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Organocatalytic Asymmetric Synthesis of β-Aryl-β-isocyano Esters

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Dedicated to Professor Alfredo Ricci on the occasion of his retirement.

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Abstract: The asymmetric addition of malonates to *in situ* generated *N*-formylimines of aromatic aldehydes was achieved under phase-transfer catalysis using *Cinchona* alkaloids-derived quaternary ammonium salts. The resulting β-formamidomalonates have been efficiently converted into β-aryl-β-isocyano esters. Their utility in the multicomponent Ugi reaction with chiral cyclic imines has been demonstrated.

Keywords: β-aryl-β-isocyano esters; imines; Mannich reaction; multicomponent reactions; organic catalysis; phase-transfer catalysis

Introduction

Isocyanide-based multicomponent reactions (IMCR)[1] are an invaluable tool for diversity-oriented synthesis,[2] granting a significant increase of structural complexity in a single step. Moreover, they allow the simultaneous introduction of several diversity inputs, whereas intramolecular modifications[3] or post-condensation transformations[4] give access to a variety of heterocyclic scaffolds.

The non-isocyanide components of classical IMCRs (aldehydes/ketones and carboxylic acids in the Passerini reaction[5] and aldehydes/ketones, carboxylic acids and amines in the Ugi reaction[1a,b]) are easily available in thousands of diverse structures, also in chiral enantiomerically pure forms. On the other hand, relatively fewer isocyanides are commercially available or easily synthesised. Most of them are achiral and unfunctionalised. A look at the recent literature on IMCRs shows that, in nearly all cases, the decorations introduced by the isocyanide component are simple achiral alkyl or cycloalkyl groups, which have a scarce exploratory value and are unlikely to act as real pharmacophores. Therefore, a broader access to functionalised and/or chiral, enantiomerically pure isocyanides would be particularly welcomed. Notable efforts in this direction have appeared just recently.[6] The only general family of enantiomerically pure isonitriles explored so far is represented by α-isocyano esters, that can be prepared in a stereoconservative way from commercially available α-amino acids.[7] They have been efficiently employed in the Passerini reaction,[8] but are more troublesome in the Ugi condensation, due to their possible racemisation or epimerisation under the reaction conditions.[9] However, recently a thorough study has demonstrated that these unwanted processes may be suppressed in most cases.[10] α-Isocyano esters may also be used in a variety of useful multicomponent reactions involving the relatively acidic α-position, but obviously in these approaches the stereochemical information is lost.[7b]

On the contrary, chiral β-isocyano esters of general formula **1** may be very useful in the convergent assembly of peptidomimetics through the Ugi reaction. They are expected to be more resistant to racemisation. Moreover, they will introduce in the final adducts two potential pharmacophores: an aryl group, capable of π-π interactions, and a carboxylate group. The latter will be able to form, after deprotection to the free carboxylate, an anion species. For example, these two moieties may be useful in the design of peptidomimetic integrin ligands.[11]

However, we could find only one report dealing with the synthesis of enantioenriched β-isocyano esters,[12] and it was of very limited scope. Thus we decided to design a general asymmetric method to

access both enantiomers of compounds **1** in high optical purity.

Results and Discussion

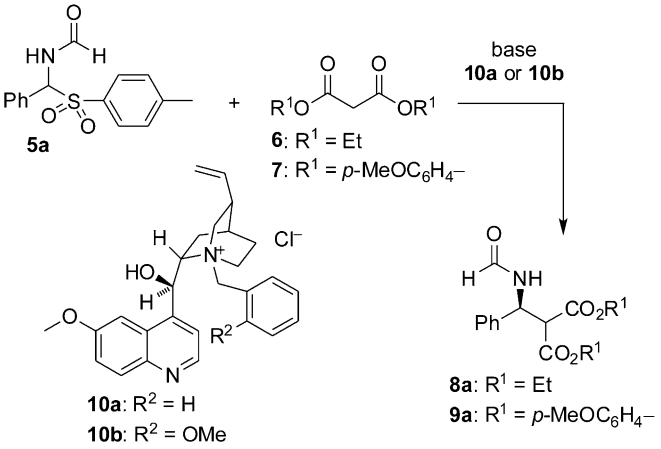
Scheme 1 shows our retrosynthetic design. β-Isocyano esters **1** are planned to be obtained through dehydration of formamides **2**, which can in turn be synthesised through an asymmetric Mannich-type addition of malonates to *N*-formylimines **4**.

However, we could not find any report on the isolation of *N*-formylimines **4** in pure form. Actually, when we attempted the preparation of **4a** from formamido sulphone **5a** (Ar = Ph),[13] under the conditions that are typically used for preparing pure *N*-Boc-imines (K_2CO_3 in THF at reflux, followed by filtration of potassium sulphinate),[14] only benzaldehyde was detected after filtration, probably because of the high hydrolytic lability of this imine. Therefore we decided to explore a one-pot strategy based on *in situ* generation of this labile imine.[15] We were particularly attracted by the excellent work by Ricci and Bernardi,[16] where they succeeded to obtain high enantiomeric excesses in the addition of malonates to *N*-Boc- or *N*-Cbz-imines, generated *in situ* from α-ureido sulphones, under asymmetric phase-transfer catalysis.[17]

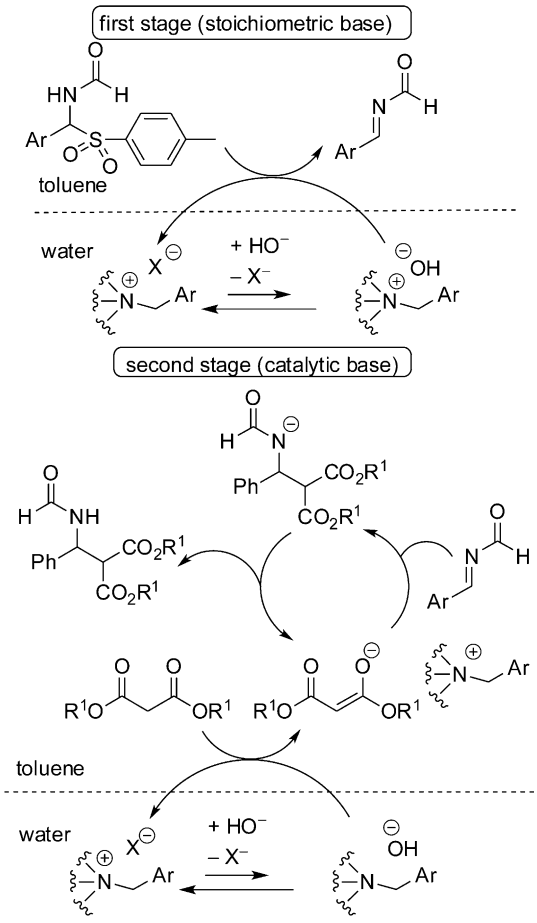
In a preliminary test, amido sulphone **5a** was dissolved in toluene and treated, at 0 °C, for 48 h, with diethyl malonate and with 6 equivalents of 50% aqueous K_2CO_3 in the presence of quinine-derived catalyst **10a** (Scheme 2). To our delight, the desired adduct **8a** was obtained in fair (65%) yield, albeit with low selectivity (23% *ee*) (*ee* = enantiomeric excess). Despite the presence of water in the reaction mixture, and the possible high hydrolytic lability, the intermediate *N*-formylimine was evidently stable enough to react with the malonate. No product derived from the addition of the malonate to benzaldehyde was detected.

A significant improvement was achieved by using malonate **7**, that was already reported by Ricci and Bernardi[16a] to enhance enantioselectivity in some critical cases. With this reagent, the *ee* rose to 50% (yield: 71%), and also the rate of reaction had significantly increased (the reaction being complete in 10 h). A further improvement (60% *ee*) was achieved by using modified catalyst **10b**, where the benzyl was replaced by an *o*-methoxybenzyl group.[16a,18]

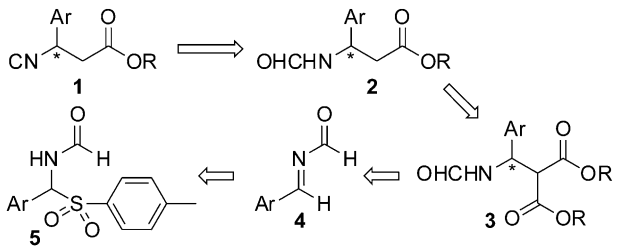
A possible mechanism is depicted in Scheme 3. In the first stage a stoichiometric quantity of the base is necessary to promote the sulphinate elimination affording the *N*-formylimine **5**. This reaction probably



Scheme 2. Organocatalytic synthesis of **8a** and **9a**.



Scheme 3. Proposed mechanism for the phase-transfer reaction.



Scheme 1. Retrosynthetic design.

takes place in the organic phase by the action of tetraalkylammonium hydroxide. Then, in the second stage, the tetraalkylammonium hydroxide deprotonates the malonate which, as a ion pair with the chiral cation, attacks the *N*-formylimine. The resulting nitrogen anion takes a proton from the malonate and thus the base, for this second stage, is only catalytic. It is important to note that this reaction also takes place, although much slower, in the absence of the catalyst. This background reaction probably involves acid-base reactions at the interface.

At this point we decided to optimise the reaction conditions with malonate **7** and catalyst **10b**.

We first studied the effect of catalyst loading, also in order to evaluate the importance of the background reaction. Surprisingly, on passing from 10 to 20 mol% loading no difference in *ee* was observed, whereas higher loadings decreased the enantioselectivity to 40%, maybe because of aggregation phenomena due to the limited solubility of the catalyst.

Thus 10 mol% catalyst loading was used for further refinements. Table 1 reports selected data for solvent screening (more data can be found in the Supporting Information). In practice, only toluene was able to afford a good enantioselectivity. The use of non-aromatic solvents (entries 3–5) resulted in a slower and poorly enantioselective reaction, but also aromatic solvents different from toluene caused a dramatic drop of enantioselectivity (entry 2). In the attempt to increase the solubility of both substrate and catalyst we also tried to add small amounts of a co-solvent, but even in the presence of only 5% of $CHCl_3$ (entry 7) the product was obtained in nearly racemic form.

By lowering the substrate concentration from 0.1 to 0.05 M a significant improvement of enantioselectivity was observed, while the yield remained unaffected (Table 1, entry 9).

Table 1. Effect of the the solvent on the enantioselective synthesis of **9a**.[a]

Entry	Solvent	Yield[b]	*ee* [%][c]
1	toluene	98%	60
2	benzene	89%	7
3	*n*-hexane	26%	5
4	MeO-*t*-Bu (MTBE)	29%	10
5	CH_2Cl_2	40%	21
6	toluene/$CHCl_3$ 9:1	91%	8
7	toluene/$CHCl_3$ 19:1	98%	7
8	toluene/CH_2Cl_2 9:1	85%	21
9	toluene[d]	97%	66

[a] Substrate concentration: 0.1 M in the organic solvent except for entry 9; base: 6 equiv. of 50% aqueous K_2CO_3 (w/w), catalyst: 10 mol%, temperature: 0 °C, time: 20 h.
[b] Isolated yield after chromatography (not optimised).
[c] Determined by HPLC on a chiral stationary phase.
[d] Substrate concentration: 0.05 M.

Table 2. Effect of base on the enantioselective synthesis of **9a**.[a]

Entry	Base[b]	Conversion[c]	*ee* [%][d]
1	50% K_2CO_3	69%	66
2	10% K_2CO_3	36%	66
3	dry K_2CO_3	64%	50
4	20% Na_2CO_3	28%	66
5	37% Cs_2CO_3	23%	37
6	1% Li_2CO_3	31%	66
7	5% $NaHBO_3$	$<10\%$	66
8	33% NH_3	30%	66
9	10% LiOH	46%	3

[a] Substrate concentration: 0.05 M in toluene; catalyst: 10%, base: 6 equiv., time: 2 h, temperature: 0 °C.
[b] w/w.
[c] Determined by NMR of the crude product.
[d] Determined by HPLC on a chiral stationary phase.

Another important parameter is represented by the nature, quantity and concentration of the base (Table 2). The screening reported in Table 2 has been carried out with a short reaction time (only 2 h) in order to also get information on the differences in rate.

In most cases the use of different aqueous bases was influential in terms of rate, but not for the *ee*. Both the countercation (compare entries 1, 4, 6) and the counteranion (compare entries 1, 7, 8) seem to be insignificant for the enantioselectivity, probably because the actual reacting species in the organic phase is the tetraalkylammonium hydroxide. Even aqueous ammonia, rarely used in this type of reactions, afforded the same enantiomeric excess (entry 8). However, a decrease of enantioselectivity was observed with cesium carbonate (entry 5) or with stronger bases (entry 9). In the absence of water (compare entries 1 and 3) a decrease of enantioselectivity was observed. In this case the reaction cannot be promoted by the tetraalkylammonium hydroxide, which might explain the difference. Taking into account the yields, aqueous K_2CO_3 turned out to be the most convenient base. Although a higher dilution (that is more water in the reaction mixture) does not seem to influence the enantioselectivity, a higher concentration (50%) granted a higher rate (entries 1 and 2).

When we studied the effect of temperature, we were rather disappointed to find that the enantioselectivity decreased upon lowering the temperature (Table 3, entries 1–4), whilst the ideal temperature remained 0 °C.

However, when we reduced the number of equivalents of base, from 6 to 1.5, a slight increase of enantioselectivity was detected at 0 °C (entries 1 and 5) but, most importantly, the expected temperature de-

Table 3. Effect of temperature and equivalents of base on the enantioselective synthesis of **9a**.[a]

Entry	Temp.	Time	Equiv. base	Conversion[b]	*ee*[c] [%]
1	0 °C	10 h	6	93%	67
2	−10 °C	10 h	6	63%	60
3	−20 °C	10 h	6	54%	54
4	−30 °C	10 h	6	<50%	54
5	0 °C	20 h	1.5	quant.	70
6	−15 °C	48 h	1.5	quant.	80
7	−15 °C	48 h	1.3	93%	82
8	−24 °C	60 h	1.5	73%	78
9	−40 °C	72 h	1.5	41%	55

[a] Substrate concentration: 0.05 M in toluene; catalyst: 10 mol%, base: 50% aqueous K_2CO_3 (w/w).
[b] Determined by NMR of the crude product.
[c] Determined by HPLC on a chiral stationary phase.

pendence was restored. The enantiomeric excess increased significantly on going down to −15 °C.

Under the best conditions (those of entry 7) the *ee* rose to 82%. A possible explanation is that the background uncatalysed reaction proceeds through reaction of the malonate with K_2CO_3 at the interface and thus its rate depends on the overall amount of base. On the contrary, in the catalysed, enantioselective reaction, the active species is continuously formed in the organic phase, and its concentration is limited by the amount of catalyst employed. Thus the effect of base concentration is stronger on the background reaction than on the catalysed one.

Interestingly, under these optimised conditions, also 33% NH_3 as the base gave a very similar enantioselectivity (83% *ee*), although with a lower conversion (44% after 48 h). A 5–10 mol% loading of the catalyst turned out to be ideal. With 5% catalyst, the *ee* decreased only slightly (80% *ee*, 84% yield), whereas with 1%, the enantioselectivity dropped markedly (54% *ee*).

Having found the best experimental conditions, we went back to try other malonates, to check if the use of **7** was really needed. Using diethyl malonate, under the conditions of entry 7 of Table 3 (48 h), the conversion was lower than 20%, showing that the aryl groups in **7** are essential for an efficient catalysis. The enantioselectivity was quite low too (26% *ee*) probably because of competition by the background reaction. With dibenzyl malonate, 30% conversion and 64% *ee* were obtained. Finally, with diphenyl malonate the conversion was good (90%), but again the enantioselectivity was inferior to **7** (67% *ee*). These data clearly demonstrate the importance for the rate of using a diaryl malonate and the higher enantioselectivity achieved with **7**.

At this point we turned our attention to catalyst engineering, preparing 23 different quaternary ammonium salts based on quinine, quinidine, dihydroquinine, cinchonine and cinchonidine (Figure 1). Selected results are reported in Table 4, whereas the full screening is described in the Supporting Information. Some of these quaternary salts were already known, whereas other ones are new.

From the results of Table 4 it appears that the presence of an *ortho* substituent on the benzyl ring is important. The effect seems more steric than electronic: catalyst **10d** with three fluorine atoms is among the

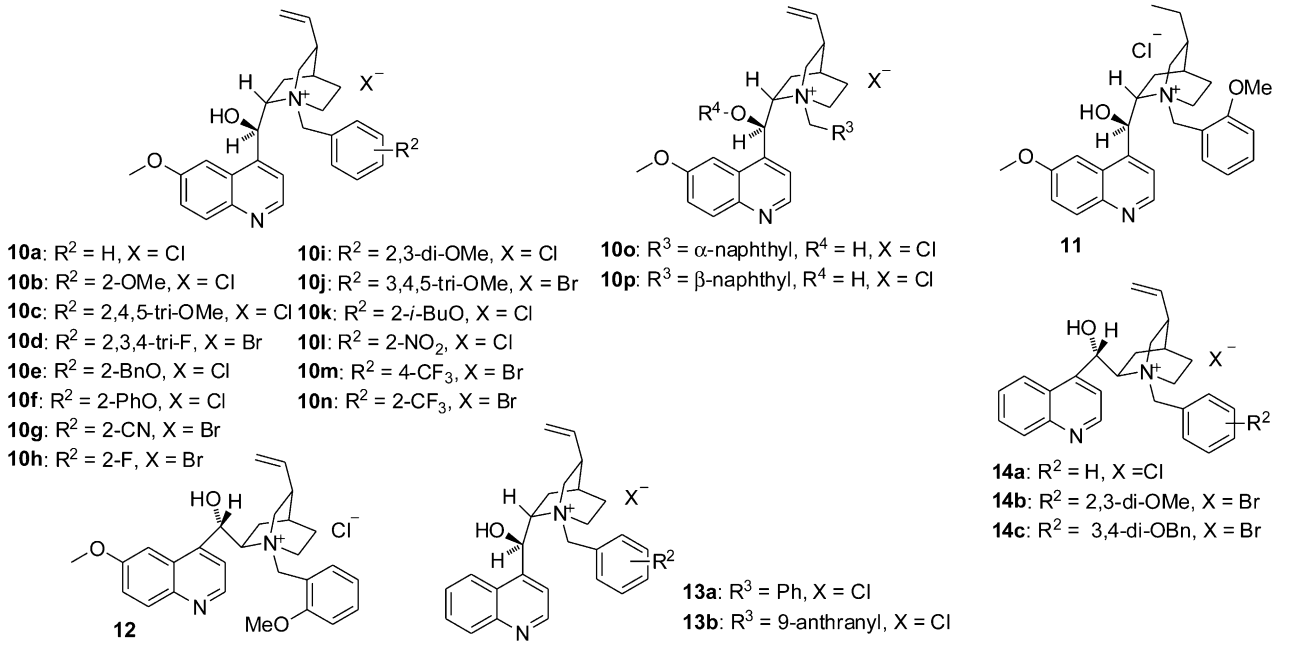


Figure 1. Catalysts tested in the asymmetric addition of malonate **7** to formylimine **4a**.

Table 4. Screening of various catalysts and conditions for the enantioselective synthesis of **9a**.[a]

Entry	Catalyst	Yield[b]	*ee* [%][c]	Configuration
1[c]	**10a**	65%	64	(*S*)
2	**10b**	88%	82	(*S*)
3	**10c**	90%	79	(*S*)
4	**10d**	72%	78	(*S*)
5	**10e**	66%	75	(*S*)
6	**10f**	95%	70	(*S*)
7	**10g**	86%	66	(*S*)
8	**10h**	62%	66	(*S*)
9	**10i**	99%	64	(*S*)
10	**10l**	65%	60	(*S*)
11	**10n**	95%	53	(*S*)
12	**11**	84%	74	(*S*)
13	**12**	76%	78	(*R*)
14	**13a**	70%	4	(*S*)
15	**14a**	66%	28	(*R*)

[a] Substrate concentration: 0.05 M in toluene; catalyst: 10 mol%, time: 48 h, base: 1.3 equiv. of 50% aqueous K_2CO_3 (w/w).
[b] Isolated yields after chromatography (unoptimised).
[c] Determined by HPLC on a chiral stationary phase.

best ones (compare entry 4 with entry 2). Thus we prepared a series of derivatives *ortho*-substituted with an alkoxy group (**10e**, **10f**, **10k**), but none of them surpassed the methoxy derivative **10b**; **10c**, having two additional methoxy groups behaved very similar to **10b** (compare entries 2 and 3).

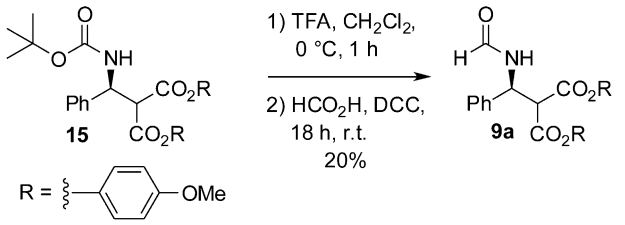
The quinoline methoxy group seems important: with catalysts derived from cinchonidine (e.g., **13a**) or cinchonine (e.g., **14a**) the enantiomeric excesses were always <28% (entries 14 and 15). Hydrogenation of the C=C double bond to give **11** gave a catalyst that was slightly less selective (entry 12). Finally, it should be noted that a nearly racemic product was observed when employing quaternary salts protected at the quinine alcoholic moiety, indicating that it is essential for selectivity.

In conclusion, after this long screening, the best catalysts turned out to be **10b**, **10c** and **10d**, with the first one being slightly superior.

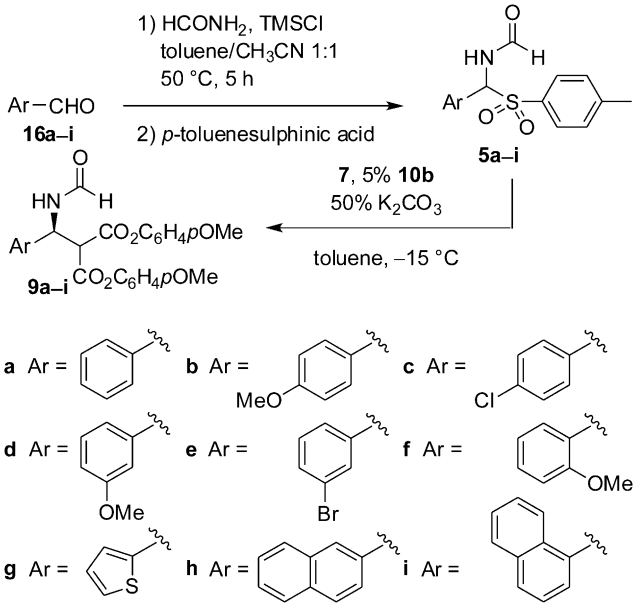
The analogue of **10b** derived from quinidine (**12**) was nearly as efficient that its diastereomer, allowing the formation in good *ee* of the (*R*) enantiomer. Various results suggest that the enantioselectivity should derive from an interaction of imine **4** and malonate **7** with the OH group, the benzyl substituent on nitrogen, and the quinoline system, with a scarce influence of the quinuclidine part and its stereogenic centres. These evidences are (i) the nearly opposite enantioselectivity of **10b** and **12**; (ii) the strong importance of the quinoline methoxy group; (iii) the essential role of the free OH group in the catalyst; and (iv) the need for aryl groups in the malonate. We think that the imine may be activated by a hydrogen bond between the nitrogen and the catalyst OH, whereas π-π interactions between the malonate aryl groups and the quinoline and the benzyl on nitrogen place the enolate selectively of one side of the imine C=N bond.

The absolute configuration of (+) **9a**, obtained with catalyst **10b**, was unambiguously demonstrated by its independent synthesis from known (*S*)**-15** (Scheme 4).[16,20]

We then proceeded to determine the scope of the reaction, using a series of formamido sulphones, synthesised from the corresponding benzaldehydes by the method developed by Sisko (Scheme 5).[13b] Table 5 reports the isolated yields after crystallisation of formamido sulphones **5** (most of them are new) and the yields and the *ee*s of the organocatalytic reaction to give **9**. It should be noted that in these reactions only 5 mol% loading of catalyst was employed. Formamido sulphone **5f**, derived from *o*-methoxybenzaldehyde, gave the highest *ee*. Also the β-naphthyl derivative **5h** gave a better *ee* than the parent unsubstituted compound **5a**.



Scheme 4. Assignment of the absolute configuration.



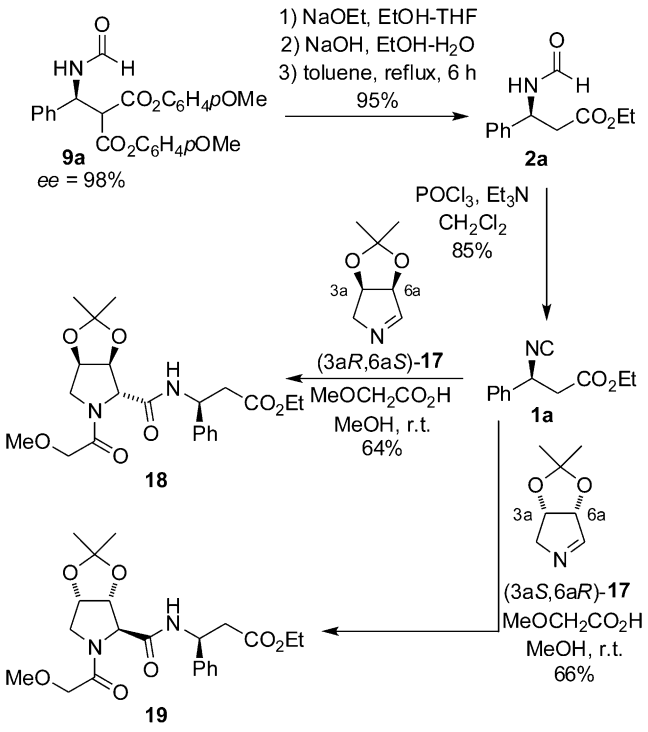
Scheme 5. Synthesis of various malonates **9a–h**.

Table 5. Enantioselective synthesis of various malonates **9**.[a]

Starting aldehyde	Ar	Yield of sulphone **5**	Yield of **9**[b]	*ee* of **9** [%][c]
16a	Ph	98%	83%	80
16b	4-$MeOC_6H_4$	91%	84%	72
16c	4-ClC_6H_4	51%	85%	60
16d	3-$MeOC_6H_4$	65%	80%	67
16e	3-BrC_6H_4	65%	87%	69
16f	2-$MeOC_6H_4$	51%	87%	90
16g	3-thienyl	78%	62%	67
16h	β-naphthyl	95%	78%	84
16i	α-naphthyl	24%	78%	70

[a] *Conditions:* catalyst: **10b** (5 mol%), 0.5 mmol of substrate in 10 mL of toluene, temp.: −15 °C, time: 48 h, base: 1.3 equiv. of 50% aqueous K_2CO_3.
[b] Isolated yields after chromatography (unoptimised).
[c] Determined by HPLC on chiral stationary phase.

The enantiomeric excess can be further improved through crystallisation. This was demonstrated in the case of compound **9a** (Scheme 6). When a sample with 80% *ee* (obtained using 5% catalyst loading, see Table 5) was dissolved in the minimum amount of CH_2Cl_2 and then diluted with *i*-PrOH, a white precipitate was slowly formed. The yield of this solid was 16%, and HPLC on a chiral stationary phase showed that it was nearly racemic (only 24% *ee*). On the other hand, the mother liquors afforded, after evaporation, in 84% yield, a solid with a lower melting point, which was found to have 98% *ee*. Thus in this case the racemate crystallises preferentially over the pure enantiomer. The overall yield of this pure enantiomer **9a** was 68% from the formamido sulphone **5a**. This procedure was carried out on a multigram scale.



Scheme 6. Synthesis of chiral isocyanide **1a** and its use in a diastereoselective Ugi reaction.

Adduct **9a** was then converted into (*S*) isocyano ester **1a** by a three-step straightforward procedure. Treatment with EtONa in EtOH gave a fast transesterification, which was followed by monohydrolysis of the resulting diethyl malonate **8a**. Upon acidification and decarboxylation, formamido ester **2a** was obtained in excellent overall yield. Finally, dehydration gave the target isocyanide **1a** in 85% yield (55% overall yield from formamido sulphone **5a**). It is worth noting that dehydration on the malonate **9a** did not afford the desired product, because of formamido group elimination, giving an alkylidenemalonate. Moreover, synthesis of the corresponding *p*-methoxyphenyl β-isocyanophenylpropionate was less efficient, because of lower yields both in the monohydrolysis and in the dehydration steps.

The above reported synthesis of **1a** is therefore well suited for the large-scale preparation of this isonitrile in nearly pure enantiomeric form. HPLC on chiral stationary phase showed an *ee* of 93%, thus slightly lower than that of starting malonate. Using the quinidine-derived catalyst **12** for the organocatalytic reaction, the (*R*) enantiomer of **9a** should be equally available.

As a first application of this chiral isocyanide, we performed (Scheme 6) a highly diastereoselective Ugi reaction with both enantiomers of imine **16**, prepared by us through a recently reported biocatalytic procedure.[11a] These imines are useful intermediates for the synthesis of conformationally biased peptidomimetics because: (i) they give complete diastereoselection (favouring the *trans* adduct) in Ugi reactions; (ii) they, and their Ugi adducts, are fairly rigid; (iii) removal of the acetal group allows modulation of the polarity and conformational behaviour of the final products.

As expected, also in this case only *trans* products were obtained. Reaction of (*S*)-**1a** with the two enan-

tiomers of imine **17** gave two distinct diastereoisomers **18** and **19**, which were clearly distinguished in HPLC, TLC, and NMR. HPLC analysis indicated a diastereomeric ratio of 94:6 (**18**) and 95:5 (**19**), which reflected the *ee*s of the starting isocyanide and imines [96% and 98% for (*3aR,6aS*)-**17** and (*3aS,6aR*)-**17**, respectively]. Pure **18** and **19** could be obtained by chromatography, since they are separable through this methodology.

Conclusions

In conclusion, we have developed a new, efficient, and short asymmetric synthesis of β-aryl-β-isocyano esters, based on an organocatalytic phase-transfer Mannich-type reaction. The readily available catalyst (derived in one step from quinine or quinidine) and the need for a relatively low loading (5 mol%) renders this methodology amenable for large-scale synthesis. The enantioselectivity obtained is significantly good, but not yet excellent. However, we have demonstrated the possibility to increase to 98% the *ee*s of the key intermediate by a simple crystallisation with only a slight loss in overall yield. These isocyano esters may find application in the stereocontrolled assembly of conformationally biased peptidomimetics through their Ugi reactions with cyclic imines. A first example of this general strategy has already been reported here.

Experimental Section

NMR spectra were taken at room temperature in $CDCl_3$ or DMSO-d_6 at 300 MHz (^{1}H), and 75 MHz (^{13}C), using as internal standards: for ^{1}H NMR in $CDCl_3$: TMS; for ^{1}H NMR in DMSO: the central peak of DMSO (2.506); for ^{13}C in $CDCl_3$ the central peak of $CDCl_3$ (at 77.02 ppm); for ^{13}C NMR in DMSO: the central peak of DMSO (39.43). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignments were also made with the aid of gCOSY and gHSQC experiments. In an ABX system, the proton A is considered upfield and B downfield. GC-MS were carried out using an HP-1 column (12 m long, 0.2 mm diameter), electron impact at 70 eV, and a mass temperature of about 170 °C. Only $m/z > 33$ were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 1.0 mL min^{-1} with initial temperature 60 °C, initial time 2 min, rate 20 °C min^{-1}, final temperature 280 °C, injection temperature 250 °C, detection temperature 280 °C. HR-MS were recorded by employing either the ESI+ or the ESI− ionisation method. IR spectra were recorded as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates and viewed under UV (254 nm) and developed with Hanessian stain [dipping into a solution of $(NH_4)_4MoO_4{\cdot}4\ H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4\ H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming] or, when specified, with ninhydrin (900 mg of ninhydrin in 300 mL *n*-BuOH and 9 mL AcOH, followed by warming). R_f values were measured after an elution of 7–9 cm. Column chromatographies were done with the "flash" methodology using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere.

General Procedure for the Preparation of Formamido Sulphones 5a–i[13b]

A solution of the starting aryl or heteroaryl aldehyde (15 mmol) in dry CH_3CN (10 mL) and dry toluene (10 mL) was treated with formamide (2.5 equiv.) and trimethylsilyl chloride (1.1 equiv.). The mixture was stirred at 50 °C for 5 h and then freshly prepared *p*-toluenesulphinic acid[13b] (1.1 equiv.) was added. The mixture was stirred for further 4 h at 50 °C. After cooling, methyl *tert*-butyl ether (10 mL) and distilled water (50 mL) were added. The mixture was cooled to 0 °C until precipitation was complete. The resulting solid was recovered by suction, washed with a little water and methyl *tert*-butyl ether, and finally thoroughly dried in a dessiccator under vacuum in the presence of P_2O_5. The purity was assessed by ^{1}H NMR. Some of these formamido sulphones were already known: **5a**,[13a,b] **5b**,[13a,b] **5d**,[21] **5f**,[21] **5g**,[13a,b] although only **5a** was fully characterised.

***N*-[(4-Methoxyphenyl)(tosyl)methyl]formamide (5b):** mp 145.2–147 °C. ^{1}H NMR [300 MHz, DMSO-d_6; 2 conformers (A and B) are present in an 81:19 ratio]: $\delta = 9.73$ (A) (d, $J =$ 10.8 Hz, 0.81 H, N*H*), 9.37 (B) (t, $J = 10.5$ Hz, 0.19 H, N*H*), 7.94 (A) (d, $J = 0.9$ Hz, 0.81 H, C*H*O), 7.87 (B) (d, $J =$ 10.5 Hz, 0.19 H, C*H*O), 7.71 (A) (d, $J = 8.4$ Hz, 1.62 H, *H ortho* to SO_2), 7.57 (B) (d, $J = 8.4$ Hz, 0.38 H, *H ortho* to SO_2), 7.48 (A) (d, $J = 8.7$ Hz, 1.62 H, *H meta* to OMe), 7.43 [d, $J = 8.4$ Hz, 2 H, *H meta* to SO_2 (A + B) + *H meta* to OMe (B)], 7.40 (B) (d, $J = 8.4$ Hz, 0.38 H, *H meta* to SO_2), 6.98 (A) (d, $J = 8.7$ Hz, 1.62 H, *H ortho* to OMe), 6.93 (B) (d, $J =$ 8.7 Hz, 0.38 H, *H ortho* to OMe), 6.33 (A) (d, $J = 10.5$ Hz, 0.81 H, ArC*H*), 6.20 (B) (d, $J = 10.5$ Hz, 0.19 H, ArC*H*), 3.78 (A) (s, 2.43 H, OCH_3), 3.76 (B) (s, 0.57 H, OCH_3), 2.41 (A + B) (s, 3 H, ArCH_3); ^{13}C NMR (75 MHz, DMSO-d_6; only the peaks of the main conformer are reported): $\delta = 160.0$ (*C*=O + *C*−OMe), 144.6, 133.5, 121.9 (quat.), 130.7 (*C meta* to OMe), 129.5 (*C meta* to SO_2), 129.0 (*C ortho* to SO_2), 113.7 (*C ortho* to OMe), 69.7 (Ar*C*H), 55.2 (O*C*H_3), 21.1 (Ar*C*H_3); IR ($CHCl_3$): $\nu = 3002$, 1693, 1609, 1484, 1304, 1178, 1142, 1081, 1026, 918 cm^{-1}; HR-MS (ESI+): $m/z =$ 342.0769; calcd. for $C_{16}H_{17}NO_4SNa$ $[M+Na]^+$: 342.0776.

(*S*)-Bis(4-methoxyphenyl) 2-[Formamido(phenyl)-methyl]malonate (9a)

A solution of **5a** (1.00 g, 3.45 mmol)[13a,b] and malonate **7**[16a] (1.31 g, 4.14 mmol) in toluene (35 mL) was treated with catalyst **10b** (336 mg, 350 μmol, 10%) and cooled to −15 °C. 50% (w/w) aqueous K_2CO_3 ($d = 1.36$) (915 μL, 4.50 mmol) was added and the mixture stirred for 48 h at −15 °C. The mixture was evaporated to dryness and immediately chromatographed through 80 g of silica (CH_2Cl_2/AcOEt from

95:5 to 85:15) to give pure **9a** as a solid; yield: 1.30 g (83%). Using 5% of catalyst, the yield was 84% and the *ee* was 80%. The *ee* was determined by chiral HPLC (Daicel Chiral pak AD 250×4.6 mm, V_{inj}=20 μL, T=40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}). R_t (*S*): 20.14; R_t (*R*): 16.49. Crystallisation of the chromatographed product (1.36 g) from CH_2Cl_2/*i*-PrOH (1:9; about 65 mL) gave a white solid (mp 143.5–145.3 °C) (yield: 210 mg), having *ee*=24%. The mother liquors, after evaporation, afforded a pale yellow solid (mp 113.8–115.7 °C) (yield: 1.06 g) which, by HPLC analysis, had an *ee*=98%. $[\alpha]_D$; +3.6 (*c* 2, $CHCl_3$). The yield of this pure enantiomer is therefore 68%. R_f 0.50 (CH_2Cl_2/AcOEt 90:10); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present in an 86:14 ratio]: δ= 8.34 (A) (s, 0.86 H, C*H*=O), 8.25 (B) (d, J=11.4 Hz, 0.14 H, C*H*=O), 7.47–7.30 [m, 5.86 H, N*H* (A)+C*H* of Ph], 7.05 (A) (d, J=9.0 Hz, 1.72 H), 6.90 (A) (d, J=9.0 Hz, 1.72 H), 6.83 (A) (s, 3.64 H), 6.25 (A) (dd, J=4.4, 9.7 Hz, 0.86 H, C*H*NH), 5.48 (B) (dd, J=5.8 Hz, 10.6 Hz, 0.14 H, C*H*NH), 4.46 (A) (d, J=4.5 Hz, 0.86 H, NHCHC*H*), 4.43 (B) (d, J= 5.8 Hz, 0.14 H, NHCHC*H*), 3.80 (A+B) (s, 3 H, OCH_3), 3.77 (A+B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ=167.1, 165.8, 160.6 (*C*=O), 157.7 (*C*–OMe), 143.6, 143.3 (*C*OCO), 137.8 (quat. Ph), 128.9 (×2), 128.2, 126.4 (×2), 122.1 (×2), 121.9 (×2), 114.6 (×2), 114.5 (×2) (aromatic *C*H), 56.4 (NHCH*C*H), 55.58, 55.56 (O*C*H$_3$), 50.2 (*C*HNH); IR ($CHCl_3$): ν=3676, 3601, 3414, 3000, 1746, 1688, 1596, 1489, 1352, 1174, 1132, 918 cm^{-1}; HR-MS (ESI+): m/z=450.1556, calcd. for $C_{25}H_{24}NO_7$ [M+H]$^+$: 450.1553.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(4-methoxyphenyl)methyl]malonate (9b): It was prepared following the procedure above described for **9a**; yield: 84%; *ee*=72% (determined by chiral HPLC on a CHIRALPAK IB column, eluant hexane/*i*-PrOH 80:20, flow 0.9 mL min^{-1}; R_t (*S*)= 51.7 min; R_t (R)=39.3 min; R_f=0.31 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −9.7 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present, in an 85:15 ratio]: δ=8.33 (A) (s, 0.85 H, C*H*=O), 8.24 (B) (d, J= 11.7 Hz, 0.15 H, C*H*=O), 7.37–7.27 (A+B) (m, 3 H, N*H*+ C*H* *meta* to OMe in Ar), 7.04 (A) (d, J=9.0 Hz, 1.70 H), 6.97–6.85 (m, 8.30 H, other aromatic C*H*), 6.18 (A) (dd, J= 4.6, 9.8 Hz, 0.85 H, C*H*NH), 5.43 (B) (dd, J=5.8 Hz, 10.3 Hz, 0.15 H, C*H*NH), 4.41 (A) (d, J=4.5 Hz, 0.86 H, NHCHC*H*), 4.39 (B) (d, J=6.0 Hz, 0.14 H, NHCHC*H*), 3.83 (B) (s, 0.45 H, OCH_3), 3.82 (A) (s, 2.55 H, OCH_3), 3.80 (A+ B) (s, 3 H, OCH_3), 3.78 (A+B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ=167.1, 165.9, 160.5 (*C*=O), 159.4, 157.7 (*C*– OMe), 143.6, 143.4 (*C*OCO), 129.9 (quat.), 127.7 (×2), 122.1 (×2), 122.0 (×2), 114.7 (×2), 114.6 (×2) 114.3 (×2) (aromatic *C*H), 56.6 (NHCH*C*H), 55.6 (×2), 55.3 (O*C*H$_3$), 49.8 (*C*HNH); IR ($CHCl_3$): ν=3670, 3597, 3410, 2997, 1747, 1688, 1599, 1493, 1171, 1132, 1023, 920 cm^{-1}; HR-MS (ESI+): m/z=480.1672, calcd. for $C_{26}H_{26}NO_8$ [M+H]$^+$: 480.1658.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(4-chlorophenyl)-methyl]malonate (9c): It was prepared following the procedure above described for **9a**; yield: 85%; *ee*=60% (determined by chiral HPLC on a Daicel Chiral pak AD 250× 4.6 mm column, V_{inj}=20 μL, T=40 °C, eluent: hexane/*i*-PrOH 40:60; flow: 0.5 mL min^{-1}). R_t (*S*): 23.90; R_t (*R*): 20.30; R_f=0.48 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −6.4 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present, in a 88:12 ratio; only selected signals of conformer B are reported]: δ=8.34 (A) (s, 0.88 H, C*H*=O), 8.23 (B) (d, J=11.7 Hz, 0.12 H, C*H*=O), 7.70 (B) (d, J=8.4 Hz, 0.12 H, N*H*), 7.43–7.35 [m, 5.86 H, N*H* (A)+C*H* of Ph], 7.04 (A) (d, J=9.3 Hz, 1.76 H), 6.90 (A) (d, J=9.0 Hz, 1.76 H), 6.86 (A) (s, 3.72 H), 6.19 (A) (dd, J=4.5, 10.0 Hz, 0.88 H, C*H*NH), 5.45 (B) (dd, J=5.7 Hz, 10.6 Hz, 0.12 H, C*H*NH), 4.41 (A) (d, J=4.5 Hz, 0.88 H, NHCHC*H*), 3.39 (B) (d, J= 5.7 Hz, 0.12 H, NHCHC*H*), 3.80 (A+B) (s, 3 H, OCH_3), 3.78 (A+B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ=167.0, 165.6, 160.6 (*C*=O), 157.8 (*C*–OMe), 143.5, 143.3 (*C*OCO), 136.4, 134.2 (quat.), 129.1 (×2), 127.9 (×2), 122.0 (×2), 121.9 (×2), 114.63 (×2), 114.58 (×2) (aromatic *C*H), 56.2 (NHCH*C*H), 55.6 (×2) (O*C*H$_3$), 49.7 (*C*HNH); IR ($CHCl_3$): ν=3673, 3605, 3412, 2994, 1747, 1687, 1598, 1486, 1193, 1134, 1019, 920 cm^{-1}; HR-MS (ESI+): m/z=484.1164, calcd. for $C_{25}H_{23}ClNO_7$ [M+H]$^+$: 484.1163.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(3-methoxyphenyl)methyl]malonate (9d): It was prepared following the procedure above described for **9a**; yield: 80%; *ee*=67% (determined by chiral HPLC on a Daicel Chiral pak AD 250× 4.6 mm column, V_{inj}=20 μL, T=40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 19.73; R_t (*R*): 16.92; R_f=0.38 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −1.6 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present, in a 85:15 ratio; only selected signals of conformer B are reported]: δ=8.34 (A) (s, 0.85 H, C*H*=O), 8.24 (B) (d, J=11.7 Hz, 0.15 H, C*H*=O), 7.36 (A) (d, J=10.2 Hz, 0.85 H, N*H*), 7.31 (A+B) (t, J=8.1 Hz, 1 H, *H meta* to OMe in Ar), 7.05 (A) (d, J=9.3 Hz, 1.70 H), 6.90 (A) (d, J= 9.0 Hz, 1.70 H), 7.08–6.80 (m, 7.60 H), 6.21 (A) (dd, J=4.5, 9.7 Hz, 0.85 H, C*H*NH), 5.44 (B) (dd, J=5.8 Hz, 10.6 Hz, 0.15 H, C*H*NH), 4.45 (A) (d, J=4.5 Hz, 0.85 H, NHCHC*H*), 4.43 (B) (d, J=5.8 Hz, 0.15 H, NHCHC*H*), 3.81 (A+B) (s, 3 H, OCH_3), 3.80 (A+B) (s, 3 H, OCH_3), 3.77 (A+B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ=167.1, 165.8, 160.6 (*C*= O), 160.0, 157.7 (×2) (*C*-OMe), 143.6, 143.4 (*C*OCO), 139.4 (quat.), 130.0, 122.1 (×2), 122.0 (×2), 118.5, 114.6 (×2), 114.5 (×2), 113.6, 112.4 (aromatic *C*H), 56.3 (NHCH*C*H), 55.60, 55.57, 55.3 (O*C*H$_3$), 50.1 (*C*HNH); IR ($CHCl_3$): ν= 3675, 3597, 3411, 3040, 2956, 1747, 1688, 1597, 1488, 1417, 1177, 1133, 1028, 921 cm^{-1}; HR-MS (ESI+): m/z=480.1658, calcd. for $C_{26}H_{26}NO_8$ [M+H]$^+$: 480.1658.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(3-bromophenyl)-methyl]malonate (9e): It was prepared following the procedure above described for **9a**; yield: 87%; *ee*=69% (determined by chiral HPLC on a Daicel Chiral pak AD 250× 4.6 mm column, V_{inj}=20 μL, T=40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 21.55; R_t (*R*): 14.08; R_f=0.49 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −1.9 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$, 2 conformers (A and B) are present in an 89:11 ratio; only selected signals of conformer B are reported]: δ=8.35 (A) (s, 0.89 H, C*H*=O), 8.24 (B) (d, J=11.4 Hz, 0.11 H, C*H*=O), 7.60 (A) (s, 0.89 H, *H ortho* to Br and CH), 7.49 (A) (dt, J=7.8 Hz), 1.3 (t, 0.89 H, *H meta* to Br and CH), 7.40 (A) (d, J=9.9 Hz, 0.89 H, N*H*), 7.37 (A) (d, J=2.6 Hz, 1.78 H, *H para* to CH), 7.29 (A) (d, J=7.8 Hz, 0.89 H, *H para* to Br), 7.05 (A) (d, J=9.0 Hz,

1.78 H), 6.91 (A) (d, J = 9.0 Hz, 1.78 H), 6.93–6.83 (m, 4 H), 6.20 (A) (dd, J = 4.2, 9.9 Hz, 0.89 H, C*H*NH), 5.45 (B) (dd, J = 5.4 Hz, 10.8 Hz, 0.11 H, C*H*NH), 4.42 (A) (d, J = 4.2 Hz, 0.89 H, NHCHC*H*), 4.40 (B) (d, J = 5.4 Hz, 0.11 H, NHCHC*H*), 3.80 (A + B) (s, 3 H, OCH_3), 3.78 (A + B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ = 167.0, 165.6, 160.6 (*C*=O), 157.8 (×2) (*C*–OMe), 143.5, 143.3 (*C*OCO), 131.4, 130.5, 129.6, 125.2, 122.0 (×2), 121.8 (×2), 114.7 (×2), 114.6 (×2) (aromatic *C*H), 123.0 (quat.), 56.1 (NHCH*C*H), 55.6 (×2) (O*C*H$_3$), 49.7 (*C*HNH); IR ($CHCl_3$): ν = 3671, 3600, 3405, 2995, 1745, 1706, 1597, 1490, 1412, 1359, 1190, 1134, 1023, 920 cm^{-1}; HR-MS (ESI+): m/z = 528.0665, calcd. for $C_{25}H_{23}BrNO_7$ $[M+H]^+$: 528.0658.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(2-methoxyphenyl)methyl]malonate (9f): It was prepared following the procedure above described for **9a**; yield: 87%; *ee* = 90% (determined by chiral HPLC on a Daicel Chiral pak AD 250 × 4.6 mm column, V_{inj} = 20 μL, T = 40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 22.51; R_t (*R*): 12.14; R_f = 0.38 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −8.0 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present in an 71:29 ratio]: δ = 8.30 (A) (s, 0.71 H, C*H*=O), 8.29 (B) (d, J = 11.7 Hz, 0.29 H, C*H*=O), 7.42–7.27 [m, 2.71 H, N*H* (A) + 2 aromatic C*H* (A + B)], 7.10–6.67 [m, 10.29 H, N*H* (B) + other aromatics], 6.37 (A) (dd, J = 6.0, 10.2 Hz, 0.71 H, C*H*NH), 5.48 (B) (dd, J = 8.1 Hz, 10.8 Hz, 0.29 H, C*H*NH), 4.67 (B) (d, J = 8.1 Hz, 0.29 H, NHCHC*H*), 4.66 (A) (d, J = 6.0 Hz, 0.71 H, NHCHC*H*), 3.96 (A + B) (s, 3 H, OCH_3), 3.79 (B) (s, 0.87 H, OCH_3), 3.78 (A) (s, 2.13 H, OCH_3), 3.770 (A) (s, 2.13 H, OCH_3); 3.767 (B) (s, 0.87 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0 (A), 166.4 (B), 166.0 (A), 165.4 (B), 164.4 (B), 160.63 (A) (*C*=O), 157.7 (B), 157.62 (B), 157.59 (A), 157.56 (A), 156.6 (B), 156.5 (A) (*C*–OMe), 143.7 (A), 143.5 (A + B), 143.4 (B) (*C*OCO), 130.3 (B), 129.6 (A), 129.2 (B), 128.5 (A), 122.1 (A) (×2), 122.04 (A) (×2), 121.98 (B) (×2), 121.8 (B) (×2), 121.1 (B), 120.8 (A), 114.6 (B) (×2), 114.5 (A) (×2), 114.4 (A + B) (×2), 111.0 (B), 110.7 (A) (aromatic *C*H), 125.3 (A), 124.9 (B) (quat.), 55.7 (B) 54.7 (A) (NHCH*C*H), 55.6 (A + B) (×3) (O*C*H$_3$), 53.9 (B), 47.4 (A) (*C*HNH); IR ($CHCl_3$): ν = 3676, 3615, 3419, 2970, 1747, 1690, 1597, 1491, 1358, 1182, 1134, 1026, 906 cm^{-1}; HR-MS (ESI+): m/z = 480.1655, calcd. for $C_{26}H_{26}NO_8$ $[M+H]^+$: 480.1658.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(3-thienyl)methyl]malonate (9g): It was prepared following the procedure above described for **9a**; yield: 62%; *ee* = 67% (determined by chiral HPLC on a Daicel Chiral pak AD 250 × 4.6 mm column, V_{inj} = 20 μL, T = 40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 22.93; R_t (*R*): 17.85; R_f = 0.37 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −2.1 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present in an 86:14 ratio; only selected signals of conformer B are reported]: δ = 8.32 (A) (s, 0.86 H, C*H*=O), 8.26 (B) (d, J = 11.7 Hz, 0.14 H, C*H*=O), 7.43 (B) (dd, J = 3.0 and 4.8 Hz, 0.14 H, C*H* of thienyl), 7.37 (A) (dd, J = 3.0 and 5.0 Hz, 0.86 H, C*H* of thienyl), 7.32–7.24 [m, 1.86 H, N*H* (A) + 1 C*H* of thienyl], 7.14 (A + B) (dd, J = 1.2 and 5.0 Hz, C*H* of thienyl), 7.05 (A) (d, J = 9.0 Hz, 1.72 H), 6.90 (A) (d, J = 9.0 Hz, 1.72 H), 6.87 (A) (s, 3.64 H), 6.29 (A) (dd, J = 4.0, 9.9 Hz, 0.86 H, C*H*NH), 5.52 (B) (dd, J = 5.2 Hz, 10.4 Hz, 0.14 H, C*H*NH), 4.47 (A) (d, J = 4.0 Hz, 0.86 H, NHCHC*H*), 4.43 (B) (d, J = 5.2 Hz, 0.14 H, NHCHC*H*), 3.80 (A + B) (s, 3 H, OCH_3), 3.78 (A + B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ = 167.1, 165.7, 160.4 (×2) (*C*=O), 157.8, 157.7 (*C*–OMe), 143.6, 143.4 (*C*OCO), 139.0 (quat. thienyl), 127.0, 126.1, 122.4, 122.1 (×2), 122.0 (×2), 114.60 (×2), 114.57 (×2) (aromatic *C*H), 55.9 (NHCH*C*H), 55.6 (×2) (O*C*H$_3$), 46.7 (*C*HNH); IR ($CHCl_3$): ν = 3676, 3594, 3412, 3002, 1748, 1687, 1596, 1490, 1357, 1171, 1132, 1041, 922 cm^{-1}; HR-MS (ESI+): m/z = 456.1129, calcd. for $C_{23}H_{22}NO_7$ $[M+H]^+$: 456.1117.

(*S*)-Bis(4-Methoxyphenyl) 2-[formamido(β-naphthyl)methyl]malonate (9h): It was prepared following the procedure above described for **9a**; yield: 78%; *ee* = 84% (determined by chiral HPLC on a Daicel Chiral pak AD 250 × 4.6 mm column, V_{inj} = 20 μL, T = 40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 24.59; R_t (*R*): 19.08; R_f = 0.43 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −38.0 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz, $CDCl_3$; 2 conformers (A and B) are present in an 86:14 ratio; only selected signals of conformer B are reported]: δ = 8.40 (A) (s, 0.86 H, C*H*=O), 8.31 (B) (d, J = 11.7 Hz, 0.14 H, C*H*=O), 7.95–7.78 (m, 4 H), 7.57–7.47 [3.86 H, m. N*H* (A) + 3 C*H* of naphthyl], 7.06 (A) (d, J = 9.0 Hz, 1.72 H), 6.90 (A) (d, J = 9.0 Hz, 1.72 H), 6.79 (A) (s, 3.64 H), 6.41 (A) (dd, J = 4.6, 9.9 Hz, 0.86 H, C*H*NH), 5.65 (B) (dd, J = 5.7 Hz, 10.5 Hz, 0.14 H, C*H*NH), 4.57 (A) (d, J = 4.6 Hz, 0.86 H, NHCHC*H*), 4.55 (B) (d, J = 5.7 Hz, 0.14 H, NHCHC*H*), 3.80 (A) (s, 2.58 H, OCH_3), 3.79 (B) (s, 0.42 H, OCH_3), 3.77 (A + B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ = 167.2, 165.9, 160.6 (*C*=O), 157.7 (*C*–OMe), 143.6, 143.3 (*C*OCO), 135.2, 133.2, 132.9 (quat. naphthyl), 128.9, 128.1, 127.7, 126.6, 126.5, 125.5, 124.2, 122.1 (×2), 121.9 (×2), 114.6 (×2), 114.5 (×2) (aromatic *C*H), 56.3 (NHCH*C*H), 55.61, 55.56 (O*C*H$_3$), 50.3 (*C*HNH); IR ($CHCl_3$): ν = 3675, 3605, 3404, 2997, 1747, 1685, 1595, 1489, 1353, 1246, 1171, 1132, 1025, 919 cm^{-1}; HR-MS (ESI+): m/z = 500.1714, calcd. for $C_{29}H_{26}NO_7$ $[M+H]^+$: 500.1709.

(*S*)-Bis(4-methoxyphenyl) 2-[formamido(α-naphthyl)methyl]malonate (9i): It was prepared following the procedure above described for **9a**; yield: 78%; *ee* = 70% (determined by chiral HPLC on a Daicel Chiral pak AD 250 × 4.6 mm column, V_{inj} = 20 μL, T = 40 °C, eluent: hexane/*i*-PrOH 25:75; flow: 0.5 mL min^{-1}); R_t (*S*): 19.39; R_t (*R*): 13.89; R_f = 0.51 (CH_2Cl_2/AcOEt 90:10); $[\alpha]_D$: −7.7 (*c* 1, $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present in an 84:16 ratio; only selected signals of conformer B are reported]: δ = 8.37 (A) (s, 0.84 H, C*H*=O), 8.31 (B) (d, J = 11.9 Hz, 0.16 H, C*H*=O), 8.26 (A) (d, J = 8.4 Hz, 0.84 H), 7.94 (A) (d, J = 8.4 Hz, 0.84 H), 7.87 (A) (d, J = 8.1 Hz, 0.84 H), 7.65–7.73 [m, 1.84 H, N*H* (A) and 1 C*H* (A + B)], 7.57 (A + B) (t, J = 7.0 Hz, 0.84 H), 7.47 (A) (t, J = 7.6 Hz, 0.84 H), 7.11 (A) (d, J = 9.0 Hz, 1.68 H), 7.04 (A) (dd, J = 3.7, 9.5 Hz, 0.84 H, C*H*NH), 6.92 (A) (d, J = 9.0 Hz, 1.68 H), 6.84–6.72 (A + B) (m, 4 H), 6.26 (B) (dd, J = 5.0 Hz, 10.4 Hz, 0.16 H, C*H*NH), 4.60 (A + B) (d, J = 3.7 Hz, 1 H, NHCHC*H*), 3.81 (A) (s, 2.52 H, OCH_3), 3.80 (B) (s, 0.48 H, OCH_3), 3.75 (A + B) (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$; only the peaks of main conformer are reported): δ = 167.3, 166.0, 160.4 (*C*=O), 157.8, 157.7 (*C*–OMe), 143.7, 143.2 (*C*OCO), 133.9, 133.2, 130.0 (quat. naphthyl), 129.4, 129.2, 127.4, 126.2, 125.1, 124.0, 122.2 (×2), 122.1, 121.9

(×2), 114.6 (×2), 114.5 (×2) (aromatic *C*H), 55.62, 55.56 (O*C*H$_3$), 55.3 (NHCH*C*H), 46.9 (*C*HNH); IR ($CHCl_3$): ν = 3675, 3602, 3411, 3001, 1745, 1688, 1597, 1488, 1420, 1355, 1183, 1132, 1024, 919 cm^{-1}; HR-MS (ESI+): m/z = 500.1724, calcd. for $C_{29}H_{26}NO_7$ $[M+H]^+$: 500.1709.

(*S*)-Ethyl 3-Formamido-3-phenylpropanoate (2a)

A solution of malonate (*S*)-**9a** (*ee* 98%; 809 mg, 1.80 mmol) in dry EtOH (32 mL) and THF (8 mL) was cooled to 0 °C, and treated with a commercial 21% (w/w) (2.68 M) solution of EtONa in absolute EtOH (800 μL, 2.14 mmol). After 30 min the cooling bath was removed and the solution further stirred for 90 min at room temperature. After addition of saturated aqueous NH_4Cl (40 mL), most of the EtOH was evaporated. The resulting mixture was extracted with AcOEt, washed with saturated NaCl, and evaporated to dryness. The crude product was chromatographed (CH_2Cl_2/AcOEt from 100:0 to 95:5) in order to separate diethyl malonate **8a** from *p*-methoxyphenol. Diethyl malonate **8a** was obtained as an oil (yield: 528 mg). It was taken up in EtOH (17.3 mL) and treated, at 0 °C, with 0.5 M aqueous NaOH (4.34 mL, 2.17 mmol). After 30 min the cooling bath was removed, and the solution stirred for further 90 min at room temperature. After addition of saturated NaCl (15 mL), and 1 M NaH_2PO_4 (15 mL), most of the EtOH was evaporated. The resulting mixture was adjusted to pH 2 by addition of 2 M HCl, and extracted with AcOEt, washed with saturated NaCl, and evaporated to dryness. It was taken up in toluene (10 mL), and refluxed for 6 h. After evaporation and chromatography, pure **2a** was obtained as a slightly yellow oil; yield: 376 mg (95%); R_f 0.30 (CH_2Cl_2/AcOEt 80:20); $[\alpha]_D$: −73.2 (*c* 1.6 $CHCl_3$); ^{1}H NMR [300 MHz., $CDCl_3$; 2 conformers (A and B) are present in an 80:20 ratio; only selected signals of conformer B are reported]: δ = 8.21 (A) (s, 0.80 H, C*H*=O), 8.15 (B) (d, J = 11.7 Hz, 0.20 H, C*H*=O), 7.40–7.20 (m, 5 H C*H* of Ph), 6.89 (A) (d, J = 8.5 Hz, 0.80 H, N*H*), 6.69 (B) (t, J = 10.6 Hz, 0.20 H, N*H*), 5.51 (A) (dt, J = 5.8 (t), 8.5 (d), 0.80 H, C*H*NH), 5.51 (B) [dt, J = 6.5 (t), 9.5 Hz (d), 0.20 H, C*H*NH], 4.12 (B) (q, J = 7.0 Hz, 0.40 H, CH_2CH$_3$), 4.07 (A) (q, J = 7.1 Hz, 1.60 H, CH_2CH$_3$), 2.93 and 2.84 [AB part of ABX syst., J = 15.7 (ab), 5.9 (ax), 6.0 (bx) Hz, 2 H, CH_2CO$_2$Et], 1.21 (B) (t, J = 6.9 Hz, 0.60 H, CH_3CH$_2$), 1.17 (A) (t, J = 7.2 Hz, 2.40 H, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$; both conformers A and B are reported): δ = 171.0 (A), 170.3 (B), 164.3 (B), 160.4 (A) (*C*=O), 140.0 (B), 139.9 (A) (quat), 129.0 (×2) (B), 128.7 (×2) (A), 128.1 (B), 127.7 (A), 126.2 (×2) (A), 126.0 (×2) (B) (aromatic *C*H), 61.1 (B), 60.9 (A) (*C*H$_2$CH$_3$), 52.7 (B), 48.2 (A) (*C*HNH), 41.6 (B), 39.9 (A) (*C*H$_2$CO$_2$Et), 14.0 (A+B) (*C*H$_3$); IR ($CHCl_3$): ν = 3419, 2969, 1722, 1685, 1485, 1375, 1164, 1019, 917 cm^{-1}; GC-MS: R_t 8.86 min; m/z = 221 (M^+, 17.2%); 192 (64.8); 176 (18.7); 175 (34.2); 147 (77.5); 146 (14.3); 134 (94.0); 131 (45.4); 119 (53.9); 106 (85.0); 104 (100.0); 103 (32.5); 79 (55.8); 77 (53.6); 51 (19.8); HR-MS (ESI+): m/z = 244.0954, calcd. for $C_{12}H_{15}NO_3Na$ $[M+H]^+$: 244.0950.

(*S*)-Ethyl 3-Isocyano-3-phenylpropanoate (1a)

A solution of formamide **2a** (360 mg, 1.63 mmol) in dry CH_2Cl_2 (12 mL) was cooled to −30 °C, and treated with Et_3N (775 μL, 5.55 mmol) and $POCl_3$ (166 μL, 1.80 mmol). The reaction mixture was stirred at this temperature for 4 h and 30 min, and then poured into saturated aqueous $NaHCO_3$, extracted with Et_2O, and chromatographed (PE/Et_2O 75:25) to give pure **1a** as a yellowish oil; yield: 283 mg (85%). This compound tends to slowly decompose upon standing in the freezer for some months. Therefore it is advisable to use it within few days after preparation. R_f 0.44 (PE/Et_2O 7:3); $[\alpha]_D$: −35.2 (*c* 1.2 $CHCl_3$); ^{1}H NMR (300 MHz., $CDCl_3$): δ = 7.45–7.32 (m, 5 H, C*H* of Ph), 5.18 (dd, J = 5.7 and 8.7 Hz, 1 H, C*H*NC), 4.27–4.10 (m, 2 H, CH_2CH$_3$), 3.01 (dd, J = 8.9 and 16.0 Hz, 1 H, C*H*HCO$_2$Et), 2.87–2.75 (m, 1 H, C*H*HCO$_2$Et), 1.26 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.8 (*C*=O), 136.0 (quat), 129.1 (×2), 128.8, 125.9 (×2) (aromatic *C*H), 61.4 (*C*H$_2$CH$_3$), 54.7 (t, J = 6.2 Hz), 43.5 (*C*HNC), 14.1 (*C*H$_3$); IR ($CHCl_3$): ν = 2984, 2143, 1727, 1598, 1371, 1350, 1183, 1005, 822 cm^{-1}; HR-MS (ESI+): m/z = 177.0915, calcd. for $C_{11}H_{13}O_2$ [M-NC]$^+$: 177.0910. The *ee* (93%) was determined by chiral HPLC (Daicel Chiral pak AD 250×4.6 mm, V_{inj} = 20 μL, T = 40 °C, eluent: hexane/*i*-PrOH 99:1; flow: 0.5 mL min^{-1}); R_t (*S*): 41.09; R_t (*R*): 37.27.

(*S*)-Ethyl 3-[(*3aS,4R,6aR*)-5-(2-Methoxyacetyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole-4-carboxamido]-3-phenylpropanoate (18)

(+)(4*S*,5*R*)-5-[(Azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl butanoate was converted, as previously described,[11a] into crude imine (*3aS,6aR*)-**17** (containing also PPh_3O). An amount of this imine corresponding to 480 μmol (calculated on the basis of the starting azidobutanoate) was dissolved in dry MeOH (1.5 mL) and treated with powdered 4 Å mol. sieves (50 mg), methoxyacetic acid (31 μL, 400 μmol), and finally with a solution of isocyanide **1a** (58 mg, 285 μmol) in MeOH (2 mL). The solution was stirred at room temperature for 48 h, and then evaporated to dryness. The crude product was taken up in AcOEt, washed with saturated aqueous $NaHCO_3$, evaporated again, and chromatographed (PE/AcOEt/acetone 46:36:18) to give pure **18** as a colourless oil; yield: 79.1 mg (64%); R_f = 0.39 (PE/AcOEt 2:8); $[\alpha]_D$: +40.1 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz., $CDCl_3$; 2 conformers A and B in 83:17 were visible): δ = 7.53 (A+B) (d, J = 8.4 Hz, 1 H, N*H*), 7.37–7.18 (A+B) (m, 5 H), 5.34 (A+B) (q, J = 7.2 Hz, 1 H, PhC*H*NH), 5.10 (A) (d, J = 6.0 Hz, 0.83 H, *H*-3a), 5.00 (B) (d, J = 5.7 Hz, 0.17 H, *H*-3a), 4.87 (A) (s, 0.83 H, *H*-4), 4.83 (A) (t, J = 5.3 Hz, 0.83 H, *H*-6a), 4.76 (B) (t, J = 5.3 Hz, 0.17 H, *H*-6a), 4.69 (B) (s, 0.17 H, *H*-4), 4.36 (B) (d, J = 13.4 Hz, 0.17 H, *H*-6), 4.15–3.96 (A+B) (m, 4 H, CH_2OMe + CH_2CH$_3$), 3.82 (A) (d, J = 12.4 Hz, 0.83 H, *H*-6), 3.46 (A) (dd, J = 4.6 and 12.4 Hz, 0.83 H, *H*-6), 3.32 (A) (s, 2.49 H, OCH_3), 3.30 (B) (s, 0.51 H, OCH_3), 3.27 (B) (dd, J = 5.1 and 13.4 Hz, 0.17 H, *H*-6), 2.92–2.75 (B) (m, 0.34 H, CH_2CO$_2$Et), 2.85 and 2.79 (A) [AB part of an ABX syst., J = 14.6 (ab), 5.6 (ax), 6.0 (bx) Hz., 1.66 H, CH_2CO$_2$Et], 1.42 (A) (s, 2.49 H, CH_3), 1.40 (B) (s, 0.51 H, CH_3), 1.32 (A) (s, 2.49 H, CH_3), 1.30 (B) (s, 0.51 H, CH_3), 1.19 (A) (t, J = 7.0 Hz, 2.49 H, CH_3CH$_2$), 1.18 (B) (t, J = 7.0 Hz, 0.51 H, CH_3CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (B), 170.4 (A), 169.2 (A), 168.6 (B), 167.8 (A), 167.7 (B) (*C*=O), 140.4 (A), 140.1 (B) (quat.), 128.8 (B) (×2), 128.7 (A) (×2), 127.9 (B), 127.6 (A), 126.2 (A) (×2), 126.1 (B) (×2) (aromatic *C*H), 111.9

(A), 111.7 (B) (O*C*O), 82.8 (B), 79.9 (A), 79.7 (A), 78.0 (B) (*C*-3a and *C*-6a), 73.1 (B), 71.6 (A) (CH_2OCH_3), 66.9 (B), 65.6 (A) (*C*-4), 60.9 (B), 60.8 (A) (CH_2CH_3), 59.0 (B), 58.9 (A) (CH_3O), 51.8 (A), 51.5 (B) (*C*-6), 50.1 (A), 49.8 (B) (*C*HNH), 40.7 (A), 40.1 (B) (CH_2CO_2Et), 26.72 (A), 26.68 (B), 24.7 (A), 24.6 (B) (H_3C-C-CH_3), 14.1 (A+B) (CH_3CH_2); IR ($CHCl_3$): $\nu = 3675$, 3613, 3008, 2969, 1726, 1668, 1512, 1476, 1424, 1384, 1331, 1228, 1203, 1128, 1042, 928 cm^{-1}; HR-MS (ESI+): $m/z = 435.2159$, calcd. for $C_{22}H_{31}N_2O_7$ $[M+H]^+$: 435.2131.

(*S*)-Ethyl 3-[(*3aR*,*4S*,*6aS*)-5-(2-methoxyacetyl)-2,2-dimethyltetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole-4-carboxamido]-3-phenylpropanoate (19)

It was prepared by the same procedure as described for **18**, but using this time crude imine (*3aR*,*6aS*)-**17** synthesized from (−)(4*R*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate;[11a] yield: 66% (colourless oil); $R_f = 0.33$ (PE/AcOEt 2:8); $[\alpha]_D$: −83.3 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz., $CDCl_3$; 2 conformers A and B in 82:18 were visible): $\delta = 7.50$ (A+B) (d, $J = 8.4$ Hz, 1H, N*H*), 7.40–7.20 (A+B) (m, 5H), 5.37 (B) [dq, $J = 6.6$ Hz (q), 8.4 (d) Hz, 0.18H, PhC*H*NH], 5.33 (A) (q, $J = 6.6$ Hz, 0.82H, PhC*H*NH), 5.06 (A) (d, $J = 5.7$ Hz, 0.82H, *H*-3a), 5.00 (B) (d, $J = 6.0$ Hz, 0.18H, *H*-3a), 4.86 (A) (t, $J = 5.4$ Hz, 0.82H, *H*-6a), 4.83 (A) (s, 0.82H, *H*-4), 4.77 (B) (t, $J = 5.3$ Hz, 0.18H, *H*-6a), 4.66 (B) (s, 0.18H, *H*-4), 4.40 (B) (d, $J = 13.5$ Hz, 0.18H, *H*-6), 4.18 and 4.09 (A) (AB syst., 1.64H, CH_2OMe), 4.04 (A) (q, $J = 7.0$, 1.64H, CH_2CH_3), 4.13–4.02 (B) (m, 0.72H, CH_2OMe and CH_2CH_3), 3.88 (A) (d, $J = 12.6$ Hz, 0.82H, *H*-6), 3.60 (A) (dd, $J = 4.6$ and 12.4 Hz, 0.82H, *H*-6), 3.46 (A) (s, 2.46H, OCH_3), 3.28 (B) (s, 0.54H, OCH_3), 3.34 (B) (dd, $J = 5.1$ and 13.5 Hz, 0.18H, *H*-6), 2.92–2.75 (B) (m, 0.36H, CH_2CO_2Et), 2.77 (A) (d, $J = 6.9$ Hz, 1.64H, CH_2CO_2Et), 1.42 (A) (s, 2.46H, CH_3), 1.40 (B) (s, 0.54H, CH_3), 1.31 (A) (s, 2.46H, CH_3), 1.30 (B) (s, 0.54H, CH_3), 1.17 (A+B) (t, $J = 7.2$ Hz, 3H, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.7$ (B), 170.5 (A), 169.5 (A), 168.7 (B), 167.9 (A), 167.6 (B) (*C*=O), 140.1 (A), 140.0 (B) (quat.), 128.8 (A+B)(x2), 127.9 (B), 127.7 (A), 126.3 (A) (× 2), 126.2 (B) (×2) (aromatic *C*H), 111.8 (A), 111.7 (B) (O*C*O), 82.9 (B), 79.8 (A), 79.7 (A), 78.0 (B) (*C*-3a and *C*-6a), 73.0 (B), 71.6 (A) (CH_2OCH_3), 67.0 (B), 65.5 (A) (*C*-4), 60.9 (B), 60.7 (A) (CH_2CH_3), 59.0 (B), 58.9 (A) (CH_3O), 51.7 (A), 51.3 (B) (*C*-6), 50.0 (A), 49.8 (B) (*C*HNH), 40.7 (A), 40.1 (B) (CH_2CO_2Et), 26.7 (A+B), 24.6 (A+B) (H_3C-C-CH_3), 14.0 (A+B) (CH_3CH_2); IR ($CHCl_3$): $\nu = 3673$, 2999, 2933, 1726, 1667, 1497, 1429, 1373, 1345, 1239, 1155, 1128, 1112, 1047, 918 cm^{-1}; HR-MS (ESI+): $m/z = 435.2144$, calcd. for $C_{22}H_{31}N_2O_7$ $[M+H]^+$: 435.2131.

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