS*,10b*RS*)-*N*-Benzyl-1-oxo-octahydro-3*H*-oxepino-[3,4:*d*]pyrrolo[1,2-*b*]isoxazolium Bromide (28): Following the general procedure described for **24**, treatment of **7** (200 mg, 1.01 mmol) with benzyl bromide (120 μL, 1.02 mmol) rendered **28** (350 mg, 0.95 mmol, 94% yield) as a yellowish solid. IR (KBr): $\tilde{\nu}$ = 3037, 2994, 2952, 2924, 2875, 1736, 1405, 1279, 1173 cm^{-1}. ^{1}H NMR (400 MHz): $\delta = 1.66$ (td, $J = 12.9$, 6.2 Hz, 1 H), 2.04 (m, 3 H), 2.39 (m, 2 H), 2.79 (m, 1 H), 2.91 (m, 1 H), 3.65 (dt, $J_{8,8} = 11.7$, $J_{8,9} \approx 5.7$ Hz, 1 H, 8-H), 4.31 (m, 2 H, 3,8-H), 4.90 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.02 (td, $J_{3,3} = J_{3,4} = 12.6$, $J_{3,4} = 5.9$ Hz, 1 H, 3-H), 5.45 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.52 (m, 3 H, 5a,10a,10b-H), 7.40 (t, $J = 7.0$ Hz, 2 H, Ar), 7.46 (t, $J = 7.0$ Hz, 1 H, Ar), 7.58 (d, $J = 7.0$ Hz, 2 H, Ar) ppm. ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 1.50$ (m, 1 H), 1.69 (m, 1 H), 2.07−2.25 (m, 5 H), 2.53 (m, 1 H), 3.65 (dt, $J_{8,8} = 13.0$, $J_{8,9} = 6.4$ Hz, 1 H, 8-H), 4.06 (dt, $J_{8,8} = 13.0$, $J_{8,9} = 7.3$ Hz, 1 H, 8-H), 4.33 (dd, $J_{3,3} = 13.2$, $J_{3,4} = 8.8$ Hz, 1 H, 3-H), 4.44 (td, $J_{3,3} \approx J_{3,4} \approx 12.6$, $J_{3,4} \approx 5.3$ Hz, 1 H, 3-H), 4.63 (br. d, $J_{10b,5a} = 7.9$ Hz, 1 H, 10b-H), 4.90 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.09 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.11 (m, 1 H, 5a-H), 5.23 (m, 1 H, 10a-H), 7.48 (m, 3 H, Ar), 7.57 (m, 2 H, Ar) ppm. ^{13}C NMR (62.5 MHz): $\delta = 20.5/24.1/26.1/29.8$ (C-4/C-5/C-9/C-10), 54.7 (C-10b), 66.1/66.4 (*C*H$_2$Ph/C-3), 69.7 (C-8), 79.9 (C-5a), 83.4 (C-10a), 127.7/129.0/130.7/132.4 (Ph), 170.7 (C-1) ppm. EIMS: $m/z = 288$ (1) [M − Br]$^+$, 197 (3), 91 (100).

(5*RS*,5a*RS*,7*RS*,10a*SR*,10b*SR*)-5-Acetoxy-*N*-benzyl-1-oxooctahydro-3*H*-oxepino[3,4:*d*]pyrrolo[1,2-*b*]isoxazolium Bromide (29): Following the general procedure described for **24**, treatment of **8** (213 mg, 0.84 mmol) with benzyl bromide (100 μL, 0.84 mmol) rendered **29** (356 mg, 0.84 mmol, 100% yield) as a yellowish solid. Decomp. 175−185 °C. IR (KBr): $\tilde{\nu}$ = 2988, 2945, 1743, 1237, 1188, 1047 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 1.81$ (m, 1 H, 4-H), 2.00−2.60 (m, 5 H, 4,9,9,10,10-H), 2.05 (s, 3 H, CH$_3$CO$_2$), 3.68 (dt, $J_{8,8} \approx 12.4$, $J_{8,9} \approx 5.9$ Hz, 1 H, 8-H), 4.06 (dt, $J_{8,8} = 12.4$, $J_{8,9} \approx 7.7$ Hz, 1 H, 8-H), 4.41 (dd, $J_{3\beta,3\alpha} \approx 13.2$, $J_{3\beta,4} = 8.8$ Hz, 1 H, 3β-H), 4.52 (td, $J_{3\alpha,3\beta} \approx J_{3\alpha,4} \approx 12.4$, $J_{3\alpha,4} \approx 7.3$ Hz, 1 H, 3α-H), 4.80 (dd, $J_{10b,5a} = 8.0$, $J_{10b,10a} = 2.2$ Hz, 1 H, 10b-H), 4.92 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 4.95 (td, $J_{5,5a} \approx J_{5,4} \approx 11.0$, $J_{5,4} \approx 6.6$ Hz, 1 H, 5-H), 5.12 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.32 (m, 1 H, 10a-H), 5.35 (t, $J_{5a,5} \approx J_{5a,10b} \approx 8.8$ Hz, 1 H, 5a-H), 7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 20.8$ (*C*H$_3$CO$_2$), 23.6/27.3/29.7 (C-4/C-9/C-10), 51.8 (C-10b), 63.4 (C-3), 66.6 (*C*H$_2$Ph), 69.0 (C-8), 70.0 (C-5), 79.8 (C-5a), 83.1 (C-10a), 128.3/128.9/130.7/132.7 (Ph), 169.4/169.6 (C-1/ CH$_3$*C*O$_2$) ppm.

(5*RS*,5a*RS*,7*RS*,10a*SR*,10b*SR*)-*N*-Benzyl-5-phenylthio-1-oxooctahydro-3*H*-oxepino[3,4:*d*]pyrrolo[1,2-*b*]isoxazolium Bromide (30): Following the general procedure described for **24**, treatment of **9** (200 mg, 0.66 mmol) with benzyl bromide (78 μL, 0.66 mmol) rendered **30** (310 mg, 0.66 mmol, 100% yield) as a white solid. Decomp. 152−166 °C. IR (KBr): $\tilde{\nu}$ = 2981, 2938, 2903, 1743, 1181 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 1.79$ (dt, $J_{4,4} = 13.5$, $J_{4,3\alpha} \approx J_{4,5} \approx 5.1$ Hz, 1 H, 4-H), 2.12 (m, 2 H, 9,9-H), 2.28 (m, 1 H, 10-H), 2.40 (m, 1 H, 4-H), 2.53 (m, 1 H, 10-H), 3.35 (m, 1 H, 5-H), 3.66 (dt, $J_{8,8} \approx 12.4$, $J_{8,9} \approx 5.9$ Hz, 1 H, 8-H), 4.07 (dt, $J_{8,8} = 12.4$, $J_{8,9} \approx 7.6$ Hz, 1 H, 8-H), 4.32 (dd, $J_{3\beta,3\alpha} \approx 13.2$, $J_{3\beta,4} = 8.0$ Hz, 1 H, 3β-H), 4.44 (td, $J_{3\alpha,3\beta} \approx J_{3\alpha,4} \approx 12.4$, $J_{3\alpha,4} = 5.1$ Hz, 1 H, 3α-H), 4.75 (dd, $J_{10b,5a} \approx 8.0$, $J_{10b,10a} \approx 1.5$ Hz, 1 H, 10b-H), 4.95 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.07 (dd, $J_{5a,5} \approx 10.2$, $J_{5a,10b} = 8.0$ Hz, 1 H, 5a-H), 5.14 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.29 (m, 1 H, 10a-H), 7.36−7.55 (m, 10 H, Ar) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 23.6/29.6$ (C-4/C-9/C-10), 45.0 (C-5), 53.1 (C-10b), 64.4 (C-3), 66.3 (*C*H$_2$Ph), 68.8 (C-8), 80.0 (C-5a), 84.6 (C-10a), 128.5/128.9/129.6/130.5/131.0/132.7/134.4 (Ar), 169.7 (C-1) ppm. $C_{23}H_{26}BrNO_3S$ (476.43) calcd. C 58.10, H 5.52, Br 16.61, N 2.95, S 6.73; found C 58.02, H 5.55, Br 16.56, N 2.99, S 6.69.

(5*RS*,5a*RS*,7*RS*,10a*SR*,10b*SR*)-5-Acetylthio-*N*-benzyl-1-oxooctahydro-3*H*-oxepino[3,4:*d*]pyrrolo[1,2-*b*]isoxazolium Bromide (31): Following the general procedure described for **24**, treatment of **10** (203 mg, 0.75 mmol) with benzyl bromide (89 μL, 0.75 mmol) rendered **31** (332 mg, 0.75 mmol, 100% yield) as a yellowish solid. Decomp. 161−170 °C. IR (KBr): $\tilde{\nu}$ = 2931, 1743, 1715, 1694, 1181 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 2.00$ (dt, $J_{4,4} = 13.9$, $J_{4,3} = J_{4,5} = 5.1$ Hz, 1 H, 4-H), 2.12 (m, 2 H, 9,9-H), 2.25 (m, 2 H, 4,10-H), 2.39 (s, 3 H, CH$_3$COS), 2.50 (m, 1 H, 10-H), 3.60 (m, 2 H, 5,8-H), 4.06 (dt, $J_{8,8} \approx 12.4$, $J_{8,9} \approx 7.3$ Hz, 1 H, 8-H), 4.39 (dd, $J_{3\beta,3\alpha} = 13.2$, $J_{3\beta,4} = 8.8$ Hz, 1 H, 3β-H), 4.53 (td, $J_{3\alpha,3\beta} \approx J_{3\alpha,4} \approx 12.4$, $J_{3\alpha,4} \approx 5.5$ Hz, 1 H, 3α-H), 4.77 (dd, $J_{10b,5a} \approx 7.7$, $J_{10b,10a} = 1.5$ Hz, 1 H, 10b-H), 4.88 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.10 (d, $J = 13.2$ Hz, 1 H, CH_2Ph), 5.23 (dd, $J_{5a,5} \approx 10.6$, $J_{5a,10b} \approx 7.7$ Hz, 1 H, 5a-H), 5.33 (ddd, $J_{10a,10} \approx 7.3$, 5.1, $J_{10a,10b} \approx 1.5$ Hz, 1 H, 10a-H), 7.40−7.53 (m, 5 H, Ph) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): $\delta = 23.7/29.2/29.7$ (C-4/C-9/C-10), 30.6 (*C*H$_3$COS), 39.7 (C-5), 53.2 (C-10b), 64.4 (C-3), 66.2 (*C*H$_2$Ph), 69.0 (C-8), 80.8 (C-5a), 83.1 (C-10a), 128.3/128.8/130.6/132.7 (Ph), 169.8 (C-1), 193.4 (CH$_3$*C*OS) ppm.

(3*RS*,4*RS*)-3-[(2*RS*)-*N*-Benzylpiperidin-2-yl]-4-hydroxyoxepan-2-one (33). General Procedure for the Reduction of *N*-Benzylisoxazolidinium Salts: Activated zinc powder (5.33 g, 81.4 mmol) was added to a solution of **24** (432 mg, 1.13 mmol) in 10% aqueous HCl (40 mL) and the mixture was sonicated for 15 min. Then the suspension was filtered, the solid washed with 10% aqueous HCl and water and the solution brought to pH 9−10 by addition of 30%

aqueous NH_3. A white solid appeared which was filtered under vacuum. The solution was then extracted with $CHCl_3$ (4 × 50 mL), the combined organic extracts were dried and the solution was concentrated to furnish **33** (343 mg, 81.4 mmol, 100% yield) as a white solid. M.p. 129−130 °C (from acetone/hexane). IR (KBr): $\tilde{\nu}$ = 3472, 2976, 2944, 2880, 1728, 1296, 1184 cm^{-1}. ^1H NMR (400 MHz): δ = 1.38 (m, 2 H), 1.60−1.84 (m, 5 H), 1.89 (m, 1 H), 2.01 (m, 1 H), 2.71 (dt, $J_{6'eq,6'ax} \approx 14.3$, $J_{6'eq,5'ax} \approx J_{6'eq,5'eq} \approx$ 4.0 Hz, 1 H, 6′eq-H), 2.81 (ddd, $J_{6'ax,6'eq}$ = 14.0, $J_{6'ax,5'ax}$ = 9.8, $J_{6'ax,5'eq}$ = 3.4 Hz, 1 H, 6′ax-H), 3.37 (dd, $J_{3,2'}$ = 11.0, $J_{3,4}$ = 2.1 Hz, 1 H, 3-H), 3.44 (dt, $J_{2',3} \approx 10.5$, $J_{2',3'} \approx 4.1$ Hz, 1 H, 2′-H), 3.81 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.95 (d, J = 13.1 Hz, 1 H, CH_2Ph), 4.21 (m, 2 H, 7,7-H), 4.44 (m, 1 H, 4-H), 7.25 (m, 1 H, Ar), 7.30 (m, 4 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 18.6/21.0/21.8 (C-3′/C-4′/C-5′), 23.5 (C-5), 33.2 (C-6), 46.4 (C-6′), 48.6 (C-3), 54.7 (C-2′), 55.4 (CH_2Ph), 65.2 (C-4), 67.2 (C-7), 127.3/128.5/128.8/139.1 (Ph), 172.8 (C-2) ppm. EIMS: m/z = 303 (1) $[M]^+$, 174 (85), 91 (100). $C_{18}H_{25}NO_3$ (303.40) calcd. C 71.24, H 8.31, N 4.62; found C 71.20, H 8.44, N 4.60.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-3-[(2*RS*)-*N*-benzylpiperidin-2-yl]-4-hydroxyoxepan-2-one (34): Following the general procedure described for **33**, reduction of **25** (164 mg, 0.37 mmol) rendered **34** (135 mg, 0.37 mmol, 100% yield) as a white solid. M.p. 141−143 °C (from $CHCl_3$/hexane). IR (KBr): $\tilde{\nu}$ = 3395, 2945, 2868, 1729, 1708, 1370, 1244, 1173, 1068 cm^{-1}. ^1H NMR (400 MHz): δ = 1.34 (m, 1 H), 1.43 (m, 1 H), 1.52−1.70 (m, 3 H), 1.92 (m, 1 H), 1.92 (dt, $J_{6\alpha,6\beta}$ = 16.5, $J_{6\alpha,7\beta} = J_{6\alpha,5}$ = 4.3 Hz, 1 H, 6α-H), 2.00 (s, 3 H, CH_3CO_2), 2.29 (ddt, $J_{6\beta,6\alpha} \approx 16.2$, $J_{6\beta,7\alpha} \approx 11.3$, $J_{6\beta,7\beta} \approx J_{6\beta,5} \approx$ 2.4 Hz, 1 H, 6β-H), 2.68 (m, 2 H, 6′,6′-H), 3.22 (dt, $J_{2',3}$ = 10.4, $J_{2',3'} \approx 4.3$ Hz, 1 H, 2′-H), 3.48 (d, $J_{3,2'}$ = 10.4 Hz, 1 H, 3-H), 3.75 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.95 (d, J = 13.1 Hz, 1 H, CH_2Ph), 4.08 (ddd, $J_{7\beta,7\alpha}$ = 13.4, $J_{7\beta,6\alpha}$ = 4.9, $J_{7\beta,6\beta}$ = 1.8 Hz, 1 H, 7β-H), 4.50 (t, $J_{7\alpha,7\beta} \approx J_{7\alpha,6\beta} \approx$ 12.2 Hz, 1 H, 7α-H), 4.63 (d, $J_{4,5}$ = 4.9 Hz, 1 H, 4-H), 5.13 (q, $J_{5,4} \approx J_{5,6\alpha} \approx J_{5,6\beta} \approx$ 4.0 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ar), 7.29 (m, 4 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 19.4/21.3/21.9 (C-3′/C-4′/C-5′), 21.0 (CH_3CO_2), 28.7 (C-6), 43.5 (C-3), 46.8 (C-6′), 53.8 (C-2′), 55.6 (CH_2Ph), 62.1 (C-7), 65.1 (C-4), 70.9 (C-5), 127.3/128.6/139.9 (Ph), 169.3 (CH_3CO_2), 172.4 (C-2) ppm. EIMS: m/z = 361 (0.4) $[M]^+$, 301 (2.5), 174 (100), 91 (57). $C_{20}H_{27}NO_5$ (361.43) calcd. C 66.45, H 7.53, N 3.88; found C 66.39, H 7.56, N 3.88.

(3*RS*,4*SR*,5*SR*)-3-[(2*RS*)-*N*-Benzylpiperidin-2-yl]-4-hydroxy-5-phenylthiooxepan-2-one (35): Following the general procedure described for **33**, reduction of **26** (658 mg, 1.34 mmol) rendered **35** (275 mg, 0.67 mmol, 50% yield) as a white solid (crystallized from $CHCl_3$/hexane) decomp. 155−170 °C. IR (KBr): $\tilde{\nu}$ = 3395, 2924, 2861, 1715, 1166, 1068, 1026 cm^{-1}. ^1H NMR (400 MHz): δ = 1.30 (m, 1 H), 1.45 (m, 1 H), 1.61 (m, 3 H), 1.91 (m, 2 H), 2.45 (dddd, $J_{6\beta,6\alpha} \approx 16.2$, $J_{6\beta,7\alpha} \approx 10.7$, $J_{6\beta,5} \approx 3.5$, $J_{6\beta,7\beta} \approx$ 1.7 Hz, 1 H, 6β-H), 2.60 (br. d, $J_{6'eq,6'ax} \approx 14.3$ Hz, 1 H, 6′eq-H), 2.91 (ddd, $J_{6'ax,6'eq} \approx 14.3$, $J_{6'ax,5'ax} \approx 11.3$, $J_{6'ax,5'eq} \approx$ 2.9 Hz, 1 H, 6′ax-H), 3.17 (m, 1 H, 2′-H), 3.62 (d, $J_{3,2'}$ = 10.4 Hz, 1 H, 3-H), 3.67 (q, $J_{5,4} \approx J_{5,6} \approx$ 4.0 Hz, 1 H, 5-H), 3.75 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.94 (d, J = 13.1 Hz, 1 H, CH_2Ph), 4.09 (br. dd, $J_{7\beta,7\alpha}$ = 13.1, $J_{7\beta,6\alpha}$ = 4.3 Hz, 1 H, 7β-H), 4.60 (dd, $J_{7\alpha,7\beta}$ = 13.1, $J_{7\alpha,6\beta}$ = 11.0 Hz, 1 H, 7α-H), 4.71 (d, $J_{4,5}$ = 3.7 Hz, 1 H, 4-H), 7.17−7.40 (m, 10 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 19.4/20.8/21.8 (C-3′/C-4′/C-5′), 28.6 (C-6), 44.1 (C-3), 46.6 (C-6′), 49.8 (C-5), 53.8 (C-2′), 56.8 (CH_2Ph), 62.9 (C-7), 66.6 (C-4), 127.0/127.2/128.4/128.7/129.1/131.2/133.3/140.1 (Ar), 172.8 (C-2) ppm. EIMS: m/z = 411 (1) $[M]^+$, 302 (5), 174 (100), 91 (53).

(3*RS*,4*RS*)-3-[(2*RS*)-*N*-Benzylpyrrolidin-2-yl]-4-hydroxyoxepan-2-one (36): Following the general procedure described for **33**, reduction of **28** (175 mg, 0.47 mmol) gave an oily residue (171 mg), which was purified by flash chromatography (eluent: $CHCl_3$/MeOH, 9:1), affording **36** (136 mg, 0.47 mmol, 99% yield) as a white solid. M.p. 129−131 °C. IR (KBr): $\tilde{\nu}$ = 3416 (br), 2952, 2924, 1729, 1447, 1398, 1286, 1230, 1166, 1103, 1061, 1019 cm^{-1}. ^1H NMR (400 MHz): δ = 1.50 (m, 1 H), 1.64 (m, 1 H), 1.73 (m, 3 H), 2.18 (m, 3 H), 2.70 (m, 2 H, 5′,5′-H), 2.80 (s, 1 H, 3-H), 3.45 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.69 (t, $J_{2',3}$ = 7.6 Hz, 1 H, 2′-H), 4.14 (t, $J_{7,7} \approx J_{7,6} \approx$ 11.9 Hz, 1 H, 7-H), 4.24 (br. s, 1 H, 4-H), 4.29 (dd, $J_{7,7}$ = 12.8, $J_{7,6}$ = 4.3 Hz, 1 H, 7-H), 4.63 (d, J = 13.1 Hz, 1 H, CH_2Ph), 5.56 (br. s, 1 H, OH), 7.22 (m, 5 H, Ph) ppm. ^{13}C NMR (62.5 MHz): δ = 23.4/24.0 (C-4′/C-5), 32.3/35.1 (C-3′/C-6), 53.6 (C-3), 54.3 (C-5′), 61.4 (CH_2Ph), 64.8/65.2 (C-2′/C-4), 68.8 (C-7), 126.8/128.4/128.8/140.2 (Ph), 174.6 (C-2) ppm. EIMS: m/z = 290 (1) $[M+1]^+$, 289 (1) $[M]^+$, 160 (100), 91 (94). $C_{17}H_{23}NO_3$ (289.37) calcd. C 70.56, H 8.01, N 4.84; found C 70.68, H 8.04, N 4.83.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-3-[(2*RS*)-*N*-benzylpyrrolidin-2-yl]-4-hydroxyoxepan-2-one (37): Following the general procedure described for **33**, reduction of **29** (105 mg, 0.25 mmol) rendered **37** (83 mg, 0.24 mmol, 97% yield) as a white solid (crystallized from $CHCl_3$/pentane). M.p. 117−120 °C. IR (KBr): $\tilde{\nu}$ = 3423, 2973, 2959, 2924, 2882, 1715, 1377, 1265, 1166, 1061 cm^{-1}. ^1H NMR (400 MHz): δ = 1.41 (m, 1 H, 3′/4′-H), 1.73 (m, 2 H, 3′/4′,4′-H), 1.96 (dt, $J_{6\alpha,6\beta} \approx 15.9$, $J_{6\alpha,7\beta} \approx J_{6\alpha,5} \approx$ 4.3 Hz, 1 H, 6α-H), 2.08 (s, 3 H, CH_3CO_2), 2.21 (m, 1 H, 3′-H), 2.39 (ddt, $J_{6\beta,6\alpha} \approx 15.9$, $J_{6\beta,7\alpha} \approx 11.6$, $J_{6\beta,5} \approx J_{6\beta,7\beta} \approx$ 2.4 Hz, 1 H, 6β-H), 2.72 (m, 2 H, 5′,5′-H), 3.03 (d, $J_{3,2'} \approx$ 1.8 Hz, 1 H, 3-H), 3.47 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.74 (td, $J_{2',3'} \approx 8.8$, $J_{2',3} \approx$ 1.8 Hz, 1 H, 2′-H), 4.07 (d, $J_{4,5}$ = 4.3 Hz, 1 H, 4-H), 4.12 (ddt, $J_{7\beta,7\alpha} \approx 13.1$, $J_{7\beta,6\alpha} \approx 4.9$, $J_{7\beta,6\beta} \approx J_{7\beta,5} \approx$ 1.2 Hz, 1 H, 7β-H), 4.44 (t, $J_{7\alpha,7\beta} \approx J_{7\alpha,6\beta} \approx$ 12.2 Hz, 1 H, 7α-H), 4.63 (d, J = 13.1 Hz, 1 H, CH_2Ph), 5.17 (q, $J_{5,4} \approx J_{5,6\alpha} \approx J_{5,6\beta} \approx$ 3.4 Hz, 1 H, 5-H), 7.25 (m, 5 H, Ph) ppm. ^{13}C NMR (62.5 MHz): δ = 20.9 (CH_3CO_2), 23.8 (C-4′), 28.6 (C-6), 31.8 (C-3′), 49.0 (C-3), 54.1 (C-5′), 61.2 (CH_2Ph), 62.2/64.3 (C-2′/C-7), 66.8 (C-4), 70.5 (C-5), 126.8/128.3/128.6/140.0 (Ph), 169.2 (CH_3CO_2), 174.0 (C-2) ppm. EIMS: m/z = 347 (0.3) $[M]^+$, 304 (0.8), 287 (1), 256 (1), 160 (100), 91 (91). $C_{19}H_{25}NO_5$ (347.41) calcd. C 65.67, H 7.26, N 4.03; found C 65.53, H 7.39, N 3.93.

(3*RS*,4*SR*,5*SR*)-3-[(2*RS*)-*N*-Benzylpyrrolidin-2-yl]-4-hydroxy-5-phenylthiooxepan-2-one (38): Following the general procedure described for **33**, reduction of **30** (251 mg, 0.53 mmol) gave an oily residue (208 mg), which was purified by flash chromatography. Elution with hexane/EtOAc, 2:1, afforded **38** (107 mg, 0.27 mmol, 51% yield). Elution with $CHCl_3$/MeOH, 9:1, afforded **40** (30 mg, 0.08 mmol, 14% yield).

38: White solid (crystallized from $CHCl_3$/pentane). M.p. 94−95 °C. IR (KBr): $\tilde{\nu}$ = 3466, 3058, 3023, 2959, 2924, 2861, 2812, 2791, 1701, 1406, 1314, 1174, 1061, 1026 cm^{-1}. ^1H NMR (400 MHz): δ = 1.41 (m, 2 H, 3′,4′-H), 1.61 (m, 1 H, 4′-H), 1.90 (ddd, $J_{6,6}$ = 16.5, $J_{6,7}$ = 5.0, $J_{6,5}$ = 2.7 Hz, 1 H, 6-H), 2.11 (m, 1 H, 3′-H), 2.54 (m, 1 H, 6-H), 2.58 (m, 2 H, 5′,5′-H), 3.22 (d, $J_{3,2'} \approx$ 1.8 Hz, 1 H, 3-H), 3.38 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.67 (ddd, $J_{2',3'}$ = 8.5, 6.7, $J_{2',3}$ = 1.8 Hz, 1 H, 2′-H), 3.73 (q, $J_{5,4} \approx J_{5,6} \approx$ 3.1 Hz, 1 H, 5-H), 4.05 (d, $J_{4,5} \approx$ 3.0 Hz, 1 H, 4-H), 4.08 (m, 1 H, 7β-H), 4.50 (dd, $J_{7\alpha,7\beta} \approx 13.1$, $J_{7\alpha,6} \approx$ 11.3 Hz, 1 H, 7α-H), 4.61 (d, J = 13.1 Hz, 1 H, CH_2Ph), 7.20 (m, 8 H, Ar), 7.34 (m, 2 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 23.9 (C-4′), 28.5 (C-6), 31.9 (C-3′), 49.4 (C-5), 49.5 (C-3), 54.5 (C-5′), 61.3 (CH_2Ph), 63.3 (C-7), 64.6 (C-2′), 68.3 (C-4), 126.8/127.5/128.3/128.8/129.2/131.4/133.0/140.1 (Ar), 174.3 (C-2) ppm. EIMS: m/z = 288 (2) $[M - PhS]^+$, 160

(100), 91 (90). $C_{23}H_{27}NO_3S$ (397.53) calcd. C 69.49, H 6.85, N 3.53, S 8.05; found C 69.49, H 6.90, N 3.42, S 8.00.

40: White solid (crystallized from acetone/hexane) decomp. 150−168 °C. IR (KBr): $\tilde{\nu}$ = 3402, 3051, 3030, 2959, 2931, 2875, 2861, 1729, 1602, 1462, 1377, 1272, 1124, 1075 cm^{-1}. ^1H NMR (400 MHz): δ = 1.86 (m, 3 H, 3′,3′,4′-H), 2.12 (m, 3 H, 6,6,4′-H), 2.47 (dt, $J_{5',5'} \approx 11.0$, $J_{5',4'} \approx 8.0$ Hz, 1 H, 5′-H), 2.99 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.30 (dd, $J_{3,4} \approx 9.0$, $J_{3,2'} \approx 4.5$ Hz, 1 H, 3-H), 3.40 (m, 2 H, 2′,5′-H), 3.47 (td, $J_{5,6} = 6.7$, $J_{5,4} = 1.8$ Hz, 1 H, 5-H), 3.84 (ddd, $J_{7,7} = 11.0$, $J_{7,6} \approx 7.0$, 4.0 Hz, 1 H, 7-H), 3.92 (ddd, $J_{7,7} = 11.0$, $J_{7,6} \approx 7.1$, 3.9 Hz, 1 H, 7-H), 4.15 (dd, $J_{4,3}$ = 8.9, $J_{4,5}$ = 1.8 Hz, 1 H, 4-H), 4.19 (d, J = 13.1 Hz, 1 H, CH_2Ph), 7.27 (m, 8 H, Ar), 7.46 (m, 2 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 22.2 (C-3′), 26.6 (C-4′), 35.8 (C-6), 45.0 (C-3), 48.2 (C-5), 51.4 (C-5′), 55.7 (*C*H_2Ph), 59.3 (C-7), 64.2 (C-2′), 72.0 (C-4), 126.4/129.2/129.3/130.1/132.0/136.5 (Ar), 177.0 (C-2) ppm. EIMS: *m*/*z* = 248 (3), 160 (76), 91 (100).

Reduction of 31: Following the general procedure described for **33**, reduction of **31** (80 mg, 0.18 mmol) gave an oily residue (68 mg), containing mainly (3*RS*,4*SR*,5*SR*)-5-acetylthio-3-[(2*RS*)-*N*-benzylpyrrolidin-2-yl]-4-hydroxyoxepan-2-one (**39**) according to NMR analysis: ^1H NMR (250 MHz): δ = 1.42 (m, 1 H, 3′/4′-H), 1.65 (m, 2 H, 3′/4′,4′-H), 1.84 (m, 1 H, 6-H), 2.17 (m, 1 H, 3′-H), 2.35 (s, 3 H, CH_3COS), 2.71 (m, 3 H, 5′,5′,6-H), 2.88 (d, $J_{3,2'}$ = 2.2 Hz, 1 H, 3-H), 3.48 (d, J = 13.2 Hz, 1 H, CH_2Ph), 3.71 (td, $J_{2',3'} \approx 8.8$, $J_{2',3} \approx 1.8$ Hz, 1 H, 2′-H), 4.08 (s, 2 H, 4,5/7-H), 4.22 (m, 2 H, 5/7,7-H), 4.62 (d, J = 13.2 Hz, 1 H, CH_2Ph), 7.25 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz) observed signals: δ = 45.8 (C-5), 50.8 (C-3), 54.4 (C-5′), 61.4 (*C*H_2Ph), 64.6/64.8 (C-2′/C-7), 68.6 (C-4), 127.0/128.5/128.9/140.0 (Ph), 173.8 (C-2) ppm. Attempts to purify this compound either by crystallisation or flash chromatography resulted in decomposition.

(5*RS*)-3-[(2*RS*)- and (5*RS*)-3-[(2*SR*)-*N*-Benzylpiperidin-2-yl]-5-[2-(benzyloxy)ethyl]-2(5*H*)-furanone (41): Benzyl bromide (410 μL, 3.45 mmol) was added dropwise to a stirred solution of **11** (703 mg, 2.22 mmol) in anhydrous THF (10 mL) at room temperature and reaction progress was monitored by ^1H NMR analysis of aliquot samples. When all the starting isoxazolidine had been consumed (3 days), the solvent was removed affording an oily residue (1.28 g). This material (504 mg) was dissolved in 10% aqueous HCl (50 mL), activated zinc powder (3.13 g, 47.9 mmol) was added and the mixture was sonicated for 30 min. Subsequently, the reaction mixture was filtered, the solid washed with 10% aqueous HCl and water, and the solution brought to pH 9−10 by addition of 30% aqueous NH_3. A white solid appeared which was filtered under vacuum. The solution was then extracted with $CHCl_3$ (4 × 50 mL), the combined organic extracts were dried and the solution was concentrated furnishing an oily residue (230 mg). Purification of this material by flash chromatography (eluent: hexane/EtOAc, 3:1) furnished **41** (77 mg, 0.20 mmol, 22% yield) as a colorless oil which solidifies on standing. IR (film): $\tilde{\nu}$ = 3065, 3030, 2931, 2854, 2798, 1757, 1455, 1103, 1075 cm^{-1}. ^1H NMR (400 MHz): δ = 1.23−1.53 (m, 4 H), 1.64 (m, 1 H, 3′/4′/5′-H), 1.76−2.03 (m, 4 H, 3′,6′ax,1′′,1′′-H), 2.84 (br. d, $J_{6'eq,6'ax} \approx 12.2$ Hz, 1 H, 6′eq-H), 2.96 (d, J = 13.4 Hz, 1 H, N-CH_2Ph), 3.10 (br. d, $J_{2',3'} \approx 9.2$ Hz, 1 H, 2′-H), 3.55 (m, 2 H, 2′′-H), 3.80 (d, J = 13.4 Hz, 1 H, N-CH_2Ph), 4.43 (s, 2 H, O-CH_2Ph), 5.04 (m, $J_{5,4} \approx J_{5,1''} \approx 6.4$ Hz, 1 H, 5-H), 7.13−7.32 (m, 11 H, Ar,4-H) ppm. ^{13}C NMR (62.5 MHz): δ = 24.2/25.6 (C-4′/C-5′), 33.7/33.9 (C-1′′/C-3′), 53.2 (C-6′), 58.6 (C-2′), 59.6 (N-*C*H_2Ph), 65.7 (C-2′′), 73.2 (O-*C*H_2Ph), 79.1 (C-5), 126.8/127.68/127.74/128.2/128.37/128.43/136.8/139.2 (Ar), 137.9 (C-3), 149.7 (C-4), 173.1 (C-2) ppm. EIMS: *m*/*z* = 391 (12) $[M]^+$, 300 (30), 91 (100). $C_{25}H_{29}NO_3$ (391.50) calcd. C 76.68, H 7.47, N 3.58; found C 76.76, H 7.55, N 3.68.

(3*RS*,4*RS*)-3-[(2*RS*)-*N*-Benzylpiperidin-2-yl]-4-(imidazol-2-ylthiocarbonyloxy)oxepan-2-one (42). General Procedure for the Thiocarbonylation of the Alcohols: A solution of TCDI (676 mg, 3.79 mmol) in THF (3 mL) was added dropwise to a stirred solution of **33** (769 mg, 2.53 mmol) in anhydrous THF (30 mL) heated at reflux under nitrogen, and reaction progress was monitored by TLC analysis (eluent: hexane/EtOAc, 2:1). When all the starting material had been consumed (6 h), the cooled solution was concentrated under vacuum. The oily residue (1.40 g) was dissolved in CH_2Cl_2 (40 mL) and the solution washed with water (4 × 30 mL). The organic layer was dried, the solvent removed and the residue crystallised in acetone/hexane to furnish **42** (867 mg, 2.10 mmol, 83% yield) as a white solid. M.p. 139−141 °C. IR (KBr): $\tilde{\nu}$ = 3135, 3114, 3065, 3037, 2988, 2945, 2861, 1729, 1469, 1384, 1328, 1293, 1237, 1159, 1110, 1047 cm^{-1}. ^1H NMR (400 MHz): δ = 1.27 (m, 1 H), 1.43 (m, 1 H), 1.52 (m, 1 H), 1.67 (m, 3 H), 1.88 (m, 2 H), 1.98 (m, 1 H), 2.61 (ddd, $J_{6'ax,6'eq} \approx 14.3$, $J_{6'ax,5'ax} \approx 11.1$, $J_{6'ax,5'eq} \approx 3.1$ Hz, 1 H, 6′ax-H), 2.72 (m, $J_{6'eq,6'ax} \approx 13.7$ Hz, 1 H, 6′eq-H), 2.91 (m, 1 H, 6-H), 3.18 (dt, $J_{2',3} \approx 11.0$, $J_{2',3'} \approx 3.7$ Hz, 1 H, 2′-H), 3.51 (d, $J_{3,2'}$ = 11.3 Hz, 1 H, 3-H), 3.78 (d, J = 12.9 Hz, 1 H, CH_2Ph), 3.83 (d, J = 12.9 Hz, 1 H, CH_2Ph), 4.38 (m, 2 H, 7,7-H), 6.39 (dd, $J_{4,5} \approx 3.8$, 2.6 Hz, 1 H, 4-H), 6.93 (m, 1 H, Im-H), 7.02 (t, J = 7.3 Hz, 1 H, Ph-H), 7.12 (t, $J \approx 7.5$ Hz, 2 H, Ph-H), 7.27 (d, $J \approx 7.0$ Hz, 2 H, Ph-H), 7.38 (br. s, 1 H, Im-H), 8.17 (br. s, 1 H, Im-H) ppm. ^{13}C NMR (62.5 MHz): δ = 18.8 (C-5′), 20.65/20.74 (C-3′/C-4′), 23.7/30.9 (C-5/C-6), 45.6/46.4 (C-3/C-6′), 53.5 (C-2′), 56.1 (*C*H_2Ph), 67.7 (C-7), 75.8 (C-4), 117.5/127.0/128.0/129.0/130.6/137.2/138.8 (Im/Ph), 171.6 (C-2), 182.5 (Im*C*SO) ppm. EIMS: *m*/*z* = 194 (8) $[M - ImCSOH - Bn]^+$, 174 (60), 91 (100). $C_{22}H_{27}N_3O_3S$ (413.53) calcd. C 63.90, H 6.59, N 10.17, S 7.74; found C 63.89, H 6.57, N 10.05, S 7.58.

3-[(2*RS*)-*N*-Benzylpiperidin-2-yl]-6,7-dihydro-2(5*H*)-oxepinone (49): When the crude product from the previous reaction was submitted to flash chromatography (eluent: hexane/EtOAc, 2:1), a product identified as **49** (60% yield) was isolated as a white solid (crystallized from acetone/hexane). M.p. 87−88 °C. IR (KBr): $\tilde{\nu}$ = 3088, 3072, 3040, 2976, 2960, 2928, 2864, 2832, 2816, 2800, 2720, 1712, 1184, 1104, 1040 cm^{-1}. ^1H NMR (400 MHz): δ = 1.20−1.50 (m, 4 H, 3′,4′ax,5′,5′-H), 1.66 (m, $J_{4'eq,4'ax}$ = 12.2 Hz, 1 H, 4′eq-H), 1.85 (m, 3 H, 6,3′,6′-H), 2.01 (dqn, $J_{6,6} \approx 13.7$, $J_{6,7} \approx J_{6,5} \approx 6.7$ Hz, 1 H, 6-H), 2.33 (m, 2 H, 5,5-H), 2.85 (br. d, $J_{6',6'} \approx 11.6$ Hz, 1 H, 6′-H), 2.90 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.05 (dd, $J_{2',3'} \approx 10.7$, 2.7 Hz, 1 H, 2′-H), 4.00 (d, J = 13.4 Hz, 1 H, CH_2Ph), 4.17 (m, 2 H, 7,7-H), 6.66 (t, $J_{4,5} \approx 6.7$ Hz, 1 H, 4-H), 7.17 (m, 1 H, Ar), 7.23 (m, 4 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 24.2 (C-5), 24.7 (C-4′), 25.4 (C-5′), 26.4 (C-6), 35.4 (C-3′), 53.3 (C-6′), 59.2 (*C*H_2Ph), 64.7 (C-2′), 66.1 (C-7), 126.6/128.1/128.3 (Ar), 134.9 (C-4), 138.0/139.6 (C-3/Ar), 171.7 (C-2) ppm. EIMS: *m*/*z* = 194 (100) $[M - Bn]^+$, 174 (23), 91 (60). $C_{18}H_{23}NO_2$ (285.38) calcd. C 75.74, H 8.13, N 4.91; found C 75.77, H 8.20, N 4.88.

(3*RS*,4*SR*,5*SR*)-5-Acetoxy-3-[(2*RS*)-*N*-benzylpiperidin-2-yl]-4-(imidazol-2-ylthiocarbonyloxy)oxepan-2-one (43): Following the general procedure described for **42**, treatment of **34** (148 mg, 0.41 mmol) with TCDI rendered **43** (140 mg, 0.30 mmol, 73% yield) as a white solid (crystallized from acetone/hexane). M.p. 149−152 °C. IR (KBr): $\tilde{\nu}$ = 3160, 3120, 3088, 3032, 2992, 2944, 2864, 1760, 1744, 1392, 1344, 1296, 1248, 1216, 1168, 1056, 1040, 1008 cm^{-1}. ^1H NMR (400 MHz): δ = 1.32 (m, 1 H, 5′-H), 1.46 (m, 1 H), 1.64 (m, 3 H), 1.90−2.20 (m, 3 H), 2.03 (s, 3 H, CH_3CO_2), 2.69 (m, 2 H, 6′,6′-H), 3.17 (dt, $J_{2',3} \approx 11.0$, $J_{2',3'} \approx 3.7$ Hz, 1 H,

2′-H), 3.78 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.84 (d, J = 13.1 Hz, 1 H, CH_2Ph), 3.87 (d, $J_{3,2'}$ = 10.4 Hz, 1 H, 3-H), 4.19 (dt, $J_{7,7} \approx$ 13.1, $J_{7,6} \approx$ 3.1 Hz, 1 H, 7-H), 4.63 (ddd, $J_{7,7} \approx$ 12.5, $J_{7,6} \approx$ 8.2, 4.0 Hz, 1 H, 7-H), 5.76 (m, 1 H, 5-H), 6.29 (br. d, $J_{4,5}$ = 4.3 Hz, 1 H, 4-H), 6.93 (s, 1 H, Im-H), 7.02 (t, $J \approx$ 7.0 Hz, 1 H, Ph-H), 7.12 (t, $J \approx$ 7.6 Hz, 2 H, Ph-H), 7.25 (d, J = 8.0 Hz, 2 H, Ph-H), 7.36 (s, 1 H, Im-H), 8.13 (s, 1 H, Im-H) ppm. ^{13}C NMR (62.5 MHz): δ = 18.7 (C-5′), 20.7/21.0 (C-3′/C-4′/CH_3CO_2), 29.2 (C-6), 40.9 (C-3), 45.9 (C-6′), 53.1 (C-2′), 55.3 (CH_2Ph), 61.7 (C-7), 65.6 (C-5), 74.6 (C-4), 117.6/126.9/128.0/128.8/130.8/137.2/138.6 (Im/Ph), 168.4 (CH$_3$CO_2), 171.0 (C-2), 182.8 (ImCSO) ppm. EIMS: m/z = 284 (6) [M − ImCSOH − OAc]$^+$, 252 (26), 174 (89), 91 (100), 43 (37). $C_{24}H_{29}N_3O_5S$ (471.57) calcd. C 61.12, H 6.20, N 8.92, S 6.74; found C 61.04, H 6.31, N 8.85, S 6.60.

(3*RS*,4*RS*)-3-[(2*RS*)-*N*-Benzylpyrrolidin-2-yl]-4-(imidazol-2-ylthiocarbonyloxy)oxepan-2-one (44): Following the general procedure described for **42**, treatment of **36** (50 mg, 0.17 mmol) with TCDI rendered an oily material (100 mg). ^{1}H NMR analysis indicated a mixture with the main component identified as **44**: ^{1}H NMR (250 MHz): δ = 1.47 (m, 1 H), 1.76 (m, 4 H), 2.17 (m, 2 H), 2.44 (m, 1 H), 2.74 (m, 3 H, 3,5′,5′-H), 3.32 (td, J = 9 and 2.5 Hz, 1 H, 2′-H), 3.50 (d, J = 12.6 Hz, 1 H, CH_2Ph), 3.77 (d, J = 12.6 Hz, 1 H, CH_2Ph), 4.31 (m, 2 H, 7,7-H), 6.32 (br. s, 1 H, 4-H), 6.95 (s, 1 H, Im-H), 7.16−7.32 (m, 5 H, Ph-H), 7.49 (s, 1 H, Im-H), 8.24 (s, 1 H, Im-H) ppm. All attempts to purify this compound led to decomposition.

(3*RS*,4*RS*,5*SR*)-5-Acetoxy-3-[(2*RS*)-*N*-benzylpyrrolidin-2-yl]-4-(imidazol-2-ylthiocarbonyloxy)oxepan-2-one (45): Following the general procedure described for **42**, treatment of **37** (51 mg, 0.15 mmol) with TCDI rendered an oily material (120 mg). ^{1}H NMR analysis indicated a mixture with the main component identified as **45**: ^{1}H NMR (250 MHz): δ = 1.52 (m, 1 H), 1.62−1.88 (m, 2 H), 2.00−2.30 (m, 3 H), 2.13 (s, 3 H, CH$_3$CO$_2$), 2.51 (dt, $J_{5',5'} \approx$ 11.4, $J_{5',4'} \approx$ 6.8 Hz, 1 H, 5′-H), 2.75 (dt, $J_{5',5'} \approx$ 11.4, $J_{5',4'} \approx$ 6.8 Hz, 1 H, 5′-H), 3.21 (d, $J_{3,2'} \approx$ 9.1 Hz, 1 H, 3-H), 3.32 (td, $J_{2',3} \approx J_{2',3'} \approx$ 9.1, $J_{2',3'} \approx$ 3.2 Hz, 1 H, 2′-H), 3.54 (d, J = 13.6 Hz, 1 H, CH_2Ph), 3.75 (d, J = 13.6 Hz, 1 H, CH_2Ph), 4.15 (dt, $J_{7,7} \approx$ 12.7, $J_{7,6} \approx$ 4.1 Hz, 1 H, 7-H), 4.50 (ddd, $J_{7,7} \approx$ 12.3, $J_{7,6} \approx$ 8.6, 3.6 Hz, 1 H, 7-H), 5.60 (m, 1 H, 5-H), 6.21 (d, $J_{4,5} \approx$ 2.3 Hz, 1 H, 4-H), 6.97 (s, 1 H, Im-H), 7.13−7.33 (m, 5 H, Ph-H), 7.45 (s, 1 H, Im-H), 8.22 (s, 1 H, Im-H) ppm. All attempts to purify this compound led to decomposition.

(3*RS*)-3-[(2*SR*)-*N*-Benzylpiperidin-2-yl]oxepan-2-one (46). General Procedure for the Reduction of Thiocarbonyl Derivatives: A solution of **42** (114 mg, 0.28 mmol) in toluene (2 mL) was added over a 30 min period to a stirred solution of Bu$_3$SnH (1.1 mL, 4.1 mmol) and AIBN (5 mg, 0.03 mmol) in anhydrous toluene (11 mL), heated at the reflux temperature under nitrogen, and reaction progress was monitored by TLC analysis (eluent: hexane/EtOAc, 2:1). When all the starting material had been consumed (35 min), the mixture was cooled and then concentrated under vacuum, affording a yellow oily residue (1.52 g), which was redissolved in acetonitrile (40 mL). This solution was washed with hexane (2 × 50 mL) and then concentrated to give a yellowish oil (108 mg). Purification by flash chromatography (eluent: hexane/EtOAc, 2:1) rendered a fraction of pure **46** (55 mg, 0.19 mmol, 70% yield) and another fraction of a 1.2:1 mixture of **46** and **49**.

46: White solid. M.p. 62−63 °C. IR (KBr): $\tilde{\nu}$ = 2931, 2854, 1722, 1152 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.22 (m, 1 H, 4-H), 1.32 (m, 1 H, 5′-H), 1.38−1.54 (m, 4 H, 5,3′,4′,5′-H), 1.56−1.73 (m, 3 H, 6,3′,4′-H), 1.83 (m, 1 H, 6-H), 1.94 (dqn, $J_{5,5} \approx$ 14.1, $J_{5,4} \approx J_{5,6} \approx$ 3.6 Hz, 1 H, 5-H), 2.41 (ddd, $J_{6',6'}$ = 14.0, $J_{6',5'}$ = 7.3, 3.7 Hz, 1 H, 6′-H), 2.52 (t, $J_{4,4}$ = 14.0, $J_{4,5} \approx$ 4.0 Hz, 1 H, 4-H), 2.65 (ddd, $J_{6',6'}$ = 14.0, $J_{6',5'}$ = 7.9, 3.7 Hz, 1 H, 6′-H), 2.85 (t, $J_{3,2} \approx J_{3,4} \approx$ 9.8 Hz, 1 H, 3-H), 2.97 (ddd, $J_{2',3} \approx$ 9.5, $J_{2',3'}$ = 6.1, 3.7 Hz, 1 H, 2′-H), 3.59 (d, J = 13.7 Hz, 1 H, CH_2Ph), 3.77 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.19 (m, 2 H, 7,7-H), 7.20 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 20.2 (C-5′), 22.6 (C-4′), 24.0 (C-3′), 24.9 (C-4), 28.4 (C-5), 28.9 (C-6), 44.2 (C-3), 48.0 (C-6′), 55.5 (CH_2Ph), 58.9 (C-2′), 68.3 (C-7), 126.7/128.2/128.5/140.2 (Ph), 176.7 (C-2) ppm. EIMS: m/z = 287 (0.6) [M]$^+$, 174 (100), 91 (45). $C_{18}H_{25}NO_2$ (287.40) calcd. C 75.21, H 8.77, N 4.88; found C 75.16, H 8.81, N 4.92.

(3*RS*,5*SR*)-5-Acetoxy-3-[(2*SR*)-*N*-benzylpiperidin-2-yl]oxepan-2-one (47): Following the general procedure described above, reduction of **43** (150 mg, 0.31 mmol) furnished **47** (84 mg, 0.24 mmol, 76% yield) as a white solid (crystallized from CHCl$_3$/pentane). M.p. 109−111 °C. IR (KBr): $\tilde{\nu}$ = 3065, 3030, 2945, 2924, 2847, 2826, 1729, 1377, 1244, 1159, 1117, 1061, 1033 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.36−1.69 (m, 6 H, 4,3′,4′,4′,5′,5′-H), 1.78 (m, 1 H, 3′-H), 1.92 (s, 3 H, CH$_3$CO$_2$), 1.97 (m, 1 H, 6-H), 2.07 (m, 1 H, 6-H), 2.47 (ddd, $J_{6',6'}$ = 13.7, $J_{6',5'} \approx$ 7.0, 3.7 Hz, 1 H, 6′-H), 2.72 (ddd, $J_{6',6'}$ = 13.7, $J_{6',5'} \approx$ 7.6, 3.6 Hz, 1 H, 6′-H), 2.90 (m, 1 H, 4-H), 2.99 (ddd, $J_{2',3} \approx$ 9.7, $J_{2',3'}$ = 6.2, 3.5 Hz, 1 H, 2′-H), 3.34 (t, $J_{3,2'} \approx J_{3,4} \approx$ 10.4 Hz, 1 H, 3-H), 3.70 (d, J = 13.7 Hz, 1 H, CH_2Ph), 3.80 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.10 (ddd, $J_{7,7}$ = 13.1, $J_{7,6} \approx$ 4.1, 2.3 Hz, 1 H, 7-H), 4.57 (t, $J_{7,7} = J_{7,6}$ = 12.2 Hz, 1 H, 7-H), 5.30 (m, 1 H, 5-H), 7.27 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 19.9 (C-5′), 21.1 (CH_3CO_2), 22.7 (C-4′), 23.5 (C-3′), 29.5 (C-4), 33.5 (C-6), 37.1 (C-3), 47.6 (C-6′), 54.8 (CH_2Ph), 58.1 (C-2′), 62.5 (C-7), 68.3 (C-5), 126.8/128.28/128.34/139.8 (Ph), 169.6 (CH$_3$CO_2), 176.2 (C-2) ppm. EIMS: m/z = 174 (100), 91 (70), 43 (15). $C_{20}H_{27}NO_4$ (345.43) calcd. C 69.53, H 7.88, N 4.06; found C 69.50, H 7.90, N 4.29.

3-(*N*-Benzylpyrrolidin-2-yl)-6,7-dihydro-2(5*H*)-oxepinone (50): Following the general procedure described above, treatment of **44** (100 mg of crude material) with Bu$_3$SnH (190 μL, 0.71 mmol) furnished an oil (291 mg). Flash chromatography of this material (eluent: hexane; then hexane/EtOAc, 1:1; then EtOAc) allowed the separation of most of the impurities. The fraction containing the product was dissolved in CHCl$_3$ and extracted with 10% aqueous HCl. The aqueous phase was basified with 30% aqueous NH$_3$ and then extracted with CHCl$_3$, furnishing **50** (23 mg, 0.08 mmol, 49% yield). IR (film): $\tilde{\nu}$ = 3065, 3030, 2959, 2868, 2791, 1722, 1462, 1398, 1356, 1321, 1279, 1223, 1173, 1103, 1068, 1040 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.71 (m, 3 H), 1.90 (m, 1 H), 2.00 (m, 1 H), 2.20 (m, 2 H), 2.36 (m, 2 H), 3.02 (ddd, $J_{5',5'}$ = 11.1, $J_{5',4'}$ = 7.3, 2.1 Hz, 1 H, 5′-H), 3.27 (d, J = 13.5 Hz, 1 H, CH_2Ph), 3.39 (br. t, $J_{2',3'}$ = 7.5 Hz, 1 H, 2′-H), 3.90 (d, J = 13.5 Hz, 1 H, CH_2Ph), 4.12 (m, 2 H, 7,7-H), 6.66 (td, $J_{4,5}$ = 6.5, J = 0.9 Hz, 1 H, 4-H), 7.25 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 22.8/24.2/26.5/33.3 (C-5/C-6/ C-3′/C-4′), 53.8 (C-5′), 58.8 (CH_2Ph), 65.8 (C-2′), 66.1 (C-7), 126.8/128.2/128.4 (Ph), 133.5 (C-4), 137.0/139.8 (C-3/Ph), 171.7 (C-2) ppm. EIMS: m/z = 272 (3) [M +1]$^+$, 271 (2) [M]$^+$, 180 (97), 160 (31), 91 (100). $C_{17}H_{21}NO_2$ (271.35) calcd. C 75.25, H 7.80, N 5.16; found C 75.19, H 7.90, N 5.03.

Reduction of 45: Following the general procedure described above, treatment of **45** (194 mg of crude material) with Bu$_3$SnH (940 μL, 3.39 mmol) furnished an oil (98 mg), which was purified by flash chromatography (eluent: hexane/EtOAc, 2:1) affording the following fractions: (5*RS*)-5-acetoxy-3-[(2*SR*)-*N*-benzylpyrrolidin-2-yl]-6,7-dihydro-2(5*H*)-oxepinone (**51**) (15 mg, 0.05 mmol, 19% yield for the two steps), (3*RS*,5*SR*)-5-acetoxy-3-[(2*SR*)-*N*-benzylpyrrolidin-

2-yl]oxepan-2-one (**48**) (7 mg, 0.02 mmol, 9% yield for the two steps), a mixture of **48** and **51** (6 mg), and **37** (17 mg, 0.05 mmol, 20% recovering).

51: ^{1}H NMR (250 MHz): δ = 1.67 (m, 2 H, 3′,4′-H), 1.92 (ddt, $J_{6,6}$ = 15.4, J = 6.6, 4.4 Hz, 1 H, 6-H), 2.00−2.30 (m, 3 H, 3′,4′,5′-H), 2.02 (s, 3 H, CH_3CO_2), 2.45 (m, 1 H, 6-H), 3.03 (ddd, $J_{5',5'} \approx$ 9.0, $J_{5',4'} \approx$ 6.2, 2.2 Hz, 1 H, 5′-H), 3.30 (d, J = 13.2 Hz, 1 H, CH_2Ph), 3.46 (dd, $J_{2',3'}$ = 8.8, 5.9 Hz, 1 H, 2′-H), 3.82 (d, J = 13.2 Hz, 1 H, CH_2Ph), 4.10 (m, 2 H, 7,7-H), 5.49 (m, 1 H, 5-H), 6.55 (d, $J_{4,5}$ = 4.4 Hz, 1 H, 4-H), 7.24 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 20.9 (CH_3CO_2), 23.0 (C-4′), 32.9/33.1 (C-6/C-3′), 53.9 (C-5′), 59.0 (CH_2Ph), 64.1/65.6 (C-7/C-2′), 69.2 (C-5), 126.9/128.2/128.7 (Ar), 133.4/136.3/139.4 (C-3/C-4/Ar), 169.9 (CH_3CO_2 and C-2) ppm. EIMS: m/z = 270 (7) [M − AcO]$^+$, 238 (27), 160 (27), 91 (100). $C_{19}H_{23}NO_4$ (329.39) calcd. C 69.27, H 7.04, N 4.25; found C 69.23, H 7.12, N 4.32.

48: Oil. IR (film): $\tilde{\nu}$ = 3072, 3032, 2959, 2924, 2875, 2861, 2798, 1736, 1370, 1244, 1159, 1061 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.60 (m, 2 H), 1.74 (m, 2 H), 1.92 (ddt, $J_{6,6} \approx$ 16.2, $J_{6,7} \approx$ 11.3, $J_{6,7} \approx J_{6,5} \approx$ 2.4 Hz, 1 H, 6-H), 2.00−2.10 (m, 2 H), 2.08 (s, 3 H, CH_3CO_2), 2.36 (m, 1 H), 2.48 (m, 1 H, 4-H), 2.88 (m, 2 H, 5′,5′-H), 3.03 (td, $J \approx$ 7.6, 4.3 Hz, 1 H, 2′-H), 3.58 (d, J = 13.4 Hz, 1 H, CH_2Ph), 3.80 (d, J = 13.4 Hz, 1 H, CH_2Ph), 4.04 (ddd, $J_{7,7} \approx$ 12.8, $J_{7,6} \approx$ 4.6, 2.4 Hz, 1 H, 7-H), 4.36 (dd, $J_{7,7} \approx$ 12.2, $J_{7,6} \approx$ 11.6 Hz, 1 H, 7-H), 5.22 (m, 1 H, 5-H), 7.20−7.32 (m, 5 H, Ar) ppm. ^{13}C NMR (62.5 MHz): δ = 21.2 (CH_3CO_2), 23.5 (C-4′), 30.3/30.4/33.4 (C-4/C-6/C-3′), 40.8 (C-3), 54.4 (C-5′), 61.3 (CH_2Ph), 62.3 (C-2′), 64.9 (C-7), 68.3 (C-5), 126.8/128.2/128.4/140.5 (Ph), 169.7 (CH_3CO_2), 176.2 (C-2) ppm. EIMS: m/z = 240 (1) [M − Bn]$^+$, 160 (62), 91 (100), 43 (20).

(3*RS*)-3-[(2*SR*)-Piperidin-2-yl]oxepan-2-one (52). General Procedure for *N*-Debenzylation: 20% $Pd(OH)_2$ (20 mg) was added to a solution of **46** (21 mg, 0.07 mmol) in MeOH (10 mL), and the mixture was submitted to a hydrogen pressure of 30 psi at room temperature. After 45 h of reaction, the mixture was filtered through Celite®, the solvent was evaporated under vacuum and the oily residue (23 mg) was purified by flash chromatography (eluent: $CHCl_3$/MeOH, 9:1) affording **52** (13 mg, 0.07 mmol, 93% yield): IR (film): $\tilde{\nu}$ = 3500−2300 (br), 3205, 2945, 2868, 2713, 2579, 2495, 2404, 1722, 1173 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.45 (m, 1 H, 4′-H), 1.56 (m, 1 H, 4-H), 1.72 (m, 2 H), 1.87 (m, 2 H, 3′,5′-H), 1.95 (m, 3 H, 6,4′,5′-H), 2.05 (m, 3 H), 2.92 (td, $J_{6'ax,6'eq} \approx J_{6'ax,5'ax} \approx$ 13.1, $J_{6'ax,5'eq} \approx$ 3.3 Hz, 1 H, 6′ax-H), 3.23 (ddd, $J \approx$ 12.2, 4.9, 2.7 Hz, 1 H, 2′-H), 3.62 (m, 1 H, 6′eq-H), 3.65 (m, 1 H, 3-H), 4.29 (dd, $J_{7,7} \approx$ 13.3, $J_{7,6} \approx$ 4.9 Hz, 1 H, 7-H), 4.39 (dd, $J_{7,7} \approx$ 12.8, $J_{7,6} \approx$ 10.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.4 (C-5′), 22.8 (C-4′), 24.5 (C-3′), 26.2/27.5/28.2 (C-4/C-5/C-6), 44.3 (C-3), 45.8 (C-6′), 59.2 (C-2′), 69.6 (C-7), 176.0 (C-2) ppm. EIMS: m/z = 197 (1) [M]$^+$, 154 (11), 84 (100).

(3*RS*,5*SR*)-5-Acetoxy-3-[(2*SR*)-piperidin-2-yl]oxepan-2-one (53): Following the same procedure described for hydrogenolysis of **46**, hydrogenolysis of **47** (37 mg, 0.11 mmol) furnished **53** (26 mg, 0.10 mmol, 96% yield): IR (film): $\tilde{\nu}$ = 3500−2400 (br), 3206, 3149, 2938, 2868, 2706, 2573, 2502, 1729, 1377, 1244, 1230, 1173, 1061 cm^{-1}. ^{1}H NMR (400 MHz): δ = 1.47 (m, 1 H, 4′-H), 1.72 (m, 1 H, 3′-H), 1.86−2.21 (m, 8 H, 4,4,6,6,3′,4′,5′,5′-H), 2.17 (s, 3 H, CH_3CO_2), 2.95 (td, $J_{6'ax,6'eq} \approx J_{6'ax,5'ax} \approx$ 12.8, $J_{6'ax,5'eq} \approx$ 4.3 Hz, 1 H, 6′ax-H), 3.18 (dt, $J_{2',3'}$ = 12.8, $J_{2',3} \approx J_{2',3'} \approx$ 2.4 Hz, 1 H, 2′-H), 3.61 (m, 1 H, 6′eq-H), 4.16 (m, 1 H, 3-H), 4.20 (ddd, $J_{7,7}$ = 13.4, $J_{7,6} \approx$ 4.0, 2.7 Hz, 1 H, 7-H), 4.71 (t, $J_{7,7} \approx J_{7,6} \approx$ 12.1 Hz, 1 H, 7-H), 5.25 (m, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 21.4 (CH_3CO_2), 22.2 (C-5′), 22.7 (C-4′), 24.0 (C-3′), 30.1 (C-4), 32.8 (C-6), 37.6 (C-3), 46.0 (C-6′), 59.0 (C-2′), 63.8 (C-7), 67.2 (C-5), 170.3 (CH_3CO_2), 175.6 (C-2) ppm.

Methyl (*E*)-6-Mesyloxyhex-2-enoate (54): A solution of methyl (*E*)-6-hydroxyhex-2-enoate[16] (400 mg, 2.78 mmol) in CH_2Cl_2 (65 mL) was added dropwise to a stirred solution of MsCl (1.7 mL, 22.0 mmol) in pyridine (6.5 mL) at 0 °C under nitrogen. After the addition (1.5 h), the mixture was stirred at room temperature for 20 h. Then the solution was washed with portions of 10% aqueous HCl (until the aqueous solution maintained an acidic pH) and with brine. The organic phase was dried and the solvent removed under vacuum. Purification of the remaining oil by flash chromatography (eluent: hexane/EtOAc, 1:1) furnished **54** (560 mg, 2.52 mmol, 91% yield) as a white solid. M.p. 30−31 °C. IR (film): $\tilde{\nu}$ = 3030, 2952, 2854, 1722, 1659, 1441, 1356, 1279, 1209, 1173 cm^{-1}. ^{1}H NMR (250 MHz): δ = 1.87 (qn, J = 6.9 Hz, 2 H, 5,5-H), 2.29 (q, J = 6.9 Hz, 2 H, 4,4-H), 2.96 (s, 3 H, CH_3SO_2), 3.67 (s, 3 H, CH_3O), 4.18 (t, J = 6.2 Hz, 2 H, 6,6-H), 5.82 (d, J = 15.5 Hz, 1 H, 2-H), 6.87 (dt, J = 15.5, 6.9 Hz, 1 H, 3-H) ppm. ^{13}C NMR (62.5 MHz): δ = 27.4/27.9 (C-4/C-5), 37.3 (CH_3SO_2), 51.4 (CH_3O), 68.6 (C-6), 122.1 (C-2), 146.7 (C-3), 166.6 (C-1) ppm. EIMS: m/z = 233 (1) [M +1]$^+$, 191 (12), 111 (71), 98 (79), 95 (35), 94 (43), 79 (37), 67 (100). $C_8H_{14}SO_5$ (222.26) calcd. C 43.23, H 6.35, S 14.40; found C 43.34, H 6.33, S 14.30.

Methyl (5*RS*,6*SR*,7*RS*)-5-Hydroxy-1-azabicyclo[5.3.0]decane-6-carboxylate (57): A stirred solution of ester **54** (541 mg, 2.44 mmol) and nitrone **55**[4b,15] (475 mg, 5.59 mmol) in $CHCl_3$ (10 mL) was heated at the reflux temperature for 24 h. The solvent was removed under vacuum and the formation of the expected mesylate **56** was confirmed by ^{1}H NMR analysis of the residue: (250 MHz, $CDCl_3$): δ = 2.16−2.51 (m, 8 H), 2.73 (s, 3 H), 3.72 (m, 3 H), 3.75 (s, 3 H), 4.16 (m, 1 H), 4.79 (dd, J = 12.4, 5.5 Hz, 1 H), 5.23 (br. s, 1 H), 5.79 (td, J = 9.7, 4.8 Hz, 1 H) ppm. Activated zinc powder (6.00 g, 91.74 mmol) was added to a solution of this residue in 10% aqueous HCl (40 mL) and the mixture was sonicated for 40 min. The mixture was then filtered, the solid washed with 10% aqueous HCl and water and the solution brought to pH 9−10 by addition of 30% aqueous NH_3. A white solid appeared which was filtered under vacuum. The solution was then extracted with $CHCl_3$ (5 × 50 mL), the combined organic extracts were dried and the solution was concentrated to furnish an oily material (717 mg). Purification by flash chromatography (eluent: $CHCl_3$/MeOH, 9:1) furnished **57** (430 mg, 2.02 mmol, 83% yield) as an oil. B.p. 80 °C (oven)/0.08 Torr. IR (film): $\tilde{\nu}$ = 3381 (br), 2931, 2875, 2798, 2748, 1743, 1440, 1201, 1159, 1096, 1054 cm^{-1}. ^{1}H NMR (250 MHz): δ = 1.50−1.70 (m, 3 H, 3,3,8-H), 1.70−2.02 (m, 4 H, 4,8,9,9-H), 2.17 (m, 1 H, 4-H), 2.37 (m, 2 H, 2,10-H), 2.84 (dd, $J_{6,7}$ = 5.9, $J_{6,5}$ = 2.7 Hz, 1 H, 6-H), 2.91−3.10 (m, 3 H, 2,7,10-H), 3.69 (s, 3 H, CH_3O), 4.18 (dt, $J_{5,4} \approx$ 7.5, $J_{5,4} \approx J_{5,6} \approx$ 2.4 Hz, 1 H, 5-H)ppm. ^{13}C NMR (62.5 MHz): δ = 22.8/24.1 (C-3/C-9), 30.0/33.9 (C-4/C-8), 51.3 (CH_3O), 52.0 (C-6), 53.6/56.5 (C-2/C-10), 62.7 (C-7), 71.5 (C-5), 173.3 (CO_2Me) ppm. EIMS: m/z = 214 (12) [M +1]$^+$, 213 (15) [M]$^+$, 196 (13), 154 (8), 110 (36), 97 (34), 96 (30), 84 (43), 83 (100), 70 (32). $C_{11}H_{19}NO_3$ (213.27) calcd. C 61.93, H 8.98, N 6.57; found C 61.87, H 9.07, N 6.55.

Methyl 1-Azabicyclo[5.3.0]dec-5-ene-6-carboxylate (58): A solution of **57** (45 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (200 μL) was added dropwise to a stirred solution of MsCl (17 μL, 0.22 mmol) in CH_2Cl_2 (50 μL) at 0 °C under nitrogen. The cooling bath was removed and the reaction mixture stirred at room temperature for 5 h. The reaction mixture was then poured into a saturated aqueous $NaHCO_3$ solution at 0 °C, the product was extracted with CH_2Cl_2,

and the organic extracts were dried. The solvent was removed under vacuum and the formation of the expected mesylate (51 mg, 0.18 mmol, 84% yield) was confirmed by ^{1}H NMR analysis of the residue (250 MHz, $CDCl_3$): δ = 1.50−1.80 (m, 4 H), 2.00 (m, 4 H), 2.37 (m, 1 H), 2.51 (m, 1 H), 2.99 (s, 3 H), 2.90−3.20 (m, 4 H), 3.68 (s, 3 H), 4.75 (m, 1 H) ppm. Potassium *tert*-butoxide (18 mg, 0.16 mmol) was added to a stirred solution of the crude mesylate (48 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) and the mixture was heated at the reflux temperature for 3 h. Water was then added, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried and the solvent evaporated under vacuum to furnish a residue (31 mg), which was purified by flash chromatography (eluent: EtOAc), affording **58** (24 mg, 0.12 mmol, 75% yield): ^{1}H NMR (250 MHz): δ = 1.45−1.95 (m, 5 H, 3,3,8,9,9-H), 2.10 (m, 1 H, 4-H), 2.37 (m, 3 H, 2,8,10-H), 2.66 (m, 1 H, 4-H), 3.16 (m, 2 H, 2,10-H), 3.44 (m, 1 H, 7-H), 3.67 (s, 3 H, CH_3O), 6.85 (ddd, J = 8.6, 3.7, 1.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.0/25.0/26.0 (C-3/C-8/C-9), 33.1 (C-4), 51.3 (CH_3O), 53.4/56.8 (C-2/C-10), 64.2 (C-7), 135.9 (C-6), 142.0 (C-5), 168.4 (CO_2Me) ppm. EIMS: m/z = 195 (33) $[M]^+$, 180 (73), 136 (100), 108 (31), 96 (42), 80 (26), 55 (24), 41 (25). HRMS (EI, 70 eV, $C_{11}H_{17}NO_2$): calcd. 195.1259; found 195.1257.

(*E*)-7-Chlorohept-3-en-2-one (59): A solution of 4-chlorobutanol (3.00 g, 27.7 mmol) in anhydrous CH_2Cl_2 (9 mL) was added dropwise to a stirred suspension of pyridinium chlorochromate (7.30 g, 33.2 mmol) in anhydrous CH_2Cl_2 (72 mL) at room temperature under nitrogen. After the addition was complete, reaction progress was monitored by TLC analysis (eluent: hexane/Et_2O, 1:1). When all the starting alcohol had been consumed (5 h), diethyl ether was added (200 mL) and stirring was continued for 10 min. The liquid phase was decanted and the remaining solid washed with Et_2O (2 × 100 mL). The combined organic fractions were filtered, the solution was concentrated under vacuum (to about 80 mL) and then filtered again through Celite®. The filtrate was transferred to a reaction vessel and 1-(triphenylphosphoranylidene)propan-2-one (13.20 g, 41.5 mmol) was added during a 1 h period, while stirring. The mixture was then stirred at room temperature overnight. Then the solvent was removed under vacuum and the remaining solid was washed with a copious amount of a warm mixture of hexane and EtO_2 (1:1). The resulting extracts were filtered and the solvent removed under vacuum, affording a yellowish oil (6.80 g), which furnished **59**[17] (2.34 g, 12.9 mmol, 58%) following purification by flash chromatography (eluent: hexane/diethyl ether, 2:1).

(5*RS*,6*RS*,7*RS*)-5-Hydroxy-1-azabicyclo[5.3.0]dec-6-yl Methyl Ketone (61): A stirred solution of ketone **59** (830 mg, 5.66 mmol) and nitrone **55**[4b,15] (720 mg, 8.47 mmol) in $CHCl_3$ (30 mL) was heated at reflux for 48 h. Removal of the solvent under vacuum rendered a brown oil (1.98 g) to which water (10 mL) and diethyl ether (10 mL) were added. The layers were separated, the organic phase was dried and the solvent removed under vacuum, affording an oily residue (343 mg). Purification of this material by flash chromatography (eluent: hexane/EtOAc, 1:1) furnished the following fractions: unchanged **59** (143 mg, 0.98 mmol, 17% recovery); (2*RS*,3*RS*,3a*RS*)-3-(3-chloropropyl)hexahydropyrrolo[1,2-*b*]-isoxazol-2-yl methyl ketone (**64**) (71 mg, 0.31 mmol, 5% yield, 7% over unrecovered **59**); and (2*RS*,3*SR*,3a*SR*)-2-(3-chloropropyl)-hexahydropyrrolo[1,2-*b*]isoxazol-3-yl methyl ketone (**65**) (54 mg, 0.23 mmol, 4% yield, 5% over unrecovered **59**). The aqueous phase was poured into a reaction vessel, 10% aqueous HCl (128 mL) and activated zinc powder (18.6 g, 0.28 mol) were added, and the mixture was sonicated for 45 min. The mixture was then filtered, the solid washed with 10% aqueous HCl and water, the solution brought to pH 9−10 by addition of 30% aqueous NH_3, and extracted with $CHCl_3$ (5 × 100 mL). The combined organic extracts were dried and the solution was concentrated to furnish an oily residue (950 mg). This material was dissolved in MeOH (5 mL) and sodium methoxide (26 mg, 0.50 mmol) was added. The mixture was heated at reflux for 2.5 h. The methanol was evaporated under vacuum, the remaining oil was redissolved in $CHCl_3$ and the solution washed with saturated aqueous $NaHCO_3$ (2 × 2 mL). The organic phase was dried and the solvent removed, affording a residue (820 mg), which furnished a by-product identified as (11-oxa-2-azatricyclo[6.2.1.0^{2,6}]undec-7-yl) methyl ketone (**66**) (45 mg, 0.23 mmol, 4% yield, 5% over unrecovered **59**) and **61** (588 mg, 2.99 mmol, 53% yield, 64% over unrecovered **59**) following separation by flash chromatography (eluent: EtOAc/30% aqueous NH_3, 99:1).

61: IR (film): $\tilde{\nu}$ = 3381 (br), 3022, 2938, 2818, 1707, 1440, 1356, 1215 cm^{-1}. ^{1}H NMR (250 MHz): δ = 1.37 (m, 1 H, 8-H), 1.49 (m, 1 H, 3-H), 1.66 (m, 3 H, 4,9,9-H), 1.95 (m, 3 H, 3,4,8-H), 2.17 (s, 3 H, CH_3CO), 2.34 (m, 2 H, 2,10-H), 2.82 (dd, $J_{6,7}$ = 9.1, $J_{6,5}$ = 4.2 Hz, 1 H, 6-H), 3.01 (m, 3 H, 2,7,10-H), 4.08 (ddd, $J_{5,4}$ = 7.7, $J_{5,6}$ = 4.2, $J_{5,4}$ = 1.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.6/23.4 (C-3/C-9), 31.00/32.6 (C-4/C-8), 31.05 (CH_3CO), 55.7/56.9 (C-2/C-10), 63.5/66.1 (C-6/C-7), 71.3 (C-5), 209.5 (CH_3CO) ppm. EIMS: m/z = 197 (9) $[M]^+$, 180 (9), 154 (18), 110 (34), 83 (100). HRMS (EI, 70 eV, $C_{11}H_{19}NO_2$): calcd. 197.1416; found 197.1412.

64: ^{1}H NMR (250 MHz): δ = 1.45−2.10 (m, 8 H, 4,4,5,5,1′,1′,2′,2′-H), 2.15 (s, 3 H, CH_3CO), 2.18 (m, 1 H, 3-H), 2.89 (ddd, $J_{6,6}$ = 13.9, $J_{6,5}$ = 8.8, 7.1 Hz, 1 H, 6-H), 3.25−3.40 (m, 2 H, 3a,6-H), 3.48 (br. t, $J \approx$ 5.9 Hz, 2 H, 3′,3′-H), 3.91 (d, $J_{2,3}$ = 8.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR (62.5 MHz): δ = 23.7/30.3/30.7/31.4 (C-4/C-5/C-1′/C-2′), 26.2 (CH_3CO), 44.5 (C-3′), 53.1 (C-3), 56.6 (C-6), 72.0 (C-3a), 88.0 (C-2), 206.9 (CH_3CO) ppm. EIMS: m/z = 234−232 (19−60) $[M+1]^+$, 233−231 (15−25) $[M]^+$, 196 (4), 190−188 (7−14), 162−160 (14−42), 124 (23), 96 (31), 86 (28), 85 (65), 70 (72), 68 (39), 55 (52), 43 (100). HRMS (EI, 70 eV, $C_{11}H_{18}ClNO_2$): calcd. 231.1026; found 231.1029.

65: ^{1}H NMR (250 MHz): δ = 1.50−2.00 (m, 8 H, 4,4,5,5,1′,1′,2′,2′-H), 2.21 (s, 3 H, CH_3CO), 2.75 (dd, $J_{3,2}$ = 8.3, $J_{3,3a}$ = 5.0 Hz, 1 H, 3-H), 2.86 (m, 1 H, 6-H), 3.33 (m, 1 H, 6-H), 3.53 (m, 2 H, 3′,3′-H), 3.78 (dt, $J_{3a,4}$ = 8.2, $J_{3a,3} \approx J_{3a,4} \approx$ 5.0 Hz, 1 H, 3a-H), 4.03 (dt, $J_{2,3}$ = 8.3, $J_{2,1'}$ = 3.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (62.5 MHz): δ = 23.9/29.2/30.3/32.1 (C-4/C-5/C-1′/C-2′), 29.4 (CH_3CO), 44.7 (C-3′), 56.7 (C-6), 68.8/69.2 (C-3/C-3a), 79.1 (C-2), 206.1 (CH_3CO) ppm. EIMS: m/z = 234−232 (8−23) $[M+1]^+$, 233−231 (7−11) $[M]^+$, 112 (15), 110 (26), 86 (78), 85 (100), 55 (55), 43 (90).

66: ^{1}H NMR (250 MHz): δ = 1.22 (m, 1 H), 1.70−2.10 (m, 7 H), 2.09 (s, 3 H, CH_3CO), 2.84 (m, 2 H, 3,7-H), 3.07 (q, J = 8.8 Hz, 1 H, 3-H), 3.61 (br. t, $J \approx$ 8.8 Hz, 1 H, 6-H), 4.57 (m, 1 H, 8-H), 4.96 (d, $J_{1,10}$ = 6.6 Hz, 1 H, 1-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.6/23.7/29.6/29.8 (C-4/C-5/C-9/C-10), 30.0 (CH_3CO), 47.7 (C-3), 50.8 (C-7), 54.9 (C-6), 74.9 (C-8), 88.4 (C-1), 207.7 (CH_3CO) ppm. EIMS: m/z = 195 (10) $[M]^+$, 152 (100), 124 (43), 110 (60), 96 (79), 83 (85), 70 (97), 55 (42), 43 (40), 41 (45).

Preparation of 61 from 7: a) A solution of MeLi (1.5 M in diethyl ether, 2.8 mL, 4.2 mmol) was added to a stirred solution of **7** (686 mg, 3.48 mmol) in anhydrous THF (70 mL) at −100 °C, under nitrogen and the mixture was stirred at the same temperature for 2 h. The solution was then poured carefully into a saturated aque-

ous solution of NH_4Cl (100 mL) at 0 °C, with vigorous stirring. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were dried and the solvent evaporated under vacuum. Purification of the residue by flash chromatography (eluent: EtOAc) furnished the following fractions: unchanged **7** (76 mg, 0.39 mmol, 11% recovery), (2*RS*,3*RS*,3a*RS*)-2-(3-hydroxypropyl)hexahydropyrrolo[1,2-*b*]isoxazol-3-yl methyl ketone (**67**) (422 mg, 1.98 mmol, 57% yield, 64% over unrecovered **7**), a 1:1.25 mixture (150 mg) of **67** and 3-[(2*RS*,3*RS*,3a*RS*)3-(1-hydroxy-1-methylethyl)hexahydropyrrolo[1,2-*b*]isoxazol-2-yl]propan-1-ol (**69**).

67: IR (film): $\tilde{\nu}$ = 3423 (br), 2966, 2931, 2875, 1714, 1595, 1525, 1426, 1356, 1046 cm^{-1}. ^1H NMR (250 MHz): δ = 1.30−2.10 (m, 8 H, 4,4,5,5,1′,1′,2′,2′-H), 2.20 (s, 3 H, CH_3CO), 2.84 (br. s, 1 H, OH), 3.11 (m, 3 H, 3,6,6-H), 3.64 (m, 2 H, 3′,3′-H), 4.06 (dt, $J_{3a,3}$ = 7.3, $J_{3a,4}$ = 5.1 Hz, 1 H, 3a-H), 4.28 (m, 1 H, 2-H) ppm. ^{13}C NMR (62.5 MHz): δ = 23.8 (C-2′), 25.7 (C-1′), 29.7 (C-5), 30.1 (*C*H_3CO), 31.7 (C-4), 57.1 (C-6), 62.1 (C-3′), 65.8 (C-3), 67.3 (C-3a), 78.2 (C-2), 205.8 (*C*OMe) ppm. EIMS: *m*/*z* = 214 (1) $[M+1]^+$, 213 (1) $[M]^+$, 196 (1), 86 (100), 85 (31), 70 (75).

69: IR (film): $\tilde{\nu}$ = 3620, 3402 (br), 2966, 2931, 2868, 1447, 1377, 1060, 1011 cm^{-1}. ^1H NMR (250 MHz): δ = 1.28 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.50−2.00 (m, 8 H, 1,1,2,2,4′,4′,5′,5′-H), 2.12 (t, $J_{3',2'} = J_{3',3a'}$ = 6.3 Hz, 1 H, 3′-H), 2.75 (br. s, 1 H, OH), 2.94 (m, 1 H, 6′-H), 3.15 (m, 1 H, 6′-H), 3.65 (m, 3 H, 3,3,3a′-H), 4.05 (ddd, $J_{2',1}$ = 9.2, $J_{2',3'}$ = 6.3, $J_{2',1}$ = 2.8 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (62.5 MHz): δ = 23.8 (C-2), 26.0 (C-1), 29.5 (CH_3), 29.9 (C-5′), 30.3 (CH_3), 33.5 (C-4′), 56.8 (C-6′), 62.4 (C-3), 63.8/65.4 (C-3′/C-3a′), 70.5 (Me_2*C*OH), 80.0 (C-2′) ppm. EIMS: *m*/*z* = 230 (1) $[M+1]^+$, 229 (2) $[M]^+$, 86 (100), 70 (69).

b) A solution of **67** (348 mg, 1.63 mmol) in anhydrous CH_2Cl_2 (45 mL) was slowly added to a solution of mesyl chloride (640 μL, 8.21 mmol) in pyridine (4 mL) at 0 °C, under nitrogen. After addition was complete, the cooling bath was removed and the mixture stirred at room temperature for 6 h. Then the solvent was evaporated under vacuum, the remaining oil was redissolved in 10% aqueous HCl (37 mL), activated zinc powder (5.39 g, 82.4 mmol) was added, and the mixture was sonicated for 45 min. Then the mixture was filtered, the solid washed with 10% aqueous HCl and water and the solution brought to pH 9−10 by addition of 30% aqueous NH_3. This solution was extracted with $CHCl_3$ (5 × 50 mL) and the combined organic extracts were dried, then concentrated to furnish an oily residue (378 mg). Purification of this material by flash chromatography (eluent: EtOAc/30% aqueous NH_3, 99:1) furnished **61** (300 mg, 1.52 mmol, 93% yield).

1-Azabicyclo[5.3.0]dec-5-en-6-yl Methyl Ketone (62): A solution of **61** (110 mg, 0.56 mmol) in anhydrous CH_2Cl_2 (250 μL) was added dropwise to a solution of mesyl chloride (46 μL, 0.59 mmol) in anhydrous CH_2Cl_2 (250 μL) at 0 °C, under nitrogen. The cooling bath was removed and the mixture was stirred at room temperature for 5 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ at 0 °C, the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 2 mL). The combined organic extracts were dried and the solvent evaporated under vacuum affording the expected mesylate (126 mg, 0.46 mmol, 82% yield), which was used in the next step without further purification. ^1H NMR (250 MHz): δ = 1.35−2.20 (m, 8 H), 2.18 (s, 3 H), 2.37 (m, 2 H), 2.81 (s, 3 H), 2.93 (m, 4 H), 4.76 (m, 1 H) ppm. Potassium *tert*-butoxide (24 mg, 0.21 mmol) was added to a solution of the crude mesylate (59 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at room temperature for 3 h. The reaction mixture was washed with water, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic extracts were dried and the solvent removed under vacuum affording a residue (38 mg), which furnished **62** (30 mg, 0.17 mmol, 79% yield) after purification by flash chromatography (eluent: $CHCl_3$/MeOH/30% aqueous NH_3, 9:1/0.1). ^1H NMR (250 MHz): δ = 1.40−1.90 (m, 5 H, 3,3,8,9,9-H), 2.04−2.50 (m, 4 H, 2,4,8,10-H), 2.24 (s, 3 H, CH_3), 2.77 (m, 1 H, 4-H), 3.05 (m, 2 H, 2,10-H), 3.37 (m, 1 H, 7-H), 6.77 (m, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.0/25.3/26.1 (C-3/C-8/C-9), 26.8 (CH_3), 33.0 (C-4), 53.3/56.7 (C-2/C-10), 64.1 (C-7), 142.0 (C-5), 147.5 (C-6), 200.8 (CH_3*C*O) ppm. Compound **62** is of low stability.

Methyl (2*RS*,3*RS*,3a*RS*)-2-(3-Hydroxypropyl)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (70): *p*-Toluenesulfonic acid (1.16 g, 6.10 mmol) was added to solution of **7** (400 mg, 2.03 mmol) in MeOH (40 mL) and the mixture was heated at the reflux temperature for 6 h. The cold solution was concentrated under vacuum, the residue was redissolved in CH_2Cl_2 (25 mL), and the solution washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, dried and the solvent removed, affording an oily residue (524 mg). Purification of this material by flash chromatography (eluent: EtOAc/MeOH, 9:1) rendered **70** (425 mg, 1.85 mmol, 91% yield): IR (film): $\tilde{\nu}$ = 3381 (br), 2952, 2875, 1736, 1440, 1377, 1286, 1201, 1166, 1061 cm^{-1}. ^1H NMR (400 MHz): δ = 1.44 (m, 1 H, 1′-H), 1.54−1.70 (m, 5 H, 4,5,1′,2′,2′-H), 1.83 (m, 1 H, 5-H), 1.95 (m, 1 H, 4-H), 2.82 (br. s, 1 H, OH), 3.03 (m, 3 H, 3,6,6-H), 3.59 (m, 2 H, 3′,3′-H), 3.66 (s, 3 H, CH_3O), 4.03 (dt, *J* = 8.5, 4.1 Hz, 1 H, 3a-H), 4.23 (ddd, *J* = 9.8, 6.9, 3.7 Hz, 1 H, 2-H) ppm. ^{13}C NMR (62.5 MHz): δ = 23.5 (C-2′), 25.8 (C-1′), 29.3 (C-5), 31.2 (C-4), 51.9 (CH_3O), 56.5 (C-6), 58.7 (C-3), 61.9 (C-3′), 66.6 (C-3a), 78.3 (C-2), 171.0 (*C*O_2Me) ppm. EIMS: *m*/*z* = 230 (1) $[M+1]^+$, 229 (1) $[M]^+$, 149 (18), 86 (100), 85 (30), 70 (68). HRMS (EI, 70 eV, $C_{11}H_{19}NO_4$): calcd. 229.1314; found 229.1310.

Methyl (5*RS*,6*RS*,7*RS*)-5-Hydroxy-1-azabicyclo[5.3.0]decane-6-carboxylate (72): A solution of **70** (425 mg, 1.85 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a stirred solution of MsCl (720 μL, 9.24 mmol) in pyridine (4.5 mL) under nitrogen and the mixture was stirred at room temperature for 6 h. Evaporation of the solvent under vacuum afforded the mesylate **71**: ^1H NMR (250 MHz): δ = 1.79−2.29 (m, 8 H), 2.80 (s, 3 H), 3.75 (s, 3 H), 3.84 (m, 3 H), 4.45 (m, 1 H), 4.80 (dd, *J* = 12.3, 5.5 Hz, 1 H), 5.08 (br. s, 1 H), 5.42 (br. t, *J* ≈ 7.1 Hz, 1 H) ppm. Activated zinc powder (6.07 g, 92.8 mmol) was added to a solution of this material in 10% aqueous HCl (42 mL) and the mixture was sonicated for 30 min. The the mixture was filtered, the solid washed with 10% aqueous HCl and water, and the solution brought to pH 9−10 by addition of 30% aqueous NH_3. A white solid appeared which was filtered under vacuum. Then the solution was extracted with $CHCl_3$ (5 × 35 mL), the combined organic extracts were dried, and the solution was concentrated affording an oily residue (533 mg). Purification of this oil by flash chromatography (eluent: EtOAc) furnished **72** (341 mg, 1.60 mmol, 86% yield) as an oil. B.p. 80 °C (oven)/0.06 Torr. IR (film): $\tilde{\nu}$ = 3402 (br), 2945, 2875, 2812, 1736, 1440, 1342, 1314, 1258, 1208, 1159, 1096 cm^{-1}. ^1H NMR (400 MHz): δ = 1.55 (m, 2 H, 3,8-H), 1.76 (m, 3 H, 8,9,9-H), 1.98 (m, 3 H, 3,4,4-H), 2.40 (m, 2 H, 2,10-H), 2.67 (dd, $J_{6,7}$ = 9.1, $J_{6,5}$ = 5.0 Hz, 1 H, 6-H), 3.00 (m, 3 H, 2,7,10-H), 3.66 (s, 3 H, CH_3O), 4.09 (ddd, $J_{5,4}$ = 7.0, $J_{5,6}$ = 5.0, $J_{5,4}$ = 2.0 Hz, 1 H, 5-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.8/23.5 (C-3/C-9), 30.9/32.7 (C-4/C-8), 51.7 (CH_3O), 55.8/57.1 (C-2/C-10), 58.8 (C-6), 64.3 (C-7), 71.8 (C-5), 173.8 (*C*O_2Me) ppm. EIMS: *m*/*z* = 213 (14) $[M]^+$, 196 (20), 182 (14), 110 (50), 97 (47), 96 (41), 84 (50), 83 (100). HRMS (EI, 70 eV, $C_{11}H_{19}NO_3$): calcd. 213.1365; found 213.1364.

Methyl (5*RS*,6*RS*,7*RS*)-5-(Imidazol-2-ylthiocarbonyloxy)-1-azabicyclo[5.3.0]decane-6-carboxylate (73): TCDI (98 mg, 0.55 mmol) was added to a stirred solution of **73** (65 mg, 0.30 mmol) in anhydrous THF (6 mL) under nitrogen, and the mixture was stirred at room temperature overnight. Then, the solvent was evaporated under vacuum and the residue re-dissolved in $CHCl_3$ (3 mL). This solution was washed with water (2 × 2 mL), dried, and the solvent removed affording a crude material (135 mg) which was used in the next step without further purification. An analytical sample of **73** was obtained by flash chromatography of this material (eluent: EtOAc/MeOH, 9:1), followed by separation of the imidazole residues by crystallisation from EtOAc/pentane and a second chromatography of the remaining oil. IR (film): $\tilde{\nu}$ = 3128, 2938, 2868, 2805, 1736, 1469, 1391, 1328, 1286, 1237, 1159, 1096 cm^{-1}. ^1H NMR (400 MHz): δ = 1.67 (m, 3 H, 3,8,9-H), 1.81 (m, 1 H, 3-H), 1.92 (m, 2 H, 8,9-H), 2.15 (m, 2 H, 4,4-H), 2.47 (m, 2 H, 2,10-H), 2.82 (ddd, $J_{7,6}$ = 9.7, $J_{7,8} \approx$ 7.9, 6.5 Hz, 1 H, 7-H), 2.96 (t, $J_{6,7} = J_{6,5}$ = 9.7 Hz, 1 H, 6-H), 3.08 (m, 2 H, 2,10-H), 3.58 (s, 3 H, CH_3O), 5.69 (td, $J_{5,4} = J_{5,6}$ = 8.9, $J_{5,4}$ = 3.8 Hz, 1 H, 5-H), 6.95 (s, 1 H, Im-H), 7.53 (s, 1 H, Im-H), 8.24 (s, 1 H, Im-H) ppm. ^{13}C NMR (62.5 MHz): δ = 22.4/22.9 (C-3/C-9), 29.3/31.0 (C-4/C-8), 51.9 (CH_3O), 53.5/57.2 (C-2/C-10), 57.8 (C-6), 61.4 (C-7), 85.5 (C-5), 117.8/130.7/136.7 (Im), 172.6 (*C*O_2Me), 182.7 (C=S) ppm. EIMS: *m*/*z* = 196 (52) $[M - ImCSO]^+$, 195 (50), 180 (89), 139 (25), 136 (100), 134 (34), 108 (28), 96 (41), 83 (31), 82 (32). $C_{15}H_{21}N_3O_3S$ (323.41) calcd. C 55.71, H 6.54, N 12.99; found C 55.69, H 6.65, N 12.71.

Methyl (6*RS*,7*SR*)-1-Azabicyclo[5.3.0]decane-6-carboxylate (74): A solution of crude **73** (prepared from 115 mg, 0.54 mmol, of **72**) in anhydrous toluene (11 mL) was added to a solution of Bu_3SnH (580 μL, 2.16 mmol) and AIBN (13 mg, 0.08 mmol) in anhydrous toluene (4 mL) at 100 °C and the mixture was heated at this temperature for 30 min. The cold solution was extracted with 10% aqueous HCl (4 × 6 mL). The combined aqueous extracts were basified to pH 9−10 with 30% aqueous NH_3 and extracted with $CHCl_3$ (5 × 10 mL). These organic extracts were dried and the solvent evaporated under vacuum affording an oily residue (118 mg), which furnished **74** (71 mg, 0.36 mmol, 67% yield for the two steps) after purification by flash chromatography (eluent: EtOAc/MeOH, 9:1). IR (film): $\tilde{\nu}$ = 2931, 2868, 2798, 1736, 1441, 1321, 1258, 1202, 1159, 1103, 1068, 1026 cm^{-1}. ^1H NMR (250 MHz): δ = 1.50 (m, 1 H), 1.60−2.06 (m, 9 H), 2.37 (m, 3 H, 2,6,10-H), 2.70 (ddd, $J \approx$ 10.0, 8.4, 6.0 Hz, 1 H, 7-H), 3.02 (m, 2 H, 2,10-H), 3.64 (s, 3 H, CH_3O) ppm. ^{13}C NMR (62.5 MHz): δ = 23.1/23.9 (C-3/C-9), 29.2/30.6/32.0 (C-4/C-5/C-8), 51.3/52.2 (C-6/CH_3O), 55.4/57.9 (C-2/C-10), 66.0 (C-7), 176.2 (*C*O_2Me) ppm. EIMS: *m*/*z* = 197 (17) $[M]^+$, 110 (47), 97 (30), 96 (89), 83 (100). HRMS (EI, 70 eV, $C_{11}H_{18}NO_2$ $[M - 1]^+$): calcd. 196.1337; found 196.1329.

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