Enantioselective Vicinal Bis-Acylation of Olefins

Léon Ghosez,*[a, b] Florence Mahuteau-Betzer,[a] Christophe Genicot,[a] Adelina Vallribera,[a] and Jean-François Cordier[a]

Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday

Abstract: A two-step sequence for the asymmetric vicinal acylation of olefins by a [2+2+1] strategy is reported. The key reaction is a [2+2] cycloaddition of an olefin to a chiral keteniminium salt derived from *N*-tosylsarcosinamide. This is followed by a regioselective Baeyer–Villiger oxidation of the resulting cyclobutanone to yield a lactol derivative that is equivalent to the product of addition of a carboxyl and a carbonyl group to the olefin. *N*-Tosylsarcosinamides derived from prolinol methyl ether and 2,5-dimethylpyrrolidine gave the best yields and diastereoselectivities. Five- and six-membered cycloolefins only gave *cis* products as expected. With seven- and eight-membered rings and *cis* 1,2-disubstituted acyclic olefins, partial or complete epimerisation of the *cis* to the *trans* adducts was observed. Facial selectivities were generally good except for terminal olefins. The oxidation step proceeded in high yields to give crystalline compounds which could usually be obtained in enantiopure form by simple recrystallisation.

Keywords: acylation · asymmetric synthesis · chiral auxiliaries · cycloaddition · keteniminium salts

Introduction

Enantiomerically pure cyclopropane and cyclobutane derivatives are attractive carbocyclic building blocks for the stereocontrolled construction of complex carbon frameworks.[1] As a result of their high angle-strain, they readily undergo reactions involving cleavage of a carbon–carbon bond of the small ring. The value of this strain-assisted synthetic strategy obviously rests upon the development of practical routes towards enantiomerically pure polysubstituted cyclopropane and cyclobutane derivatives. Recent years have witnessed considerable interest in the development of efficient catalysts for asymmetric cyclopropanations.[2] On the contrary, catalytic asymmetric [2+2] cycloadditions are still few and limited in scope.[3] Therefore, asymmetric syntheses of cyclobutane derivatives rely upon the use of a chiral reactant. Thus, cyclobutane derivatives of high enantiomeric purities have been obtained from cycloadditions involving olefins carrying chiral substituents.[4]

The cycloaddition of an olefin to a ketene or a keteniminium salt can be regarded as the most successful reaction for the preparation of four-membered carbocyclic compounds. Reactions involving ketenes bearing a chiral substituent only led to poor or modest facial selectivities.[5] On the other hand, previous work from our laboratory demonstrated that [2+2] cycloadditions of olefins with 2,2-disubstituted keteniminium salts generated from *N*-acyl-(*S*)-prolinol methyl ether proceeded with high stereoselectivities.[6] Since then, inter- and intramolecular cycloadditions of in situ-generated keteniminium salts have been successfully used in asymmetric syntheses.[7]

These findings led us to design a two-step sequence that formally amounts to the regio- and stereoselective attachment of a carboxylic and a carbonyl group to an unactivated olefin (Scheme 1). To the best of our knowledge, such a transformation is unprecedented.

In this sequence the two new carbon–carbon bonds are formed in a cycloaddition step involving a keteniminium salt. This is followed by a regioselective insertion of an oxygen atom through a Baeyer–Villiger oxidation.[1e] The keteniminium reagent was selected on the basis of the following criteria: 1) the carbon–carbon double bond should carry an electron-donating group to secure an efficient control of the regiochemistry of the oxidation step and generate a masked aldehyde group in the final product, 2) it should carry an efficient chiral auxiliary which can be easily removed after the

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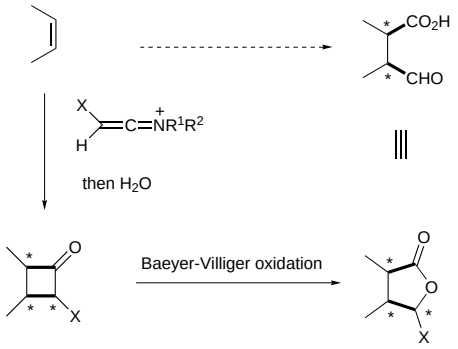
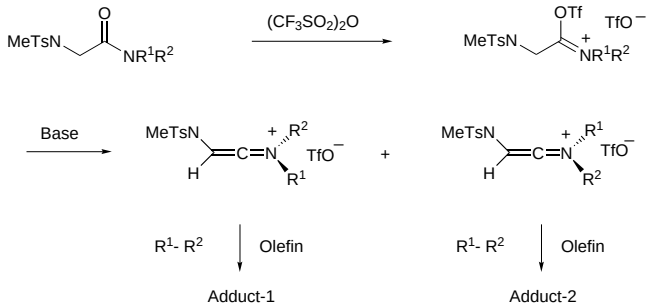


Scheme 1. Asymmetric vicinal bis-acylation of an olefin. X = electron-donating group; R^1, R^2 = chiral substituents.

cycloaddition step. Preliminary studies in the racemic series led to the selection of *N*-TsMe as the most practical group for fulfilment of the first requirement.[8] We now report full details of our studies related to the selection of the chiral reagent, and the preparative scope of this method for the asymmetric vicinal acylation of olefins.[9]

Results and Discussion

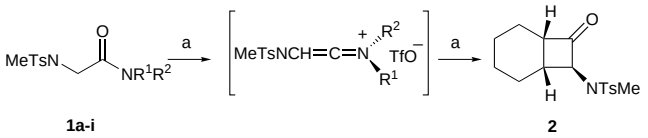
Selection of a chiral auxiliary: The in situ method of generation of keteniminium salts involves the treatment of *N*-tosylsarcosinamides with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (Scheme 2). Only one



R^1, R^2 = chiral groups

Scheme 2. The problem of diastereomeric keteniminium salts.

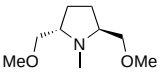
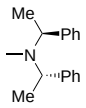
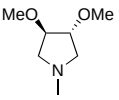
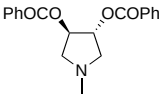
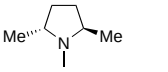
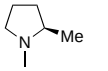
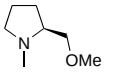
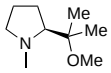
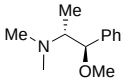
diastereomer can be formed if the chiral auxiliary has C_2 symmetry. On the other hand, chiral sarcosinamides without C_2 symmetry can lead to diastereomeric keteniminium salts that could react with different facial selectivities. We decided to examine the behaviour of a representative series of sarcosinamides **1a–i** derived from readily available enantiopure amines[10] in a model reaction with cyclohexene (Scheme 3, Table 1). Sarcosinamides **1a–i** were treated with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane or 1,2-dichloroethane containing a fourfold excess of cyclohexene. The crude adducts were hydrolyzed in a heterogeneous H_2O/CCl_4 mixture. Organic phases were subjected to flash chromatography, and all fractions containing bicyclo[4.2.0]octan-7-one (**2**) were combined and analysed



1a-i **2**

Scheme 3. Selection of a chiral auxiliary. a) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, cyclohexene then H_2O/CCl_4.

Table 1. Cycloadditions of cyclohexene with keteniminium salts derived from *N*-methyl-*N*-tosylsarcosinamides **1a–i**.

1	$-N(R^1)R^2$	Yield of **2** [%]	*ee* [%]	Remarks
a		0	–	decomposition products
b		0	–	decomposition products
c		80	42	
d		36	33	
e		81	93	
f		78	90	
g		70	92	
h		0	–	ester **3** (62%)
i		20	52	

by HPLC (Chiralpack AD) and/or ^1H NMR spectroscopy in the presence of $Eu(hbfc)_3$.

Since the formation of diastereomeric keteniminium salts could obviously be avoided by using a C_2-symmetric chiral auxiliary, we first examined a series of *N*-tosylsarcosinamide **1a–e** derived from C_2-symmetric enantiopure amines (Table 1). In contrast to earlier observations on related intramolecular cycloadditions,[7b] no cycloadduct was obtained from **1a**. A complex mixture was also formed from the sterically hindered amide **1b**. These failures illustrate a problem associated with the use of C_2-symmetric ligands or auxiliaries, that is the presence of a substituent on both diastereotopic faces leads to a decrease of reactivity with respect to the corresponding ligand or auxiliary lacking C_2 symmetry. Putting the substituents further away from the

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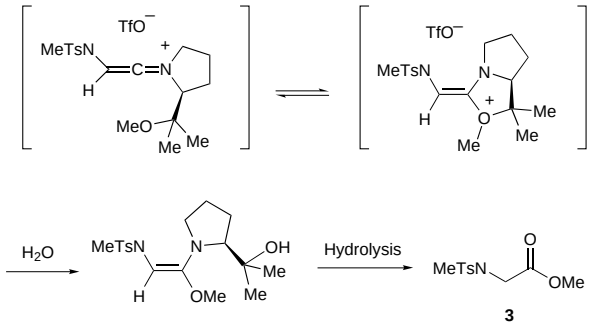
reacting centre (as in **1c–d**) restored the reactivity of the keteniminium salts. However, cycloaddition occurred with low enantiomeric excesses. The best compromise was reached by using sarcosinamide **1e** derived from 2,5-dimethylpyrrolidine. The corresponding keteniminium salt underwent cycloaddition to cyclohexene to give cyclobutanone **2** in excellent yield and with high enantiomeric purity.

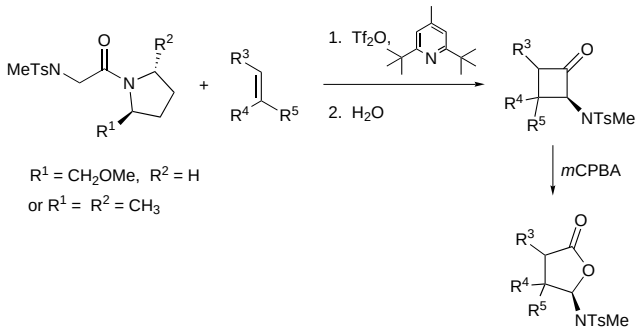
Unexpectedly excellent yields and high facial discrimination were observed from *N*-tosylsarcosinamides **1f–g** derived from 2-methylpyrrolidine and prolinol methyl ether which both lack C_2 symmetry. Increasing the size of the nitrogen substituent (such as in **1h**) was detrimental to the cycloaddition reaction and led to the formation of *N*-tosylsarcosine methyl ester (**3**). This can be explained by an intramolecular cyclisation favoured by the Thorpe–Ingold effect of the two methyl groups (Scheme 4). Sarcosinamide **1i** derived from an acyclic amine gave **2** in poor yields and low *ee*.



Scheme 4. Mechanism of formation of **3**.

Generalisation: To assess the versatility and scope of the cycloaddition reaction, we have examined the reaction of a wide variety of olefins with keteniminium salts generated from **1e** and **1g** (Scheme 5). The resulting cyclobutanones were oxidized to the corresponding lactones with *m*-CPBA. The ring expansion was totally regioselective in all cases, as expected from a sulfonamide substituent acting as an electron-releasing group. The results are summarised in Table 2.

Five- and six-membered cycloolefins (entries a–d) gave good yields of *cis-exo* cyclobutanones with high enantiomeric purities. Both chiral inductors gave similar results. To establish that the *exo* adduct was not produced by epimerisation of an initially formed *endo* adduct, **4-*exo*** was left with



Scheme 5. Sequence for the vicinal bis-acylation of an olefin.

triethylamine until the *exo*:*endo* ratio remained constant (Scheme 6). This experiment indicated that at equilibrium, the mixture still contained 25% of the *endo* isomer. Also, when the cycloaddition to cyclohexadiene was stopped after 10 minutes (instead of three hours), only the *exo* isomer was formed. This experimentally confirmed that the *exo* product was kinetically favoured.

With cycloheptene and *cis*-cyclooctene (Table 2), the cycloaddition reaction was accompanied by an inversion of configuration at the ring junction (*cis* → *trans*). Inversion was complete with the C_2-symmetric chiral auxiliary (entries e–f). With the derivatives of prolinol, the amount of inversion increased with ring size. Enantiomeric purities of both *cis*- and *trans*-cyclobutanones derived from cycloheptene were high with the two chiral auxiliaries. In the case of *cis*-cyclooctene, only the C_2-chiral auxiliary gave a high facial selectivity. The keteniminium salt derived from prolinol methyl ether reacted with moderate facial selectivities.

A similar inversion of configuration was observed in the cycloadditions of *cis*-butene and *cis*-β-methylstyrene. Here again, the C_2-symmetric chiral auxiliary led to practically complete inversion of configuration and high enantiomeric excesses of the *trans*-cyclobutanone. Interestingly, the reaction of *trans*-butene gave the *trans*-cyclobutanone of configuration opposite to that of the *trans* enantiomer obtained from *cis*-butene.

The prolinol-derived amide reacted with terminal olefins without facial discrimination. On the other hand, the C_2-symmetric chiral auxiliary gave a better, albeit moderate selectivity. The facial selectivity increased with the size of the substituent (Table 2, entry l versus entry k).

All cyclobutanones were converted in high yields into the corresponding lactones, which could be easily purified and enantiomerically enriched by recrystallisation. The absolute configuration of **17** was established by correlation with the previously reported enantiomerically pure corresponding lactone **27** (Scheme 7).[11] The configuration of the *trans* adduct resulting from the cycloaddition to *cis*-butene was correlated with that of the known diol **28**.[12] This allowed us to assign configurations for all cyclobutanones and lactols.

The above results can be explained on the basis of our present knowledge of the mechanism of the cycloaddition reaction. The absence of a lone pair on nitrogen in keteniminium salts suppresses the nucleophilicity at C-2 which accounts for the 1,2-dipolar character of ketenes and ketenimines (Scheme 8).[13]

FMO analysis led to a mechanistic scenario in which the keteniminium salt reacts with the olefin as a carbenoid (Scheme 9) to form a homoallylic carbocation ($HOMO_{olef}\cdots LUMO_{ket}$, strong interactions) stabilized by an interaction with the olefinic bond of the former keteniminium salt ($HOMO_{ket}\cdots LUMO_{olef}$, weak interaction).

Then, a rotation around the C–N bond regenerates a nucleophilic double bond which attacks the cationic centre to form a cyclobutaniminium salt. This mechanism provided satisfactory explanations to most experimental observations in the racemic series. Recently, more refined models have been proposed to account for the results of asymmetric cycloadditions. Early ab initio calculations indicated that, in

Table 2. Enantioselective vicinal bis-acylation of olefins.

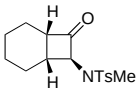
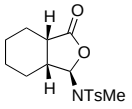
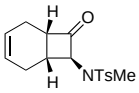
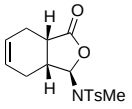
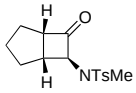
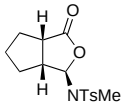
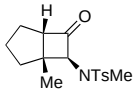
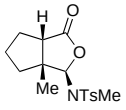
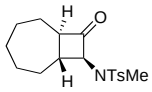
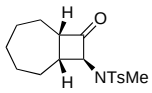
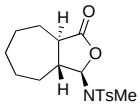
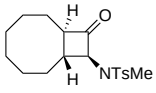
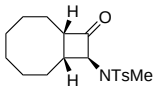
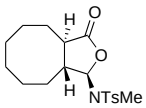
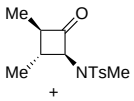
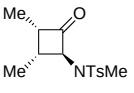
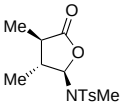
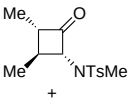
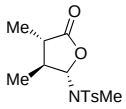
Entry	Olefin	Cyclobutanone	From **1g** Yield [%]	From **1e** (*ee* %)[a]	Lactone	Yield [%]	*ee* [%][a,b]
a		 **2**	70 (92)	81 (93)	 **15**	93	93
b		 **4**	71 (86)	–	 **16**	92	86
c		 **5**	63 (89)	75 (91)	 **17**	95 → 78[c]	91- ≫ 98[c]
d		 **6**	44 (92)	32 (95)	 **18**	80 → 61[c]	95- ≫ 98[c]
e		 +  **7**	20 (92) 20 (86)	52 (98) 0 (–)	 **19**	90	98
f		 +  **8**	66 (74) 23 (52)	66 (92) 0 (–)	 **20**	95	92
g		 +  **9**	46 (83) 15 (84)	71 (96) 2 (–)	 **21**	96 → 86[c]	96 – ≫ 98[c]
h		 +	64 (80)	51 (68)	 **22**	92	68

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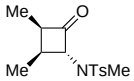
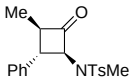
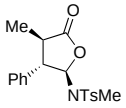
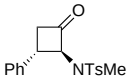
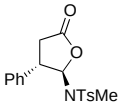
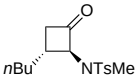
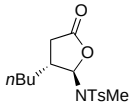
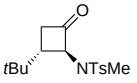
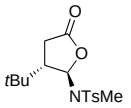
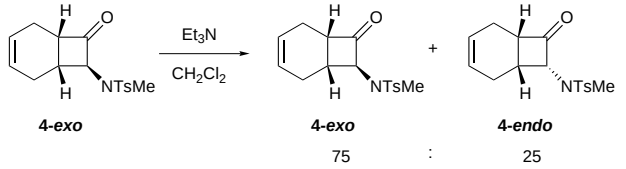
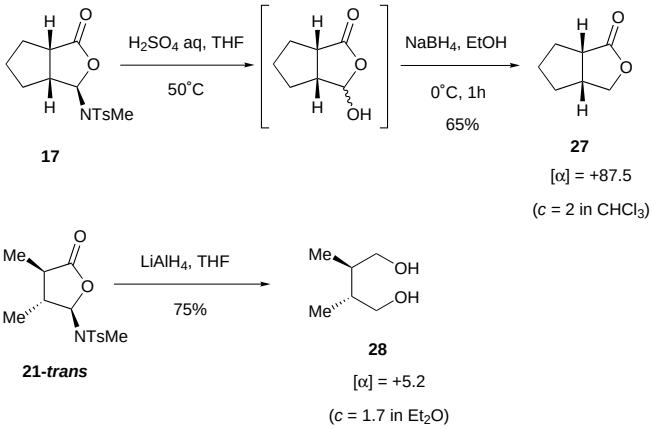
Table 2. (Continued)

Entry	Olefin	Cyclobutanone	From **1g** Yield [%]	From **1e** (ee %)[a]	Lactone	Yield [%]	*ee* [%][a,b]
		 **10**	5 (–)	0 (–)			
i		 **11**	–	74 (86)	 **23**	92 → 65[c]	86- ≫ 98[c]
j		 **12**	66 (0)	80 (31)	 **24**	97	31
k		 **13**	58 (0)	70 (48)	 **25**	95	48
l		 **14**	–	65 (76)	 **26**	89– > 71[c]	76– ≫ 95[c]

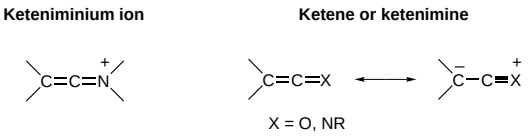
[a] Except where otherwise stated, *ee* was measured by HPLC (column chiralpack AD) on the isolated product. [b] Lactone *ee* was identical to that of the corresponding cyclobutanone. [c] After purification by recrystallisation.



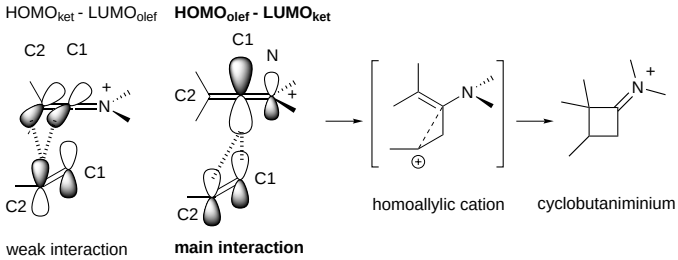
Scheme 6. Equilibration of cyclobutanones **4-*exo*** and **4-*endo***.



Scheme 7. Determination of the absolute configurations of **17** and **21-*trans***.

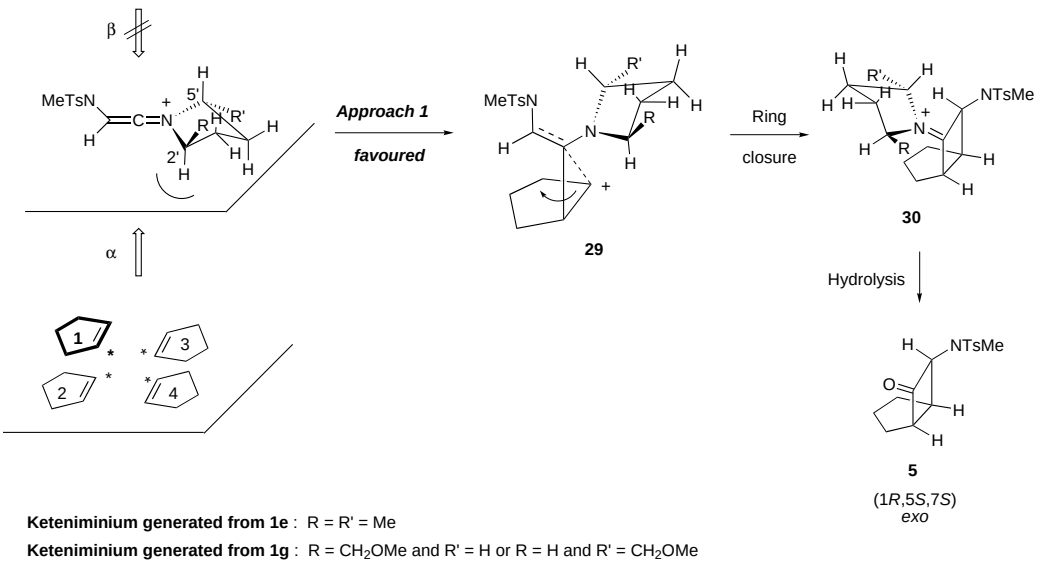


Scheme 8. Electronic structure of keteniminium ions versus ketenes and ketenimines.



Scheme 9. Mechanism of [2+2] cycloaddition between a keteniminium salt and an olefin.

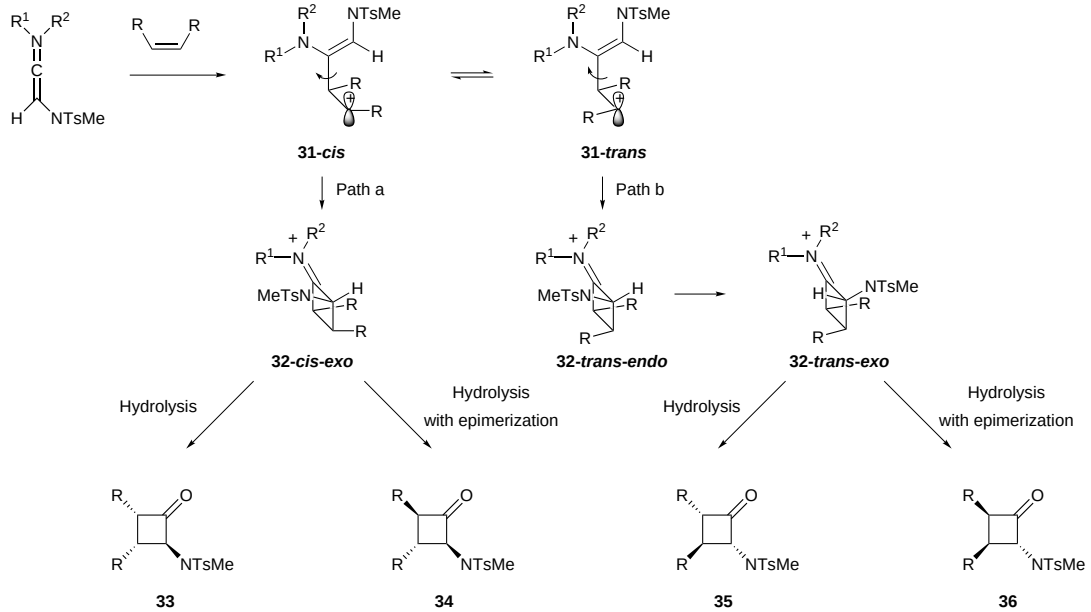
pyrrolidine-derived keteniminium salts, the ring adopted a twisted conformation with the 2- and 5-substituents in pseudoequatorial position (Scheme 10).[14] All approaches of the olefin from the β-face of the keteniminium salt suffer from steric repulsions with the bulky *N*-TsMe group and axial hydrogen atoms of the pyrrolidine ring. This should also be



Scheme 10. Stereochemistry of the cycloaddition of keteniminium salts derived from **1e** and **1g** with cyclic olefins.

the case for approaches 3 and 4 from the α-side which would lead to steric interactions with two axial hydrogen atoms of the ring. The model suggests that approach 1 should be preferred to approach 2 which suffers from an interaction with the axial hydrogen atom at C-2′. Thus, the preferred homoallylic cation should be **29**. Rotation around the C–C and C–N bonds generates an enamine, which is able to cyclise to give **30**. Hydrolysis then leads to enantiomer **5**, which is observed experimentally. This rough mechanistic model has been recently refined by an ab initio study of the potential energy surface of the reaction path.[15, 16] Nevertheless, the qualitative mechanistic analysis of Scheme 10 already accounts for all experimental observations. In particular it explains that both the C_2-symmetric keteniminium salt ($R = R' = CH_3$) and the diastereoisomeric keteniminium salts ($R = CH_2OMe$, $R' = H$ and $R = H$, $R' = CH_2OMe$) reacted with very similar facial selectivities.

Cyclopentene and cyclohexene only gave the *cis*-fused adducts as expected. With larger cycloolefins or with *cis* disubstituted acyclic olefins, the cycloadditions yielded some (or only) *trans*-fused cyclobutanones (Table 2, entries e, f, g and i). The obvious explanation would be an epimerisation of this asymmetric carbon atom α to the carbonyl group during the hydrolysis step (Scheme 11, path a). This explanation accounts for the fact that more epimerisation is found in the hydrolysis of the cyclobutaniminium **32-*cis-exo*** derived from 2,5-dimethylpyrrolidine because its hydrolysis is slower. If this explanation is correct, both *cis*- and *trans*-fused adducts should be formed in identical enantiomeric excesses, within experimental errors. This is indeed the case for the cycloheptene and the *cis*-2-butene adducts. However, an epimerisation after cycloaddition does not account for the observation that diastereoisomeric cyclobutanones **8-*cis-exo*** and **8-*trans-exo*** are formed in significantly different enantiomeric



Scheme 11. Stereochemical leak observed for the cycloaddition of keteniminium salt derived from **1g** with acyclic *cis* olefins.

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excesses. This implies that some epimerisation must have occurred before the formation of the second carbon–carbon bond in the cycloaddition reaction. In both cases, isomerisation of the cycloolefin had to be rejected, since the *trans* olefin is very unstable relative to the *cis* isomer. The best hypothesis is that an inversion of configuration occurred at the level of the intermediate homoallylic (cyclopropylcarbinyl) cation **31-*cis***. This leads to **31-*trans***, which undergoes the cyclisation to **32-*trans-endo***. As we have seen, *endo* isomers were never observed. This is easily understood, since **32-*trans-endo*** should be much less stable than **32-*trans-exo*** as a result of the interaction of the bulky *N*-TsMe group with the vicinal alkyl substituent in the *endo* isomer. This is by no means inconsistent with the fact that the equilibrium mixture for cyclobutanone **4** is 75% *exo* and 25% *endo* (Scheme 6). Indeed, here, the epimerisation occurs as the level of the iminium salt. Hydrolysis would lead to **35** (the enantiomer of **34**) or hydrolysis with epimerisation would lead to **36** (the enantiomer of **33**). Thus, the occurrence of path b should lower the enantiomeric excesses of the *cis*- and *trans*-cyclobutanones, as observed. A similar situation has been observed in our early studies on the cycloaddition of a chiral keteniminium salt bearing two methyl groups at C-2.[7a]

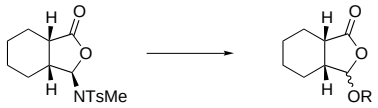
In the case of terminal olefins, the absence of facial discrimination observed in the reaction of prolinol-derived amide with terminal olefins could result from the possibility for approaches other than 1 (Scheme 10). Also, with these olefins, isomerisation of **31-*cis*** to **31-*trans*** would eventually lead to a mixture of enantiomers (Scheme 11).

Conclusion

In summary, we have established an unprecedented two-step sequence for the enantioselective addition of a carboxyl and a carbonyl group (in a protected cyclic form) to the vicinal carbon atoms of an olefin. The method works very well (good yields, high enantiomeric purities) with *cis* cyclic olefins and with *cis*-1,2-disubstitued acyclic olefins. The sequence is highly stereoselective but not stereospecific: cyclopentene and cyclohexene only formed *cis* adducts, while cycloheptene, *cis*-cyclooctene and *cis*-2-butene only produced the *trans* adducts. The method uses readily available chiral auxiliaries that can be recovered. The final products are crystalline. One recrystallisation gives the enantiopure adducts without much loss of material. The *N*-TsMe substituent can be easily exchanged for a hydroxyl or an alkoxyl group as shown for the transformation of **15** into **37a–c**, which are cyclic derivatives of the corresponding adducts of a carbonyl and a carboxyl group to the olefin (Table 3).

The ready access to α-*N*-methyltosyl cyclobutanones in high enantiomeric purities could be further exploited as illustrated by our recent discovery that they can be readily transformed in cyclopentenones of high enantiomeric purities.[17]

Table 3. Transformation of **15** to **37a–c**.



15 **37a-c**

37	Conditions	OR	Yield [%]	*endo*:*exo*
a	H_2SO_4 0.5 M, THF 50 °C, 72 h	OH	89	10:90
b	MeOH, cat. TsOH, 60 °C	OCH_3	80	15:85
c	cyclohexanol (1.1 equiv), cat. TsOH, 1,2-dichloroethane, 60 °C	OC_6H_{11}	63	0:100

Experimental Section

General methods: ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian Gemini-200 or 300 spectrometers at 200 MHz or 300 MHz at room temperature. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz or 75 MHz at room temperature. Chemical shifts are given in ppm relative to $(CH_3)_4Si$ (0 ppm, ^{1}H) or $CDCl_3$ (77.0 ppm, ^{13}C). Mass spectra were obtained on a Finnigan MAT-TSQ 700 spectrometer. IR spectra were recorded on a BIO-RAD TFS 135 FT-IR spectrophotometer. All absorption values are expressed in wavenumbers (cm^{-1}). $[\alpha]_D$ values were obtained on a Perkin–Elmer 241 MC polarimeter. Melting points are uncorrected. Enantiomeric excesses were measured on HPLC with a Millipore Waters 600 Controller, UV Millipore Waters 486 as detector and fitted with Diacel Chiralpack-AD, -AS analytical column. TLC was run on silica gel 60 F_{254} coated aluminium plates. Column chromatography was performed with silica gel 40 (230–400 μm, Merck). All solvents were distilled before use. All reagents were of reagent grade.

General procedure for the preparation of chiral sarcosinamides: Thionyl chloride was added to a solution of *N*-tosylsarcosine in 1,2-dichloroethane. The mixture was heated at reflux for 2 h. Evaporation of the solvent yielded crude *N*-tosylsarcosyl chloride that was used without purification. At 0 °C, a fourfold excess of this crude material was added to a heterogeneous mixture of the amine hydrochloride in dichloromethane and 20% aqueous NaOH. The mixture was stirred overnight, and the phases were decanted. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were washed with brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography.

Sarcosinamide (1a): *N*-Tosylsarcosine (5 g, 20 mmol), thionyl chloride (1.7 mL, 20 mmol), (2*S*,5*S*)-2,5-dimethoxymethylpyrrolidine hydrochloride[10b] (1.0 g, 5 mmol) and 20% aqueous NaOH (6.2 mL) gave **1a** (1.95 g, 99%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 4.33 (d, $J = 15.2$ Hz, 1H), 3.72 (d, $J = 15.2$ Hz, 1H), 4.30–4.20 (m, 2H), 3.50–3.25 (m, 4H), 3.35 (s, 3H), 3.03 (s, 3H), 2.84 (s, 3H), 2.43 (s, 3H), 2.17–1.76 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 167.0$, 143.2, 134.5, 129.4, 127.4, 74.7, 71.0, 58.9, 58.7, 57.2, 56.9, 52.6, 35.4, 27.2, 25.4, 21.3; IR (neat): $\tilde{\nu} = 3000$, 2950, 1660, 1600, 1180 cm^{-1}; MS (EI): *m*/*z* (%): 385 (10), 198 (100), 155 (58), 91 (80).

Sarcosinamide (1b): *N*-Tosylsarcosine (18.6 g, 80 mmol), thionyl chloride (6.0 mL, 84 mmol), (*S*,*S*)-α,α'-dimethylbenzylamine[10c] (5 g, 20 mmol) and 20% aqueous NaOH (23 mL) gave **1b** (9.6 g, 93%). $[\alpha]_D^{20} = +64.3$ ($c = 1.8$ in $CHCl_3$); m.p. 146 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.4$ Hz, 2H), 7.40–7.10 (m, 12H), 5.29 (m, 2H), 4.05 (d, $J = 14.8$ Hz, 1H), 3.53 (d, $J = 14.8$ Hz, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 1.88 (s, 6H); IR (neat): $\tilde{\nu} = 3000$, 2950, 1660, 1600, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 451 (5), 198 (100), 155 (53), 91 (37); elemental analysis calcd (%) for $C_{26}H_{30}O_3N_2S$: C 69.33, H 6.66, N 6.22, S 7.11; found: C 69.23, H 6.51, N 6.18, S 7.12.

Sarcosinamide (1c): *N*-Tosylsarcosine (5.8 g, 24 mmol), thionyl chloride (1.9 mL, 26 mmol), (3*S*,4*S*)-dimethoxypyrrolidine hydrochloride[10a] (1 g, 6 mmol) and 20% aqueous NaOH (7.2 mL) gave **1c** (2.1 g, 96%). $[\alpha]_D^{20} = +2.9$ ($c = 1.7$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.4$ Hz, 2H), 7.40–7.30 (d, $J = 8.4$ Hz, 2H), 3.90–3.42 (m, 8H), 3.40 (s, 3H), 3.36 (s, 3H), 2.78 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$):

δ = 166.4, 144.2, 134.2, 130.2, 128.1, 74.7, 71.0, 57.6, 57.5, 53.5, 49.9, 49.6, 36.0, 22.1; IR (neat): $\tilde{\nu}$ = 3000, 2950, 2840, 1660, 1600, 1360, 1180 cm^{-1}; MS (EI): *m*/*z* (%): 357 (8), 198 (25), 155 (42), 91 (64).

Sarcosinamide (1d): The general procedure was modified to avoid saponification of the ester groups. The 20% aqueous NaOH solution was replaced by a 10% aqueous $NaHCO_3$ solution. *N*-Tosylsarcosine (2.8 g, 12 mmol), thionyl chloride (1.4 mL, 15 mmol), (*S*,*S*)-3,4-bis(phenylacetoxy)pyrrolidine[10f] (830 mg, 3 mmol) and 10% aqueous $NaHCO_3$ (13 mL) afforded **1d** (970 mg, 65%). $[\alpha]_D^{20}$ = +24.4 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.1 Hz, 2H), 7.40–7.10 (m, 12H), 5.20 (br dd, 2H), 3.90–3.50 (m, 10H), 2.70 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.9, 169.8, 165.7, 143.7, 133.5, 132.9 (×2), 129.6, 128.9, 128.5, 127.4, 127.2, 75.0, 73.0, 52.6, 49.9 (×2), 40.8 (×2), 35.3, 21.3; IR (neat): $\tilde{\nu}$ = 1745, 1655 cm^{-1}.

Sarcosinamide (1e): *N*-Tosylsarcosine (35 g, 144 mmol), thionyl chloride (11.6 mL, 158 mmol), (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride[10e] (5 g, 36 mmol) and 20% aqueous NaOH (43 mL) afforded **1e** (10.9 g, 94%). $[\alpha]_D^{20}$ = −33.7 (*c* = 1.5 in $CHCl_3$); m.p. 76 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.28–4.12 (m, 2H), 4.21 (d, *J* = 14.8 Hz, 1H), 3.48 (d, *J* = 14.8 Hz, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 2.17–1.47 (m, 4H), 1.89 (d, 3H), 1.08 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.2, 144.1, 134.7, 130.1, 128.1, 53.9, 53.3, 52.9, 35.9, 31.3, 28.9, 22.0, 21.8, 19.1; IR (neat): $\tilde{\nu}$ = 3000, 2950, 1660, 1600 cm^{-1}; MS (EI): *m*/*z* (%): 325 (12), 198 (68), 155 (60), 91 (63); elemental analysis calcd (%) for $C_{16}H_{24}O_3N_2S$: C 59.26, H 7.41, N 8.64, S 9.88; found: C 59.41, H 7.53, N 8.55, S 9.94.

Sarcosinamide (1f): *N*-Tosylsarcosine (10 g, 41 mmol), thionyl chloride (3.0 mL, 41 mmol), (2*S*)-2-methylpyrrolidine[10g] (2.3 g, 27 mmol) and 20% aqueous NaOH (10 mL) afforded **1f** (5.1 g, 60%). $[\alpha]_D^{20}$ = +24.8 (*c* = 0.6 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.30–4.00 (m, 1H), 3.88 (d, *J* = 14.6 Hz, 1H), 3.80–3.40 (m, 2H), 3.67 (d, *J* = 14.6 Hz, 1H), 2.86 (s, 3H), 2.80 (s, 3H), 2.43 (s, 3H), 2.20–1.80 (m, 4H), 1.24 (d, *J* = 3.4 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.9, 143.4, 134.3, 129.4, 127.4, 53.2, 52.8, 52.5, 51.7, 46.3, 45.5, 35.5, 35.2, 33.1, 31.5, 23.9, 21.3, 21.2, 20.9, 19.1; IR (neat): $\tilde{\nu}$ = 3000, 2950, 1660, 1600 cm^{-1}; MS (EI): *m*/*z* (%): 311 (1), 198 (52), 155 (100), 91 (16); elemental analysis calcd (%) for $C_{15}H_{22}O_3N_2S$: C 58.04, H 7.14, N 9.02, S 10.33; found: C 57.98, H 7.20, N 8.90, S 10.41.

Sarcosinamide (1g): *N*-Tosylsarcosine (8.5 g, 35 mmol), thionyl chloride (2.8 mL, 38.5 mmol), (2*S*)-methoxymethylpyrrolidine hydrochloride[10a] (1 g, 9 mmol) and 20% aqueous NaOH (11 mL) afforded **1g** (2.9 g, 98%). $[\alpha]_D^{20}$ = −49.4 (*c* = 1.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.20 (m, 1H), 4.26 (d, *J* = 15.2 Hz, 1H), 3.96 (d, *J* = 14.7 Hz, 1H), 3.82 (d, *J* = 15.2 Hz, 1H), 3.70 (d, *J* = 14.7 Hz, 1H), 3.65–3.49 (m, 4H), 3.35 (s, 3H), 3.32 (s, 3H), 2.86 (s, 3H), 2.81 (s, 3H), 2.43 (s, 3H), 2.14–1.80 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 165.4, 144.1, 143.3, 134.2, 133.7, 129.3, 129.2, 127.2, 127.1, 74.2, 71.6, 58.6, 56.7, 56.2, 52.6, 51.6, 46.7, 45.4, 35.6, 35.1, 28.3, 26.8, 24.0, 21.4, 21.2; IR (neat): $\tilde{\nu}$ = 3000, 2950, 1660, 1600, 1360, 1180 cm^{-1}; MS (EI): *m*/*z* (%): 339 (5), 198 (96), 185 (100), 155 (77), 91 (97); elemental analysis calcd (%) for $C_{16}H_{24}O_4N_2S$: C 56.45, H 7.11, N 8.23; found: C 56.19, H 7.14, N 8.05.

Sarcosinamide (1h): *N*-Tosylsarcosine (6.8 g, 28 mmol), thionyl chloride (2.3 mL, 31 mmol), (2*S*)-(1-methoxy-1-methyl)-1-ethylpyrrolidine hydrochloride[10d] (1 g, 7 mmol) and 20% aqueous NaOH (9 mL) afforded **1h** (2.5 g, 98%). $[\alpha]_D^{20}$ = −36.8 (*c* = 1.7 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.33 (m, 1H), 4.09 (d, *J* = 15.0 Hz, 1H), 3.84 (m, 1H), 3.70 (d, *J* = 15.0 Hz, 1H), 3.58 (m, 1H), 3.15 (s, 3H), 2.87 (s, 3H), 2.80 (s, 3H), 2.42 (s, 3H), 2.05–1.80 (m, 4H), 1.13 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.1, 166.6, 143.3, 143.0, 135.1, 134.2, 129.5, 127.4, 78.8, 78.5, 65.2, 63.7, 53.0, 52.0, 49.1, 48.7, 47.2, 46.6, 35.9, 35.5, 27.5, 24.9, 24.8, 24.7, 22.6, 22.1, 21.7, 21.4, 18.3; IR (neat): $\tilde{\nu}$ = 3000, 2950, 1660, 1600, 1360, 1180 cm^{-1}; MS (EI): *m*/*z* (%): 369 (11), 198 (100), 155 (42), 91 (43).

Sarcosinamide (1i): a) *N*-Tosylsarcosine (42 g, 160 mmol), thionyl chloride (12 mL, 160 mmol), (1*R*,2*S*)-ephedrine (6.6 g, 40 mmol) and 20% aqueous NaOH (10 mL) afforded (1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-1-(*N*-tosylsarcosyl)ethylamine (10.9 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.40–7.26 (m, 7H), 4.82 (d, *J* = 4.8 Hz, 1H), 4.68 (d, *J* = 7.8 Hz, 1H), 4.47 (qd, *J* = 7.0, 4.8 Hz, 1H), 4.20 (dq, *J* = 7.8, 6.8 Hz, 1H), 3.92 (d, *J* = 14.7 Hz, 1H), 3.65 (d, *J* = 14.7 Hz, 1H), 2.90 (s, 3H), 2.80 (s, 3H), 2.58 (s, 3H), 2.50 (s, 3H), 2.43 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.0, 143.8, 141.9, 134.0, 129.7, 128.4, 127.8, 127.7, 126.3, 76.8, 58.0, 53.0, 35.2, 32.6, 21.5, 12.1; MS (EI): *m*/*z* (%): 391 (6), 283 (100), 198 (90), 155 (20), 91 (10); elemental analysis calcd (%) for $C_{20}H_{26}O_4N_2S$: C 61.51, H 6.71, N 7.17, S 8.21; found: C 61.47, H 6.57, N 7.16, S 7.91.

b) Sodium hydride 58% (0.50 g, 12 mmol) was added to a cold solution of (1*S*,2*R*)-2-hydroxy-1-methyl-2-phenyl-1-(*N*-tosylsarcosyl)ethylamine (3.12 g, 8 mmol) and dimethylsulfate (570 µL, 6 mmol) in THF (30 mL). The mixture was then heated at reflux overnight. A solution of brine (10 mL) was added then at room temperature. The compound was extracted with dichloromethane. The organic phases were washed with water, then dried over $MgSO_4$, filtered and concentrated in vacuo. Crystallisation of the residue in ethyl acetate afforded **1i** (1.40 g, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.55 (m, 3H), 7.40–7.20 (m, 6H), 4.61 (p, *J* = 6.9 Hz, 1H), 4.20 (d, *J* = 6.9 Hz, 1H), 4.15–4.05 (m, 2H), 3.89 (d, *J* = 14.5 Hz, 1H), 3.87 (d, *J* = 14.5 Hz, 1H), 3.52 (d, *J* = 14.5 Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H), 2.98 (s, 3H), 2.80 (s, 3H), 2.51 (s, 3H), 2.43 (s, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.9, 166.5, 143.6, 143.4, 139.0, 138.9, 134.2, 134.1, 129.6, 129.4, 128.5, 128.3, 127.8, 127.5, 127.0, 126.9, 85.8, 85.0, 57.2, 57.0, 56,9, 54.7, 52.8, 51.8, 35.1, 34.8, 31.0, 28.3, 21.4, 15.1, 12.5; MS (EI): *m*/*z* (%): 405 (10), 283 (100), 198 (60), 155 (10), 91 (4); elemental analysis calcd (%) for $C_{21}H_{28}O_4N_2S$: C 62.35, H 6.97, N 6.92, S 7.93; found: C 62.11, H 6.95, N 6.82, S 7.70.

General procedure for the [2+2] cycloaddition-hydrolysis sequence: Triflic anhydride (1.2 equiv) was added to a 0.1 M solution of amide (1 equiv) in 1,2-dichloroethane at 0 °C. After 5 min, the mixture was treated with a 0.3 M solution of 1.1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine and 4 equiv of olefin in 1,2-dichloroethane at 0 °C. After 3 h at room temperature, the solvent was removed, and the solid residue was taken up in a biphasic mixture of water and carbon tetrachloride. After 12 h at room temperature, the two layers were separated, and the aqueous layer was extracted three times with carbon tetrachloride. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography on silica gel (AcOEt/cyclohexane 2:8).

(1*R*,6*S*,8*S*)-8-(Methyltosylamino)bicyclo[4.2.0]octan-7-one (2): a) Compound **1c** (500 mg, 1.36 mmol), triflic anhydride (275 µL, 1.63 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (307 mg, 1.49 mmol) and cyclohexene (550 µL, 6.16 mmol) afforded **2** (335 mg, 80%, 42% *ee*).

b) Compound **1d** (845 mg, 1.69 mmol), triflic anhydride (340 µL, 2.03 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (420 mg, 2.03 mmol) and cyclohexene (685 µL, 6.76 mmol) afforded **2** (185 mg, 36%, 33% *ee*).

c) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (347 mg, 1.69 mmol) and cyclohexene (625 µL, 6.16 mmol) afforded **2** (382 mg, 81%, 93% *ee*). $[\alpha]_D^{20}$ = +68.5 (*c* = 1.0 in $CHCl_3$).

d) Compound **1g** (500 mg, 2.46 mmol), triflic anhydride (495 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (555 mg, 1.69 mmol) and cyclohexene (995 µL, 6.16 mmol) afforded **2** (317 mg, 70%, 92% *ee*).

e) Compound **1i** (410 mg, 1.00 mmol), triflic anhydride (205 µL, 1.20 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (250 mg, 1.20 mmol) and cyclohexene (205 µL, 2 mmol) afforded **2** (60 mg, 20%, 52% *ee*).

Compound 2: Colourless solid; m.p. 93 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.34 (dd, *J* = 9.5, 2.2 Hz, 1H), 2.84 (m, 1H), 2.76 (s, 3H), 2.50 (m, 1H), 2.44 (s, 3H), 2.11–1.04 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 204.7, 143.8, 136.0, 129.8, 127.3, 69.7, 49.0, 30.6, 27.0, 22.2, 22.1, 21.9, 21.3, 20.3; IR (neat): $\tilde{\nu}$ = 2950, 2850, 1785, 1360, 1170 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{21}O_3NS$: C 62.51, H 6.89, N 4.56; found: C 62.73, H 6.85, N 4.69; HPLC (AD column; eluent EtOH; flow: *v* = 0.35 mL min^{-1}; λ = 254 nm): 15.9 min (1*S*,6*R*,8*R*) and 21.0 min (1*R*,6*S*,8*S*).

(1*R*,6*S*,8*S*)-8-(Methyltosylamino)bicyclo[4.2.0]oct-3-en-7-one (4): Compound **1g** (9.0 g, 26.4 mmol), triflic anhydride (5.4 mL, 31.7 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (6.0 g, 29.0 mmol) and cyclohexadiene (5 mL, 52.9 mmol) afforded **4** (5.75 g, 71%, 86% *ee*) as a colourless solid. $[\alpha]_D^{20}$ = +56.5 (*c* = 1.7 in CH_2Cl_2); m.p. 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.00–5.92 (m, 1H), 5.90–5.82 (m, 1H), 4.88 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.18 (tt, *J* = 9.9, 3.0 Hz,

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1H), 2.78 (s, 3H), 2.85–2.75 (m, 1H), 2.43 (s, 3H), 2.40–1.15 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.0$, 143.6, 135.9, 129.6, 127.3, 126.3, 126.2, 74.5, 50.7, 31.7, 28.4, 23.8, 21.5, 21.2; IR (neat): $\tilde{\nu} = 2924$, 2841, 1780, 1341, 1148 cm^{-1}; MS (EI): *m*/*z* (%): 277 (100), 225 (28), 155 (24), 122 (60), 91 (80); elemental analysis calcd (%) for $C_{16}H_{19}O_3NS$: C 62.93, H 6.27, N 4.59, S 10.50; found: C 62.95, H 6.37, N 4.62, S 10.47; HPLC (AD column; eluent EtOH; flow: $v = 0.35$ mL min^{-1}; $\lambda = 254$ nm): 15.9 min (1*S*,6*R*,8*R*) and 18.3 min (1*R*,6*S*,8*S*).

(1*R*,5*S*,7*S*)-7-(Methyltosylamino)bicyclo[3.2.0]heptan-6-one (5): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (347 mg, 1.70 mol) and cyclopentene (680 µL, 7.70 mmol) afforded **5** (340 mg, 75%, 91% *ee*).

b) Compound **1g** (100 mg, 0.30 mmol), triflic anhydride (60 µL, 0.35 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (67 mg, 0.32 mmol) and cyclopentene (130 µL, 1.5 mmol) afforded **5** (55 mg, 63%, 89% *ee*) as a colourless oil. $[\alpha]_D^{20} = +24.8$ ($c = 1.1$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 4.68 (dd, $J =$ 5.1, 3.3 Hz, 1H), 3.35 (m, 1H), 2.84 (m, 1H), 2.75 (s, 3H), 2.44 (s, 3H), 2.03–1.63 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.7$, 143.8, 135.7, 129.8, 127.5, 74.6, 60.7, 35.8, 32.4, 31.4, 28.6, 25.2, 21.3; IR (neat): $\tilde{\nu} = 2950$, 2850, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 294 (8), 265 (100), 155 (20), 110 (56), 91 (20); elemental analysis calcd (%) for $C_{15}H_{19}O_3NS$: C 61.41, H 6.53, N 4.77; found: C 61.52, H 6.59, N 4.88; HPLC (AD column; eluent EtOH; flow: $v = 0.35$ mL min^{-1}; $\lambda = 254$ nm): 16.6 min (1*S*,5*R*,7*R*) and 21.8 min (1*R*,5*S*,7*S*).

(1*R*,5*S*,7*S*)-1-Methyl-7-(methyltosylamino)bicyclo[3.2.0]heptan-6-one (6): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (347 mg, 1.70 mmol) and 1-methylcyclopentene (810 µL, 7.70 mmol) afforded **6** (155 mg, 32%, 95% *ee*).

b) Compound **1g** (500 mg, 1.47 mmol), triflic anhydride (300 µL, 1.77 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (330 mg, 1.62 mmol) and 1-methylcyclopentene (770 µL, 7.35 mmol) afforded **6** (210 mg, 44%, 90% *ee*) as a colourless oil. $[\alpha]_D^{20} = +65.8$ ($c = 0.3$ in CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 4.57 (d, $J = 3.0$ Hz, 1H), 2.88 (m, 1H), 2.85 (s, 3H), 2.42 (s, 3H), 2.35–1.45 (m, 6H), 1.35 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 207.9$, 143.7, 135.8, 129.4, 127.2, 75.0, 66.3, 45.1, 40.6, 34.1, 29.2, 26.4, 21.6, 19.1; IR (neat): $\tilde{\nu} =$ 3050, 2950, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 307 (8), 225 (28), 155 (8), 123 (100), 91 (63); elemental analysis calcd (%) for $C_{16}H_{21}O_3NS$: C 62.54, H 6.84, N 4.56, S 10.42; found: C 62.38, H 7.06, N 4.43, S 10.26; HPLC (AD column; eluent EtOH; flow: $v = 0.35$ mL min^{-1}; $\lambda = 254$ nm): 14.8 min (1*S*,5*R*,7*R*) and 18.6 min (1*R*,5*S*,7*S*).

(1*R*,7*S*,9*S*)-9-(Methyltosylamino)bicyclo[5.2.0]nonan-8-one (7-*cis*) and (1*R*,7*R*,9*S*)-9-(methyltosylamino)bicyclo[5.2.0]nonan-8-one (7-*trans*): a) Compound **1e** (300 mg, 0.92 mmol), triflic anhydride (190 µL, 1.11 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (210 mg, 1.02 mmol) and cycloheptene (230 µL, 1.80 mmol) afforded **7-*trans*** (154 mg, 52%, 98% *ee*). $[\alpha]_D^{20} = -67.4$ ($c = 0.3$ in $CHCl_3$).

b) Compound **1g** (575 mg, 1.70 mmol), triflic anhydride (340 µL, 2.00 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (380 mg, 1.90 mmol) and cycloheptene (395 µL, 3.40 mmol) afforded of a mixture of **7-*cis*** and **7-*trans*** (155 mg, 39%) in the ratio 1:1 (86% *ee* for **7-*cis*** and 92% *ee* for **7-*trans***). **7-*cis*** ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.79$ (d, $J = 8.0$ Hz, 2H), 6.82 (d, $J =$ 8.0 Hz, 2H), 4.86 (dd, $J = 7.9$, 2.4 Hz, 1H), 2.60–2.50 (m, 1H), 2.52 (s, 3H), 2.30–2.20 (m, 1H), 2.00–1.85 (m, 1H), 1.89 (s, 3H), 1.60–0.75 (m, 9H); **7-*trans*** ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.79$ (d, $J = 8.0$ Hz, 2H), 6.82 (d, $J =$ 8.0 Hz, 2H), 4.78 (d, $J = 9.1$ Hz, 1H), 2.58 (s, 3H), 2.05–1.85 (m, 2H), 1.90 (s, 3H), 1.65–1.55 (m, 1H), 1.50–0.95 (m, 9H); **7-*cis*** ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.0$, 143.4, 135.9, 129.7, 127.3, 74.9, 59.7, 36.0, 31.8, 32.2, 30.1, 30.0, 28.2, 26.5, 21.5; **7-*trans*** ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.3$, 143.6, 135.9, 129.7, 127.3, 71.7, 57.5, 35.2, 31.8, 32.7, 31.5, 29.4, 27.7, 25.6, 21.5; IR (neat): $\tilde{\nu} = 2923$, 2857, 1778, 1340, 1157 cm^{-1}; MS (EI): *m*/*z* (%): 293 (84), 225 (16), 185 (12), 155 (54), 138 (60), 91 (100); elemental analysis calcd (%) for $C_{17}H_{23}O_3NS$: C 63.52, H 7.21, N 4.35, S 9.97; found: C 63.46, H 7.25, N 4.27, S 10.03; HPLC (AD column; eluent *i*PrOH/hexane 10:90; flow: $v =$ 1.00 mL min^{-1}; $\lambda = 254$ nm): 18.3 min (1*S*,7*R*,9*R*), 20.7 min (1*S*,7*S*,9*R*), 22.4 min (1*R*,7*S*,9*S*) and 60.8 min (1*R*,7*R*,9*S*).

(1*R*,8*S*,10*S*)-10-(Methyltosylamino)bicyclo[6.2.0]decan-9-one (8-*cis*) and (1*R*,8*R*,10*S*)-10-(methyltosylamino)bicyclo[6.2.0]decan-9-one (8-*trans*): a) Compound **1e** (1.0 g, 3.1 mmol), triflic anhydride (620 µL, 3.7 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (700 mg, 3.4 mmol) and *cis*-cyclooctene (845 µL, 6.2 mmol) afforded **8-*trans*** (680 mg, 66%, 92% *ee*). $[\alpha]_D^{20} = -56.1$ ($c = 0.4$ in CH_2Cl_2).

b) Compound **1g** (575 mg, 1.70 mmol), triflic anhydride (340 µL, 2.00 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (380 mg, 1.90 mmol) and *cis*-cyclooctene (440 µL, 3.40 mmol) afforded a mixture of **8-*cis*** and **8-*trans*** (330 mg, 58%) in the ratio 1:3 (52% *ee* for **8-*cis*** and 74% *ee* for **8-*trans***). **8-*cis*** ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.83$ (d, $J = 8.3$ Hz, 2H), 6.82 (d, $J =$ 8.3 Hz, 2H), 4.88 (dd, $J = 8.5$, 2.3 Hz, 1H), 2.55 (s, 3H), 2.34 (m, 1H), 2.00–1.85 (m, 3H), 1.88 (s, 3H), 1.60–1.35 (m, 5H), 1.15 (m, 4H); **8-*trans*** ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.81$ (d, $J = 8.3$ Hz, 2H), 6.82 (d, $J = 8.3$ Hz, 2H), 4.81 (dd, $J = 8.8$, 1.9 Hz, 1H), 2.57 (s, 3H), 2.10–2.00 (m, 1H), 2.00–1.90 (m, 1H), 1.88 (s, 3H), 1.70–1.30 (m, 7H), 1.20–0.75 (m, 5H); **8-*cis*** ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.2$, 143.2, 137.3, 129.8, 127.6, 75.1, 58.3, 35.3, 31.3, 28.6, 26.2, 26.1, 25.7, 25.2, 24.6, 20.7; **8-*trans*** ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 203.6$, 143.2, 137.3, 129.8, 127.6, 74.5, 57.1, 37.0, 35.1, 31.0, 28.4, 28.0, 27.5, 27.3, 26.6, 20.7; IR (neat): $\tilde{\nu} = 2923$, 2853, 1774, 1340, 1154 cm^{-1}; MS (EI): *m*/*z* (%): 307 (100), 225 (16), 185 (28), 91 (64); elemental analysis calcd (%) for $C_{18}H_{25}O_3NS$: C 64.44, H 7.51 N 4.18, S 9.56; found: C 64.20, H 7.54, N 4.02, S 9.82; HPLC (AS followed by AD; eluent *i*PrOH/hexane 10:90; flow: $v = 1.00$ mL min^{-1}; $\lambda = 254$ nm): 26.2 min (1*S*,8*R*,9*R*), 31.2 min (1*R*,8*S*,9*S*), 33.1 min (1*S*,8*S*,9*R*) and 49.0 min (1*R*,8*R*,9*S*).

(2*S*,3*R*,4*R*)-3,4-Dimethyl-2-(*N*-methyl-*N*-tosylamino)cyclobutanone (9-*trans*) and (2*S*,3*R*,4*S*)-3,4-dimethyl-2-(*N*-methyl-*N*-tosylamino)cyclobutanone (9-*cis*): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.70 mmol) and *cis*-butene (330 µL, 6.00 mmol) afforded **9-*cis*** and **9-*trans*** (316 mg, 73%) in a ratio 3:97. The enantiomeric excess was determined on lactone **21** (96% *ee* for **9-*trans***).

b) Compound **1g** (500 mg, 1.50 mmol), triflic anhydride (300 µL, 1.77 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (330 mg, 1.62 mmol) and *cis*-butene (330 µL, 6.00 mmol) afforded a mixture of **9-*cis*** and **9-*trans*** (253 mg, 61%) in the ratio 1:3. Enantiomeric excess was determined on lactone **21** (83% *ee* for **9-*trans*** and 84% *ee* for **9-*cis***). **9-*trans*** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 4.88 (dd, $J = 8.7$, 2.0 Hz, 1H), 2.73 (s, 3H), 2.56 (dqd, $J = 8.8$, 7.1, 2.0 Hz, 1H), 2.42 (s, 3H), 1.94 (ddq, $J = 8.8$, 8.7, 6.5 Hz, 1H), 1.37 (d, $J = 7.1$ Hz, 3H), 1.11 (d, $J = 6.5$ Hz, 3H); **9-*cis*** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 4.82 (dd, $J = 8.7$, 2.7 Hz, 1H), 2.96 (dqd, $J = 10.4$, 7.9, 2.7 Hz, 1H), 2.74 (s, 3H), 2.62 (dqd, $J = 10.4$, 8.7, 6.9 Hz, 1H), 2.42 (s, 3H), 1.22 (d, $J = 7.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H); **9-*trans*** ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 207.7$, 143.7, 135.8, 129.8, 127.4, 74.1, 53.9, 33.3, 31.2, 21.5, 18.6, 11,7; **9-*cis*** ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 205.0, 143.7, 135.9, 129.8, 127.4, 75.4, 50.9, 31.4, 28.6, 21.5, 13.2, 9.9; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1785, 1340, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 282 (44); elemental analysis calcd (%) for $C_{14}H_{19}O_3NS$: C 59.79, H 6.76, N 4.98, S 11.34; found: C 59.90, H 6.88, N 4.95, S 11.46.

(2*S*,3*S*,4*S*)-3,4-Dimethyl-2-(*N*-methyl-*N*-tosylamino)cyclobutanone (10-*trans*) and (2*S*,3*S*,4*R*)-3,4-dimethyl-2-(*N*-methyl-*N*-tosylamino)cyclobutanone (10-*cis*): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.70 mmol) and *trans*-butene (330 µL, 6.00 mmol) afforded **10-*trans*** (224 mg, 51%). Enantiomeric excess was determined on lactone **22** (68% *ee*).

b) Compound **1g** (250 mg, 0.75 mmol), triflic anhydride (150 µL, 0.89 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (165 mg, 0.80 mmol) and *trans*-butene (165 µL, 3.00 mmol) afforded a mixture of **10-*cis*** and **10-*trans*** (143 mg, 69%) in the ratio 8:92. Enantiomeric excess was determined on lactone **22** (80% *ee* for **10-*trans***).

(2*S*,3*S*,4*R*)-4-Methyl-2-(*N*-methyl-*N*-tosylamino)-3-phenylcyclobutanone (11): Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.70 mmol) and β-*cis*-methylstyrene (990 µL, 7.70 mmol) afforded **11** (388 mg, 74%). Enantiomeric excess was determined on lactone **23** (86% *ee*). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.48$ (d, $J = 8.3$ Hz, 2H), 7.40–7.20 (m, 5H), 7.12 (d, $J = 8.3$ Hz, 2H), 5.48 (dd, $J = 8.8$, 2.4 Hz, 1H), 3.08 (m, 1H), 3.04 (dd, $J = 8.9$, 8.8 Hz, 1H), 2.82 (s, 3H), 2.36 (s, 3H), 1.23 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.2$, 143.4, 139.7, 135.4, 128.9, 128.7, 127.4, 127.1, 74.6, 55.2, 42.5, 31.2, 21.5, 12.4; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850,

1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 343 (21), 225 (19), 188 (49), 159 (40), 155 (16), 91 (63); elemental analysis calcd (%) for $C_{19}H_{21}O_3NS$: C 66.47, H 6.12, N 4.08; found: C 66.65, H 6.35, N 4.03.

(2*S*,3*R*)-2-(Methyltosylamino)-3-phenylcyclobutanone (12): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.70 mmol) and styrene (880 µL, 7.70 mmol) afforded **12** (406 mg, 80%). Enantiomeric excess was determined on lactone **24** (31% *ee*).

b) Compound **1g** (500 mg, 1.50 mmol), triflic anhydride (300 µL, 1.77 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (332 mg, 1.62 mmol) and styrene (845 µL, 7.37 mmol) afforded **12** (320 mg, 66%) as a colourless solid. Enantiomeric excess was determined on lactone **24** (0% *ee*). Compound **12**: m.p. 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J =$ 8.4 Hz, 2H), 7.35–7.25 (m, 5H), 7.15 (d, $J = 8.4$ Hz, 2H), 5.45 (dd, $J = 8.8$, 1.5 Hz, 1H), 3.60 (t, $J = 9.5$ Hz, 1H), 3.03 (dtd, $J = 17.0$, 9.5, 1.5 Hz, 2H), 2.75 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 201.4$, 143.5, 135.4, 129.6, 128.8, 127.2, 127.1, 126.7, 77.0, 47.6, 34.4, 31.2, 21.5; IR (neat): $\tilde{\nu} =$ 3050, 2950, 2850, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 329 (7), 287 (62), 91 (84).

(2*S*,3*R*)-3-*n*-Butyl-2-(methyltosylamino)cyclobutanone (13): a) Compound **1e** (500 mg, 1.54 mmol), triflic anhydride (310 µL, 1.85 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (345 mg, 1.70 mmol) and 1-hexene (955 µL, 7.70 mmol) afforded **13** (330 mg, 70%). Enantiomeric excess was determined on lactone **25** (48% *ee*).

b) Compound **1g** (500 mg, 1.50 mmol), triflic anhydride (300 µL, 1.77 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (332 mg, 1.62 mmol) and 1-hexene (955 µL, 7.70 mmol) afforded **13** (263 mg, 58%) as a colourless solid. Enantiomeric excess was determined on lactone **25** (0% *ee*). Compound **13**: m.p. 62 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.71$ (d, $J =$ 8.3 Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 4.91 (d, $J = 7.7$ Hz, 1H), 2.74 (s, 3H), 2.70 (m, 1H), 2.40 (s, 3H), 2.53–2.25 (m, 2H), 1.90–1.50 (m, 2H), 1.50–1.20 (m, 4H), 0.90 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 202.0$, 143.3, 135.7, 129.4, 127.0, 74.7, 45.4, 34.4, 30.8, 30.0, 29.7, 22.2, 21.1, 13.6; IR (neat): $\tilde{\nu} =$ 3050, 2950, 2850, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 310 (4), 224 (75), 155 (60), 126 (100), 91 (60); elemental analysis calcd (%) for $C_{16}H_{23}O_3NS$: C 62.13, H 7.44, N 4.53, S 10.36; found: C 61.98, H 7.60, N 4.35, S 10.57.

(2*S*,3*S*)-3-*tert*-Butyl-2-(methyltosylamino)cyclobutanone (14): Compound **1e** (250 mg, 0.77 mmol), triflic anhydride (155 µL, 0.93 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (165 mg, 0.85 mmol) and 1-*tert*-butylethylene (500 µL, 7.70 mmol) afforded **14** (154 mg, 65%) as a colourless oil. Enantiomeric excess was determined on lactone **26** (76% *ee*). Compound **14**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 5.20 (d, $J = 8.8$ Hz, 1H), 2.75 (s, 3H), 2.58–2.32 (m, 3H), 2.44 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 202.7$, 144.3, 136.6, 130.4, 128.0, 71.1, 41.7, 41.2, 32.4, 31.4, 27.6, 22.3; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 224 (100), 155 (37), 126 (15), 91 (43); elemental analysis calcd (%) for $C_{16}H_{23}O_3NS$: C 62.13, H 7.44, N 4.53, S 10.36; found: C 61.87, H 7.61, N 4.35, S 10.61.

General procedure for the Baeyer–Villiger oxidation of the cycloadducts: *m*-CPBA (1.1 equiv) was added to a 0.01M mixture of cyclobutanone (1 equiv) and sodium bicarbonate (3 equiv) in dichloromethane at 0 °C. The solution was stirred for about one hour (reaction time checked by TLC). The solution was washed with a 5% sodium thiosulfate solution, and the aqueous layer was extracted twice with dichloromethane. The organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The product was purified by flash chromatography or recrystallisation from hexane/EtOH.

(1*R*,6*S*,9*R*)-9-(Methyltosylamino)-8-oxabicyclo[4.3.0]octan-7-one (15): Compound **2** (328 mg, 1.30 mmol), *m*-CPBA (267 mg, 1.55 mmol) and $NaHCO_3$ (437 mg, 5.20 mmol) afforded **15** (375 mg, 93%, 93% *ee*) as a colourless solid. $[\alpha]_D^{20} = -14.7$ ($c = 1.0$ in $CHCl_3$); m.p. 103 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 6.20 (d, $J = 7.6$ Hz, 1H), 2.76 (s, 3H), 2.67 (m, 1H), 2.53 (m, 1H), 2.43 (s, 3H), 1.92–1.34 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.8$, 143.3, 134.4, 129.9, 127.8, 88.8, 39.5, 37.1, 27.7, 24.2, 23.3, 23.2, 21.8, 21.6; IR (neat): $\tilde{\nu} = 2950$, 2850, 1880, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 323 (5), 214 (100), 155 (22), 91 (24); elemental analysis calcd (%) for $C_{16}H_{21}O_4NS$: C 59.42, H 6.54, N 4.33; found: C 59.13, H 6.50, N 4.25; HPLC (AD column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 6.4 min (1*S*,6*R*,9*S*) and 13.7 min (1*R*,6*S*,9*R*).

(1*R*,6*S*,9*R*)-9-(Methyltosylamino)-8-oxabicyclo[4.3.0]oct-3-en-7-one (16): Compound **4** (200 mg, 0.65 mmol), *m*-CPBA (180 mg, 0.98 mmol) and $NaHCO_3$ (235 mg, 2.00 mmol) afforded **16** (193 mg, 92%, 86% *ee*) as a colourless solid. $[\alpha]_D^{20} = +4.9$ ($c = 1.4$ in CH_2Cl_2); m.p. 137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 2H), 5.97 (d, $J = 7.0$ Hz, 1H), 5.92 (m, 2H), 3.00–2.75 (m, 1H), 2.80–2.60 (m, 1H), 2.73 (s, 3H), 2.43 (s, 3H), 2.40–2.20 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 177.3$, 144.2, 134.5, 129.8, 127.8, 126.3, 125.9, 91.6, 37.6, 36.6, 27.9, 22.6, 22.6, 21.5; IR (neat): $\tilde{\nu} = 2923$, 2847, 1781, 1341, 1168 cm^{-1}; MS (EI): *m*/*z* (%): 321 (8), 214 (100), 155 (16), 91 (8); elemental analysis calcd (%) for $C_{16}H_{19}O_4NS$: C 59.80, H 5.96, N 4.36, S 9.98; found: C 59.65, H 6.02, N 4.26, S 9.86; HPLC (AD column; eluent *i*PrOH/hexane 1:9; flow: $v =$ 0.70 mL min^{-1}; $\lambda = 220$ nm): 4.6 min (1*S*,6*R*,9*S*) and 6.0 min (1*R*,6*S*,9*R*).

(1*R*,5*S*,8*R*)-8-(Methyltosylamino)-7-oxabicyclo[3.3.0]octan-6-one (17): Compound **5** (340 mg, 1.16 mmol), *m*-CPBA (240 mg, 1.40 mmol) and $NaHCO_3$ (390 mg, 4.64 mmol) afforded **17** (280 mg, 78% after recrystallisation, 98% *ee*) as a colourless solid. $[\alpha]_D^{20} = -63.6$ ($c = 1.1$ in $CHCl_3$); m.p. 144 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 6.00 (d, $J = 3.1$ Hz, 1H), 3.08 (m, 1H), 2.83 (m, 1H), 2.71 (s, 3H), 2.43 (s, 3H), 2.18–1.40 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 178.7, 144.2, 134.5, 129.8, 127.8, 93.3, 44.8, 44.2, 33.3, 31.4, 27.9, 25.2, 21.5; IR (neat): $\tilde{\nu} = 2950$, 2850, 1790, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 309 (7); elemental analysis calcd (%) for $C_{16}H_{21}O_4NS$: C 58.23, H 6.19, N 4.53; found: C 57.77, H 6.50, N 4.25; HPLC (AD column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 7.1 min (1*S*,5*R*,8*S*) and 20.4 min (1*R*,5*S*,8*R*).

(1*R*,5*S*,8*R*)-1-Methyl-8-(methyltosylamino)-7-oxabicyclo[3.3.0]octan-6-one (18): Compound **6** (209 mg, 0.68 mmol), *m*-CPBA (140 mg, 0.82 mmol) and $NaHCO_3$ (230 mg, 2.72 mmol) afforded **18** (134 mg, 61% after recrystallisation, 98% *ee*) as a colourless solid. $[\alpha]_D^{20} = -87.8$ ($c = 1.2$ in $CHCl_3$); m.p. 118 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 6.03 (s, 1H), 2.64 (s, 3H), 2.63 (m, 1H), 2.41 (s, 3H), 2.09 (m, 2H), 1.84–1.24 (m, 4H), 1.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 179.0$, 144.0, 134.8, 129.8, 124.4, 93.5, 50.5, 50.4, 41.9, 29.5, 29.3, 24.0, 21.5, 21.3; IR (neat): $\tilde{\nu} = 2950$, 2850, 1950, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 323 (11), 214 (100), 155 (30); elemental analysis calcd (%) for $C_{16}H_{21}O_4NS$: C 59.44, H 6.50, N 4.33, S 9.91; found: C 59.42, H 6.53, N 4.31, S 9.88; HPLC (AD column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 6.5 min (1*S*,5*R*,8*S*) and 46.4 min (1*R*,5*S*,8*R*).

(1*R*,7*R*,10*R*)-10-(Methyltosylamino)-9-oxabicyclo[5.3.0]decan-8-one (19): Compound **7-*trans*** (200 mg, 0.62 mmol), *m*-CPBA (160 mg, 0.93 mmol) and $NaHCO_3$ (225 mg, 1.87 mmol) afforded **19** (190 mg, 90%, 98% *ee*) as a colourless solid. $[\alpha]_D^{20} = -84.5$ ($c = 0.4$ in CH_2Cl_2); m.p. 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 2H), 5.87 (d, $J = 9.3$ Hz, 1H), 2.73 (s, 3H), 2.53 (td, $J = 11.2$, 5.2 Hz, 1H), 2.42 (s, 3H), 2.30–2.20 (m, 1H), 2.15–2.00 (m, 1H), 2.15–2.00 (m, 1H), 1.85–1.20 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.9$, 144.2, 135.1, 129.8, 127.8, 90.5, 45.9, 45.1, 29.1, 27.9, 27.7, 27.6, 26.9, 26.0, 21.5; IR (neat): $\tilde{\nu} = 2933$, 2852, 1775, 1345, 1160 cm^{-1}; MS (EI): *m*/*z* (%): 337 (8), 214 (72), 155 (12), 44 (100); HRMS: *m*/*z* calcd for $C_{17}H_{23}O_4NS$: 337.1348; found: 337.1345; HPLC (AD column; eluent *i*PrOH/hexane 1:9; flow: $v = 1$ mL min^{-1}; $\lambda =$ 220nm): 16.4 min (1*S*,7*S*,10*S*) and 25.7 min (1*R*,7*R*,10*R*).

(1*R*,8*R*,11*R*)-11-(Methyltosylamino)-10-oxabicyclo[6.3.0]undecan-9-one (20): Compound **8-*trans*** (120 mg, 0.35 mmol), *m*-CPBA (130 mg, 0.54 mmol) and $NaHCO_3$ (130 mg, 1.07 mmol) afforded **20** (115 mg, 95%, >92% *ee*) as a colourless solid. $[\alpha]_D^{20} = -83.8$ ($c = 0.6$ in CH_2Cl_2); m.p. 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 5.80 (d, $J = 8.6$ Hz, 1H), 2.70 (s, 3H), 2.47 (td, $J = 10.5$, 4.4 Hz, 1H), 2.43 (s, 3H), 2.35–2.00 (m, 4H), 1.95–1.60 (m, 4H), 1.60–1.30 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.9$, 144.1, 136.6, 129.8, 127.8, 91.2, 45.7, 44.9, 31.0, 29.8, 27.9, 27.1, 27.0, 25.2, 25.1, 21.5; IR (neat): $\tilde{\nu} = 2936$, 1773, 1344, 1167 cm^{-1}; MS (EI): *m*/*z* (%): 351 (10), 307 (10), 214 (100), 155 (12), 108 (6), 91 (24); HRMS: *m*/*z* calcd for $C_{17}H_{23}O_4NS$: 351.1504; found: 351.1513; HPLC (AD column with a silica column; eluent *i*PrOH/hexane 5:95; flow: $v = 1$ mL min^{-1}; $\lambda =$ 220nm): 32.3 min (1*S*,8*S*,11*S*) and 44.0 min (1*R*,8*R*,11*R*).

(2*R*,3*R*,4*R*)-2,3-Dimethyl-4-(methyltosylamino)butyrolactone (21): Compound **9-*trans*** (120 mg, 1.06 mmol), *m*-CPBA (220 mg, 1.27 mmol) and $NaHCO_3$ (355 mg, 4.25 mmol) afforded **21** (322 mg, 96%) in mixture with a minor *cis* isomer (ratio 98:2). After recrystallisation from ethanol/hexane,

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21 was obtained as a single isomer in 86% (>98% *ee*) as a colourless solid. $[\alpha]_D^{20} = -53.5$ ($c = 1.0$ in $CHCl_3$); m.p. 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 5.98 (d, $J = 7.8$ Hz, 1H), 2.82–2.50 (m, 2H), 2.74 (s, 3H), 2.45 (s, 3H), 1.24 (d, $J = 7.7$ Hz, 3H), 1.17 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 176.5$, 144.6, 135.0, 130.3, 128.2, 91.7, 43.0, 42.1, 28.3, 22.0, 14.4, 13.2; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1950, 1620, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 297 (10), 307 (10), 214 (100), 155 (37), 91 (33); elemental analysis calcd (%) for $C_{14}H_{19}O_4NS$: C 56.56, H 6.39, N 4.71, S 10.77; found: C 56.45, H 6.49, N 4.59, S 10.94; HPLC (AD column with a silica column; eluent EtOH; flow: $v = 0.5$ mL min^{-1}; $\lambda = 254$nm): 12.5 min (2*S*,3*S*,4*S*) and 25.0 min (2*R*,3*R*,4*R*).

(2*S*,3*S*,4*S*)-2,3-Dimethyl-4-(methyltosylamino)butyrolactone (22): Compound **10-*trans*** (224 mg, 0.75 mmol), *m*-CPBA (155 mg, 0.90 mmol) and $NaHCO_3$ (255 mg, 3.00 mmol) afforded **22** (216 mg, 92%, 68% *ee*). HPLC (AD column with a silica column; eluent EtOH; flow rate: 0.5 mL min^{-1}; $\lambda = 254$ nm): 12.5 min (2*S*,3*S*,4*S*) and 25.0 min (2*R*,3*R*,4*R*).

(2*R*,3*S*,4*R*)-2-Methyl-4-(methyltosylamino)-3-phenylbutyrolactone (23): Compound **11** (368 mg, 1.07 mmol), *m*-CPBA (220 mg, 1.27 mmol) and $NaHCO_3$ (355 mg, 4.25 mmol) afforded **23** (355 mg, 92%, 86% *ee*). After recrystallisation from ethanol/hexane, **23** was obtained as a colourless solid (250 mg, 65%, 98% *ee*). $[\alpha]_D^{20} = -19.4$ ($c = 1.0$ in $CHCl_3$); m.p. 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.2$ Hz, 2H), 7.44–7.23 (m, 7H), 6.36 (d, $J = 9.2$ Hz, 1H), 3.17 (dd, $J = 12.3$, 9.2 Hz, 1H), 2.91 (m, 1H), 2.81 (s, 3H), 2.39 (s, 3H), 1.24 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.9$, 144.9, 135.5, 135.3, 130.0, 129.6, 128.7, 128.0, 127.9, 91.0, 53.3, 43.6, 28.7, 22.3, 13.8; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1790, 1620, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 359 (4), 331 (19), 118 (100), 91 (28); elemental analysis calcd (%) for $C_{19}H_{21}O_4NS$: C 63.51, H 5.85, N 3.90, S 8.91; found: C 63.57, H 5.90, N 3.84, S 9.00; HPLC (AD column with a silica column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 7.6 min (2*R*,3*S*,4*R*) and 10.9 min (2*S*,3*R*,4*S*).

(3*S*,4*R*)-4-(Methyltosylamino)-3-phenylbutyrolactone (24): Compound **12** (374 mg, 1.14 mmol), *m*CPBA (235 mg, 1.36 mmol) and $NaHCO_3$ (380 mg, 4.60 mmol) afforded **24** (382 mg, 97%, 31% *ee*) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.4$ Hz, 2H), 7.47–7.22 (m, 7H), 6.38 (d, $J = 8.4$ Hz, 1H), 3.66 (ddd, $J = 10.4$, 9.6, 8.4 Hz, 1H), 2.92 (ddd, $J = 17.7$, 10.4, 9.6 Hz, 2H), 2.81 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 173.1$, 144.0, 136.6, 134.6, 129.9, 129.4, 128.3, 127.9, 127.1, 92.7, 44.0, 36.2, 27.8, 21.3; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1785, 1600, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 345 (20), 317 (10), 104 (100), 91 (11); elemental analysis calcd (%) for $C_{18}H_{19}O_4NS$: C 62.59, H 5.54, N 4.05; found: C 62.46, H 5.46, N 3.90; HPLC (AD column with a silica column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 17.5 min (3*S*,4*R*) and 19.8 min (3*R*,4*S*).

(3*R*,4*R*)-3-*n*-Butyl-4-(methyltosylamino)butyrolactone (25): Compound **13** (330 mg, 1.07 mmol), *m*CPBA (220 mg, 1.28 mmol) and $NaHCO_3$ (360 mg, 4.27 mmol) afforded **25** (330 mg, 95%, 48% *ee*) as a colourless solid. M.p. 86 °C; ^{1}H NMR (200 MHz, C_6D_6): $\delta = 7.80$ (d, $J = 8.3$ Hz, 2H), 6.80 (d, $J = 8.3$ Hz, 2H), 5.90 (d, $J = 8.6$ Hz, 1H), 2.30 (s, 3H), 2.02 (dd, $J = 16.3$, 7.7 Hz, 1H), 1.85 (s, 3H), 1.70 (m, 1H), 1.49 (dd, $J = 16.3$, 9.9 Hz, 1H), 1.20–0.70 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 173.6$, 144.1, 134.5, 129.7, 127.7, 92.4, 39.0, 34.8, 31.6, 29.2, 27.9, 22.4, 21.4, 13.7; IR (neat): $\tilde{\nu} = 3050$, 2950, 2850, 1785, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 325 (5), 214 (100), 155 (34), 91 (42); elemental analysis calcd (%) for $C_{16}H_{23}O_4NS$: C 59.08, H 7.08, N 4.31, S 9.84; found: C 58.88, H 7.05, N 4.15, S 9.88; HPLC (AD column with a silica column; eluent EtOH/hexane 1:1; flow: $v = 1$ mL min^{-1}; $\lambda = 254$ nm): 6.0 min (3*R*,4*R*) and 9.7 min (3*S*,4*S*).

(3*S*,4*R*)-3-*tert*-Butyl-4-(methyltosylamino)butyrolactone (26): Compound **14** (154 mg, 0.50 mmol), *m*CPBA (105 mg, 0.60 mmol) and $NaHCO_3$ (170 mg, 2.00 mmol) afforded **26** (144 mg, 89%, 76% *ee*). After recrystallisation from ethanol/hexane, **26** was obtained as colourless solid (130 mg, 80%, 95% *ee*). M.p. 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.3$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 6.25 (d, $J = 6.0$ Hz, 1H), 2.70 (s, 3H), 2.46–2.36 (m, 3H), 2.43 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 173.9$, 143.9, 134.4, 129.5, 127.6, 89.4, 48.2, 31.9, 30.5, 27.6, 26.6, 21.3; IR (neat) $\tilde{\nu} = 3050$, 2950, 2850, 1950, 1360, 1170 cm^{-1}; MS (EI): *m*/*z* (%): 325 (12), 214 (100), 155 (24), 91 (39); elemental analysis calcd (%) for $C_{16}H_{23}O_4NS$: C 59.08, H 7.08, N 4.31, S 9.84; found: C 58.91, H 7.10, N 4.18, S 9.93; HPLC (AD column with a silica column; eluent EtOH; flow: $v = 0.5$ mL min^{-1}; $\lambda = 254$ nm): 12.8 min (3*S*,4*R*) and 14.8 min (3*R*,4*S*).

(1*S*,5*S*)-7-Oxabicyclo[3.3.0]octan-6-one (27): Lactone **17** (150 mg, 0.49 mmol) in a 0.5 M aqueous solution of H_2SO_4 (1.5 mL) was heated at 50 °C in THF (3 mL) for 2 d. The solvent was removed in vacuo and dichloromethane (5 mL) and water (5 mL) were added. The organic phase was separated and the aqueous phase was extracted twice with dichloromethane (5 mL). Organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was dissolved in ethanol (10 mL) and the solution was cooled to 0 °C. $NaBH_4$ (20 mg, 0.49 mmol) was added to this solution. The mixture was stirred for 1 h at room temperature. The solvent was removed in vacuo, and dichloromethane (5 mL) and a 1 M solution of aqueous HCl (5 mL) was added. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane (5 mL). The organic phases were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (AcOEt/heptane 10:90) to afford **27** (40 mg, 65%). RN: 113428-55-0. $[\alpha]_D^{20} = +87.5$ ($c = 2.0$ in $CHCl_3$).

(2*R*,3*R*)-2,3-Dimethyl-1,4-butanediol (28): Lactone **21-*trans*** (150 mg,0.51 mmol) dissolved in THF (5 mL) was added to a suspension of $LiAlH_4$ (57 mg, 1.51 mmol) in THF (5 mL). The mixture was heated at reflux for 2 h and was then cooled to 0 °C for the addition of water (2 mL). The white precipitate was filtered, then dissolved in THF (10 mL) and heated for 10 min. The precipitate was filtered. The organic phases were combined and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (AcOEt) to afford **28** (44 mg, 75%). RN: 127-53-15-0. $[\alpha]_D^{20} = +5.2$ ($c = 1.7$, Et_2O).

(1*S,6*S**)-9-Hydroxy-8-oxabicyclo[4.3.0]octan-6-one (37a)**: RN: 65641-39-6. Lactone **15** (500 mg, 1.54 mmol) in a 0.5 M aqueous solution of H_2SO_4 (3 mL) was heated at 50 °C in THF (5 mL) for 2 days. The solvent was removed in vacuo and dichloromethane (5 mL) and water (5 mL) were added. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane (5 mL). Organic phases were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexane 1:9) to afford the title compound (211 mg, 89%). The ^{1}H NMR was consistent with that reported in literature.[18]

(1*S,6*S**)-9-Methoxy-8-oxabicyclo[4.3.0]octan-6-one (37b)**: Lactone **15** (150 mg, 0.46 mmol) and a catalytic amount of *p*-TsOH were heated at 60 °C in methanol (10 mL) for 12 h. The reaction mixture was washed, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexane 1:9) to afford the title compound (62 mg, 80%) as a mixture of *endo* and *exo* isomers in a ratio 15:85. **37b-*endo*** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.30$ (d, $J = 4.5$ Hz, 1H), 3.56 (s, 3H), 2.67 (m, 1H), 2.36 (m, 1H), 2.10–1.00 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 178.1$, 106.6, 57.9, 40.3, 38.7, 22.6, 22.5, 22.5, 21.3; **37b-*exo*** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.95$ (s, 1H), 3.45 (s, 3H), 2.90 (m, 1H), 2.51 (m, 1H), 2.10–1.00 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 178.4, 107.4, 56.3, 40.7, 37.0, 25.6, 22.8, 22.3, 22.2; IR (neat): $\tilde{\nu} = 2950$, 2850, 1780 cm^{-1}; MS (EI): *m*/*z* (%): 139 (6), 126 (19), 82 (100), 79 (71).

(1*S,6*S**)-9-Cyclohexanoxy-8-oxabicyclo[4.3.0]octan-6-one (37c)**: Lactone **15** (150 mg, 0.46 mmol), cyclohexanol (46 mg, 0.51 mmol) and a catalytic amount of *p*-TsOH were heated at 60 °C in 1,2-dichloroethane (5 mL) for 12 h. The reaction mixture was washed, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/hexane 1:9) to afford the title compound (70 mg, 65%). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.62$ (s, 1H), 3.83 (m, 1H), 2.99 (m, 1H), 2.18 (m, 1H), 2.10–1.00 (m, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 178.2, 104.3, 51.0, 41.1, 37.4, 33.1, 31.4, 25.5, 25.2, 23.7, 23.6, 22.9, 22.4, 22.3; IR (neat): $\tilde{\nu} = 2950$, 2850, 1770 cm^{-1}; MS (IC–): *m*/*z* (%): 237 (100).

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