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Synthesis of 2-Azabicyclo[4.1.0]heptanes through Stereoselective Cyclopropanation Reactions

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Unsaturated δ-lactams are cyclopropanated with the aid of diazo compound decomposition catalysed by metal complexes. A study of the reaction conditions, stereochemical outcome and group protection is reported. The resulting bicyclic products are related to bioactive compounds. Transformation into thiolactams facilitates the separation of the different isomers obtained and the removal of the protecting group. The cyclopropanation reaction works with diverse diazo compounds.

Introduction

The synthesis of highly functionalized chiral cyclopropanes is of interest because many biologically active compounds contain cyclopropane moieties.[1,2] These units are also present in important synthetic intermediates, especially for the synthesis of condensed polycycles and molecules of higher complexity, and have attracted considerable interest in medicinal chemistry, due to their potential to control conformation by restricting the number of rotational degrees of freedom. Most recent synthetic efforts have focused on stereoselective cyclopropanation reactions.[3]

On the other hand, the syntheses of many 2-pyridine-containing compounds[4] have been developed because these moieties are contained in potent antitumor,[5] antiviral[6] and antimicrobial[7] agents. We envisioned that 2-pyridones fused with cyclopropane rings might present interesting biological activities or be useful intermediates in syntheses of bioactive products.[8] In particular, certain amidines derived from tetrahydro-2-pyridones have shown high inhibitory activities against nitric oxide synthase (NOS). Identification of potent and selective inhibitors of iNOS (the inducible isoform of NOS) has been the subject of intense interest because of their therapeutic potential in the treatment of diseases mediated by overexpression of nitric oxide (NO). This need has been met through the design of a rigid ligand bearing a cyclopropane unit fused to a cyclic amidine. A good example of such a system is ONO-1714, a selective iNOS inhibitor currently undergoing evaluation in a Phase II clinical trial.[9]

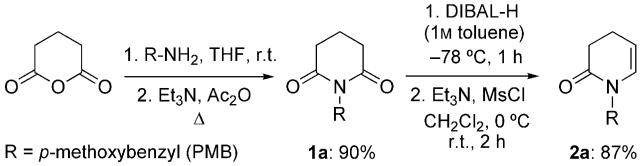
We therefore set out to develop efficient synthetic strategies for the construction of 2-azabicyclo[4.1.0]heptanes. For the key cyclopropanation step we chose transition-metal-catalysed decomposition of diazo compounds. Intermolecular cyclopropanation mediated by $Rh_2(OAc)_4$ or $Cu(OAc)_2$ continues to provide a powerful tool for the construction of constrained systems from diazo precursors, with high levels of diastereoselectivity. Many related chiral metal complexes are able to give high enantioselectivities.[10]

In a previous paper we presented our preliminary results on cyclopropanation of unsaturated lactams, based on the use of a number of metal catalysts to decompose diazo compounds.[11] Initial attempts, however, were thwarted by our inability to cleave the protecting group from the lactam efficiently.

We now present all the synthetic details for the developed highly stereoselective intermolecular cyclopropanation and describe its scope and limitations, together with the effects of varying the catalyst and the protecting group.

Results and Discussion

In order to conduct an extended study of the cyclopropanation of compounds **2**, we optimised the supply of these materials by means of the route shown in Scheme 1. Our aim was to study the influence of the protecting group on



R = *p*-methoxybenzyl (PMB)	**1a**: 90%	**2a**: 87%
R = 2,4-dimethoxybenzyl (Dmob)	**1b**: 89%	**2b**: 98%
R = benzyl (Bn)	**1c**: 91%	**2c**: 92%
R = *o*-*tert*-butylphenyl (*o*-*t*BuPh)	**1d**: 93%	**2d**: 80%
R = *p*-methoxyphenyl (PMP)	**1e**: 93%	**2e**: 92%

Scheme 1. Synthesis of substrates **2a**–**e**.

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the yield and selectivity of the cyclopropanation step, as well as the feasibility of the deprotection step.

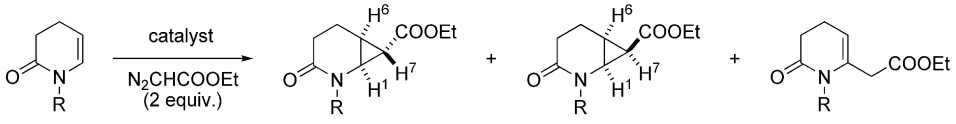
The compounds **2a**–**e** were prepared by a procedure described by Kawanaka,[12] with certain modifications. After aminolysis of glutaric anhydride and formation of the imides **1a**–**e** we carried out the reduction of **1a**–**e** with DIBAL-H.[13] For the subsequent dehydration step we treated the intermediates with mesyl chloride in the presence of triethylamine as the base, which resulted in the formation of compounds **2** in 73–87% overall yields from glutaric anhydride.

We next examined a set of conditions for cyclopropanation with ethyl diazoacetate (EDA, Table 1). Firstly, some conventional achiral catalysts were used. In all reactions with compound **2a**, the two diastereomeric cyclopropanes *trans*-**3a** and *cis*-**3a** were isolated together with unreacted starting material and a minor compound which was assigned as the insertion product **4**. Temperature, solvent, catalyst loading and reagent ratios were examined. Catalyst loading produced only slight variation in yields, and was fixed at 4% because no significant improvement was observed on increasing this value (Entries 1–3). Use of rhodium acetate gave better results than that of other metal acetates such as palladium or copper (Entries 2 and 4–5). Solvent and reaction temperature were chosen according to conventional reaction conditions described in the literature.[10] CH_2Cl_2 gave the best results, and levels of conversion were not improved by increasing temperature (Entries 6–7). EDA was added slowly by pump syringe. Several addition periods were tested and 4 h were fixed as the best option, with longer addition periods not producing any improvement (Entry 8). At this point we had achieved a good diastereomeric ratio, although chemical yields were still not satisfactory. In all the reactions, the major compound was *trans*-**3a**; stereochemical assignment was carried out by means of n.O.e. experiments.[14]

The conditions shown in Entry 1 were then used with a selection of chiral catalysts. When using chiral complexes we were pleased to observe a general improvement in the yields. In particular, copper complexes gave good results, maintaining high diastereomeric ratios. These catalysts were prepared in situ by treatment of CuOTf with the ligands **5**–**7** depicted in Figure 1.[15] In addition, two rhodium catalysts were used (Entries 12–13),[16] but these gave worse results than those obtained with copper in terms of global yield, *dr* and *ee*. The enantiomeric excesses were measured by chiral HPLC (see Exp. Sect.). As shown in Entries 10 and 11, these *ee* values are low, although it is interesting that the major enantiomers are different in the reactions of Entries 10 and 11.

The conditions listed in Entry 11 were selected for reactions with substrates **2b**–**e** (Entries 14 and 16–18). With compound **2b** the chemical yields of cyclopropane **3b** were slightly lower than for **2a**, with a decrease in diastereoselectivity also being observed (Entry 14). We therefore tried a different Cu^I complex, with ligand **6** (Entry 15), but obtained a lower level of conversion. These conditions, however gave *trans*-**3b** with a moderate *ee* (33%), whereas the

Table 1. Reaction conditions for the cyclopropanation of enamides **2a**–**e**.



2a–e *trans*-**3a–e** *cis*-**3a–e** **4a,b**

Entry[a]	R	Substrate	Catalyst	mol-% cat.	Solvent	Time addition	Yield [%][b] **2**	*trans*-**3**	*cis*-**3**	**4**	% *dr*[c] *trans*/*cis*	% *ee* *trans*-**3**[d]
1	PMB	**2a**	$Rh_2(OAc)_4$	1	CH_2Cl_2	2 h	27	25	15	6	66:33	–
2	PMB	**2a**	$Rh_2(OAc)_4$	4	CH_2Cl_2	4 h	25	45	5	5	90:10	–
3	PMB	**2a**	$Rh_2(OAc)_4$	8	CH_2Cl_2	4 h	26	32	20	5	57:43	–
4	PMB	**2a**	$Cu(OAc)_2$	4	CH_2Cl_2	4 h	32	19	10	8	67:33	
5	PMB	**2a**	$Pd_2(OAc)_4$	4	CH_2Cl_2	4 h	75	>5	–	–	–	
6[e]	PMB	**2a**	$Rh_2(OAc)_4$	4	CH_2Cl_2	4 h	29	35	11	8	71:29	–
7	PMB	**2a**	$Rh_2(OAc)_4$	4	pentane	4 h	24	27	15	6	61:39	–
8	PMB	**2a**	$Rh_2(OAc)_4$	4	CH_2Cl_2	8 h	29	25	19	5	60:40	–
9	PMB	**2a**	CuOTf/**5**	1:1	CH_2Cl_2	4 h	20	59	6	6	82:18	40
10	PMB	**2a**	CuOTf/**6**	1:1	CH_2Cl_2	4 h	28	52	4	7	87:13	75
11	PMB	**2a**	CuOTf/**7**	1:1	CH_2Cl_2	4 h	18	62	10	5	78:22	–55
12	PMB	**2a**	Rh_2[2S-DOSP]$_4$[13]	1	CH_2Cl_2	4 h	29	25	20	7	56:44	0
13	PMB	**2a**	Rh_2[2S-TBSP]$_4$[13]	1	CH_2Cl_2	4 h	31	28	14	8	60:40	0
14	Dmob	**2b**	CuOTf/**7**	1:1	CH_2Cl_2	4 h	20	47	25	5	62:38	15
15	Dmob	**2b**	CuOTf/**6**	1:1	CH_2Cl_2	4 h	57	26	9	7	73:27	33
16	Bn	**2c**	CuOTf/**7**	1:1	CH_2Cl_2	4 h	40	25	<5	–	81:19	n.c.[f]
17	*o*-*t*BuPh	**2d**	CuOTf/**7**	1:1	CH_2Cl_2	4 h	30	25	<5	–	75:25	n.c.[f]
18	PMP	**2e**	CuOTf/**7**	1:1	CH_2Cl_2	4 h	18	55	<5	–	85:15	n.c.[f]

[a] The reactions were carried out under argon, with EDA (2 equiv.) slowly added by syringe pump. [b] Of pure product, with correct analytical and spectroscopic data. [c] % *dr* was determined by ^1H NMR examination of the crude mixture. [d] % *ee* was determined by HPLC analysis with a CHIRAL-AGP (100 × 4.0 mm) column. [e] All reactions were carried out at room temp. except for that of Entry 6, which was performed under reflux. [f] n.c.: not calculated.

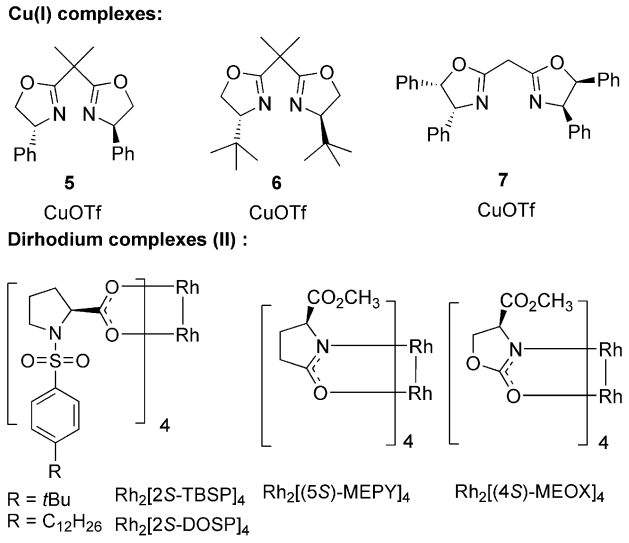
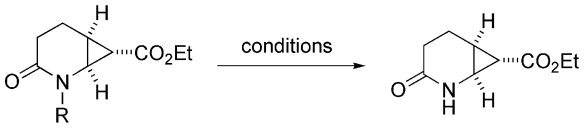


Figure 1. Chiral catalytic systems used.

Table 2. Deprotection reactions of **3a**–**e**.



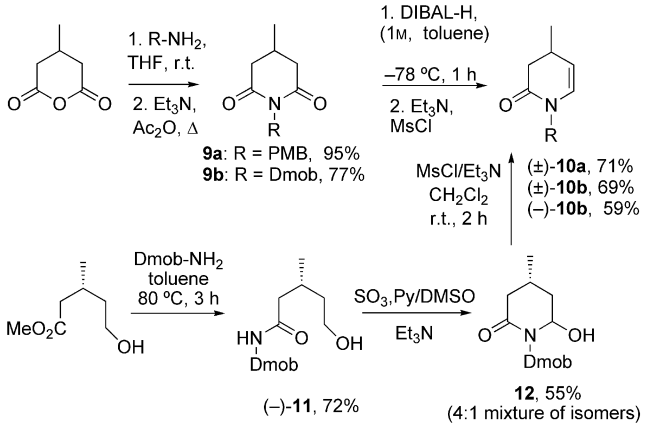
Entry	R	Reagent	Conditions	Yield [%]
1	PMB	TFA	80 °C, 48 h	20
2	PMB	H_2, Pd/C	AcOEt/MeOH, 50 °C, 94 h	n.r.[a]
3	PMB	$AlCl_3$	anisole, r.t.	n.r.[a]
4	PMB	$BF_3{\cdot}OEt_2$	anisole, 100 °C, 35 h	dec.[b]
5	PMB	CAN[c]	CH_3CN/H_2O (7:3)	dec.
6	PMB	DDQ[d]	CH_2Cl_2/H_2O	n.r.[a]
7	Dmob	TFA	80 °C, 16 h	36
8	Bn	H_2, Pd/C	AcOH/EtOH, r.t.	n.r.[a]
9	Bn	$AlCl_3$	benzene, r.t.	n.r.[a]
10	Bn	Na/NH_3	THF, r.t.	n.r.[a]
11	*o*-*t*BuPh	CAN[c]	CH_3CN/H_2O (7:3), r.t.	dec.[b]
12	PMP	CAN[c]	CH_3CN/H_2O (7:3), r.t.	dec.[b]

[a] n.r.: no reaction. [b] dec.: decomposition. [c] CAN: ceric(IV) ammonium nitrate. [d] DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone.

reaction of Entry 14 had given only 15% *ee*. Cyclopropanation of **2c** and **2d** proceeded with low levels of conversion, with large amounts of starting materials being recovered. Compounds *trans*-**3c** and *trans*-**3d** were isolated in low yields (Entries 16–17). Finally, the PMP-protected product *trans*-**3e** was obtained with a good yield and diastereoselectivity (Entry 18). From these results we can conclude that PMB and Dmob are the groups that give better chemical yields, with PMB being the one that gives better selectivity.

We next checked the feasibility of removing the protecting group (Table 2). Many experimental procedures for the removal of the PMB group have been reported in the literature. We started by treating *trans*-**3a** with TFA at 80 °C (Entry 1), which sluggishly gave a crude product from which only a 20% yield of the desired product *trans*-**8** could be isolated (Entry 1). Attempted hydrogenolysis or treatment with $AlCl_3$ produced no observable reaction (Entries 2 and 3). On the other hand, use of $BF_3{\cdot}OEt_2$ or CAN resulted in extensive decomposition of the starting compound (Entries 4 and 5). A final attempt with DDQ failed to produce any deprotection (Entry 6). We next subjected compound *trans*-**3b** to treatment with TFA and observed a much cleaner reaction that gave *trans*-**8** in 36% yield (Entry 7). We then examined the elimination of the benzyl group from *trans*-**3c**. Unfortunately none of the conditions tested (attempted hydrogenolysis, treatment with $AlCl_3$ or reductive NH_3/Na conditions, Entries 8–10) provided any conversion into the unprotected lactam. Finally both *trans*-**3d** and *trans*-**3e** were treated with CAN, which led to complex reaction mixtures (Entries 11 and 12). We therefore selected Dmob as the best protecting group, although without yet having achieved a satisfactory result in the deprotection step.

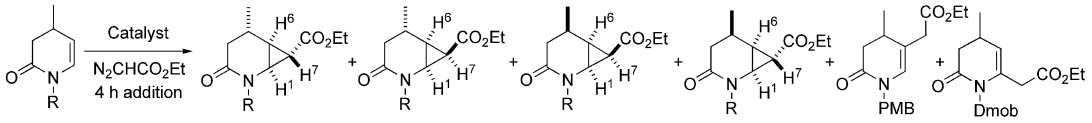
Our following target was the cyclopropanation of 4-substituted lactams. As a model system we selected the substrates **10a** and **10b** (Scheme 2), because these lactams bear methyl substituents as present in ONO-1714.[9] The methyl group at the 4-position is thought to be important for biological activity.[9] We prepared the two starting lactams with PMB and Dmob as protecting groups by a methodology similar to that used for the substrates **2**. In addition we prepared the enantiomerically pure substrate (–)-**10b** from methyl (3*R*)-5-hydroxy-3-methylpentanoate, which was subjected to aminolysis to yield the compound (–)-**11** (72%).[11] Oxidation of the hydroxy group formed the cyclic hemiaminal **12** as a mixture of diastereomers, which upon dehydration gave the desired lactam (–)-**10b** in 59% yield.



Scheme 2. Synthesis of the substrates **10a**, **10b** and (–)-**10b**.

We carried out cyclopropanations of these unsaturated lactams under the previously determined best reaction conditions (Table 1, Entry 2). Use of the chiral catalysts with the racemic substrates resulted in the observation of slight kinetic resolution. Compound (±)-**10a** was thus treated under the conditions indicated in Table 3, giving mixtures of the four possible diastereomers **13a**, with the *anti-trans* isomer in all cases being the major one. A small amount of the insertion compound **14** was also obtained. This time,

Table 3. Reaction conditions for cyclopropanations of the enamides (±)-**10a**, (±)-**10b** and (–)-**10b**.



Entry	Substrate	R	Catalyst	mol-% cat.	Yield [%][a] **10**	**13** combined	*anti-trans*-**13**	*anti-cis*-**13**	**14/15**	% *dr*[b]	% *ee* *anti-trans*[c]
1	(±)-**10a**	PMB	$Rh_2(OAc)_4$	4	30	60	36	18	8	57:28:8:7	–
2	(±)-**10a**	PMB	$Cu(OAc)_2$	4	22	72	41	16	6	63:13:18:6	–
3	(±)-**10a**	PMB	CuOTf/**6**	1:1	30	41	25	10	2	80:12:0:0	18
4	(±)-**10a**	PMB	CuOTf/**7**	1:1	18	72	50	10	7	57:25:12:6	14
5	(±)-**10a**	PMB	Rh_2[(4*S*)-MEOX]$_4$	1:1	28	70	30	36	5	39:52:9:0	9
6	(±)-**10a**	PMB	Rh_2[(5*S*)-MEPY]$_4$	1:1	31	66	32	29	5	49:35:13:3	18
7	(±)-**10b**	Dmob	CuOTf/**6**	1:1	72	–	12	4	12	71:29:0:0	16
8	(±)-**10b**	Dmob	CuOTf/**7**	1:1	33	–	54	6	7	90:10:0:0	0
9	(–)-**10b**	Dmob	$Rh_2(OAc)_4$	4	38	–	23	12	>5	65:35:0:0	>99
10	(–)-**10b**	Dmob	CuOTf/**7**	1:1	28	–	52	>5	4	95:05:0:0	>99

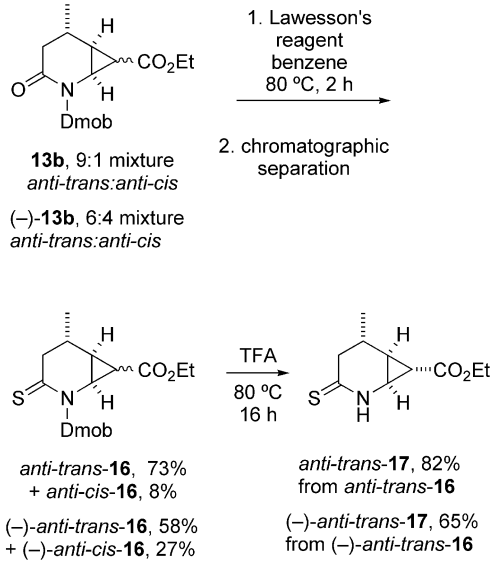
[a] Of pure product, with correct analytical and spectroscopic data. [b] % *dr* was determined by ^{1}H NMR examination of the crude mixture. [c] % *ee* was determined by HPLC analysis with a CHIRAL-AGP (100 × 4.0 mm) column.

insertion of EDA occurred in the 5-position of the ring. This surprising change in the regiochemistry of the insertion product is evident from the chemical shift value of the remaining olefinic proton. We do not have an explanation for this result because the presence of a methyl group should have favoured the same result as for **2a** [i.e., insertion at C–H(6)]. Good results in terms of global yield were obtained with $Cu(OAc)_2$ (Entry 2), although still with poor diastereoselectivity.

When using chiral catalysts, we observed good levels of conversion. The best result, in terms both of total yield and of diastereoselectivity, was achieved with the complex CuOTf/**7** (Entry 4, Table 3). The major product, *anti-trans*-**13a**, was isolated in 50% yield as a pure scalemic compound (14% *ee*). The overall yield of this reaction was 72%. All the isomers could be separated and independently characterized by use of n.O.e. experiments to assign relative stereochemistry.[17] Two chiral rhodium catalysts, selected from the most frequently used in the literature, and different from those tested with previous substrates, because those had given unsatisfactory results, were used with (±)-**10a**. Rh_2[(4*S*)-MEOX]$_4$[18] and Rh_2[(5*S*)-MEPY]$_4$[19] (Entries 5 and 6) gave cyclopropanes in similar chemical yields, although the diastereoselectivity was lower than for copper catalysts. Interestingly, in the reaction in the presence of Rh_2[(4*S*)-MEOX]$_4$ the major product was *anti-cis*-**13a**. On the other hand cyclopropanation of (±)-**10b** gave similar results in terms of chemical yield but with good diastereoselection. Only *anti* products could be detected under the two sets of reaction conditions used (Entries 7 and 8), and compound *anti-trans*-**13b** was strongly predominant in the crude mixtures, especially with CuOTf/**7** as the catalyst. One problem in these two reactions was the separation of the two **13b** isomers, which could not be completely achieved. The major product *anti-trans*-**13b** was isolated in 54% yield (Entry 8), whereas *anti-cis*-**13b** was obtained as a 5:2 mixture with the major isomer. Finally (–)-**10b** was treated with $Rh_2(OAc)_4$ as the catalyst and moderate conversion into a mixture of the two (–)-**13b** *anti* isomers was observed (Entry 9), with recovery of starting material (38%). The reaction in the presence of CuOTf/**7** gave (–)-*anti-trans*-**13b** in 52% yield with the *anti-cis* isomer also being detectable in the crude mixture (Entry 10). The insertion byproduct in all the reactions with substrate **10b** was **15**, involving a C–H insertion at the 6-position.

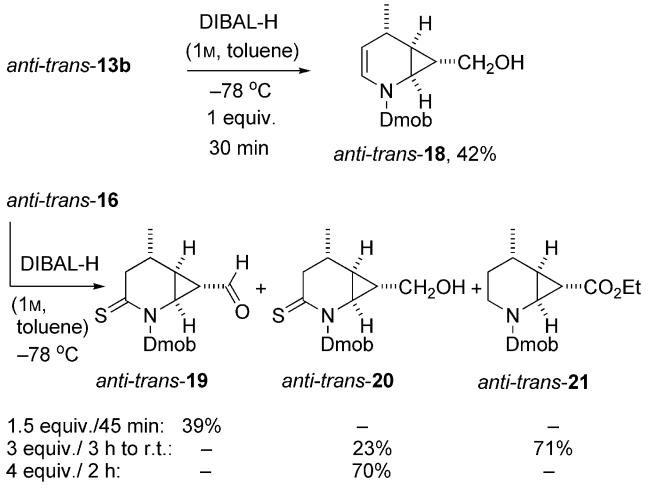
One possible solution to achieving efficient deprotection of the bicyclic compounds synthesized above was to carry out a functional group transformation; this might, in addition, also favour a cleaner isomer separation. We decided to convert the lactam group into a thiolactam, because this group allows many further modifications. The synthesis of possibly active products such as amidines[11] or iminosugar-derived compounds could therefore be envisioned. The mixture of *anti-trans*-**13b** and *anti-cis*-**13b** (9:1) obtained in the reaction of Entry 8, Table 3, was thus transformed into the corresponding thioamido derivatives by treatment with Lawesson's reagent (Scheme 3). We were pleased to obtain the corresponding mixture of isomeric thiolactams, which could be separated to give a 73% yield of *anti-trans*-**16** and an 8% yield of *anti-cis*-**16**. In addition, removal of the Dmob group with TFA gave *anti-trans*-**17** in 82% yield. In view of this pleasing result we subjected the corresponding mixture of enantiomerically pure (–)-*anti-trans*-**13b** and its *anti-cis* isomer to the same transformation and obtained (–)-*anti-trans*-**16** and (–)-*anti-cis*-**16** in high yields. The first isomer was deprotected efficiently to give (–)-*anti-trans*-**17**.

Our next goal was to explore different substitution at the 7-position in the bicyclic system. The first idea was to reduce the ester group selectively. Unfortunately, treatment of *anti-trans*-**13b** with DIBAL-H (1 equiv.) resulted in the formation of compound *anti-trans*-**18** (Scheme 4) in 42% yield with recovery of starting material. We thus studied the reduction of the corresponding thioamide. With this sub-



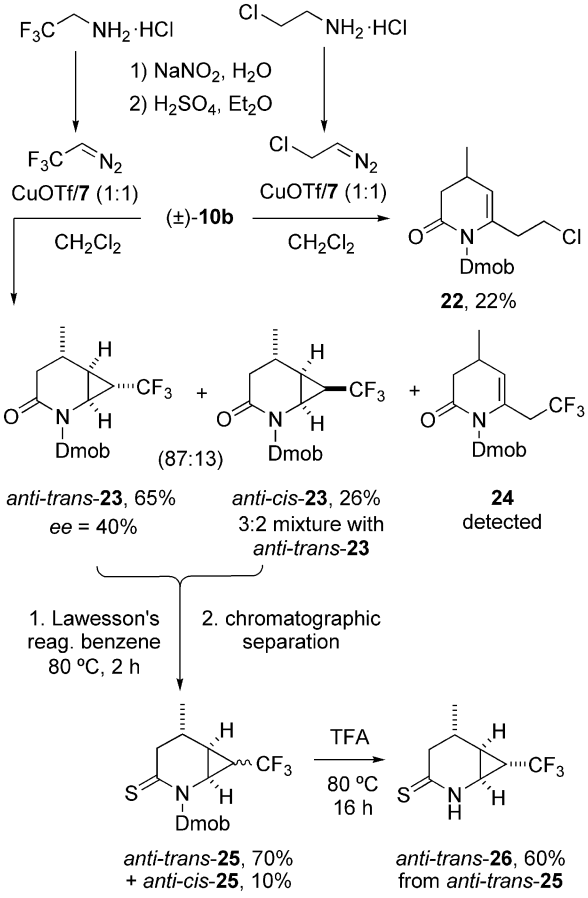
Scheme 3. Conversion to compounds **17**.

strate we were able to isolate three different products, depending on the amount of DIBAL-H used. With 1.5 equiv. the only product formed, albeit in low yield, was the aldehyde *anti-trans*-**19**. An increase to 3 equiv. did not improve the result, and when the mixture was allowed to come room temp. after the addition of the reagent we obtained a mixture of *anti-trans*-**20** and *anti-trans*-**21**, meaning competition from the thiolactam group, which is reduced at higher temperatures. Finally, use of DIBAL-H (4 equiv.) at low temperature allowed the isolation of *anti-trans*-**20** as the only reaction product in good yield (70%).



Scheme 4. Reduction of *anti-trans*-**13b** and *anti-trans*-**16**.

One interesting extension of this work was a study of the cyclopropanation reaction with other diazo compounds. We thus subjected the substrate (±)-**10b** to treatment with 2-chlorodiazoethane and 1,1,1-trifluorodiazoethane, both reagents prepared in situ from the corresponding ethylamine hydrochlorides by reported methodology.[21] Treatment with 2-chlorodiazoethane produced no cyclopropanes but a low yield of the insertion product **22** (Scheme 5). On the other hand, on treatment with the trifluoromethyl-containing diazo compound, we were pleased to obtain a mixture of the cyclopropanes *anti-trans*-**23** and *anti-cis*-**23** together with a small amount of the corresponding insertion product **24**. Separation of the isomers allowed the isolation of a 65% yield of *anti-trans*-**23** as a scalemic product with *ee* = 40%. The minor isomer *anti-cis*-**23** could not be completely separated, so we proceeded as in the previous cases, transforming the mixture of isomers as obtained from the cyclopropanation reaction into the corresponding thiolactams. These could be efficiently separated to give *anti-trans*-**25** (70%) and *anti-cis*-**25** (10%).[22] The major isomer was further deprotected to give *anti-trans*-**26** in good yield (60%).



Scheme 5. Synthesis of trifluoromethyl-substituted cyclopropanes.

Conclusions

In conclusion, an efficient and highly diastereoselective intermolecular cyclopropanation reaction has allowed the synthesis of new potentially active bicyclo[4.1.0] compounds. The transformation of the lactam group into the thiolactam system has revealed a convenient way to improve isomer separation and deprotection efficiency. The resulting structures are related to active compounds and can

further be easily functionalised. Investigation of the biological activities of the newly synthesized compounds is currently underway.

Experimental Section

Syntheses of compounds **9a** and (±)-**10a** are described in the literature.[9,12]

General Procedure for the Formation of the Imides 1a–e: The appropriate amine (37.00 mmol) was added at room temperature to a stirred solution of glutaric anhydride (35.00 mmol) in THF (60 mL) and the system was stirred for 30 min. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was diluted with EtOAc (25 mL). The resulting mixture was treated with HCl (1 M, 20 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine (30 mL), dried with anhydrous magnesium sulfate and concentrated to afford a residue, which was used for the subsequent reaction without further purification.

Et_3N (51.00 mmol) was added at room temperature to a stirred solution of the compound obtained above in Ac_2O (10 mL). The reaction mixture was heated at 80 °C for 1 h. After completion of the reaction, the mixture was allowed to cool to room temperature and the solvents were evaporated. The residue was diluted with EtOAc (10 mL). The organic layer was washed with aqueous HCl (1 M, 30 mL), saturated aqueous sodium hydrogen carbonate (30 mL) and brine (30 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

1-(4-Methoxybenzyl)piperidine-2,6-dione (1a): This compound was obtained as a yellow pale oil (7.100 g, 90%, hexane/EtOAc 7:3) by the General Procedure for the formation of imides, from glutaric anhydride (4.000 g, 35.38 mmol) and 4-methoxybenzylamine (5.36 mL, 37.39 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84–1.92 (m, 2 H), 2.66 (t, J = 6.6 Hz, 4 H), 3.78 (s, 3 H), 4.88 (s, 2 H), 6.80–6.83 (m, 2 H), 7.34 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 32.5, 41.7, 54.9, 113.4, 129.3, 130.0, 158.5, 172.8 ppm. IR (film): $\tilde{\nu}$ = 3440, 2970, 2.880, 1730, 1660, 1576, 1510 cm^{-1}. MS (ESI): m/z = 255.92 [M + Na]$^+$. $C_{13}H_{15}NO_3$ (233.27): calcd. C. 66.94, H 6.48, N 6.00; found C 66.84, H 6.41, N 6.21.

1-(2,4-Dimethoxybenzyl)piperidine-2,6-dione (1b): This compound was obtained as a white solid (7.100 g, 89%, hexane/EtOAc 3:7) by the General Procedure for the formation of imides, from glutaric anhydride (4.000 g, 35.38 mmol) and 2,4-dimethoxybenzylamine (5.60 mL, 37.39 mmol); m.p. 115–123 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91–1.96 (m, 2 H), 2.66 (t, J = 6.6 Hz, 4 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.9 (s, 2 H), 6.35–6.39 (m, 2 H), 6.87 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1, 30.9, 32.92, 37.8, 55.2, 55.3, 98.4, 103.8, 117.3, 128.0, 158.0, 159.8, 172.4, 172.8 ppm. IR (film): $\tilde{\nu}$ = 3394, 2980, 1722, 1660, 1598, 1576 cm^{-1}. $C_{14}H_{17}NO_4$ (263.12): calcd. C 63.87, H 6.51, N 5.32; found C 63.93, H 6.50, N 5.28.

1-Benzylpiperidine-2,6-dione (1c): This compound was obtained as a colourless oil (1.610 g, 91%, hexane/EtOAc 3:7) by the General Procedure for the formation of imides, from glutaric anhydride (1.000 g, 8.76 mmol) and benzylamine (1.16 mL, 9.26 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.96 (m, 2 H), 2.68 (t, J = 6.0 Hz, 4 H), 4.93 (s, 2 H), 7.21–7.35 (m, 5 H) ppm. IR (film): $\tilde{\nu}$ = 3365, 2962, 1734, 1655, 1598, 1580 cm^{-1}.

1-(2-*tert*-Butylphenyl)piperidine-2,6-dione (1d): This compound was obtained as a colourless oil (1.990 g, 93%, hexane/EtOAc 3:7) by the General Procedure for the formation of imides, from glutaric anhydride (1.000 g, 8.76 mmol) and 2-*tert*-butylphenylamine (1.22 mL, 9.26 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 2.07–2.16 (m, 2 H), 2.83 (t, J = 6.6 Hz, 4 H), 6.82 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.29 (dt, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.37 (dt, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.58 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 3380, 2965, 1734, 1655, 1598, 1580 cm^{-1}.

1-(4-Methoxyphenyl)piperidine-2,6-dione (1e): This compound was obtained as a colourless oil (1.800 g, 93%, hexane/EtOAc 3:7) by the General Procedure for the formation of imides, from glutaric anhydride (1.000 g, 8.76 mmol) and 4-methoxyphenylamine (1.10 mL, 9.26 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02–2.11 (m, 2 H), 2.78 (t, J = 6.6 Hz, 4 H), 3.79 (s, 3 H), 6.93–7.00 (m, 4 H) ppm. IR (film): $\tilde{\nu}$ = 3380, 2965, 1734, 1655, 1598, 1580 cm^{-1}.

1-(2,4-Dimethoxybenzyl)-4-methylpiperidine-2,6-dione (9b): This compound was obtained as a white solid (3.200 g, 77%, hexane/EtOAc 3:1) by the General Procedure for the formation of imides, from glutaric anhydride (2.000 g, 15.74 mmol) and 2,4-dimethoxybenzylamine (2.54 mL, 16.50 mmol); m.p. 80–85 °C (EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.6 Hz, 3 H), 2.26–2.35 (m, 3 H), 2.77 (dd, J_1 = 14.3, J_2 = 3.0 Hz, 2 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.88 (s, 2 H), 6.34–6.39 (m, 2 H), 6.85 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 24.4, 24.5, 37.9, 40.7, 55.3, 55.4, 98.4, 103.8, 117.4, 128.3, 158.0, 159.9, 172.0 ppm. IR (film): $\tilde{\nu}$ = 3390, 2920, 2810, 1720, 1660, 1600, 1580 cm^{-1}. $C_{15}H_{19}NO_4$ (277.13): calcd. C 64.80, H 6.72, N 5.15; found C 63.93, H 6.50, N 5.28.

(3*R*)-*N*-(2,4-Dimethoxybenzyl)-5-hydroxy-3-methylpentanamide [(–)-11]: 2,4-Dimethoxybenzylamine (5.4 mL, 36.64 mmol) was added to a stirred solution of methyl (3*R*)-5-hydroxy-3-methylpentanoate[11] (5.000 g, 34.22 mmol) in toluene (60 mL) and the system was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc/hexane 3:2) to afford (–)-**11** (5.400 g, 79%) as a pale yellow oil. $[\alpha]_D^{25}$ = –4.10 (c = 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.0 Hz, 3 H), 1.22 (d, J = 7.1 Hz, 1 H), 1.43–1.54 (m, 2 H), 2.07–2.11 (m, 2 H), 3.58–3.64 (m, 2 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 4.33 (d, J = 5.5 Hz, 1 H), 5.90–5.93 (m, 2 H), 6.43 (d, J = 8.2 Hz, 2 H), 7.14 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 27.0, 38.9, 39.5, 43.7, 55.3, 55.4, 60.3, 98.5, 103.8, 118.6, 130.6, 158.5, 160.5, 172.4 ppm. IR (film): $\tilde{\nu}$ = 3358, 2146, 1730, 1660, 1598, 1576 cm^{-1}. $C_{15}H_{23}NO_4$ (281.16): calcd. C 64.03, H 8.24, N 4.98; found C 64.13, H 8.34, N 4.93.

(4*R*)-1-(2,4-Dimethoxybenzyl)-6-hydroxy-4-methylpiperidin-2-one (12): Et_3N (5.56 mL, 40.20 mmol) and sulfur trioxide pyridine complex (6.940 g, 43.60 mmol) were added at 0 °C under argon to a stirred solution of (–)-**11** (2.300 g, 8.18 mmol) in DMSO (15 mL). After stirring for 5 h at room temperature the reaction mixture was quenched with water (4 mL). The mixture was then treated with HCl (1 M, 7 mL) and extracted with EtAcO (3 × 20 mL). The organic layer was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:1) to afford (–)-**12** (1.370 g, 55%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.0 Hz, 3 H), 1.58–1.62 (m, 2 H), 1.96–1.98 (m, 2 H), 2.51–2.58 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.20 (d, J = 14.8 Hz, 1 H), 4.35 (d, J = 2.7 Hz, 1 H), 5.15 (d, J = 14.8 Hz, 1 H), 6.43 (m, 2 H), 7.17 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 23.9, 37.5, 40.4, 42.2, 55.3, 55.4,

79.3, 98.4, 104.1, 117.7, 130.8, 158.7, 160.2, 169.5 ppm. IR (film): $\tilde{\nu}$ = 3258, 2951, 2810, 1734, 1580, 1500, 1479, 1439, 1413, 1312, 1297, 1281, 1249, 1182, 1170, 1100, 1065, 1026, 974, 931 cm^{-1}. $C_{15}H_{21}NO_4$ (279.15): calcd. C 64.50, H 7.58, N 5.01; found C 64.43, H 7.50, N 5.17.

General Procedure for the Formation of the Enamides 2a-e: DIBAL-H (12.50 mmol, 1 M solution in toluene) was added dropwise at –78 °C to a stirred solution of the appropriate imide **1** (6.40 mmol) in CH_2Cl_2 (22.66 mL) After the mixture had been stirred for 1 h at –78 °C, H_2O (12 mL), followed by NaOH (2 N, 3.7 mL) were cautiously added and the reaction mixture was poured into a saturated solution of Rochelle's salt (90 mL). The mixture was then extracted with CH_2Cl_2 (4 × 30 mL). The combined extracts were then washed with brine (35 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield a crude residue, which was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

Et_3N (22.71 mmol) was added at 0 °C to a solution of the previously obtained hydroxyamide (7.50 mmol) in CH_2Cl_2 (7.5 mL), followed by methanesulfonyl chloride (mesyl chloride, 8.06 mmol). The reaction mixture was stirred at room temperature for 2 h, then washed with H_2O (7.5 mL), a saturated solution of $NaHCO_3$ (7.5 mL) and brine (7.5 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield a crude residue, which was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

1-(4-Methoxybenzyl)-3,4-dihydropyridin-2(1*H*)-one (2a): The corresponding hydroxyamide was obtained from the imide **1a** (1.000 g, 4.28 mmol) and DIBAL-H (8.36 mL, 8.4 mmol) as an orange oil (0.850 g, 85%, hexane/EtOAc 1:1) by the General Procedure for the reduction with DIBAL-H. Compound **2a** was obtained from the previous intermediate (2.260 g, 9.6 mmol) as a colourless oil (1.810 g, 87%, hexane/EtOAc 7:3) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27–2.53 (m, 2 H), 2.55 (t, J = 7.7 Hz, 2 H), 3.77 (s, 3 H), 4.60 (s, 2 H), 5.08–5.13 (m, 1 H), 5.98–6.02 (m, 1 H), 6.83 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 31.2, 48.2, 55.2, 106.4, 114.0, 129.0, 129.2, 129.3, 158.9, 169.3 ppm. IR (film): $\tilde{\nu}$ = 2290, 2815, 1655, 1605, 1590, 1405 cm^{-1}. MS (ESI): m/z = 239.94 $[M + Na]^+$. $C_{13}H_{15}NO_2$ (217.11): calcd. C 71.87, H 6.96, N 6.45; found C 71.90, H 7.11, N 6.28.

1-(2,4-Dimethoxybenzyl)-3,4-dihydropyridin-2(1*H*)-one (2b): The corresponding hydroxyamide was obtained as an orange oil (5.540 g, 59%, hexane/EtOAc 1:1) by the General Procedure for the reduction with DIBAL-H, from the imide **1b** (1.700 g, 6.46 mmol) and DIBAL-H (12.50 mL, 6.46 mmol). Compound **2b** was obtained from the previous intermediate (0.200 g, 0.75 mmol) as a colourless oil (0.810 g, 98%, hexane/EtOAc 3:1) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24–2.28 (m, 2 H), 2.51 (t, J = 7.7 Hz, 2 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 4.58 (s, 2 H), 5.01–5.06 (m, 1 H), 6.06 (m, 1 H), 6.38–6.40 (m, 2 H), 7.12 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 31.4, 43.4, 55.2, 55.3, 98.3, 104.0, 105.5, 117.7, 130.0, 130.3, 158.3, 160.2, 169.4 ppm. IR (film): $\tilde{\nu}$ = 3050, 3010, 2999, 1612, 1552, 1503, 1452 cm^{-1}. $C_{14}H_{17}NO_3$ (247.12): calcd. C 68.00, H 6.93, N 5.66; found C 68.32, H 7.11, N 5.70.

1-Benzyl-3,4-dihydropyridin-2(1*H*)-one (2c): The corresponding hydroxyamide was obtained from the imide **1c** (1.000 g, 4.92 mmol) and DIBAL-H (9.84 mL, 9.84 mmol), as a pale yellow pale oil (0.830 g, 82%, hexane/EtOAc 1:2), by the General Procedure for the reduction with DIBAL-H. Compound **2c** was obtained from the previous intermediate (1.000 g, 4.87 mmol) as a colourless oil (0.82 g, 92%, hexane/EtOAc 7:3) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33–2.38 (m, 2 H), 2.61 (t, J = 7.7 Hz, 2 H), 4.70 (s, 2 H), 5.13–5.17 (m, 1 H), 6.00–6.04 (m, 1 H), 7.23–7.36 (m, 5 H) ppm. IR (film): $\tilde{\nu}$ = 2290, 2845, 1650, 1590, 1405, 1390 cm^{-1}.

1-(2-*tert*-Butylphenyl)-3,4-dihydropyridin-2(1*H*)-one (2d): The corresponding hydroxyamide was obtained from the imide **1d** (1.000 g, 4.08 mmol) and DIBAL-H (8.16 mL, 8.16 mmol) as an orange oil (0.760 g, 76%, hexane/EtOAc 1:1) by the General Procedure for the reduction with DIBAL-H. Compound **2d** was obtained from the previous intermediate (1.000 g, 4.04 mmol) as a colourless oil (0.740 g, 80%, hexane/EtOAc 7:3) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 2.43–2.49 (m, 2 H), 2.65–2.71 (m, 2 H), 5.21–5.31 (m, 1 H), 6.04–6.09 (m, 1 H), 6.99 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.56 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 2290, 2845, 1650, 1590, 1405, 1390 cm^{-1}.

1-(4-Methoxyphenyl)-3,4-dihydropyridin-2(1*H*)-one (2e): The corresponding hydroxyamide was obtained from the imide **1d** (1.000 g, 4.56 mmol) and DIBAL-H (9.12 mL, 9.12 mmol) as an orange oil (0.730 g, 73%, hexane/EtOAc 1:1) by the General Procedure for the reduction with DIBAL-H. Compound **2e** was obtained from the previous intermediate (1.000 g, 4.52 mmol) as a colourless oil (0.840 g, 92%, hexane/EtOAc 7:3) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 2.43–2.49 (m, 2 H), 2.65–2.71 (m, 2 H), 5.21–5.31 (m, 1 H), 6.04–6.09 (m, 1 H), 6.99 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.25–7.28 (m, 2 H), 7.56 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 2290, 2845, 1650, 1590, 1405, 1390 cm^{-1}.

(±)-1-(2,4-Dimethoxybenzyl)-4-methyl-3,4-dihydropyridin-2(1*H*)-one [(±)-10b]: The corresponding hydroxyamide was obtained from the imide **9b** (3.500 g, 13.40 mmol) and DIBAL-H (13.40 mL, 13.40 mmol) as a colourless oil (3.100 g, 74%) and as an inseparable mixture of diastereomers (4:1, hexane/EtOAc 3:2) by the General Procedure for the reduction with DIBAL-H. Compound (±)-**10b** was obtained from the previous intermediate (1.000 g, 3.58 mmol) as a colourless oil (0.700 g, 69%, hexane/EtOAc 3:1) by the General Procedure for the dehydration. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.7 Hz, 3 H), 2.21–2.28 (m, 1 H), 2.55–2.60 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.55 (d, J = 15.1 Hz, 1 H), 4.62 (d, J = 15.1 Hz, 1 H), 4.93–4.97 (m, 1 H), 6.02 (dd, J_1 = 7.8, J_2 = 1.5 Hz, 1 H), 6.39–6.42 (m, 2 H), 7.11 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 26.9, 39.7, 43.3, 55.3, 55.3, 98.3, 104.0, 112.2, 117.8, 128.7, 130.3, 158.3, 160.3, 169.2 ppm. IR (film): $\tilde{\nu}$ = 3060, 2930, 2710, 1730, 1610, 1580, 1500 cm^{-1}. $C_{15}H_{19}NO_3$ (261.14): calcd. C 68.94, H 7.33, N 5.36; found C 67.00, H 7.27, N 5.46.

(4*S*)-1-(2,4-Dimethoxybenzyl)-4-methyl-3,4-dihydropyridin-2(1*H*)-one [(–)-10b]: Et_3N (5.42 mmol) was added at 0 °C to a solution of **12** (0.500 g, 1.79 mmol) in CH_2Cl_2 (1.8 mL), followed by methanesulfonyl chloride (mesyl chloride, 1.82 mmol). The reaction mixture was stirred at room temperature for 2 h, washed with H_2O (1.8 mL), a saturated solution of $NaHCO_3$ (1.8 mL) and brine (1.8 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to yield an oil. The crude residue was purified by column chromatography on silica gel (EtOAc/hexane 3:1) to afford (–)-**10b** (0.240 g, 59%) as a colourless oil. $[\alpha]_D^{25}$ = –152.00 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.7 Hz, 3 H), 2.23–2.29 (m, 1 H), 2.53–2.59 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.54 (d, J = 14.6 Hz, 1 H), 4.61 (d, J = 14.6 Hz, 1 H), 4.93–4.97 (m, 1 H), 6.02 (dd, J_1 = 7.9, J_2 = 1.2 Hz, 1 H), 6.39–6.41 (m, 2 H), 7.11 (d, J = 9.3 Hz, 1 H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 20.1, 26.9, 39.7, 43.3, 55.2, 55.3, 98.3, 103.9, 112.2, 117.8, 128.7, 130.3, 158.3, 160.2, 169.2 ppm. IR (film): $\tilde{\nu}$ = 2990, 2220, 1750, 1600, 1505, 1450 cm^{-1}. $C_{15}H_{19}NO_3$ (261.14): calcd. C 68.94, H 7.33, N 5.36; found C 69.00, H 7.15, N 5.21.

General Procedures for Cyclopropanation Reactions

Method A – General Procedure for Cyclopropanation Reactions with Rhodium(II) Acetate: A solution of rhodium(II) acetate (4 mol-%) in anhydrous CH_2Cl_2 (3 mL) was added under argon to a stirred solution of the appropriate enamide **2** (1.60 mmol) in anhydrous CH_2Cl_2 (4 mL). An anhydrous CH_2Cl_2 solution (10 mL) of ethyl diazoacetate (3.80 mmol) was then added to the reaction mixture by syringe pump, at 30 °C under argon, over the course of 4 h at room temperature. The mixture was stirred for an additional 8 h, filtered through celite and concentrated under reduced pressure to yield a crude residue that was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

Method B – General Procedure for Cyclopropanation Reactions with Copper(I) Complexes: Copper(I) trifluoromethanesulfonate benzene (0.029 mmol, 1 mol-%) and the corresponding chiral bis-oxazolidine ligand (0.027 mmol, 1 mol-%) were combined under argon in a dry box with addition of anhydrous CH_2Cl_2 (3 mL). The solution was stirred for 1 h at room temperature. The reaction mixture was filtered through a 0.2 mm filter, and the filtrate was added to a solution of **2** (1.60 mmol) in anhydrous CH_2Cl_2 (4 mL). The reaction flask was stoppered with a septum. An anhydrous CH_2Cl_2 solution (10 mL) of ethyl diazoacetate (2 equiv.) was added to the reaction mixture by syringe pump, under argon at room temperature, over the course of 4 h. The mixture was stirred for an additional 1 h, filtered through celite and concentrated under reduced pressure to yield a crude residue that was purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

Cyclopropanation of 2a with EDA: A crude residue containing a mixture of isomers (78:22) was obtained (Table 1, Entry 11) by cyclopropanation Method B from the enamide **2a** (0.200 g, 0.90 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.09 mmol) and CuOTf (0.09 mmol) and ethyl diazoacetate (1.8 mmol), with an addition time of 4 h. Compounds *trans*-**3a** (0.170 g, 62%), *cis*-**3a** (0.028 g, 10%) and **4a** (0.014 g, 5%) were all obtained as colourless oils (hexane/EtOAc 3:1) .

Ethyl (1*S,6*S**,7*S**)-2-(4-Methoxybenzyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*trans*-3a):** $[\alpha]_D^{25}$ = +9.90 (*c* = 0.14, $CHCl_3$, scalemic, *ee* = 55%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.44–1.47 (m, 1 H, 7-H), 1.61–1.73 (m, 1 H, CH_2), 1.92–1.97 (m, 1 H, 6-H), 2.19–2.22 (m, 1 H, CH_2), 2.24–2.48 (m, 2 H, CH_2, CH_2), 2.97 (dd, J_1 = 8.8, J_2 = 2.7 Hz, 1 H, 1-H), 3.77 (s, 3 H, OCH_3), 4.05 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.42 (d, *J* = 14.3 Hz, 1 H, CH_2), 4.69 (d, *J* = 14.3 Hz, 1 H, CH_2), 6.82 (d, *J* = 8.8 Hz, 2 H, ArH), 7.18 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.6, 21.7, 30.7, 30.8, 40.4, 48.5, 55.1, 60.6, 113.8, 128.6, 129.9, 158.9, 170.3, 170.9 ppm. IR (film): $\tilde{\nu}$ = 2999, 2910, 1720, 1651, 1610, 1510 cm^{-1}. MS (ESI): *m*/*z* = $[M + Na]^+$: 326.10. $C_{17}H_{21}NO_4$ (303.15): calcd. C 67.31, H 6.98, N 4.62; found C 68.00, H 6.93, N 4.70. The *ee* was determined by HPLC with a CHIRAL-AP (100 × 4.0 mm) column and 9% propan-2-ol/sodium phosphate buffer (pH 7.0, 10 mM) as mobile phase; flow rate = 0.9 mL min^{-1}; retention time for *trans*-**3a**: 2.45 min for first enantiomer and 3.15 min for second enantiomer.

Ethyl (1*S,6*S**,7*R**)-2-(4-Methoxybenzyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*cis*-3a):** $[\alpha]_D^{25}$ = +10.90 (*c* = 0.12, $CHCl_3$, scalemic). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.73–1.78 (m, 2 H, CH_2), 1.88–1.93 (m, 1 H, 7-H), 2.15–2.23 (m, 1 H, 6-H), 2.37–2.43 (m, 2 H, CH_2), 3.03 (dd, J_1 = 8.2, J_2 = 6.3 Hz, 1 H, 1-H), 3.60 (d, *J* = 14.3 Hz, 1 H, CH_2), 3.83 (s, 3 H, OCH_3), 4.11 (q, *J* = 7.1 Hz, 2 H, CH_2), 5.32 (d, *J* = 14.3 Hz, 1 H, CH_2), 6.88 (d, *J* = 8.8 Hz, 2 H, ArH), 7.23–7.27 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 20.7, 21.7, 30.7, 31.0, 40.5, 48.6, 55.2, 60.7, 113.9, 128.8, 130.1, 158.9, 169.0, 171.7 ppm. MS (ESI): *m*/*z* = 326.21 $[M + Na]^+$. $C_{17}H_{21}NO_4$ (303.15): calcd. C 67.31, H 6.98, N 4.62; found C 67.22, H 6.93, N 4.70.

Ethyl 2-[1-(4-Methoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]-acetate (4a): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H), 1.52–1.63 (m, 2 H), 1.93–2.00 (m, 2 H), 3.30–3.51 (m, 2 H), 3.77 (s, 3 H), 3.90 (d, *J* = 14.3 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.10–4.13 (m 1 H), 4.42 (d, *J* = 14.3 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H) ppm. IR (film): $\tilde{\nu}$ = 2999, 2910, 1720, 1651, 1610, 1510, 1420, 1280 cm^{-1}. $C_{17}H_{21}NO_4$ (303.15): calcd. C 67.31, H 6.98, N 4.62; found C 67.26, H 7.02, N 4.56.

Cyclopropanation of 2b with EDA: A crude residue containing a mixture of isomers (62:38) was obtained (Table 1, Entry 14) by cyclopropanation Method B from the enamide **2b** (0.400 g, 1.6 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.016 mmol) and CuOTf (0.016 mmol) and ethyl diazoacetate (3.2 mmol), with an addition time of 4 h. Compounds *trans*-**3b** (0.250 g, 47%), *cis*-**3b** (0.150 g, 25%) and **4b** (0.027 g, 5%) were all obtained (hexane/EtOAc 3:1) as colourless oils.

Ethyl (1*S,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*trans*-3b):** $[\alpha]_D^{25}$ = –3.32 (*c* = 0.054, $CHCl_3$, scalemic, *ee* = 15%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.44 (dd, J_1 = 5.0, J_2 = 2.7 Hz, 1 H, 7-H), 1.61–1.69 (m, 1 H, CH_2), 1.89–1.92 (m, 1 H, 6-H), 2.14–2.18 (m, 1 H, CH_2), 2.29–2.38 (m, 2 H, CH_2), 3.02 (dd, J_1 = 8.8, J_2 = 2.2 Hz, 1 H, 1-H), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.02 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.63 (d, *J* = 14.3 Hz, 1 H, CH_2), 4.56 (d, *J* = 14.3 Hz, 1 H, CH_2), 6.40–6.41 (m, 2 H, ArH), 7.17 (d, *J* = 8.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.0, 21.7, 30.7, 30.9, 40.8, 43.3, 55.1, 55.3, 60.5, 98.2, 104.1, 117.1, 131.1, 158.7, 160.5, 170.5, 171.2 ppm. IR (film): $\tilde{\nu}$ = 2900, 2820, 1740, 1650, 1600, 1580, 1520 cm^{-1}. $C_{18}H_{23}NO_5$ (333.16): calcd. C 64.85, H 6.95, N 4.20; found C 65.00, H 6.89, N 4.32. The *ee* was determined by HPLC with a CHIRAL-AP (100 × 4.0 mm) column and 9% propan-2-ol/sodium phosphate buffer (pH 7.0. 10 mM) as mobile phase; flow rate = 0.9 mL min^{-1}; retention time for *trans*-**3b**: 3.02 min for first enantiomer and 3.85 min for second enantiomer.

Ethyl (1*S,6*S**,7*R**)-2-(2,4-Dimethoxybenzyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*cis*- 3b):** $[\alpha]_D^{25}$ = +9.90 (*c* = 0.06, $CHCl_3$, scalemic). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.62 (dd, *J* = 8.8, J_2 = 6.6 Hz, 1 H, 7-H), 1.79–1.83 (m, 1 H, 6-H), 2.14–2.18 (m, 2 H, CH_2), 2.31–2.34 (m, 2 H, CH_2), 3.02 (dd, J_1 = 7.7, J_2 = 6.6 Hz, 1 H, 1-H), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.86 (d, *J* = 14.3 Hz, 1 H, CH_2), 4.08 (q, *J* = 7.1 Hz, 2 H, CH_2), 4.96 (d, *J* = 14.3 Hz, 1 H, CH_2), 6.39–6.40 (m, 2 H, ArH), 7.17 (d, *J* = 8.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.4, 21.3, 30.2, 30.4, 40.3, 42.8, 54.5, 54.6, 60.0, 97.7, 103.8, 116.6, 131.8, 158.2, 160.0, 170.0, 170.7 ppm. IR (film): $\tilde{\nu}$ = 2900, 2820, 1740, 1650, 1600, 1580, 1520 cm^{-1}. $C_{18}H_{23}NO_5$ (333.16): calcd. C 64.85, H 6.95, N 4.20; found C 64.76, H 6.87, N 4.31.

Ethyl 2-[1-(2,4-Dimethoxybenzyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]acetate (4b): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3 H), 1.92–2.01 (m, 2 H), 2.25–2.38 (m, 1 H), 2.47–2.51 (m, 1 H), 3.36–3.48 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.15 (d, *J* = 14.8 Hz, 1 H), 4.54 (t, *J* = 4.9 Hz, 1 H),

5.03 (d, J = 14.8 Hz, 1 H), 6.38–6.42 (m, 2 H), 7.15 (d, J = 8.8 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 2900, 2820, 1740, 1650, 1600, 1580, 1520 cm^{-1}. MS (ESI): m/z = 356.38 [M + Na]$^+$. $C_{18}H_{23}NO_5$ (333.16): calcd. C 64.85, H 6.95, N 4.20; found C 64.76, H 6.88, N 4.13.

Ethyl (1*S,6*S**,7*S**)-2-Benzyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*trans*-3c):** This compound was obtained as a mixture of isomers (81:19) by cyclopropanation Method B (Table 1, Entry 16) from the enamide **2c** (0.200 g, 1.1 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.016 mmol) and CuOTf (0.016 mmol) and ethyl diazoacetate (2.1 mmol), with a time of addition of 4 h. The crude residue contained *trans*-**3c** (0.072 g, 25%) as a colourless oil (hexane/EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H), 1.47–1.48 (m, 1 H), 1.65–1.73 (m, 1 H), 1.92–2.02 (m, 1 H), 2.21–2.30 (m, 1 H), 2.32–2.50 (m, 2 H), 3.37 (dd, J_1 = 8.8, J_2 = 2.1 Hz, 1 H, 1-H), 4.05 (q, J = 7.1 Hz, 2 H, CH_2), 4.08 (d, J = 14.3 Hz, 1 H), 4.72 (d, J = 14.3 Hz, 1 H), 7.26–7.30 (m, 5 H) ppm. IR (film): $\tilde{\nu}$ = 2999, 2910, 1720, 1651, 1610, 1510 cm^{-1}.

Ethyl (1*S,6*S**,7*S**)-2-(2-*tert*-Butylphenyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*trans*-3d):** This compound was obtained as a mixture of isomers (75:25) by cyclopropanation Method B (Table 1, Entry 17) from the enamide **2d** (0.210 g, 0.9 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.091 mmol) and CuOTf (0.091 mmol) and ethyl diazoacetate (1.8 mmol), with a time of addition of 4 h, The crude residue contained *trans*-**3d** (0.070 g, 25%) as a pale yellow oil (hexane/EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H), 1.41 (s, 9 H), 2.14–2.22 (m, 3 H), 2.29–4.41 (m, 2 H), 2.52–2.57 (m, 1 H), 3.30 (dd, J_1 = 7.1, J_2 = 4.9 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 7.02 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H), 7.23–7.29 (m, 2 H), 7.56 (dd, J_1 = 7.7, J_2 = 1.6 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 3010, 2934, 1720, 1651, 1620, 1510 cm^{-1}.

Ethyl (1*S,6*S**,7*S**)-2-(4-Methoxyphenyl)-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*trans*-3e):** This compound was obtained as a mixture of isomers (85:15) by cyclopropanation Method B (Table 1, Entry 18), from the enamide **2e** (0.210 g, 1.0 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.098 mmol) and CuOTf (0.098 mmol) and ethyl diazoacetate (1.8 mmol), with a time of addition of 4 h. The crude residue contained *trans*-**3e** (0.150 g, 55%) as a yellow pale oil (hexane/EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H), 1.84–1.92 (m, 2 H), 2.08–2.13 (m, 1 H), 2.29–2.49 (m, 1 H), 2.51–2.61 (m, 2 H), 3.37 (dd, J_1 = 8.8, J_2 = 2.7 Hz, 1 H), 3.79 (s, 3 H), 4.05 (q, J = 7.1 Hz, 2 H), 6.88–6.91 (m, 2 H), 7.20 (d, J = 9.3 Hz, 2 H) ppm. IR (film): $\tilde{\nu}$ = 2999, 2910, 1720, 1651, 1610, 1510 cm^{-1}.

Cyclopropanation of (±)-10a with EDA: A crude residue containing a mixture of isomers (57:25:12:6) was obtained (Table 2, Entry 4) by cyclopropanation Method B from the enamide (±)-**10a** (0.200 g, 0.9 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.086 mmol) and CuOTf (0.086 mmol) and ethyl diazoacetate (1.73 mmol), with a time of addition of 4 h. Compounds *anti-trans*-**13a** (0.130 g, 50%), *anti-cis*-**13a** (0.027 g, 10%), *syn-trans*-**13a** (0.016 g, 8%), *syn-cis*-**13a** (0.008 g, 4%) and **14** (0.019 g, 7%) were all obtained as colourless oils (hexane/EtOAc 3:1).

Ethyl (1*S,5*S**,6*S**,7*S**)-2-(4-Methoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-trans*-13a):** $[\alpha]_D^{25}$ = +12.60 (c = 0.34, $CHCl_3$, scalemic, 14% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.6 Hz, 3 H, CH_3), 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 1.45 (dd, J_1 = 5.0, J_2 = 2.7 Hz, 1 H, 7-H), 1.57–1.64 (m, 1 H, 6-H), 1.81–1.98 (m, 1 H, CH), 2.13–2.26 (m, 2 H, CH_2), 2.93 (dd, J_1 = 8.3, J_2 = 2.7 Hz, 1 H, 1-H), 3.78 (s, 3 H, OCH_3), 4.09 (q, J = 7.1 Hz, 2 H, CH_2), 4.37 (d, J = 14.3 Hz, 1 H, CH_2), 4.72 (d, J = 14.3 Hz, 1 H, CH_2), 6.79–6.82 (m, 2 H, ArH), 7.15 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.2, 27.6, 30.1, 31.3, 39.4, 40.4, 48.3, 55.2, 60.7, 113.9, 128.7, 129.9, 159.0, 170.6, 171.1 ppm. IR (film): $\tilde{\nu}$ = 3010, 2990, 1720, 1670, 1550 cm^{-1}. MS (ESI): m/z = 340.41 [M + Na]$^+$. $C_{18}H_{23}NO_4$ (317.16): calcd. C 68.12, H 7.30, N 4.41; found C 68.07, H 7.25, N 4.53.

Ethyl (1*S,5*S**,6*S**,7*R**)-2-(4-Methoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-cis*-13a):** $[\alpha]_D^{25}$ = +9.51 (c = 0.10, $CHCl_3$, scalemic). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.6 Hz, 3 H, CH_3), 1.24 (t, J = 7.1 Hz, 3 H, CH_3), 1.39–1.46 (m, 1 H, 6-H), 1.74 (dd, J_1 = 9.1, J_2 = 6.6 Hz, 1 H, 7-H), 2.12 (dd, J_1 = 12.6, J_2 = 2.7 Hz, 1 H, CH_2), 2.35 (dd, J_1 = 15.4, J_2 = 4.4 Hz, 1 H, CH_2), 2.55–2.65 (m, 1 H, CH), 2.94 (dd, J_1 = 8.5, J_2 = 6.6 Hz, 1 H, 1-H), 3.50 (d, J = 14.3 Hz, 1 H, CH_2), 3.79 (s, 3 H, OCH_3), 4.07 (q, J = 7.1 Hz, 2 H, CH_2), 5.26 (d, J = 14.3 Hz, 1 H, CH_2), 6.80–6.83 (m, 2 H, ArH), 7.25 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.1, 23.3, 24.2, 25.8, 38.0, 40.4, 48.2, 55.3, 60.7, 113.8, 128.9, 130.0, 159.0, 169.1, 171.7 ppm. IR (film): $\tilde{\nu}$ = 3010, 2990, 1720, 1670, 1550 cm^{-1}. MS (ESI): m/z = 340.02 [M + Na]$^+$. $C_{18}H_{23}NO_4$ (317.16): calcd. C 68.12, H 7.30, N 4.41; found C 68.09, H 7.21, N 4.32.

Ethyl (1*S,5*R**,6*S**,7*S**)-2-(4-Methoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*syn-trans*-13a):** $[\alpha]_D^{25}$ = –6.32 (c = 0.10, $CHCl_3$, scalemic). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (d, J = 6.6 Hz, 3 H, CH_3), 1.20 (t, J = 7.1 Hz, 3 H, CH_3), 1.65 (dd, J_1 = 5.5, J_2 = 2.7 Hz, 1 H, 7-H), 1.71–1.79 (m, 1 H, CH), 1.83–1.94 (m, 1 H, 6-H), 2.42–2.51 (m, 2 H, CH_2), 3.03 (dd, J_1 = 8.8, J_2 = 2.7 Hz, 1 H, 1-H), 3.77 (s, 3 H, OCH_3), 4.05 (q, J = 7.1 Hz, 2 H, CH_2), 4.59 (s, 2 H, CH_2), 6.83–6.86 (m, 2 H, ArH), 7.18 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.2, 22.6, 23.1, 24.3, 36.7, 39.0, 49.8, 55.2, 60.6, 113.8, 129.7, 130.2, 159.0, 169.6, 169.7 ppm. IR (film): $\tilde{\nu}$ = 3010, 2990, 1720, 1670, 1550 cm^{-1}. MS (ESI): m/z = 340.21 [M + Na]$^+$. $C_{18}H_{23}NO_4$ (317.16): calcd. C 68.12, H 7.30, N 4.41; found C 68.16, H 7.28, N 4.51.

Ethyl (1*S,5*R**,6*S**,7*R**)-2-(4-Methoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*syn-cis*-13a):** $[\alpha]_D^{25}$ = +15.81 (c = 0.07, $CHCl_3$, scalemic). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.6 Hz, 3 H, CH_3), 1.19 (t, J = 7.1 Hz, 3 H, CH_3), 1.64 (dd, J_1 = 7.2, J_2 = 7.1 Hz, 1 H, 7-H), 2.36–2.43 (m, 2 H, CH, CH_2), 2.53–2.57 (m, 2 H, CH_2, 6-H), 3.11 (dd, J_1 = 7.2, J_2 = 7.1 Hz, 1 H, 1-H), 3.79 (s, 3 H, OCH_3), 4.03 (q, J = 7.1 Hz, 2 H, CH_2), 4.45 (d, J = 14.3 Hz, 1 H, CH_2), 4.82 (d, J = 14.3 Hz, 1 H, CH_2), 6.84 (d, J = 8.8 Hz, 2 H, ArH), 7.25 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.2, 22.5, 23.0, 24.2, 36.7, 39.0, 49.7, 55.2, 60.5, 113.7, 129.0, 130.2, 159.0, 169.5, 169.6 ppm. IR (film): $\tilde{\nu}$ = 3010, 2990, 1720, 1670, 1550 cm^{-1}. MS (ESI): m/z = 340.62 [M + Na]$^+$. $C_{18}H_{23}NO_4$ (317.16): calcd. C 68.12, H 7.30, N 4.41; found C 68.10, H 7.18, N 4.35.

Ethyl 2-[1-(4-Methoxybenzyl)-4-methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl]acetate (14): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, J = 6.6 Hz, 3 H), 1.22 (t, J = 7.1 Hz, 3 H), 2.33 (dd, J_1 = 16.0, J_2 = 4.4 Hz, 1 H), 2.44–2.69 (m, 1 H), 2.76 (dd, J_1 = 16.0, J_2 = 6.6 Hz, 1 H), 2.94 (d, J = 16.5 Hz, 1 H), 3.02 (d, J = 16.5 Hz, 1 H), 3.79 (s, 3 H), 4.12 (q, J = 7.1 Hz, 2 H), 4.45 (d, J = 14.8 Hz, 1 H), 4.75 (d, J = 14.8 Hz, 1 H), 5.85 (s, 1 H), 6.83–6.86 (m, 2 H), 7.16 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 17.4, 29.7, 37.4, 38.9, 48.2, 55.2, 60.9, 114.0, 117.8, 126.2, 129.1, 159.0, 168.5, 171.4 ppm. IR (film): $\tilde{\nu}$ = 2999, 2910, 1720, 1651, 1610, 1510, 1420, 1300 cm^{-1}. $C_{18}H_{23}NO_4$ (317.16): calcd. C 68.12, H 7.30, N 4.41; found C 68.23, H 7.19, N 4.44.

Cyclopropanation of (±)-10b with EDA: A crude residue containing a mixture of isomers (90:10:0:0) was obtained (Table 2, Entry 8) by cyclopropanation Method B from the enamide (±)-**10b** (0.500 g, 1.9 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.019 mmol) and CuOTf (0.019 mmol) and ethyl diazoacetate (3.80 mmol), with time of addition of 4 h. Compound *anti-trans*-**13b** (0.360 g, 54%), a mixture (5:2, 0.040 g, 6%) of *anti-cis*-**13b** with *anti-trans*-**13b** and compound **15** (0.046 g, 7%) were all obtained (hexane/EtOAc 4:1–1:2) as colourless oils.

Ethyl (1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-trans*-13b):** $[a]_D^{25}$ = +6.25 (*c* = 0.08, $CHCl_3$, scalemic). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.20 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.42 (dd, J_1 = 5.0, J_2 = 3.3 Hz, 1 H, 7-H), 1.53–1.60 (m, 1 H, 6-H), 1.81–1.86 (m, 1 H, CH), 2.14–2.18 (m, 2 H, CH_2), 2.98 (dd, J_1 = 8.8, J_2 = 2.7 Hz, 1 H, 1-H), 3.70 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.07 (q, *J* = 7.3 Hz, 2 H, CH_2), 4.50 (d, *J* = 14.0 Hz, 1 H, CH_2), 4.62 (d, *J* = 14.0 Hz, 1 H, CH_2), 6.37–6.40 (m, 2 H, ArH), 7.14 (d, *J* = 8.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.1, 27.8, 30.0, 31.2, 39.4, 40.6, 42.9, 55.1, 55.2, 60.5, 98.1, 104.0, 117.0, 131.5, 158.6, 160.4, 171.2, 182.6 ppm. IR (film): $\tilde{\nu}$ = 2975, 1730, 1706, 1661, 1602, 1576, 1500, 1455 cm^{-1}. $C_{19}H_{25}NO_5$ (347.17): calcd. C 65.69, H 7.25, N 4.03; found C 65.77, H 7.13, N 4.01.

Ethyl 2-[1-(2,4-Dimethoxybenzyl)-4-methyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]acetate (15): ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.87–1.97 (m, 1 H), 2.23–2.28 (m, 1 H), 2.50–2.57 (m, 1 H), 3.35–3.50 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.05–4.12 (m, 3 H), 4.50 (d, *J* = 7.1 Hz, 1 H), 5.02 (d, *J* = 14.8 Hz, 1 H), 6.39–6.40 (m, 2 H), 7.15 (d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 21.0, 22.3, 35.0, 40.6, 41.3, 55.0, 55.1, 61.5, 97.9, 103.7, 103.9, 117.9, 130.3, 130.5 ppm. 158.2, 159.8, 169.8, 169.9 ppm. IR (film): $\tilde{\nu}$ = 2900, 2820, 1740, 1650, 1600, 1470, 1500, 980 cm^{-1}. MS (ESI): *m*/*z* = 348.13 $[M + H]^+$. $C_{19}H_{25}NO_5$ (347.17): calcd. C 65.69, H 7.25, N 4.03; found C 65.72, H 7.31, N 3.98.

Cyclopropanation of (–)-10b with EDA: a) A crude residue containing a mixture of isomers (95:5:0:0) was obtained (Table 2, Entry 10) by cyclopropanation Method B from the enamide (–)-**10b** (0.400 g, 1.5 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.015 mmol) and CuOTf (0.015 mmol) and ethyl diazoacetate (3.06 mmol), with a time of addition of 4 h. Compounds (–)-*anti-trans*-**13b** (0.160 g, 52%) and (–)-**15** (0.021 g, 4%) were obtained (hexane/EtOAc 3:1) as yellow oils. **b)** A crude residue containing a mixture of isomers (65:35:0:0) was obtained (Table 2, Entry 9) by cyclopropanation Method A from the enamide (–)-**10b** (0.400 g, 1.5 mmol), rhodium(II) acetate (0.06 mmol) and ethyl diazoacetate (3.06 mmol), with a time of addition of 4 h. Compound (–)-*anti-trans*-**13b** (0.073 g, 23%) and a mixture (5:2) of *anti-cis*-**13b** with (–)-*anti-trans*-**13b** (0.037 g,12%) were obtained (hexane/EtOAc 3:1) as yellow oils.

Ethyl (1*S*,5*S*,6*S*,7*S*)-2-(2,4-Dimethoxybenzyl)-5-methyl-3-oxo-2-azabicyclo[4.1.0]heptane-7-carboxylate [(–)-*anti-trans*-13b]: $[a]_D^{25}$ = –25.20 (*c* = 0.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.22 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.43 (dd, J_1 = 4.9, J_2 = 3.1 Hz, 1 H, 7-H), 1.55–1.69 (m, 1 H, 6-H), 1.80–1.90 (m, 1 H, CH), 2.14–2.20 (m, 2 H, CH_2), 2.99 (dd, J_1 = 9.1, J_2 = 3.1 Hz, 1 H, 1-H), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.06 (q, *J* = 7.3 Hz, 2 H, CH_2), 4.52 (d, *J* = 14.0 Hz, 1 H, CH_2), 4.64 (d, *J* = 14.0 Hz, 1 H, CH_2), 6.39–6.42 (m, 2 H, ArH), 7.16 (d, *J* = 9.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 21.2, 27.9, 30.1, 31.2, 39.5, 40.7, 42.9, 55.1, 55.3, 60.5, 98.2, 104.1, 117.1, 131.5, 158.7, 160.5, 171.7, 171.3 ppm. IR (film): $\tilde{\nu}$ = 2970, 2810, 2220, 1740, 1605, 1580, 1360 cm^{-1}. $C_{19}H_{25}NO_5$ (347.17): calcd. C 65.69, H 7.25, N 4.03; found C 65.55, H 7.09, N 4.1.

Ethyl (4*R*)-2-[1-(2,4-Dimethoxybenzyl)-4-methyl-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]acetate [(–)-15]: $[a]_D^{25}$ = –10.00 (*c* = 0.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3 H), 1.19 (t, *J* = 7.4 Hz, 3 H), 1.86–1.96 (m, 1 H), 2.21–2.31 (m, 1 H), 2.50–2.57 (m, 1 H), 3.28–3.52 (m, 2 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.11–4.23 (m, 3 H), 4.51 (s, 1 H), 5.02 (d, *J* = 15.4 Hz, 1 H), 6.39–6.41 (m, 2 H), 7.15 (d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 21.0, 22.3, 35.0, 40.6, 41.3, 55.0, 55.1, 61.5, 97.9, 103.7, 103.9, 117.9, 130.3, 130.5, 158.2, 159.8, 169.8, 169.9 ppm. IR (film): $\tilde{\nu}$ = 2810, 2230, 2070, 1740, 1651, 1492, 1460 cm^{-1}. $C_{19}H_{25}NO_5$ (347.17): calcd. C 65.69, H 7.25, N 4.03; found C 65.57, H 7.31, N 3.97.

6-(2-Chloroethyl)-1-(2,4-dimethoxybenzyl)-4-methyl-3,4-dihydropyridin-2(1*H*)-one (22): This compound (0.142 g, 22%) was obtained by cyclopropanation Method B from the enamide (±)-**10b** (0.500 g, 1.9 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.019 mmol) and CuOTf (0.019 mmol) and 2-chlorodiazoethane[21] (19.0 mmol, 0.3 M solution in Et_2O), with a time of addition of 8 h, as a yellow pale oil (hexane/EtOAc 7:3). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H), 1.16–1.32 (m, 1 H), 1.86–1.96 (m, 2 H), 2.25–2.31 (m, 1 H), 2.54 (d, *J* = 1.7 Hz, 1 H), 3.60–3.65 (m, 2 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.15 (d, *J* = 14.6 Hz, 1 H), 4.58 (s, 1 H), 5.04 (d, *J* = 14.6 Hz, 1 H), 6.39–6.41 (m, 2 H), 7.15–7.19 (m, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 35.2, 40.7, 41.7, 42.8, 55.2, 55.3, 64.4, 98.3, 104.2, 104.3, 118.0, 129.5, 131.0, 158.5, 160.1, 170.1 ppm. IR (film): $\tilde{\nu}$ = 3317, 2949, 1648, 1609, 1507, 1456, 1340, 1266, 1255, 1153, 1039 cm^{-1}. $C_{17}H_{22}ClNO_3$ (323.13): calcd. C 63.06, H 6.85, N 4.33; found C 63.03, H 6.71, N 4.27.

(1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-7-(trifluoromethyl)-2-azabicyclo[4.1.0]heptan-3-one (*anti-trans*-23):** A crude residue containing a mixture of isomers (87:130:0:0) was obtained by cyclopropanation Method B from the enamide (±)-**10b** (0.500 g, 1.9 mmol), the copper(I) complex formed by the bis-oxazolidine **7** (0.019 mmol) and CuOTf (0.019 mmol) and 1,1,1-trifluorodiazoethane[21] (3.8 mmol, 0.25 M solution in Et_2O), with a time of addition of 4 h. Compound *anti-trans*-**23** (0.510 g, 65%) and a mixture (3:2) of *anti-cis*-**23**/*anti-trans*-**23** (0.220 g, 23%) were obtained as colourless oils (hexane/EtOAc 3:1). *anti-trans*-**23**: $[a]_D^{25}$ = +20.02 (*c* = 0.07, $CHCl_3$, scalemic, *ee* = 40%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.36–1.41 (m, 1 H, 6-H), 1.43–1.48 (m, 1 H, 7-H), 1.87–1.94 (m, 1 H, CH), 2.17–2.30 (m, 2 H, CH_2), 2.94 (dd, J_1 = 8.8, J_2 = 2.9 Hz, 1 H, 1-H), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.41 (d, *J* = 14.1 Hz, 1 H, CH_2), 4.83 (d, *J* = 14.1 Hz, 1 H, CH_2), 6.43–6.46 (m, 2 H, ArH), 7.22 (d, *J* = 9.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.0 (q, *J* = 2.8 Hz), 29.9, 30.2 (q, *J* = 36 Hz), 34.8 (q, *J* = 3.8 Hz), 39.5, 42.5, 55.1, 55.4, 98.2, 104.2, 117.2, 123.4 (q, *J* = 270 Hz), 131.7, 158.7, 160.5, 170.7 ppm. IR (film): $\tilde{\nu}$ = 2975, 1730, 1706, 1661, 1602, 1576, 1500, 1455 cm^{-1}. $C_{17}H_{20}F_3NO_3$ (343.34): calcd. C 59.47, H 5.87, N 4.08; found C 59.36, H 6.01, N 4.14.

Reduction of Ethoxycarbonylcyclopropanes

[(1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]hept-3-en-7-yl]methanol (*anti-trans*-18):** Compound *anti-trans*-**18** (0.017 g, 42%) was obtained (hexane/EtOAc 3:2) as a pale yellow oil by the General Procedure for the reduction with DIBAL-H from *anti-trans*-**13b** (0.050 g, 0.14 mmol) and DIBAL-H (0.15 mL, 0.15 mmol), reaction time, temperature: 30 min, –78 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.4 Hz, 3 H), 1.21–

1.23 (m, 1 H), 1.50–1.53 (m, 1 H), 1.98–2.01 (m, 1 H), 2.12 (dd, J_1 = 15.9, J_2 = 5 Hz, 1 H), 2.62 (dd, J_1 = 15.9, J_2 = 4.4 Hz, 1 H), 2.83 (d, J = 8.8 Hz, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.13 (d, J = 14.8 Hz, 1 H), 4.83–4.86 (m, 1 H), 5.11 (d, J = 14.8 Hz, 1 H), 5.60 (d, J = 9.3 Hz, 1 H), 6.36–6.45 (m, 2 H), 7.21–7.24 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 23.6, 30.4, 46.0, 46.3, 50.0, 55.3, 55.4, 68.1, 98.4, 103.4, 104.0, 115.8, 128.8, 131.5, 158.7, 160.5 ppm. IR (film): $\tilde{\nu}$ = 2960, 1730, 1706, 1500, 1455, 1256, 1113 cm^{-1}. MS (ESI): m/z = 312.17 $[M + Na]^+$. $C_{17}H_{23}NO_3$ (289.17): calcd. C 70.56, H 8.01, N 4.84; found C 70.44, H 7.94, N 4.96.

(1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carbaldehyde (*anti-trans*-19):** Compound *anti-trans*-**19** (0.010 g, 39%) was obtained (hexane/EtOAc 1:1) as a yellow pale oil by the General Procedure for the reduction with DIBAL-H from *anti-trans*-**16** (0.050 g, 0.14 mmol) and DIBAL-H (0.21 mL, 0.21 mmol), reaction time, temperature: 45 min, –78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.7 Hz, 3 H), 1.20–1.23 (m, 1 H), 1.80–1.83 (m, 1 H), 1.88–1.91 (m, 1 H), 2.63 (dd, J_1 = 15.9, J_2 = 10.4 Hz, 1 H), 2.98 (dd, J_1 = 15.9, J_2 = 3.6 Hz, 1 H), 3.19 (dd, J_1 = 7.9, J_2 = 3.0 Hz, 1 H), 3.73 (s, 3 H), 3.78 (s, 3 H), 5.19 (d, J = 14.0 Hz, 1 H), 5.30 (d, J = 14.0 Hz, 1 H), 6.41–6.45 (m, 2 H), 7.35 (d, J = 7.9 Hz, 1 H), 9.33 (d, J = 2.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 29.3, 30.1, 39.9, 44.2, 49.7, 49.9, 55.3, 55.4, 98.3, 104.4, 115.8, 132.0, 157.9, 160.8, 197.1, 200.1 ppm. IR (film): $\tilde{\nu}$ = 3010, 2980, 1724, 1706, 1661, 1602, 1500, 1455 cm^{-1}. MS (ESI): m/z = 342.31 $[M + Na]^+$. $C_{17}H_{21}NO_3S$ (319.12): calcd. C 63.92, H 6.63, N 4.39; found C 63.76, H 6.43, N 4.57.

(1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-7-(hydroxymethyl)-5-methyl-2-azabicyclo[4.1.0]heptane-3-thione (*anti-trans*-20):** Compound *anti-trans*-**20** (0.061 g 70%) was obtained (hexane/EtOAc 1:1) as a yellow pale oil by the General Procedure for the reduction with DIBAL-H, from *anti-trans*-**16** (0.010 g, 0.27 mmol) and DIBAL-H (1.1 mL, 1.08 mmol), reaction time, temperature: 2 h, –78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, J = 6.7 Hz, 3 H), 1.20–1.22 (m, 1 H), 1.70–1.79 (m, 2 H), 2.44–2.48 (m, 1 H), 2.51–2.60 (m, 1 H), 2.95 (dd, J_1 = 15.2, J_2 = 3.6 Hz, 1 H), 3.07 (dd, J_1 = 11.6; J_2 = 7.3 Hz, 1 H), 3.43 (dd, J_1 = 11.6, J_2 = 4.9 Hz, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.97 (d, J = 14.0 Hz, 1 H), 5.56 (d, J = 14.0 Hz, 1 H), 6.43–6.46 (m, 2 H), 7.39 (d, J = 9.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 24.6, 30.4, 32.7, 38.4, 49.7, 50.3, 55.3, 55.7, 63.1, 98.7, 104.8, 116.4, 131.5, 158.4, 160.7, 201.0 ppm. IR (film): $\tilde{\nu}$ = 3440, 2950, 1860, 1590, 1500, 1210 cm^{-1}. $C_{17}H_{23}NO_3S$ (321.14): calcd. C 63.52, H 7.21, N 4.36; found C 63.56, H 7.43, N 4.58.

Ethyl (1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-trans*-21):** Compound *anti-trans*-**21** (0.057 g, 71%) was obtained as a yellow pale oil, together with *anti-trans*-**20** (0.021 g, 23%) (hexane/EtOAc 1:1) by the General Procedure for the reduction with DIBAL-H, from *anti-trans*-**16** (0.010 g, 0.27 mmol) and DIBAL-H (0.83 mL, 0.83 mmol), reaction time, temperature: 3 h, –78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.7 Hz, 3 H), 1.20 (t, J = 6.6 Hz, 3 H), 1.42–1.45 (m, 1 H), 1.56–1.57 (m, 1 H), 1.78–1.81 (m, 2 H), 2.16–2.21 (m, 1 H), 2.46–2.51 (m, 1 H), 3.00 (dd, J_1 = 8.5, J_2 = 2.4 Hz, 1 H), 3.61–3.73 (m, 1 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.05 (q, J = 6.6 Hz, 2 H), 4.52 (d, J = 14.3 Hz, 1 H), 4.65 (d, J = 14.3 Hz, 1 H), 6.40–6.42 (m, 2 H), 7.16 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 21.2, 27.9, 28.0, 30.1, 31.2, 39.6, 40.7, 42.9, 55.2, 55.3, 60.6, 98.2, 104.1, 117.1, 131.6, 158.7, 160.5, 170.6 ppm. IR (film): $\tilde{\nu}$ = 3330, 2830, 2810, 1530, 1510, 1400, 1120 cm^{-1}. $C_{19}H_{27}NO_4$ (333.19): calcd. C 68.44, H 8.16, N 4.20; found C 68.35, H 8.10, N 4.07. 4.58.

General Procedure for the Formation of Thioamides: Lawesson's reagent (0.80 mmol) was added to a stirred solution of the appropriate lactam (1.10 mmol) in benzene (10 mL). The reaction mixture was stirred at 80 °C for 2 h, concentrated under reduced pressure and purified by flash chromatography on silica gel (hexane/EtOAc mixtures).

Synthesis of 16: Isomers *anti-trans*-**16** (0.350 g, 73%) and *anti-cis*-**16** (0.037 g, 8%) were obtained as yellow pale oils (hexane/EtOAc 3:1) by the General Procedure for the formation of thioamides, from a mixture (9:1) of *anti-trans*-**13b** and *anti-cis*-**13b** (0.380 g, 1.13 mmol).

Ethyl (1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-trans*-16):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.6 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H), 1.52–1.54 (m, 1 H), 1.67–1.74 (m, 1 H), 1.75–1.80 (m, 1 H), 2.62 (dd, J_1 = 15.9, J_2 = 10.4 Hz, 1 H), 2.97 (dd, J_1 = 16.4, J_2 = 3.8 Hz, 1 H), 3.08 (dd, J_1 = 8.2; J_2 = 2.2 Hz, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.95 (q, J = 7.1 Hz, 2 H), 5.11 (d, J = 14.1 Hz, 1 H), 5.30 (d, J = 14.1 Hz, 1 H), 6.41–6.43 (m, 2 H), 7.31 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.6, 28.7, 29.3, 30.9, 41.7, 49.7, 50.4, 55.2, 55.3, 60.8, 98.3, 104.2, 115.6, 131.8, 158.7, 160.9, 172.1, 200.9 ppm. IR (film): $\tilde{\nu}$ = 2930, 2820, 1730, 1610, 1585, 1410, 1205 cm^{-1}. MS (ESI): m/z = 386.50 $[M + Na]^+$. $C_{19}H_{25}NO_4S$ (363.15): calcd. C 62.78, H 6.93, N 3.85; found C 62.56, H 7.13, N 4.04.

Ethyl (1*S,5*S**,6*S**,7*R**)-2-(2,4-Dimethoxybenzyl)-5-methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-cis*-16):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, J = 6.6 Hz, 3 H, CH_3), 1.19 (t, J = 7.3 Hz, 3 H, CH_3), 1.51–1.62 (m, 1 H, 7-H), 1.72 (dd, J_1 = 9.1, J_2 = 6.7 Hz, 1 H, 6-H), 2.41–2.53 (m, 2 H, CH_2, CH), 3.07 (dd, J_1 = 7.9, J_2 = 6.7 Hz, 1 H, 1-H), 3.13 (d, J = 11.6 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.07 (q, J = 7.3 Hz, 2 H, CH_2), 4.30 (d, J = 14.6 Hz, 1 H, CH_2), 5.86 (d, J = 14.6 Hz, 1 H, CH_2), 6.40–6.43 (m, 2 H, ArH), 7.25 (d, J = 8.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 21.4, 23.1, 25.3, 27.1, 39.31, 50.2, 51.0, 55.3, 55.4, 60.7, 98.3, 104.0, 115.6, 131.5, 158.8, 160.6, 168.8, 203.1 ppm. IR (film): $\tilde{\nu}$ = 2930, 2820, 1730, 1610, 1585, 1410, 1205 cm^{-1}. $C_{19}H_{25}NO_4S$ (363.15): calcd. C 62.78, H 6.93, N 3.85; found C 62.89, H 6.98, N 3.98.

Synthesis of (–)-16: Isomers (–)-*anti-trans*-**16** (0.071 g, 58%) and (–)-*anti-cis*-**16** (0.031 g, 27%) were obtained as yellow pale oils (hexane/EtOAc 3:1) by the General Procedure for the formation of thioamides from a mixture (6:4) of (–)-*anti-trans*-**13b** and *anti-cis*-**13b** (0.120 g, 0.38 mmol).

(1*S*,5*S*,6*S*,7*S*)-Ethyl-2-(2,4-dimethoxybenzyl)-5-methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate [(–)-*anti-trans*-16]: $[\alpha]_D^{25}$ = –184.00 (c = 0.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (d, J = 6.7 Hz, 3 H), 1.20 (t, J = 7.3 Hz, 3 H), 1.52–1.54 (m, 1 H), 1.69–1.73 (m, 1 H), 1.76–1.80 (m, 1 H), 2.64 (dd, J_1 = 15.8, J_2 = 10.3 Hz, 1 H), 2.95 (dd, J_1 = 15.8, J_2 = 3.6 Hz, 1 H), 3.08 (dd, J_1 = 7.9, J_2 = 2.4 Hz, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 3.98 (q, J = 7.3 Hz, 2 H), 5.14 (d, J = 14.0 Hz, 1 H), 5.31 (d, J = 14.0 Hz, 1 H), 6.40–6.43 (m, 2 H), 7.31 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.6, 28.7, 29.3, 30.8, 41.7, 49.7, 50.4, 55.2, 55.3, 60.8, 98.3, 104.2, 115.6, 131.8, 158.7, 160.9, 170.6, 200.8 ppm. IR (film): $\tilde{\nu}$ = 2910, 2830, 1720, 1610, 1580, 1405, 1205, 1035 cm^{-1}. $C_{19}H_{25}NO_4S$ (363.15): calcd. C 62.78, H 6.93, N 3.85; found C 62.77, H 6.86, N 3.91.

(1*S*,5*S*,6*S*,7*R*)-Ethyl-2-(2,4-dimethoxybenzyl)-5-methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate [(–)-*anti-cis*-16]: $[\alpha]_D^{25}$ = –48.00 (c = 0.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10

(d, J = 6.1 Hz, 3 H, CH_3), 1.25 (t, J = 7.3 Hz, 3 H, CH_3), 1.51–1.59 (m, 1 H, 7-H), 1.72 (dd, J_1 = 9.1, J_2 = 6.7 Hz, 1 H, 6-H), 2.40–2.53 (m, 2 H, CH_2, CH), 3.07 (dd, J_1 = 7.9, J_2 = 6.7 Hz, 1 H, 1-H), 3.13 (d, J = 11.6 Hz, 1 H, CH_2), 3.74 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.12 (q, J = 7.3 Hz, 2 H, CH_2), 4.27 (d, J = 14.6 Hz, 1 H, CH_2), 5.83 (d, J = 14.6 Hz, 1 H, CH_2), 6.39–6.42 (m, 2 H, ArH), 7.23 (d, J = 9.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 21.4, 23.13, 25.3, 27.0, 39.3, 50.2, 51.1, 55.3, 55.4, 60.7, 98.3, 104.1, 115.6, 131.6, 158.8, 160.6, 168.8, 203.1 ppm. IR (film): $\tilde{\nu}$ = 2960, 2910, 1720, 1610, 1590, 1410, 1290, 1260, 1210, 1060 cm^{-1}. $C_{19}H_{25}NO_4S$ (363.15): calcd. C 62.78, H 6.93, N 3.85; found C 62.66, H 7.10, N 3.79.

Synthesis of 25: Isomers *anti-trans*-**25** (0.290 g, 70%) and *anti-cis*-**25** (0.029 g, 10%) were obtained as yellow pale oils (hexane/EtOAc 4:1) by the General Procedure for the formation of thioamides, from a mixture (87:13) of *anti-trans*-**23** and *anti-cis*-**23** (0.400 g, 1.20 mmol).

(1*S,5*S**,6*S**,7*S**)-2-(2,4-Dimethoxybenzyl)-5-methyl-7-(trifluoromethyl)-2-azabicyclo[4.1.0]heptan-3-one (*anti-trans*-25):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.8 Hz, 3 H), 1.51–1.57 (m, 2 H), 1.82–1.87 (m, 1 H), 2.62 (dd, J_1 = 16.1; J_2 = 10.3 Hz, 2 H), 2.94 (dd, J_1 = 15.6, J_2 = 3.9 Hz, 1 H), 3.12 (dd, J_1 = 8.8, J_2 = 3.5 Hz, 1 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 4.93 (d, J = 14.1 Hz, 1 H), 4.63 (d, J = 14.1 Hz, 1 H), 6.42–6.44 (m, 2 H), 7.43 (d, J = 9.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 23.1 (q, J = 2.3 Hz), 28.8, 29.5 (q, J = 36 Hz), 36.5 (q, J = 3.8 Hz), 49.5, 49.7, 55.2, 55.3, 98.3, 104.3, 115.7, 125.9 (q, J = 270 Hz), 131.7, 158.7, 160.9, 201.0 ppm. IR (film): $\tilde{\nu}$ = 2931, 2810, 1688, 1600, 1597, 1500, 1465, 1380, 1355, 1250 cm^{-1}. $C_{17}H_{20}F_3NO_2S$ (359.12): calcd. C 56.81, H 5.61, N 3.90, S 8.92; found C 56.69, H 5.56, N 3.98, S 8.97.

(1*S,5*S**,6*S**,7*R**)-2-(2,4-Dimethoxybenzyl)-5-methyl-7-(trifluoromethyl)-2-azabicyclo[4.1.0]heptan-3-one (*anti-cis*-25):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.8 Hz, 3 H, CH_3), 1.43–1.51 (m, 1 H, 6-H), 1.57–1.66 (m, 1 H, 7-H), 2.11–2.14 (m, 1 H, CH), 2.50 (dd, J_1 = 15.5, J_2 = 12.7 Hz, 1 H, CH_2), 3.03 (dd, J_1 = 7.3, J_2 = 2.5 Hz, 1 H, 1-H), 3.12 (dd, J_1 = 15.6, J_2 = 3.4 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.22 (d, J = 14.6 Hz, 1 H, CH_2), 6.13 (d, J = 14.6 Hz, 1 H, CH_2), 6.42–6.44 (m, 2 H, ArH), 7.30 (d, J = 9.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 23.8 (q, J = 2.8 Hz), 25.3 (q, J = 34.6 Hz), 30.2 (q, J = 3.8 Hz), 36.2, 50.0, 50.9, 55.3, 55.4, 98.3, 104.1, 115.4, 131.1, 134.3 (q, J = 272.0 Hz), 158.7, 160.6, 202.8 ppm. IR (film): $\tilde{\nu}$ = 2925, 2810, 1690, 1608, 1580, 1500, 1450, 1380, 1352, 1250 cm^{-1}. $C_{17}H_{20}F_3NO_2S$ (359.12): calcd. C 56.81, H 5.61, N 3.90, S 8.92; found C 56.62, H 5.58, N 3.97, S 8.88.

General Procedure for Removal of the 2,4-Dimethoxybenzyl (Dmob) Group: A solution of the appropriate thioamide (0.33 mmol) in trifluoroacetic acid (0.60 mmol) was heated at reflux for 16 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane mixtures).

Ethyl (1*S,5*S**,6*S**,7*S**)-5-Methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate (*anti-trans*-17):** Compound *anti-trans*-**17** (0.580 g, 82%) was obtained as a pale yellow oil (hexane/EtOAc 4:1) by the General Procedure, from *anti-trans*-**16** (0.120 g, 0.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.6 Hz, 3 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.76–1.80 (m, 1 H), 1.82–1.85 (m, 1 H), 1.96–2.08 (m, 1 H), 2.55 (dd, J_1 = 16.5, J_2 = 7.3 Hz, 1 H), 2.75 (dd, J_1 = 17.1, J_2 = 5.5 Hz, 1 H), 3.18–3.23 (m, 1 H), 4.13 (q, J = 7.3 Hz, 2 H), 8.45 [s(a), 1 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.8, 25.7, 27.7, 29.1, 37.7, 45.4, 61.1, 170.6, 199.7 ppm. IR (film): $\tilde{\nu}$ = 1940, 1745, 1630, 1550, 1430, 1300, 1290 cm^{-1}. MS (ESI): m/z = 214.05 [M + H]$^+$. $C_{10}H_{15}NO_2S$ (213.08): calcd. C 56.31, H 7.09, N 6.57; found C 56.27, H 7.01, N 6.43.

Ethyl (1*S*,5*S*,6*S*,7*S*)-5-Methyl-3-thioxo-2-azabicyclo[4.1.0]heptane-7-carboxylate [(–)-*anti-trans*-17]: Compound (–)-*anti-trans*-**17** (0.040 g, 65%) was obtained as a pale yellow oil (hexane/EtOAc 4:1) by the General Procedure from (–)-*anti-trans*-**16** (0.100 g, 0.3 mmol). $[\alpha]_D^{25}$ = –30.43 (c = 0.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.6 Hz, 3 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.76–1.80 (m, 1 H), 1.82–1.85 (m, 1 H), 1.96–2.08 (m, 1 H), 2.55 (dd, J_1 = 16.5, J_2 = 7.3 Hz, 1 H), 2.75 (dd, J_1 = 17.1, J_2 = 5.5 Hz, 1 H), 3.18–3.23 (m, 1 H), 4.13 (q, J = 7.3 Hz, 2 H), 8.45 [s(a), 1 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.8, 25.7, 27.7, 29.1, 37.7, 45.4, 61.1, 170.6, 199.7 ppm. IR (film): $\tilde{\nu}$ = 1940, 1745, 1630, 1550, 1430, 1300, 1290 cm^{-1}. MS (ESI): m/z = 214.05 [M + H]$^+$. $C_{10}H_{15}NO_2S$ (213.08): calcd. C 56.31, H 7.09, N 6.57; found C 56.33, H 6.96, N 6.44.

(1*S,5*S**,6*S**,7*S**)-5-Methyl-7-(trifluoromethyl)-2-azabicyclo-[4.1.0]heptane-3-thione (*anti-trans*-26):** Compound *anti-trans*-**26** (0.840 g, 60%) was obtained as a pale yellow oil (hexane/EtOAc 9:1) by the General Procedure from *anti-trans*-**25** (0.240 g, 0.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, J = 6.8 Hz, 3 H), 1.55–1.59 (m, 1 H), 1.72–1.75 (m, 1 H), 1.89–2.00 (m, 1 H), 2.54 (dd, J_1 = 16.6, J_2 = 7.8 Hz, 1 H), 2.74 (dd, J_1 = 16.6, J_2 = 4.9 Hz, 1 H), 3.07 (d, J = 8.8 Hz, 1 H), 8.80 [s(a), 1 H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 (q, J = 2.8 Hz), 20.0, 27.5, 28.2 (q, J = 36.0 Hz), 32.0 (q, J = 3.8 Hz), 45.3, 124.2 (q, J = 270.0 Hz), 203.1 ppm. IR (film): $\tilde{\nu}$ = 3110, 3000, 1533, 1445, 1390, 1330, 1274, 1070 cm^{-1}. MS (ESI): m/z = 209.91 [M + H]$^+$. $C_8H_{10}F_3NS$ (209.05): calcd. C 45.92, H 4.82, N 6.69, S 15.33; found C 46.01, H 4.67, N 6.74, S 15.27.

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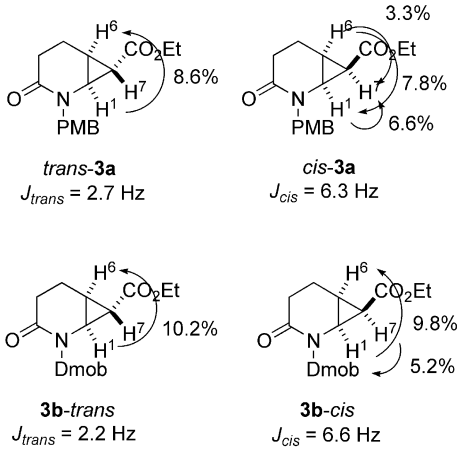

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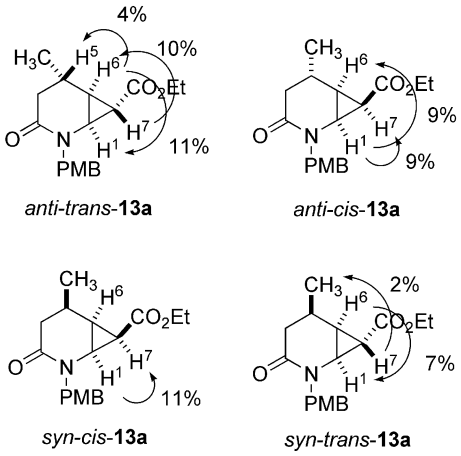

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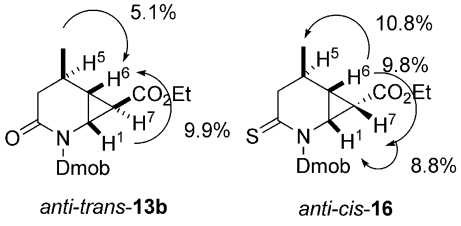

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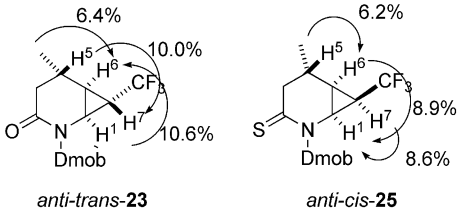

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