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Enantio- and Diastereoselective Synthesis of Highly Substituted Benzazepines by a Multicomponent Strategy Coupled with Organocatalytic and Enzymatic Procedures

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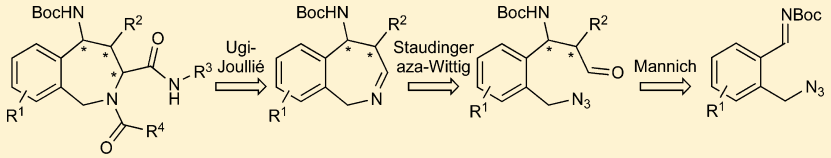
Supporting Information

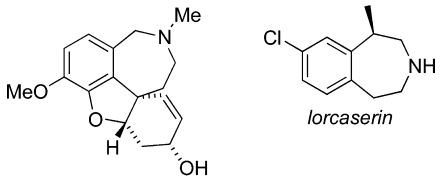


ABSTRACT: Enantiomerically pure 4,5-dihydro-1*H*-benzo[*c*]azepines with three contiguous stereogenic centers have been assembled by convergent strategy with a good control of diastereoselectivity. The two steps are as follows: an asymmetric organocatalytic Mannich reaction performed on Boc-imines of *o*-(azidomethyl)benzaldehydes, followed by a one-pot Staudinger/aza-Wittig/Ugi–Joullié sequence. The latter reaction represents one of the first examples of diastereoselective Ugi three-component reaction on a seven-membered cyclic imine. The *o*-azidomethylbenzaldehydes have been synthesized employing a simple and efficient chemoenzymatic strategy from commercially available building blocks.

INTRODUCTION

The benzazepine scaffold is a privileged structure in medicinal chemistry and can be found in many biologically active compounds. Some of them are the active pharmaceutical ingredient (API) of marketed drugs, such as galanthamine, used to treat mild to moderate Alzheimer's disease and lorcaserin, a weight-loss drug (Scheme 1). Within this heterocyclic group, 2-benzazepines have been deeply investigated in the last decades, and recently several interesting biological properties have been reported. For example, they can act as kinase inhibitors,[1] histone deacetylase inhibitors,[2] glycine transporter 1 inhibitors (antipsychotic drugs),[3] selective PPARδ agonists,[4] and inhibitors of factor Xa (anticoagulants),[5] and they may also be involved in new drug therapies to treat skin wounds.[6]

Scheme 1. Examples of APIs Containing a Benzazepine Scaffold



While a huge variety of substituents has been introduced on the benzene ring and on the heterocyclic nitrogen, the diversity of the appendages on the seven-membered heterocyclic ring has been little explored to date and very few enantio- and/or diastereoselective approaches to these scaffolds have been reported. In particular, compounds with a nitrogen substituent at C5 and a carboxy moiety at C3 are unknown. Many different approaches for assembling this heterocycle are known. Within the most recent papers, two different ring closures to give the 2-benzazepine skeleton, based on a Friedel–Crafts reaction, have been described: the first one couples 3-arylpropionamides and formaldehyde,[6] and the second one involves a 7-endo selective cyclization of vinyloxirane.[7] In addition, other approaches have been reported in recent years, including, for example, ring-closing metathesis[8] and lactamization.[9,10]

In this paper, we present a new stereoselective approach to an unprecedented class of chiral seven-membered 2-benzazepines, namely 4,5-dihydro-1*H*-benzo[*c*]azepine of general structure **1**, characterized by three adjacent stereogenic centers. The synthetic strategy, depicted in Scheme 2, allows the introduction of at least four diversity points.

The key step in our synthetic plan is the three-component Ugi–Joullié reaction[11,12] using chiral, enantiomerically pure, cyclic imines **2**. This Ugi three-component reaction has recently emerged as a powerful method for synthesizing in a stereocontrolled way and, in just one step, various druglike nitrogen heterocycles. Two diversity points are embodied by the appendages derived from the isocyanide and carboxylic acid components. The third diversity point is the heterocyclic scaffold itself resulting from the cyclic imine. In order to fully explore the scaffold diversity, efficient and short synthetic pathways to access a variety of chiral cyclic imines with different ring size in enantiomerically pure form are needed. For this purpose, the ideal methodology would be diversity-oriented as

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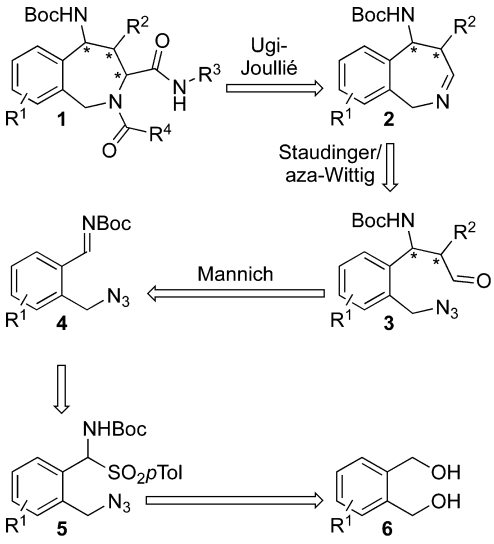
Scheme 2. Retrosynthetic Analysis



well, allowing the introduction of additional diversity points during the construction of the cyclic imines.

Most examples of the Ugi–Joullié reaction on enantiomerically pure substrates reported to date involve chiral pyrrolines, which have been obtained either by a Staudinger/aza-Wittig reaction on acyclic precursors, derived from the chiral pool[12−17] or through enzymatic desymmetrizations[18,19] or by biocatalytic oxidation of *meso*-pyrrolidines.[20,21] On the other hand, chiral six-membered cyclic imines have been mostly used as racemates[22,23] and only in few cases in enantiomerically pure form.[24−27] In most cases, although not always, a good control of the diastereoselectivity has been observed. All the chiral five-membered or six-membered cyclic imines employed to date in Ugi–Joullié reactions have been prepared in a target-oriented way, without the possibility of introducing diversity prior to the multicomponent reaction.

In the last years, we have been particularly interested in the use of isocyanide multicomponent reactions for the synthesis of seven-membered heterocycles, which represent a typical privileged scaffold in medicinal chemistry. In this context, we are developing diversity-oriented and enantioselective approaches to dihydrobenz(oxa)azepines to be used as input in the Ugi–Joullié reaction. We have recently reported a first successful achievement of this strategy, where the imine was constructed by joining a salicylaldehyde derivative with a chiral alcohol using a Mitsunobu reaction.[28,29] This has represented the first example of a diastereoselective Ugi–Joullié reaction on a seven-membered cyclic imine. While in that work the stereochemistry of the dihydrobenzoxazepine was controlled by the starting chiral alcohol, in this report we decided to follow a truly enantioselective approach.

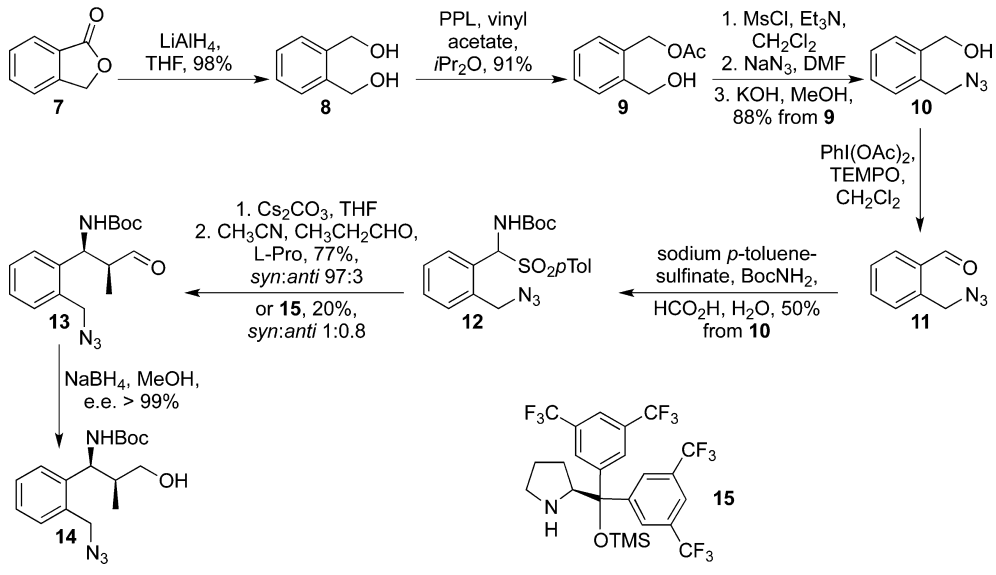
To accomplish the enantioselective synthesis of imine **2** we planned to apply an organocatalytic methodology, involving an asymmetric Mannich reaction on Boc-protected imines **4**, to give *β*-amino aldehydes **3**. This methodology allows to introduce two diversity points and requires just two synthetic steps from readily available ureido sulfones **5**. The latter intermediates can be prepared through an efficient sequence where the two alcoholic moieties of **6** are differentiated by a chemoenzymatic approach.

RESULTS AND DISCUSSION

In an exploratory study we chose to synthesize first aldehyde **13** (Scheme 3). For our purposes we needed to differentiate the two equivalent hydroxy groups of 1,2-phenylenedimethanol **8**, obtained in nearly quantitative yield from commercially available phthalide **7**. Every attempt to selectively manipulate just one of the hydroxy groups under classical chemical conditions gave poor results[30] until we discovered that an enzymatic acylation mediated by supported porcine pancreatic lipase[31] is able to afford monoacetate **9** in excellent yield.

Starting from this monoacetate, azido alcohol **10**[30] was obtained in excellent overall yield and without the need of any purification. The following oxidation to give **11** was successfully performed using catalytic tetraproylammonium perruthenate (TPAP) even with only 2% of the catalyst but with a 2 days reaction time.[32] However, a shorter reaction time (2 h) and comparable yields were obtained using a more practical (no dry solvents nor inert atmosphere needed) and less expensive

Scheme 3. Organocatalytic Synthesis of Mannich Product 13



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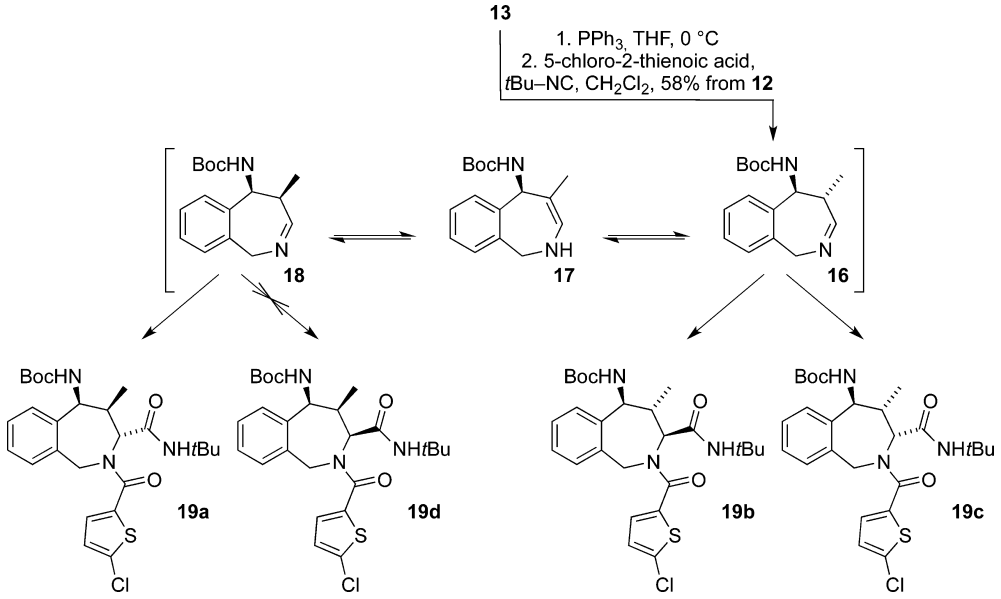
Scheme 4. Stereoselective Ugi–Joullié Reaction from Chiral Aldehyde 13



oxidant, which is catalytic TEMPO (2,2,6,6-tetramethyl-1-piperidinyl oxide, free radical) in the presence of (diacetoxyiodo)benzene as stoichiometric oxidant.[33]

Also thanks to the high yield (>90%) and to the purity of aldehyde **11**, we decided not to isolate it because of its volatility, and after a rapid filtration over silica gel, the concentrated solution was directly used for the synthesis of ureidosulfone **12**. The standard method to prepare these ureido sulfones,[34,35] using a large excess of aldehyde, was not practical in this case. After several attempts, we finally obtained good results using an excess of sodium *p*-toluenesulfinate and isolating **12** in pure form by precipitation after sonication of the crude reaction mixture. It is worth noting that pure **12** was obtained in 44% overall yield from monoacetate **9** (five steps) using a single final purification operation (precipitation). The base-mediated elimination step to give the key Boc-protected imine **4** (R^1 = H) was not trivial as well, and only cesium carbonate at 40 °C[19] was successful.[36] The following Mannich reaction was directly performed using either L- or D-proline as the catalyst, according to List's protocol,[34,35] and the respective aldehydes **13** or *ent*-**13** were isolated in 77% overall yield from **12**. The ee, determined by HPLC on chiral stationary phase on the corresponding alcohol **14**,[37] was >99% for both enantiomers. The absolute and relative stereochemistry of **13** and its enantiomer were established according to literature precedent.[38]

Also the diastereoselectivity, if determined by NMR on the crude aldehyde, was excellent, but after chromatography, a significant degree of epimerization occurred. In our experience, **13** has a stronger tendency to epimerize than other similar products devoid of the azido group. We also tried the one-pot elimination–Mannich reaction, starting from **12**, following the procedure reported by Córdova (KF as base).[39] In our hands, the reaction was sluggish, and starting **12** was completely consumed only after 63 h. In addition, crude **13** was an equimolar mixture of *syn* (ee 80%) and *anti* stereoisomers, and the isolated yield was only around 30%. The extended reaction time and the coexistence of an easily epimerizable aldehyde with a base may explain the lack of diastereoselectivity, while we have no explanation for the formation of several byproducts and for the low ee observed.

In order to gain access to the *anti* stereoisomer of **13**, we tried the "complementary" Jørgensen–Hayashi catalyst **15**, known to induce the opposite relative stereochemistry with respect to proline in both aldol and Mannich reactions.[38] This catalyst showed poor activity: after 10 days only 20% of **13** was isolated with a 1:0.8 *anti*:*syn* ratio, while the prevailing product was aldehyde **11**, arising from the decomposition of the Boc-imine. For reasons that will become clear below, we decided not to pursue further the synthesis of *anti* isomers.

To avoid the epimerization of **13**, we decided to investigate the following transformations on the crude aldehyde (Scheme 4). The Staudinger/aza-Wittig reaction is an efficient method for the construction of carbon–nitrogen double bonds.[40] The possibility of coupling the Staudinger reduction of azides with the aza-Wittig reaction in a one-pot sequence has been applied to the synthesis of five- and six-membered cyclic imines[14−16,18,24] but never to build a seven-membered ring.

The conditions previously developed in our group for the sequential Staudinger/aza-Wittig/Ugi–Joullié reaction[18] did not afford any trace of the expected products. An extensive investigation of the reaction outcome, by repeatedly recording proton spectra of the reaction mixture in the appropriate deuterated solvent (THF or toluene), unequivocally demonstrated the instability of imine **16**. After careful optimization (see Table 1), we found that the most important factor was a very short reaction time (30 min) for the Staudinger/aza-Wittig reaction. For this step we found that PPh_3 at 0 °C in THF represents the best conditions. However, the following MCR could not be performed in THF because the reaction was too slow in this solvent.[15,29] On the other hand, the use of methanol, one of the solvents of choice for the Ugi reaction, for both steps, afforded **19** only in traces. Eventually, the best results were obtained by a quick evaporation of THF, followed by addition of methylene chloride, a solvent often used in MCRs on other cyclic imines.[15,20,41] The possible competition with the Passerini reaction, favored by less polar solvents,[42] was not a problem, since we were working on a preformed imine. In

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Table 1. Optimization of the Staudinger/Aza-Wittig/Ugi–Joullié Protocol on 13

entry	phosphine	temp (°C) (Staudinger/ aza-Wittig)	solvent (Ugi)[a]	dr (**19a**:**19b**:**19c**)[b]	yield of **19**[c] (%)
1	PPh_3	rt	MeOH	52:28:20	19
2	PPh_3	rt	CH_2Cl_2	59:27:14	18
3	PPh_3	rt	CF_3CH_2OH	48:27:25	13
4	PPh_3	rt	toluene	54:30:16	14
5	PPh_3	0	CH_2Cl_2	64:22:14	58
6	PMe_3	0	CH_2Cl_2	37:42:21	26
7	PBu_3	0	CH_2Cl_2	43:37:20	8
8[d]	PPh_3	0	CH_2Cl_2	69:20:11	54

[a]All reactions performed at rt. [b]By HPLC. [c]Isolated yields from **12** of the whole stereoisomeric mixture of **19**. [d]Results of the one-pot procedure from **12** to **13** using KF as base.

the end, we were able to obtain a good overall yield of benzazepines **19** (58% from **12** for four steps).

As far as stereoselectivity was concerned, we expected the formation of two diastereomers, hopefully in a good ratio, thanks to the close position of the preexisting stereogenic centers.

We were therefore quite surprised when the crude reaction mixture displayed the presence of three isobaric (HPLC–MS) compounds, with one of them highly prevailing. The major stereoisomer was very easily separated from the other two by chromatography, whereas the obtainment in pure form of the other two was rather difficult, but eventually feasible. Analysis of ^1H and ^{13}C NMR spectra, also supported by computational methods, allowed us to assign structures **19a** to the major product and **19b** and **19c** to the minor ones (a detailed discussion is reported in the Supporting Information). Starting from **13**, we expected to obtain **19b** and **19c**, but the prevailing product was **19a** instead, with the opposite configuration at C_4 (with respect to **16**). The most likely explanation of our experimental results is an equilibration between the two epimeric imines **16** and **18**, through the enamine **17**.

This hypothesis is corroborated by semiempirical calculations carried out on **16**, **17**, and **18** (see the Supporting Information), which indicated the following order of stability: **17** > **18** ≈ **16**. Moreover, when we started from a nearly 1:1 *syn*/*anti* mixture of aldehydes (derived from the poorly stereoselective one-pot Mannich reaction accomplished in the presence of potassium fluoride), the diastereomeric ratio between **19a**, **19b**, and **19c** was nearly the same (Table 1, entry 8).

This result suggests a fast pre-equilibrium between the three species. Due to this equilibration, the search for an appropriate organocatalyst able to afford the *anti* stereoisomer of **13** was useless. From our evidence we cannot decide whether the preference for diastereomer **19a** relative to **19b,c** derives from the fact that pre-equilibrium favors **18** (thermodynamic control) or from a faster reaction of **18** compared to **16** (kinetic control). However, we guess that the second hypothesis is more likely, in view of the similar energy of **16** and **18** as deduced from our calculations. From the stereochemical results it is clear that *cis* imine **18** undergoes a highly diastereoselective Ugi–Joullié reaction (**19d** was not detected at all), whereas the reaction of the corresponding epimeric *trans* imine **16** is less diastereoselective. The calculations reported in the Supporting Information indicate that both imines **16** and **18** should exist essentially in a single conformation, depicted in Figure 1. In **18** attack from the bottom, leading to **19a**, is

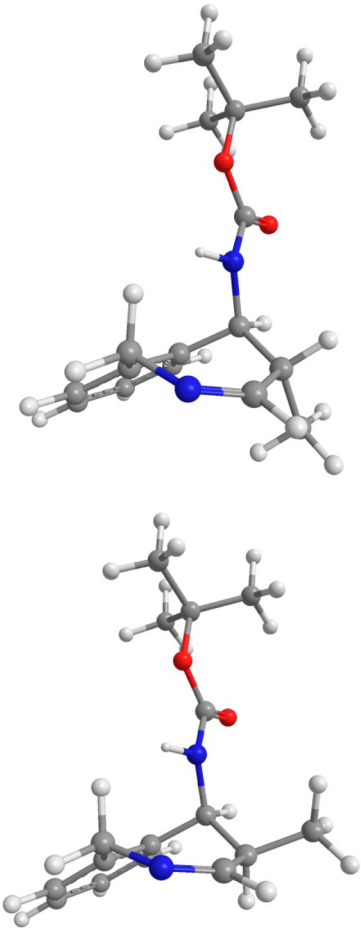

Figure 1. Preferred conformation of cyclic imines **16** (top) and **18** (bottom).

expected to be highly favored. On the other hand, for *trans* imine **16**, a clear preference for one of the two diastereotopic faces can not be envisaged because the upper face is encumbered by the axial NH(Boc) group, whereas the lower face is encumbered by the axial methyl group. This fact probably makes reaction of **16** slower compared to **18**.

Eventually, under the best conditions, the major stereoisomer **19a** was obtained in 64% ratio with respect to the other two (entry 5). We also demonstrated, by ^1H NMR of Mosher amides derived from **19a**, that its ee corresponds with that determined on the Mannich aldehyde **13** (through the corresponding alcohol **14**).

In order to study the scope of our procedure, apart from using diverse aldehydes, isocyanides, and carboxylic acids, we also planned to synthesize different ureido sulfones, characterized by the presence of a derivatizable group on the aromatic ring. We therefore targeted regioisomers **26** and **27** (Scheme 5) through a regiodivergent approach starting from 5-bromophthalide **20** that was reduced with $LiBH_4$ to avoid the loss of bromine from the aromatic ring, which occurred in part using $LiAlH_4$ instead. This time, the two hydroxy groups are no longer equivalent, and therefore, a problem of regioselectivity arose. We again found valuable help in the enzymatic catalysis, and some representative results are reported in Table 2 (more information is available in the Supporting Information). Several parameters have been varied: the reaction (acylation or hydrolysis), the lipase, and its amount with respect to substrate, temperature, and reaction time.

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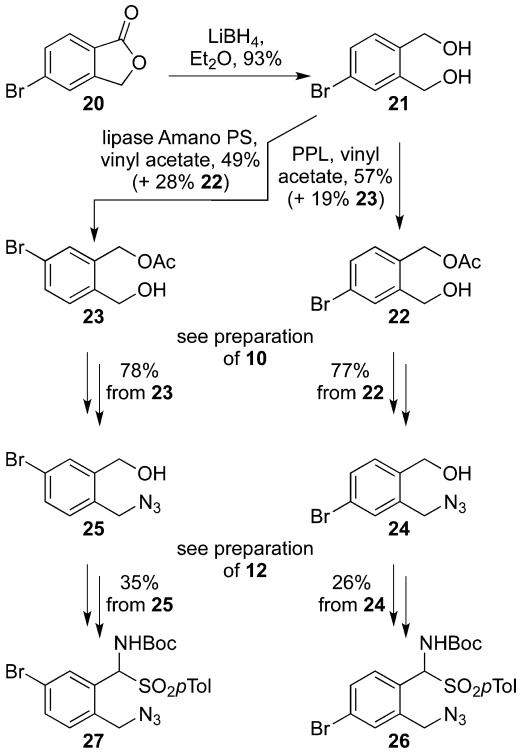
Scheme 5. Synthesis of Ureido Sulfones 26 and 27



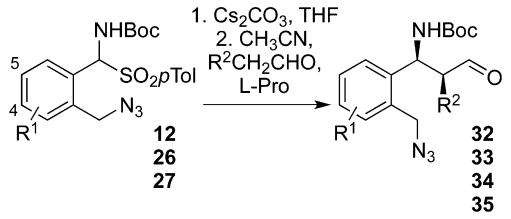
We were not able to obtain a single regioisomer unless at a very high degree of conversion, but this was at the expense of the yield. Eventually, the best compromise was a conversion around 50%, which implies an acceptable ratio between the two regioisomers in such a way that the chromatographic separation becomes straightforward enough. Depending on the lipase, the acylation afforded preferentially **22** (vinyl acetate as acyl donor) and **28** (vinyl butyrate as acyl donor) or **23** (vinyl acetate) and **29** (vinyl butyrate): with supported PPL and CAL **22** and **28** prevailed (entries 2, 4, and 5). On the contrary, supported lipase Amano PS[43] and lipase Amano AK gave larger amounts of **23** and **29** (entries 1 and 3).

We also studied the monohydrolysis of either diacetate **30** or dibutyrate **31**, prepared by standard acylation of **21** in 93% and 89% yield. The results were less encouraging, and most of all, this strategy is less convenient from the point of view of step and atom economy. Therefore, for preparative reactions, we preferred to perform acetylations.

The transformation of **22** and **23** into **26** and **27** followed exactly the same strategy reported in Scheme 3 on compound **9**. The yields of ureido sulfones **26** and **27** were in this case lower, most likely for the difficulty to precipitate them from the reaction mixture.

Another point of diversity that was considered is the aldehyde to be used as donor in the organocatalytic Mannich reaction. Using hydrocinnamaldehyde we obtained comparable results with only a small decrease of diastereoselectivity starting from the bromine-bearing ureido sulfones **26** and **27** (Scheme 6).[44] On the contrary, when we switched to the branched

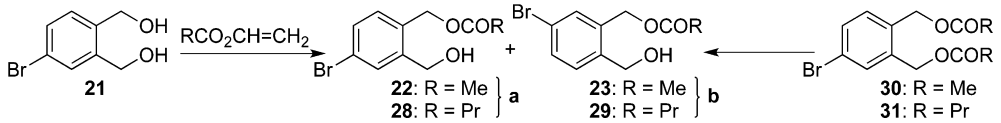
Scheme 6. Scope of the Organocatalytic Mannich Reaction



isovaleraldeyde, no reaction occurred at all with ureidosulfone **12**. This aldehyde was chosen hoping to obtain a cyclic imine less prone to be converted into the enamine. However, the observed result is really unexpected as isovaleraldehyde behaves as a good donor with several Boc-imines with different substituents on the aromatic ring (also in *ortho* position) but lacking the azidomethyl group.[19]

The possibility of increasing the diversity is ensured by the Ugi–Joullié reaction: actually, we synthesized a small library of 4,5-dihydro-1*H*-benzo[c]azepines by changing, in addition to the cyclic imine, the isocyanide and the carboxylic acid. Contrary to what we have done in the optimization step, we preferred to isolate and purify the Mannich aldehyde. Even if a bit longer, this procedure allowed to obtain the final products with a higher overall yield and a higher degree of purity. Thanks to the fact that the diastereomeric ratio of the final products is independent from the *syn*/*anti* ratio of the Mannich product,

Table 2. Regioselective Enzymatic Monoacyclation of Diol 21 or Monohydrolysis of Diesters 30 and 31



entry	subs	products	lipase[a]	solvent	lipase/substrate (mg/mmol)	temp (°C)	time (h)	a:b[b]	yield (a + b)[b] (%)	conv[b,c] (%)
1	**21**	**22, 23**	S-Amano PS	vinyl acetate	22	10	2	37:63	77	60
2	**21**	**22, 23**	S-PPL	vinyl acetate	65	20	2	75:25	76	50
3	**21**	**28, 29**	Amano AK	vinyl butyrate	22	0	6	0:100	40	80
4	**21**	**28, 29**	S-PPL	vinyl butyrate	44	10	24	100:0	66	67
5	**21**	**28, 29**	CAL	vinyl butyrate	22	10	6	68:32	76	62
6	**30**	**22, 23**	CAL	buffer/iPr_2O[d]	29	20	15	21:79	20	85
7	**31**	**28, 29**	CAL	buffer/iPr_2O[d]	29	10	19	12:88	25	33

[a]Key: lipase Amano PS, from *Burkholderia cepacia*; lipase Amano AK, from *Pseudomonas fluorescens*; PPL, lipase from porcine pancreas; CAL, lipase from *Candida anctartica*; S-PPL or S-Amano PS, lipase supported on Celite. [b]Determined by ^{1}H NMR. [c]Conversion is the ratio of acylated hydroxy groups vs initially present hydroxy groups (acylation) or the ratio of hydrolyzed acyl groups vs initially present acyl groups (hydrolysis). [d]pH (buffer): 7.0; ratio (buffer/cosolvent): 9:1.

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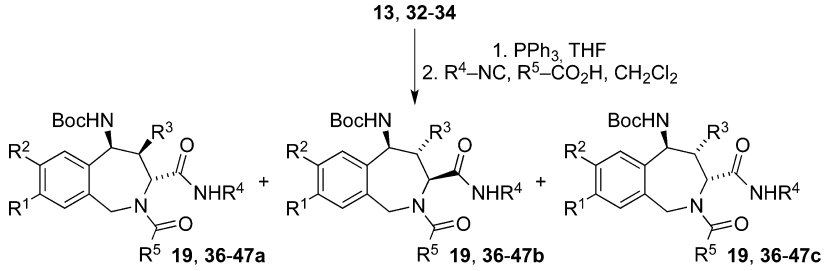
Table 3. Scope of the Staudinger/Aza-Wittig reaction Followed by Ugi–Joullié Reaction



entry	aldehyde	product	R^1	R^2	R^3	R^4	R^5	yield (**a**)[a] (%)	yield (**a** + **b** + **c**)[a,b] (%)	ratio (**a**:**b**:**c**)[c]
1	**13**	**19**	H	H	Me	*t*-Bu	5-chloro-2-thienyl	53	83	64:22:14
2	**13**	**36**	H	H	Me	*n*-Bu	3-Br-C_6H_4	48	76	63:28:9
3	**13**	**37**	H	H	Me	*n*-Bu	Ph	60	86	70:23:7
4	**13**	**38**	H	H	Me	2,6-(Me_2)-C_6H_3	Et	55	84	65:31:4
5	**13**	**39**	H	H	Me	CH_2CO_2Et	Et	53	83	64:36[d]
6	**13**	**40**	H	H	Me	cyclohexyl	*S*-BnCHNHFmoc	48	68	70:17:13
7	**13**	**41**	H	H	Me	nC_5H_{11}	*S*-*i*PrCHNHCbz	55	78	70:21:9
8	**13**	**42**	H	H	Me	Bn	$MeOCH_2$	55	73	75:19:6
9	**32**	**43**	H	H	Bn	*t*-Bu	5-chloro-2-thienyl	42	69	61:30:9
10	**32**	**44**	H	H	Bn	Me	3-OMe-C_6H_4	47	70	67:30:3
11	**33**	**45**	Br	H	Bn	CH_2CO_2Et	Ph	33	46	72:24:4
12	**33**	**46**	Br	H	Bn	Bn	$CH_2NHFmoc$	47	57	82:18[d]
13	**34**	**47**	H	Br	Bn	*t*-Bu	Et	30	41	73:19:8

[a]Isolated yield after chromatography. [b]With the exception of **19b** and **19c**, isolated only as analytical samples, in all other cases **b** and **c** have been obtained as a mixture, because of impossible chromatographic separation. [c]For **19** determined by HPLC on the crude mixture. In the other cases, the ratio **a**:(**b** + **c**) was determined by weight after chromatography (**b** + **c** coeluted), whereas the ratio **b**:**c** was determined by HPLC (the two isomers have been recognized through MS detection for their *m*/*z* ratio). Since they have not been isolated and characterized, the fact that **b** is the prevailing one is only guessed. [d]The **b**:**c** ratio has not been determined because the diastereomers are not separated in HPLC.

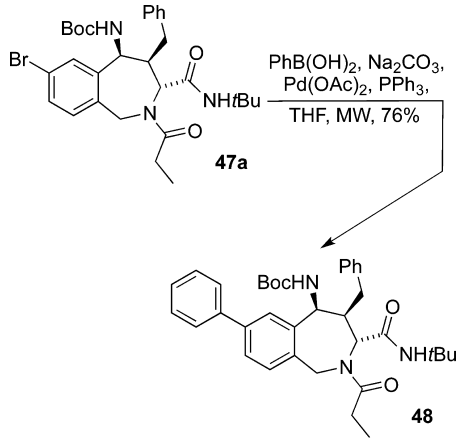
the partial epimerization during the first chromatography does not influence the stereochemical outcome of the reaction.

The results of the library synthesis are summarized in Table 3. Different isocyanides (including aliphatic, aromatic, branched aliphatic, and functionalized ones) and carboxylic acids (including aliphatic, aromatic and heteroaromatic ones, and also *N*-protected amino acids) have been combined with different aldehydes. The overall yields of the Staudinger/aza-Wittig-MCR protocol are good and, in most cases, excellent.

In all cases, we obtained a mixture of the previously described diastereomers, with stereoisomer **a**, which was very easily obtained in pure form by chromatography, always prevailing. The average ratio **a**:(**b** + **c**) ranges from a minimum of 2:1 up to around 5:1 (entry 12). Within the minor stereoisomers, one of them, presumably **b**, is sometimes highly prevailing.[45] The noticeable variety of the decorations introduced in these scaffolds demonstrates the robustness of this highly convergent methodology.

We also wanted to demonstrate that the presence of a bromine atom on the aromatic ring (**47a**) may be exploited for further derivatization. As shown in Scheme 7, the possibility of forming a new $C(sp^2)–C(sp^2)$ bond by means of a Suzuki coupling (**48**) has been fully proved.

Scheme 7. Suzuki Reaction on Compound 47a



CONCLUSION

In conclusion, we developed a new method for fast assembly of a new family of seven-membered heterocycles. Our strategy relies on the possibility of synthesizing, in high enantiomeric excess, unknown custom-made azido aldehydes by an organocatalytic procedure. These aldehydes then undergo a chemically efficient and operationally simple one-pot sequence involving a Staudinger/aza-Wittig reaction followed by an Ugi–Joullié coupling. This enables, after easy chromatography, the isolation in good overall yield of a single stereoisomer (out of eight) of a new heterocyclic structure endowed with three contiguous stereogenic centers. It is also worth noting that the sequence from the *o*-azido benzyl alcohols **10**, **24**, and **25** to the final products requires just two separation steps and that the final products can be further derivatized using the NHBoc group or the bromine present on derivatives **45**, **46**, or **47**.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were taken in $CDCl_3$ or in DMSO-d_6 at 300 MHz (^1H) and 75 MHz (^{13}C) using, as internal standard, TMS (^1H NMR in $CDCl_3$; 0.000 ppm), the central peak of DMSO (^1H NMR in DMSO-d_6; 2.506 ppm), the central peak of $CDCl_3$ (^{13}C in $CDCl_3$; 77.02 ppm), or the central peak of DMSO

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(^{13}C in DMSO-d_6; 39.43 ppm). 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 the B proton is considered downfield. IR spectra were recorded as $CHCl_3$ solutions or directly on solid, oil, or foamy samples, with the ATR (attenuated total reflectance) technique. TLC analyses were carried out on silica gel plates, viewed at UV (λ = 254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming), or (only for compounds **13**, **32**–**34**) with ninhydrin (ninhydrin (900 mg) in *n*-BuOH (300 mL) and AcOH (9 mL), followed by warming. R_f values were measured after an elution of 7–9 cm. GC–MS were carried out using an HP-1 column (12 m long, 0.2 mm wide), 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 with initial temperature 50 °C, initial time 2 min, rate 20 °C/min, final temperature 260 °C, inj temperature 250 °C, det temperature 280 °C. HPLC analyses for the determination of enantiomeric ratios were performed on a DAICEL Chiral Pak AD 250 × 4.6 mm column, at 25–28 °C with a flow of 1 mL/min (UV detection at λ = 220 nm). HPLC–MS analyses were performed on Synergi Hydro RP 150 × 3 mm column, at 30 °C with a flow of 0.5 mL/min (where not otherwise stated). For MS the ESI+ ionization method was used. HRMS were performed employing an ESI+ ionization method and TOF as analyzer. Column chromatography was performed with the "flash" methodology using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. All reactions employing dry solvents were carried out under a nitrogen atmosphere. Amano PS and AK enzymes were a kind gift of Amano-Mitsubishi Italia. Lipase from *Candida antarctica* (Novozym 435) was a kind gift of Novo Nordisk.

1,5-Benzenedimethanol (8). To a suspension of $LiAlH_4$ (3.33 g, 87.69 mmol) in Et_2O (130 mL) at 0 °C under nitrogen atmosphere was added dropwise (30 min) a solution of phthalide (6.43 g, 48.71 mmol) in dry THF (30 mL). The mixture was allowed to reach room temperature over a period of 3 h, and then it was cooled to 0 °C and carefully quenched with a solution of NaOH (3.99 g, 13.4 mL of H_2O; added dropwise in 45 min). The mixture was diluted with THF (40 mL), stirred for 3 h, filtered on a sintered funnel, and washed with THF. In order to fully recover the product, which in part remains adsorbed on the aluminates, they were dissolved in 1 M HCl (20 mL) and extracted with EtOAc (3 × 40 mL). The organic phase was dried over Na_2SO_4 and united with the THF filtrate above. Evaporation to dryness gave **8** (6.58 g, 98%) as a white solid: mp 68.1–69.4 °C. The analytical data conform to those reported in literature.[46]

2-(Hydroxymethyl)benzyl Acetate (9). Diol **8** (5.54 g, 40.1 mmol) was dissolved in vinyl acetate (60 mL) and diisopropyl ether (120 mL) and treated with 2.00 g of pig pancreatic lipase (PPL, Sigma) supported on Celite as previously described.[31] [(SPPL-4): 1 g of this supported enzyme corresponds to 0.23 g of crude PPL]. After being stirred for 40 h at rt (when the amounts of starting **8** and of its diacetate seem equal at TLC), the suspension was filtered through a sintered funnel. The filtrate was evaporated and chromatographed (PE/Et_2O 75:25) to give pure **9** as an oil (6.60 g, 91%). A partial characterization of **9** has already been reported.[47] R_f = 0.40 (PE/Et_2O 25:75). IR: see literature. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.50–7.30 (m, 4 H); 5.24 (s, 2 H, CH_2OAc); 4.76 (d, J = 6.0 Hz, 2 H, CH_2OH); 2.10 (s, 3 H, CH_3CO); 2.07 (t, J = 6.0 Hz, 1 H, OH). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 170.8 (C=O), 139.3, 133.8 (quat), 129.8, 128.9, 128.8, 128.2 (aromatic CH), 63.9 (CH_2OAc), 62.9 (CH_2OH), 21.0 (CH_3). GC–MS (initial temp 80 °C, initial time 2 min, rate 20 °C/min, final temp 260 °C): t_R 6.36 min. m/z: 162 (M^+–18, 1.1); 120 (100); 119 (58); 92 (5.4); 91 (33); 77 (13); 65 (6.8); 51 (4.4); 43 (31). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.7; H, 6.8.

2-(Azidomethyl)benzyl Alcohol (10). A solution of monoacetate **9** (6.06 g, 33.6 mmol) in dry CH_2Cl_2 (100 mL) was cooled to −30 °C and treated with Et_3N (6.10 mL, 43.72 mmol) and methanesulfonyl chloride (3.12 mL, 40.36 mmol). The mixture was stirred for 2 h, and then it was treated with saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The crude was taken up in dry DMF (34 mL), treated with NaN_3 (4.37 g, 67.26 mmol), stirred for 18 h at room temperature, diluted with H_2O (100 mL), and extracted with Et_2O (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. To a solution of this crude in MeOH (200 mL) at 0 °C was added a 1 M solution of KOH in MeOH (50.5 mL, 50.5 mmol). The reaction mixture was stirred for 1 h at 0 °C and then treated with saturated aqueous NH_4Cl (100 mL), and most of the MeOH was evaporated under reduced pressure. The aqueous phase was extracted with Et_2O (3 × 80 mL), washed with H_2O (80 mL), dried (Na_2SO_4), and concentrated to give azido alcohol **10** as a colorless oil (4.83 g, 88%). The analytical data conform to those reported in literature.[48]

***tert*-Butyl ((4-Methylsulfonyl)(2-azidomethyl)phenyl)-carbamate (12).** To a solution of (2-azidomethyl)benzyl alcohol (**10**) (4.04 g, 24.8 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyl oxide, free radical, 387 mg, 2.48 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was added (diacetoxyiodo)benzene (8.79 g, 27.3 mmol). The solution was stirred for ca. 10 min and then for 1 h at room temperature. The reaction mixture was diluted with $Na_2S_2O_3$ 0.4 M solution (50 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with saturated aq $NaHCO_3$ (80 mL), dried (Na_2SO_4), and concentrated. The residue was filtered through a column of silica gel (60 g) and eluted with 4:1 PE–Et_2O to give a solution of 2-(azidomethyl)benzaldehyde (**11**) that was concentrated to about 5–6 mL at about 100 mbar (it was not completely evaporated at higher vacuum because of its relative volatility). After dilution with methanol (10 mL), H_2O (20 mL), sodium *p*-toluenesulfinate (5.30 g, 29.7 mmol), *tert*-butyl carbamate (2.90 g, 24.8 mmol), and finally, formic acid (1.12 mL, 29.7 mmol) were added. The reaction mixture was vigorously stirred at room temperature for 48 h, diluted with H_2O (30 mL), and sonicated for 30 min. The resulting fine crystalline solid was filtered through a sintered funnel and washed first with H_2O and then with Et_2O/pentane to give ureidosulfone **12a** as a white powder (5.16 g, 12.4 mmol, 50%). This compound was relatively stable as a solid at low temperature but tended to rapidly decompose in solution in the presence of traces of water. Therefore, only fast ^{1}H NMR were recorded. For the same reason, HRMS (ESI+) and elemental analysis were not feasible. Only *p*-toluenesulfinic acid was detected at HRMS. Mp: 124.1–124.7. IR (ATR): ν = 3372, 2987, 2953, 2227, 2100, 1701, 1508, 1491, 1463, 1455, 1433, 1363, 1338, 1315, 1307, 1290, 1278, 1244, 1159, 1140, 1083, 1047, 1019 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 8.32 (d, J = 8.2 Hz, 2H, *H* ortho to SO_2), 7.62–7.55 (m, 1H, aromatic *H*), 7.49–7.36 (m, 3H, aromatic *H*), 7.35 (d, J = 8.2 Hz, 2H, *H* meta to SO_2), 6.29 and 5.85 (AB syst, J = 10.7 Hz, 2H, ArC*H* and N*H*), 4.66 and 4.48 (AB syst, J = 14.1 Hz, 2H, CH_2N_3), 2.43 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$).

***tert*-Butyl ((3*R*,4*R*,5*S*)-3-(*tert*-Butylcarbamoyl)-2-(5-chlorothiophene-2-carbonyl)-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (19a) and Its Diastereoisomers 19b and 19c.** Ureidosulfone **12** (388 mg, 0.93 mmol) in dry THF (9 mL) was treated, under a nitrogen atmosphere, with Cs_2CO_3 (763 mg, 2.34 mmol). The mixture was warmed at 40 °C and stirred for 2 h, then filtered on a sintered funnel, washed with CH_2Cl_2, and concentrated. The residue was dissolved in dry CH_3CN (9 mL), cooled to 0 °C, and treated with propanal (142 μL, 1.98 mmol) and L-proline (23 mg, 0.198 mmol) for 44 h at 0 °C. The crude was then diluted with H_2O, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The dr was determined as 97:3 on the crude by ^{1}H NMR. The residue was eluted from a column of silica gel with 6:1 PE/EtOAc to give **13** (229 mg, 77%), which was directly submitted to the next Staudinger/aza-Wittig/Ugi–Joullié sequence (due to the partial epimerization during the purification step it was not possible to characterize **13**). This crude aldehyde (229 mg, 0.72 mmol) was dissolved in dry THF (18 mL). Triphenylphosphine (227 mg, 0.86 mmol) was added at room temperature. The reaction mixture was stirred for 30 min and then rapidly concentrated under reduced pressure. The residue was immediately dissolved in CH_2Cl_2 (1.8 mL) and treated with 5-

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chloro-2-thienoic acid (129 mg, 0.79 mmol) and *tert*-butyl isocyanide (90 μL, 0.79 mmol). Then it was stirred at room temperature for 18 h, diluted with saturated aq $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated. The diastereomeric ratio was determined as 64:22:14 (**19a**:**19b**:**19c**) by reversed-phase HPLC on this crude mixture: t_R (**19a**) = 8.44 min, t_R (**19b**) = 6.80 min, t_R (**19c**) = 5.85 min. The crude product was purified by chromatography using 6:1 PE−Et_2O to give first **19a** (198 mg, 53% from **13**, 41% from **12**) as a white foam and then the mixture of **19b** and **19c** (112 mg, 30% from **13**, 23% from **12**). Analytically pure samples of **19b** and **19c** were obtained by repeated chromatographies on silica gel using 4:1 PE/EtOAc. **(3*R*,4*R*,5*S*) Diastereomer 19a**. R_f = 0.57 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ +81.5 (*c* 1.1, $CHCl_3$). IR (ATR): ν = 3343, 2969, 2932, 1703, 1673, 1610, 1588, 1543, 1481, 1431, 1389, 1364, 1315, 1222, 1153, 1101, 1065, 1009 cm^{-1}. ^1H NMR (d6-DMSO-d_6, 70 °C): δ = 7.56 (broad s, 1H, N*H*tBu), 7.28−7.15 (m, 4H, aromatic *H*), 7.11 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 7.05 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 6.69 (broad s, 1H, N*H*Boc), 5.17 (d, *J* = 9.3 Hz, 1H, H-5), 5.08, 4.84 (AB syst, *J* = 16.1 Hz, 2H, H-1), 4.61 (d, *J* = 6.5 Hz, 1H, H-3), 2.64 (dq, J_d = 6.5, J_q = 6.3 Hz, 1H, H-4), 1.42 (s, 9H, Boc), 1.34 (s, 9H, C(CH_3)$_3$), 0.74 (broad s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 70 °C): δ = 168.9, 163.0, 154.8 (3 C═O), 139.9, 136.0, 134.7, 131.5 (quat), 128.3, 126.9, 126.5, 126.2 (aromatic *C*H), 77.8 (*C*(CH_3)$_3$), 61.9 (C-3), 54.2 (C-5), 50.2 (quat), 48.3 (C-1), 37.9 (C-4), 28.1 (CH_3 of *t*Bu), 27.8 (CH_3 of Boc), 14.4 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{35}ClN_3O_4S$ 520.2037, found 520.2043. **(3*R*,4*R*,5*S*) Diastereomer 19b**. R_f = 0.40 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ −74.1 (*c* 1.6, $CHCl_3$). IR (ATR): ν = 3340, 2972, 1707, 1671, 1600, 1518, 1455, 1431, 1390, 1364, 1244, 1163, 1046, 1010 cm^{-1}. ^1H NMR (DMSO-d_6, 70 °C): δ = 7.33−7.18 (m, 5H, NH*t*Bu and aromatic *H*), 7.14 (d, *J* = 9.6 Hz, 1H, N*H*Boc), 7.10 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 7.08 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 5.21, 4.82 (AB syst, *J* = 16.3 Hz, 2H, H-1), 4.59 (d, *J* = 6.9 Hz, 1H, H-3), 4.55 (dd, *J* = 9.6, 8.7 Hz, 1H, H-5), 2.73 (ddq, *J* = 8.7, 6.9, 6.6 Hz, 1H, H-4), 1.41 (s, 9H, Boc), 1.22 (s, 9H, C(CH_3)$_3$), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 70 °C): δ = 168.8, 162.8, 155.7 (3 C═O), 140.0, 136.3, 134.3, 132.1 (quat), 128.5, 126.8, 126.7, 126.4 (aromatic CH), 77.6 (*C*(CH_3)$_3$), 62.9 (C-3), 54.8 (C-5), 50.1 (quat), 49.2 (C-1), 37.8 (C-4), 27.9 (CH_3 of *t*Bu), 27.8 (CH_3 of Boc), 15.7 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{35}ClN_3O_4S$ 520.2037, found 520.2048. **(3*R*,4*S*,5*S*) Diastereomer 19c**. R_f = 0.38 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ −16.8 (*c* 1.2, $CHCl_3$). IR (ATR): ν = 2968, 1667, 1615, 1531, 1429, 1366, 1260, 1200, 1131, 1009 cm^{-1}. ^1H NMR (DMSO-d_6, 70 °C): δ = 7.33−7.13 (m, 5H, NH*t*Bu and aromatic *H*), 7.12 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 7.09 (d, *J* = 4.0 Hz, 1H, *H* thienyl), 6.24 (broad d, *J* = 7.7 Hz, 1H, N*H*Boc), 4.99 (dd, *J* = 8.7, 7.2 Hz, 1H, H-5), 4.98, 4.87 (AB syst, *J* = 16.7 Hz, 2H, H-1), 4.80 (d, *J* = 6.0 Hz, 1H, H-3), 2.83 (d of quint, J_q = 7.2, J_d = 6.0 Hz, 1H, H-4), 1.39 (s, 9H, Boc), 1.23 (s, 9H, C(CH_3)$_3$), 1.06 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 70 °C): δ = 168.6, 162.7, 155.9 (C═O), 138.5, 136.6, 136.0, 131.9 (quat), 131.2, 128.7, 128.0, 127.5, 127.1, 126.7 (aromatic CH), 77.9 (*C*(CH_3)$_3$), 59.8 (C-3), 57.1 (C-5), 50.1 (quat), 49.6 (C-1), 36.5 (C-4), 28.2 (CH_3 of *tert*But), 27.9 (CH_3 of Boc), 14.9 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{35}ClN_3O_4S$ 520.2037, found 520.2041.

(2*S*,3*S*) 3-(2-(Azidomethyl)phenyl)-3-*tert*-butoxycarbonylamino-2-methylpropanol (14). Crude aldehyde **13** (0.24 mmol), obtained as described above, was diluted with MeOH (1 mL) and treated with $NaBH_4$ (13.6 mg, 0.36 mmol) at 0 °C. After being stirred for 30 min, the reaction mixture was diluted with H_2O, extracted with EtOAc, dried (Na_2SO_4), and concentrated. The crude residue was purified by silica gel column chromatography with PE/EtOAc 5:2 to give **14** (41 mg, 54% from **12**) as a colorless oil. HPLC on chiral stationary phase: hexane/*i*PrOH 95:5. t_R = 28.80 min (t_R of *ent*-**14** prepared using D-proline: 25.10 min); ee > 98%. $[\alpha]^{20}_D$ +15.2 (*c* 1.5, $CHCl_3$). IR (ATR): ν = 3353, 2974, 2932, 2097, 1687, 1646, 1525, 1365, 1289, 1247, 1160, 1075, 1031 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.39−7.22 (m, 4H, aromatic *H*), 5.21−5.09 (m, 1H, H-3), 5.11 (d, *J* = 9 Hz, 1H, N*H*), 4.63, 4.52 (AB syst, *J* = 13.8 Hz, 2H, CH_2N_3), 3.50−3.33 (m, 2H, CH_2OH), 3.17−3.05 (broad s, 1H, OH), 2.08−1.93 (m, 1H, H-2), 1.42 (s, 9H, C(CH_3)$_3$), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 156.1 (C═O), 139.9, 132.9 (2 quat), 130.1, 128.6, 127.4, 126.4 (4 aromatic CH), 80.1 (*C*(CH_3)$_3$), 64.7 (C-1), 52.3 (CH_2N_3), 50.1 (C-3), 41.0 (C-2), 28.3 (C(CH_3)$_3$), 11.3 (CH_3). HRMS (ESI+) *m*/*z*: [M + Na]$^+$ calcd for $C_{16}H_{24}N_4O_3Na$ 343.1746, found 343.1743.

Determination of Enantiomeric Excess of Diastereomer 19a. Product **19a** (10 mg, 24 μmol), obtained using L-proline as the catalyst for the Mannich step, was treated with 1:2 TFA/CH_2Cl_2 (1.5 mL). The mixture was stirred at room temperature for 30 min and then coevaporated with *n*-heptane. The crude was solubilized in dry CH_2Cl_2 (1 mL) and treated with 4-(dimethylamino)pyridine (DMAP) (12 mg, 96 μmol) and (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (7 μL, 36 μmol). The mixture was stirred at room temperature for 1 h and then it was concentrated. The crude was purified by preparative TLC (PE−Et_2O 2:3) to give the corresponding Mosher amides. The ee (97.3%) was determined by reversed-phase HPLC on the (*S*) Mosher amide, obtained starting from the (*R*) Mosher chloride. Conditions: column phenyl C6 150 × 3 mm, 3 μm. Flow: 0.34 mL/min. Temperature: 25 °C, isocratic elution with MeOH/H_2O 70:30, Detection: UV (280 nm). t_R 36.59 min. t_R of (*R*) amide: 34.47 min (see the Supporting Information for the HPLC chromatograms).

4-Bromo-1,2-benzenedimethanol (21). To a suspension of $LiBH_4$ (0.45 g, 20.65 mmol) in Et_2O (30 mL) at 0 °C under a nitrogen atmosphere was added dropwise (30 min) a solution of 5-bromophthalide (2.00 g, 9.39 mmol) in dry THF (35 mL). The mixture was allowed to reach room temperature and was stirred for 44 h. Then the mixture was cooled to 0 °C, carefully quenched with a saturated solution of NH_4Cl (50 mL; added dropwise in 20 min), and extracted with Et_2O (60 mL) and EtOAc (60 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was eluted from a column of silica gel with 2:1 EtOAc−Et_2O to give **21** (1.89 g, 93%) as a white solid. Mp: 73.1−74.0 °C. The analytical data conform to those reported in the literature.[49]

4-Bromo-2-(hydroxymethyl)benzyl Acetate (22). To a solution of diol **21** (1.85 g, 8.55 mmol) in vinyl acetate (104 mL) at 20 °C, porcine pancreatic lipase supported on Celite as described in literature (SPPL-4)[31] (2.44 g; 1 g of this supported enzyme corresponds to 0.23 g of crude Lipase) was added. The reaction mixture was stirred at 20 °C for 2 h, filtered through a sintered funnel, and washed with CH_2Cl_2 (100 mL). The filtrate was concentrated (regioisomers ratio 75:25 by ^1H NMR analysis of the crude), and the residue was eluted from a column of silica gel with PE/Et_2O (2:3) to give first **22** (1.16 g, 52%) as a white solid and then a mixture of **22** and **23** (0.53 g, 24%) as a white solid. Further chromatography of these mixed fractions afforded other 110 mg of **22**. The overall yield was 1.27 g, 57%. R_f = 0.43 (PE/Et_2O 3:7). Mp: 40.3−41.0 °C. IR (ATR): ν = 3230, 2866, 1728, 1689, 1482, 1455, 1404, 1385, 1360, 1254, 1207, 1176, 1104, 1086, 1051, 1025, 802 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.61 (d, *J* = 2.1 Hz, 1H, H-2), 7.44 (dd, *J* = 8.1, 2.1 Hz, 1H, H-6), 7.25 (d, *J* = 8.1 Hz, 1H, H-5), 5.14 (s, 2H, CH_2OAc), 4.72 (d, *J* = 5.4 Hz, 2H, CH_2OH), 2.20 (t, *J* = 5.4 Hz, 1 H, OH), 2.09 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 170.8 (*C*═O), 141.3, 132.5 (quat), 131.4, 131.3, 130.9 (aromatic *C*H), 122.8 (quat), 63.2 (*C*H_2OAc), 62.2 (*C*H_2OH), 20.9 (*C*H_3). GC−MS: t_R 9.19 min. *m*/*z*: 200 (M^+ −60, 62, (^{81}Br)), 199 (29), 198 (M^+ −60, 62, (^{79}Br)), 197 (24), 171 (8.3), 169 (8.8), 92 (18), 91 (33), 90 (14), 89 (16), 78 (8.0), 77 (13), 65 (9.1), 63 (9.9), 51 (9.5), 43 (100), 39 (7.0). HRMS (ESI+) *m*/*z*: [M + H]$^+$ calcd for $C_{10}H_{12}BrO_3$ 258.9970, found 258.9975.

5-Bromo-2-(hydroxymethyl)benzyl Acetate (23). *Preparation of the Catalyst.* Amano PS lipase (from *Burkholderia cepacia*) (3.00 g) was suspended in 0.067 M pH 7 buffer (phosphate) (50 mL) and immediately treated with Hyflo Supercel (10 g). The suspension was magnetically stirred for 15 min at rt and then allowed to stand still for 9 h. The resulting suspension was frozen at −25 °C while gently manually stirring. The frozen mixture was then lyophilized at 10^{-2} mbar. The resulting solid was removed from the flask, gently ground,

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and further stripped at 10^{-2} mbar in a desiccator over P_2O_5. Yield = 13.452 g. Thus, 1 g of this supported catalyst corresponds to 0.223 g of native Amano PS.

To a solution of diol **21** (1.10 g, 5.07 mmol) in vinyl acetate (60 mL) at 10 °C was added lipase Amano PS supported on Celite as described above (0.47 g). The reaction mixture was stirred at 10 °C for 2 h, filtered through a sintered funnel, and washed with CH_2Cl_2 (80 mL). The filtrate was concentrated (regioisomers ratio 37:63 by ^{1}H NMR analysis of the crude), and the residue was eluted from a column of silica gel with PE/Et_2O (2:3) to give first a mixture of **22** and **23** (0.64 g, 49%) as a white solid and then **23** (0.37 g, 28%) as a white solid. A second chromatography of the mixed fractions afforded other 0.22 g of **23**. Overall yield: 0.59 g (45%). R_f = 0.35 (PE/Et_2O 3:7). Mp: 70.2−71.1 °C; IR (ATR): ν = 3507, 3071, 2930, 2872, 2808, 1726, 1595, 1567, 1482, 1454, 1428, 1406, 1378, 1360, 1313, 1245, 1210, 1179, 1114, 1086, 1042, 989 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.53 (d, J = 2.1 (meta) Hz, 1H, H-2), 7.46 (dd, J = 8.1 (ortho), 2.1 (meta) Hz, 1H, H-6), 7.29 (d, J = 8.1 Hz, 1H, H-5), 5.17 (s, 2H, CH_2OAc), 4.69 (d, J = 5.7 Hz, 2H, CH_2OH), 2.20 (t, J = 5.4 Hz, 1H, OH), 2.11 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 170.7 (C═O), 137.8, 135.9 (quat), 132.1, 131.6, 130.3 (aromatic CH), 121.8 (quat), 62.9 (CH_2OAc), 62.2 (CH_2OH), 20.9 (CH_3). GC−MS: t_R 9.12 min. m/z: 200 (M^+ − 60, 36, (^{81}Br)), 199 (25), 198 (M^+ −60, 38, (^{79}Br)), 197 (23), 171 (6.7), 169 (6.8), 92 (14), 91 (30), 90 (14), 89 (16), 78 (8.3), 77 (14), 65 (14), 64 (10), 63 (11), 51 (10), 50 (4.9), 44 (4.6), 43 (100), 39 (7.3). HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}BrO_3$ 258.9970, found 258.9973.

(2-(Azidomethyl)-4-bromophenyl)methanol (24). Compound **24** was prepared using the same procedure described for **10**, starting from 0.97 g of **22**. Oil. Yield from **22**: 77%. R_f = 0.42 (PE/EtOAc 3:2); IR (ATR): ν = 3331, 2885, 2093, 1594, 1568, 1482, 1450, 1400, 1339, 1285, 1244, 1216, 1174, 1116, 1084, 1042, 1005, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.50 (s, 1H, H-3), 7.48 (dd, J = 7.8 (ortho), 2.1 (meta) Hz, 1H, H-5), 7.30 (d, J = 7.8 Hz, 1H, H-6), 4.69 (broad d, J = 3.6 Hz, 2H, CH_2OH). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 137.8, 135.8 (quat), 132.3, 131.7, 130.6 (aromatic CH), 122.0 (quat), 62.5 (CH_2OH), 51.8 (CH_2N_3). GC−MS: t_R 8.94 min. m/z: 214 (M^+ −29, 6.3, (^{81}Br)), 212 (M^+ −29, 6.2, (^{79}Br)), 198 (21), 169 (6.4), 157 (5.9), 133 (10), 116 (69), 104 (18), 89 (100), 77 (81), 63 (54), 51 (68), 39 (49). HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_8H_8BrN_3NaO$ 263.9748, found 263.9755.

(2-(Azidomethyl)-5-bromophenyl)methanol (25). Compound **25** was prepared using the same procedure described for **10**, starting from 740 mg of **23**. Oil. Yield from **23**: 78%. R_f = 0.41 (PE/EtOAc 3:2). IR (ATR): ν = 3359, 2927, 2099, 1594, 1481, 1403, 1246, 1014 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.61 (d, J = 2.1 Hz, 1H, H-6), 7.46 (dd, J = 8.1 (ortho), 2.1(meta) Hz, 1H, H-4), 7.21 (d, J = 8.1 Hz, 1H, H-3), 4.72 (d, J = 4.2 Hz, 2H, CH_2OH), 4.41 (d, 2H, CH_2N_3), 1.95 (t, J = 4.2 Hz, 1H, OH). ^{13}C NMR (DCl_3, 25 °C): δ = 141.1, 132.3 (quat), 131.8, 131.3, 131.2 (aromatic CH), 122.8 (quat), 62.4 (CH_2OH), 51.9 (CH_2N_3); GC−MS: t_R 9.10 min; m/z: 214 (M^+ − 29, 7.6, (^{81}Br)), 212 (M^+ − 29, 7.3, (^{79}Br)), 198 (30), 169 (6.6), 157 (6.5), 133 (9.3), 116 (71), 104 (19), 92 (60), 89 (100), 77 (99), 63 (58), 51 (71), 39 (41). HRMS (ESI+) m/z: $[M + Na]^+$ calcd for $C_8H_8BrN_3NaO$ 263.9748, found 263.9764.

***tert*-Butyl ((4-Methylsulfonyl)(2-azidomethyl-4-bromo)-phenyl)carbamate (26).** Compound **26** was obtained as a white powder in 26% yield starting from 550 mg of **24**, using the same procedure above-described for **12**. This compound was relatively stable as a solid at low temperature, but tended to rapidly decompose in solution in the presence of traces of water. Therefore only fast ^{1}H NMR were recorded. For the same reason HRMS (ESI+) and elemental analysis were not feasible. Mp: 173.4−174.5 °C. IR (ATR): ν = 3353, 2956, 2098, 1698, 1595, 1516, 1483, 1365, 1335, 1316, 1307, 1249, 1181, 1162, 1143, 1082 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.83 (d, J = 8.2 Hz, 2H, *H* ortho to SO_2), 7.63−7.56 (m, 2H, aromatic *H*), 7.46−7.34 (m, 3H, aromatic *H*), 6.20 and 5.70 (AB syst, J = 10.4 Hz, 2H, ArC*H* and N*H*), 4.65 and 4.49 (AB syst, J = 14.4 Hz, 2H, CH_2N_3), 2.44 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$).

***tert*-Butyl ((4-Methylsulfonyl)(2-azidomethyl-5-bromo)-phenyl)carbamate (27) (R = 4-Br).** Compound **27** was obtained as a white powder in 35% yield starting from 400 mg of **25**, using the same procedure above-described for **12**. This compound was relatively stable as a solid at low temperature but tended to rapidly decompose in solution in the presence of traces of water. Therefore, only fast ^{1}H NMR were recorded. For the same reason HRMS (ESI+) and elemental analysis were not feasible. Mp: 134.3−136.0 °C. IR (ATR): ν = 3353, 2956, 2098, 1698, 1595, 1516, 1483, 1365, 1361, 1271, 1249, 1162, 1144, 1083 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.83 (d, J = 8.1 Hz, 2H, *H* ortho to SO_2), 7.67 (broad s, 1H, aromatic *H*), 7.57 (dd, J = 8.1 (ortho), 1.8 (meta) Hz, 1H, aromatic *H*), 7.37 (d, J = 8.1 Hz, 2H, *H* meta to SO_2), 7.28 (d, J = 8.1 Hz, 1H, aromatic *H*), 6.22 and 5.70 (AB syst, J = 10.5 Hz, 2H, ArC*H* and N*H*), 4.63 and 4.47 (AB syst, J = 14.1 Hz, 2H, CH_2N_3), 2.45 (s, 3H, CH_3), 1.25 (s, 9H, $C(CH_3)_3$).

1,2-Bis(acetoxymethyl)-4-bromobenzene (30). A solution of diol **21** (1.89 g, 8.70 mmol) in dry CH_2Cl_2 (17 mL) was cooled to 0 °C and treated with pyridine (3.5 mL, 43.50 mmol) and acetic anhydride (2.5 mL, 26.10 mmol). The mixture was allowed to reach room temperature in 1 h and stirred at this temperature for 11 h, and then it was was treated with 1 M HCl (40 mL) and extracted with CH_2Cl_2 (2 × 80 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give **30** (2.43 g, 93%) as a white solid, pure enough for characterization. R_f = 0.71 (PE/EtOAc 6:4). Mp: 38.5−39.7 °C (CH_2Cl_2). IR (ATR): ν = 2937, 2166, 1735, 1597, 1573, 1485, 1460, 1378, 1362, 1260, 1230, 1179, 1110, 1091, 1044 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.56 (d, J = 1.8 (meta) Hz, 1H, H-2), 7.47 (dd, J = 8.4 (ortho), 1.8 (meta) Hz, 1H, H-6), 7.28 (d, J = 8.4 Hz, 1H, H-5), 5.15 (s, 2H, CH_2OAc), 5.13 (s, 2H, CH_2OAc), 2.12 (s, 3H, CH_3), 2.09 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 170.5 (C═O), 136.7, 133.2 (quat), 132.3, 131.6, 131.4 (aromatic CH), 122.6 (quat), 63.1 (CH_2OAc), 62.8 (CH_2OAc), 20.9 (CH_3). GC−MS: t_R 9.54 min. m/z: 242 (M^+ −60, 6.1, (^{81}Br)), 240 (M^+ − 60, 6.1, (^{79}Br)), 200 (23), 198 (25), 89 (5.2), 43 (100). HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{12}H_{14}BrO_4$ 301.0075, found 301.0084.

1,2-Bis(butyryloxymethyl)-4-bromobenzene (31). A solution of diol **21** (0.50 g, 2.30 mmol) in dry CH_2Cl_2 (25 mL) was cooled to 0 °C and treated with Et_3N (1.7 mL, 12.19 mmol) and butyryl chloride (0.5 mL, 4.83 mmol). The mixture was allowed to reach room temperature for 2 h, and then it was was treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with 9:1 PE/EtOAc to give **31** (0.73 g, 89%) as colorless oil. R_f = 0.70 (PE/EtOAc 8:2). IR (ATR): ν = 2965, 2876, 1736, 1597, 1571, 1487, 1458, 1417, 1382, 1303, 1252, 1165, 1087, 1042 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.55 (d, J = 2.1 (meta) Hz, 1H, H-2), 7.46 (dd, J = 8.1 (ortho), 2.1 (meta) Hz, 1H, H-6), 7.26 (d, J = 8.1 Hz, 1H, H-5), 5.15 (s, 2H, ArCH_2O), 5.13 (s, 2H, ArCH_2O), 2.35 (t, J = 7.2 Hz, 2H, OCH_2), 2.32 (t, J = 7.5 Hz, 2H, OCH_2), 1.74−1.57 (m, 4H, 2 OCH_2CH_2), 0.95 (t, J = 7.5 Hz, 3H, CH_3), 0.94 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 173.1, 173.0 (C═O), 136.8, 133.4 (quat), 132.1, 131.4, 131.2 (aromatic CH), 122.5 (quat), 62.9, 62.6 (CH_2O), 36.0 (OCH_2CH_2), 18.3 (CH_2CH_3), 13.6 (CH_3). GC−MS: t_R 11.17 min. m/z: 270 (M^+ − 86; 0.86 (^{81}Br)), 268 (M^+ − 86; 0.86 (^{79}Br)), 71 (100), 44 (8.4), 43 (33), 40 (5.7). HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}BrO_4$ 357.0701, found 357.0695

***tert*-Butyl ((3*R*,4*R*,5*S*)-2-(3-Bromobenzoyl)-3-(butylcarbamoyl)-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)-carbamate (36a).** Compound **36a** was prepared from 300 mg of ureidosulfone **12** (0.72 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. *n*-Butyl isocyanide and 3-bromobenzoic acid have been use in the Ugi−Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/Et_2O to give first **36a** (149 mg, 48% from **13**, 37% from **12**) as a white foam and a mixture of **36b** and **36c** (87 mg, 22% from **13**) (foam). **36a**. R_f = 0.50 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ −16.3 (c 1.0, $CHCl_3$). IR (ATR): ν = 3317, 2967, 2931, 1655, 1621, 1560, 1516, 1454, 1422, 1364, 1291,

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1246, 1160, 1069 cm^{-1}. ^1H NMR ($CDCl_3$, 40 °C): δ = 7.57 (ddd, J = 8.0 (ortho), 1.7, 1.1 (meta) Hz, 1H, *H* ortho to C═O), 7.48 (broad d, J = 7.5 Hz, 1H, *H* ortho to CHNHBoc), 7.30 (t, J = 7.5 Hz, 1H, *H* meta to CHNHBoc), 7.27−7.19 (m, 2H, aromatic *H*), 7.18 (t, J = 8.0 Hz, 1H, *H* meta to Br), 7.03 (broad d, J = 8.0 Hz, 1H, *H* ortho to Br), 6.68 (broad d, J = 7.5 Hz, 1H, *H* ortho to CH_2), 6.60 (broad t, J = 4.9 Hz, 1H, N*H*nBu), 5.19 (d, J = 10.1 Hz, 1H, H-5), 4.99, 4.16 (AB syst, J = 17.2 Hz, 2H, H-1), 4.69 (d, J = 10.8 Hz, 1H, H-3), 4.47 (broad d, J = 10.1 Hz, 1H, N*H*Boc), 3.33 (dt, J = 6.6, 4.9 Hz, 2H, CH_2NH), 3.04 (dq, J = 10.8, 6.5 Hz, 1H, H-4), 1.61−1.33 (m, 4H, 2 CH_2 *n*Bu), 1.46 (s, 9H, Boc), 1.17 (broad d, J = 6.6 Hz, 3H, CH_3), 0.97 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 40 °C): δ = 171.1, 169.2, 155.9 (C═O), 140.2, 136.6, 136.4 (quat), 133.7, 131.9, 130.3, 129.9, 128.2, 127.7, 125.4 (aromatic CH), 122.4, 80.1 (quat), 59.4 (C-3), 57.7 (C-5), 50.6 (C-1), 39.2 (CH_2), 35.5 (C-4), 31.6 (CH_2), 28.4 (CH_3 of Boc), 20.0 (CH_2), 16.8 (CH_3), 13.7 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{28}H_{37}BrN_3O_4$ 558.1967, found 558.1972.

***tert*-Butyl ((3*R*,4*R*,5*S*)-2-Benzoyl-3-(butylcarbamoyl)-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (37a).** Compound **37a** was prepared from 300 mg of ureidosulfone **12** (0.72 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. *n*-Butyl isocyanide and benzoic acid have been use in the Ugi−Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/Et_2O to give first **37a** (160 mg, 60% from **13**, 46% from **12**) as a pale yellow foam and a mixture of **37b** and **37c** (69 mg, 26% from **13**, 20% from **12**) as a yellow foam. **37a**: R_f = 0.50 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ +0.4 (c 0.5, $CHCl_3$). IR (ATR): ν = 3316, 2969, 2932, 1711, 1665, 1619, 1577, 1517, 1494, 1447, 1418, 1365, 1232, 1160 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.49 (broad d, J = 7.5 Hz, 1H, *H* ortho to CHNHBoc), 7.43 (dt, J = 7.5 (ortho), 1.0 (meta) Hz, 1H, aromatic *H*), 7.37−7.24 (m, 3H, aromatic *H*), 7.16 (dt, J = 7.5 (ortho), 1.1 (meta) Hz, 1H, aromatic *H*), 7.11 (broad d, J = 7.3 Hz, 2H, aromatic *H*), 6.81 (broad t, J = 5.5 Hz, 1H, N*H*nBu), 6.66 (broad d, J = 7.5 Hz, 1H, *H* ortho to CH_2), 5.19 (broad d, J = 10.0 Hz, 1H, H-5), 4.96, 4.23 (AB syst, J = 17.1 Hz, 2H, H-1), 4.73 (broad d, J = 10.8 Hz, 1H, H-3), 4.60 (broad d, J = 10.0 Hz, 1H, N*H*-Boc), 3.41−3.24 (m, 2H, CH_2 *n*Bu), 3.03 (dq, J = 10.8, 6.4 Hz, 1H, H-4), 1.61−1.33 (m, 4H, 2 CH_2 *n*Bu), 1.44 (s, 9H, Boc), 1.12 (broad d, J = 6.4 Hz, 3H, CH_3), 0.96 (t, J = 7.3 Hz, 3H, CH_3 *n*Bu). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 172.8, 169.3, 155.9 (C═O), 140.2, 136.7, 134.5 (quat), 131.9, 130.6, 128.1, 127.9, 127.6, 127.4, 127.1 (aromatic CH), 79.8 (quat), 59.2 (C-3), 57.6 (C-5), 50.5 (C-1), 39.0 (CH_2 *n*Bu), 35.3 (C-4), 31.5 (CH_2 *n*Bu), 28.3 (CH_3 Boc), 19.9 (CH_2 *n*Bu), 16.8 (CH_3), 13.6 (CH_3 *n*Bu). HPLC−MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{28}H_{38}N_3O_4$ 480.2862, found 480.2868.

***tert*-Butyl ((3*R*,4*R*,5*S*)-3-((2,6-Dimethylphenyl)carbamoyl)-4-methyl-2-propionyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (38a).** Compound **38a** was prepared from 300 mg of ureidosulfone **12** (0.72 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. 2,6-Dimethylphenylisocyanide and propanoic acid have been use in the Ugi−Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/Et_2O to give first **38a** (146 mg, 55% from **13**, 42% from **12**) as an pale yellow foam and a mixture of **38b** and **38c** (77 mg, 29% from **13**, 22% from **12**) (foam) (this mixture was found by HPLC to contain indeed 10% of **38a**). **38a**. R_f = 0.52 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ +8.6 (c 1.0, $CHCl_3$). IR (ATR): ν = 3303, 2972, 1686, 1628, 1426, 1365, 1231, 1206, 1158, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 40 °C): δ = 7.72 (broad s, 1H, N*H*(CH_3)$_2$Ph), 7.47 (broad d, J = 7.1 Hz, 1H, *H* ortho to CHNHBoc), 7.29 (dt, J = 7.1 (ortho), 1.5 (meta) Hz, 1H, *H* meta to CHNHBoc), 7.22 (dt, J = 7.1 (ortho), 1.5 (meta) Hz, 1H, *H* meta to CH_2), 7.10 (broad d, J = 7.1 Hz, 1H, *H* ortho to CH_2), 7.10−7.03 (m, 3H, aromatic *H*), 5.17 (broad d, J = 10.4 Hz, 1H, H-5), 4.99 (d, J = 10.9 Hz, 1H, H-3), 4.96, 4.39 (AB syst, J = 17.4 Hz, 2H, H-1), 4.38 (broad d, J = 10.4 Hz, 1H, N*H*Boc), 3.07 (dq, J = 10.9, 6.6 Hz, 1H, H-4), 2.48, 2.23 (AB part of ABX_3 syst, J = 15.0, 7.5 Hz, 2H, CH_2), 2.19 (s, 6H, 2 CH_3), 1.46 (s, 9H, Boc), 1.24 (broad d, J = 6.6 Hz, 3H, CH_3), 1.12 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 40 °C: δ = 174.5, 168.0, (C═O), 140.5, 135.6, 135.1, 133.6 (quat), 132.3, 128.3, 128.2, 127.6, 127.5, 127.3 (aromatic CH), 79.9 (quat), 58.3 (C-3), 57.8 (C-5), 48.2 (C-1), 35.0 (C-4), 28.4 (CH_3 of Boc), 26.9 (CH_2), 18.3 (2 CH_3), 16.7 (CH_3), 9.3 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{28}H_{38}N_3O_4$ 480.2862, found 480.2862.

Ethyl 2-((3*R*,4*R*,5*S*)-5-((*tert*-Butoxycarbonyl)amino)-4-methyl-2-propionyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-3-carboxamido)acetate (39a). Compound **39a** was prepared from 300 mg of ureidosulfone **12** (0.72 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. Ethyl isocyanoacetate and propanoic acid have been use in the Ugi−Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/EtOAc to give first **39a** (136 mg, 53% from **13**, 41% from **12**) as an pale yellow foam and a mixture of **39b** and **39c** (77 mg, 30% from **13**, 23% from **12**) (foam). **39a**. R_f = 0.55 (PE/EtOAc 1:1). $[\alpha]^{20}_D$ −26.9 (c 2.2, $CHCl_3$). IR (ATR): ν = 3318, 2978, 2938, 1742, 1683, 1631, 1495, 1425, 1366, 1231, 1198, 1160, 1067, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.45 (broad d, J = 7.2 Hz, 1H, *H* ortho to CHNHBoc), 7.27 (dt, J = 7.2 (ortho), 1.4 (meta) Hz, 1H, *H* meta to CHNHBoc), 7.22 (dt, J = 7.2 (ortho), 1.5 (meta) Hz, 1H, *H* meta to CH_2), 7.10 (broad d, J = 7.2 Hz, 1H, *H* ortho to CH_2), 6.88 (broad t, J = 5.4 Hz, 1H, N*H*CH_2CO_2Et), 5.14 (broad d, J = 10.3 Hz, 1H, H-5), 4.87 (broad s, 1H, H-3), 4.86, 4.39 (AB syst, J = 17.4 Hz, 2H, H-1), 4.43 (broad s, 1H, N*H*Boc), 4.20 (q, J = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.06 (dd, J = 18.0, 6.2 Hz, 1H, CH_2COOEt), 3.96 (dd, J = 18.0, 5.6 Hz, 1H, CH_2CO_2Et), 2.97 (dq, J = 12.8, 6.5 Hz, 1H, H-4), 2.48, 2.17 (AB part of ABX_3 syst, J = 14.9, 7.3 Hz, 2H, CH_2CH_3), 1.44 (s, 9H, Boc), 1.28 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (broad s, 3H, CH_3), 1.07 (q, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 174.5, 170.3, 169.3, 155.9 (C═O), 140.2, 135.6 (quat), 132.0, 128.1, 127.6, 127.4 (aromatic CH), 79.7 (quat), 61.3 (CH_2CH_3), 57.7 (C-3), 57.5 (C-5), 48.1 (C-1), 41.2 (CH_2NH), 35.2 (C-4), 28.3 (CH_3 of Boc), 26.8 (CH_2), 16.4 (CH_3), 14.1 (CH_3), 9.1 (CH_3). HPLC−MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{24}H_{36}N_3O_6$ 462.2609, found 462.2604.

***tert*-Butyl ((3*R*,4*R*,5*S*)-3-(Cyclohexylcarbamoyl)-4-methyl-2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (40a).** Compound **40a** was prepared from 200 mg of ureidosulfone **12** (0.48 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. Cyclohexyl isocyanide and Fmoc-L-phenylalanine have been use in the Ugi−Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/Et_2O to give first **40a** (137 mg, 48% from **13**, 37% from **12**) as a pale yellow foam and a mixture of **40b** and **40c** (57 mg, 20% from **13**, 15% from **12**) (foam). **40a**. R_f = 0.57 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ +32.1 (c 1.0, $CHCl_3$). IR (ATR): ν = 3303, 2931, 2854, 1709, 1631, 1492, 1449, 1391, 1365, 1332, 1247, 1228, 1158, 1066, 1031 cm^{-1}. ^1H NMR ($CDCl_3$, 40 °C): δ = 7.77 (broad d, J = 7.5 Hz, 2H, aromatic *H*), 7.59−7.52 (m, 2H, aromatic *H*), 7.41 (t, J = 7.5 Hz, 2H, aromatic *H*), 7.35−7.23 (m, 9H, aromatic *H*), 7.05−6.94 (m, 3H, aromatic *H*), 6.74 (broad s, 1H, aromatic *H*), 6.29 (broad d, J = 7.9 Hz, 1H, N*H*cyclohexyl), 5.22 (broad d, J = 8.5 Hz, 1H, N*H*Fmoc), 5.02 (broad d, J = 9.8 Hz, 1H, H-5), 4.96−4.77 (m, 3H, Hα and 2 H-1), 4.49−4.29 (m, 3H, H-3 and CH_2 Fmoc), 4.19 (t, J = 6.7 Hz, 1H, C*H* Fmoc), 3.80−3.60 (m, 2H, C*H* cyclohexyl and N*H*Boc), 2.94 (dq, J = 10.8, 6.3 Hz, 1H, H-4), 2.83−2.66 (m, 2H, CH_2Ph), 1.90−1.03 (m, 10H, cyclohexyl), 1.46 (s, 9H, Boc), 1.02 (broad s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 40 °C): δ = 171.9, 168.0, 155.7 (C═O), 143.6, 143.5, 141.2, 139.6, 135.8, 135.3 (quat), 132.1, 128.5, 128.1, 127.7, 127.4, 127.0, 126.6, 124.9, 119.9 (aromatic CH), 79.5 (quat), 67.3 (CH_2 Fmoc), 58.8 (C-3), 57.1 (C-5), 52.0 (CH Fmoc), 48.0 (Cα), 47.7 (C-1), 47.1 (CH_2 Fmoc), 38.4 (CH_2 Ph), 35.2 (C-4), 32.8, 32.6, 25.4, 24.5 (CH_2 cyclohexyl), 28.3 (CH_3 Boc), 16.3 (CH_3). HPLC−MS: see Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{47}H_{55}N_4O_6$ 771.4129, found 771.4122.

***tert*-Butyl ((3*R*,4*R*,5*S*)-2-((*S*)-2-(((Benzyloxy)carbonyl)amino)-3-methylbutanoyl)-4-methyl-3-(pentylcarbamoyl)-2,3,4,5-tetrahydro-1*H*-benzo[c]azepin-5-yl)carbamate (41a).** Compound **41a** was prepared from 200 mg of ureidosulfone **12** (0.48 mmol)

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through aldehyde **13**, following the typical procedure described above for **19a**. Pentyl isocyanide and Cbz-L-valine have been used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/Et_2O to give first **41a** (127 mg, 55% from **13**, 42% from **12**) as an pale yellow foam and a mixture of **41b** and **41c** (53 mg, 23%, 18% from **12**) (foam). **41a**. R_f = 0.46 (PE/Et_2O 1:1). $[\alpha]^{20}_D$ +10.3 (*c* 1.0, $CHCl_3$). IR (ATR): ν = 3319, 2964, 2931, 2873, 1713, 1634, 1497, 1454, 1433, 1366, 1233, 1160, 1068, 1044, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.48–7.21 (m, 9H, aromatic *H*), 6.40 (broad s, 1H, N*H*pentyl), 5.25 (broad d, *J* = 9.2 Hz, 1H, N*H*Val), 5.17, 5.07 (AB syst, *J* = 12.2 Hz, 2H, CH_2 Cbz), 5.07–4.69 (m, 3H, H-5 and 2 H-1), 4.55 (broad s, 1H, H-3), 4.43 (dd, *J* = 8.8, 6.5 Hz, 1H, Hα Val), 4.26 (broad s, 1H, N*H*-Boc), 3.33–3.14 (m, 2H, CH_2 pentyl), 3.02 (dq, *J* = 12.9, 6.6 Hz, 1H, H-4), 1.57–1.21 (m, 5H, C*H* Val and 2 CH_2pentyl), 1.40 (s, 9H, Boc), 1.12 (broad s, 3H, CH_3), 0.88 (t, *J* = 6.6 Hz, 3H, CH_3pentyl), 0.75 (d, *J* = 6.5 Hz, 3H, CH_3Val), 0.54 (d, *J* = 6.5 Hz, 3H, CH_3Val). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 173.0, 168.8, 156.3, 155.7 (C=O), 140.0, 135.9, 135.6 (quat), 131.7, 128.5, 128.3, 128.2, 127.9, 127.6, 127.5 (aromatic *C*H), 79.5 (quat), 67.1 (CH_2 Cbz), 58.9 (C-3), 57.6 (C-5), 56.4 (*C*Hα), 48.1 (C-1), 39.3 (CH_2 pentyl), 35.1 (C-4), 30.7 (*C*H Val), 28.9, 28.8 (2 CH_2 pentyl), 28.2 (CH_3 Boc), 22.1 (CH_2 pentyl), 19.4 (CH_3Val), 16.8 (CH_3), 13.9 (CH_3 pentyl). HPLC–MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{51}N_4O_6$ 623.3813, found 623.3809.

***tert*-Butyl ((3*R*,4*R*,5*S*)-3-(Benzylcarbamoyl)-2-(2-methoxyacetyl)-4-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (42a).** Compound **42a** was prepared from 200 mg of ureidosulfone **12** (0.48 mmol) through aldehyde **13**, following the typical procedure described above for **19a**. Benzyl isocyanide and methoxyacetic acid have been used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/EtOAC to give first pure **42a** (90 mg) as a pale yellow foam and then a mixture of **42a**, **42b**, and **42c** (40 mg) (foam). HPLC (see the Supporting Information) showed that the percent of **42a** in this mixture was 24%. Thus, the yield of **42a** was calculated to be 98 mg, 55% from **13**, or 42% from **12**, whereas the yield of **4ab** + **42c** was 32 mg, 18% from **13**, 14% from **12**. **42a**. R_f = 0.33 (PE/EtOAc 1:1). $[\alpha]^{20}_D$ −26.6 (*c* 1.0, $CHCl_3$). IR (ATR): ν = 3307, 2971, 2931, 1709, 1645, 1495, 1454, 1432, 1365, 1336, 1239, 1159, 1126 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.44 (broad d, *J* = 7.2 Hz, 1H, *H* ortho to CHNHBoc), 7.36–7.17 (m, 7H, aromatic *H*), 7.07 (broad d, *J* = 7.2 Hz, 1H, *H* ortho to CH_2), 6.73 (t, *J* = 6.0 Hz, 1H, N*H*CH_2Ph), 5.14 (broad d, *J* = 10.1 Hz, 1H, H-5), 4.99, 4.34 (AB syst, *J* = 17.7 Hz, 2H, H-1), 4.74 (d, *J* = 10.6 Hz, 1H, H-3), 4.52, 4.36 (AB part of ABX syst, *J* = 14.8, 6.0, 6.0 Hz, 2H, NHCH_2Ph), 4.47 (broad s, 1H, N*H*Boc), 4.14, 3.86 (AB syst, *J* = 14.2 Hz, 2H, CH_2OMe), 3.26 (s, 3H, OCH_3), 3.02 (dq, *J* = 10.6, 6.3 Hz, 1H, H-4), 1.43 (s, 9H, Boc), 1.14 (broad d, *J* = 6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 169.6, 169.2, 155.9 (C=O), 139.9, 137.8, 135.2 (quat), 131.9, 128.6, 128.2, 127.7, 127.5, 127.4 (aromatic CH), 79.7 (quat), 71.1 (CH_2OMe), 59.0 (OCH_3), 58.1 (C-3), 57.4 (C-5), 47.3 (C-1), 43.36 (CH_2Ph), 35.1 (C-4), 28.3 (CH_3 of Boc), 16.4 (CH_3). HPLC–MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{36}N_3O_5$ 482.2662, found 482.2655.

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-Benzyl-3-(*tert*-butylcarbamoyl)-2-(5-chlorothiophene-2-carbonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (43a).** Compound **43a** was prepared from 230 mg of ureidosulfone **12** (0.55 mmol) through aldehyde **32**, following the typical procedure described above for **19a**. Hydrocinnamaldehyde was used for the Mannich reaction. The dr of this reaction was determined as 96:4 by ^1H NMR of the crude. The crude was purified by chromatography with 6:1 PE/EtOAc to give **32** (71%) as a pale yellow oil. *tert*-Butyl isocyanide and 5-chloro-2-thienoic acid were then used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 4:1 PE/Et_2O to give first **43a** (98 mg, 42% from **32**, 30% from **12**) as a white foam and then with EtOAc to give a mixture of **43b** and **43c** (63 mg, 27% from **32**, 19% from **12**). **43a**. R_f = 0.45 (PE/Et_2O 2:1). $[\alpha]^{20}_D$ +62.4 (*c* 1.1, $CHCl_3$). IR (ATR): ν = 2963, 1681, 1600, 1531, 1429, 1365, 1259, 1161, 1017 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.52–7.43 (m, 2H, aromatic *H*), 7.39–7.15 (m, 6H, aromatic *H*), 7.03–6.97 (m, 1H, aromatic *H*), 6.88 (broad d, *J* = 4.1 Hz, 1H, *H* thienyl), 6.81 (broad s, 1H, N*H*tBu), 6.79 (d, *J* = 4.1 Hz, 1H, *H* thienyl), 5.23 (d, *J* = 9.9 Hz, 1H, H-5), 5.09, 4.69 (AB syst, *J* = 17.4 Hz, 2H, H-1), 4.67 (d, *J* = 11.1 Hz, 1H, H-3), 4.37 (broad d, *J* = 9.9 Hz, 1H, N*H*Boc), 3.07 (dd, *J* = 11.1, 10.2 Hz, 1H, H-4), 2.67 (broad d, *J* = 12.9 Hz, 1H, CH_2Ph), 2.54 (broad dd, *J* = 12.9, 10.2 Hz, 1H, CH_2Ph), 1.46 (s, 9H, Boc), 1.40 (s, 9H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 168.0, 164.3, 155.8 (C=O), 140.6, 139.5, 136.4, 136.2, 135.4 (quat), 132.5, 129.7, 129.1, 128.4, 128.1, 127.8, 127.3, 126.4, 126.3 (aromatic CH), 79.9 (quat), 59.7 (C-3), 52.9 (C-5), 51.5 (quat), 50.5 (C-1), 43.6 (C-4), 35.5 (CH_2Ph), 28.7 (CH_3 of Boc), 28.3 (CH_3 of *t*Bu). HPLC–MS: see the Supporting Information. HRMS (ESI+) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{39}ClN_3O_4S$ 596.2346, found 596.2350.

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-Benzyl-2-(3-methoxybenzoyl)-3-(methylcarbamoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (44a).** Compound **44a** was prepared from 255 mg of ureidosulfone **12** (0.61 mmol) through aldehyde **32**, following the typical procedure described above for **19a**. Hydrocinnamaldehyde was used for the Mannich reaction. The dr of this reaction was determined as 96:4 by ^1H NMR of the crude. The crude was purified by chromatography with 6:1 PE/EtOAc to give **32** (71%) as a pale yellow oil. Methyl isocyanide and 3-methoxybenzoic acid were then used in the Ugi-Joullié reaction. The residue was eluted from a column of silica gel with 1:1 PE/EtOAc to give first **44a** (111 mg, 47% from **32**, 33% from **12**) as a white foam and a mixture of **44b** and **44c** (54 mg, 23% from **32**, 16% from **12**) (foam). **44a**. R_f = 0.36 (PE/EtOAc 1:1). $[\alpha]^{20}_D$ +2.4 (*c* 0.7, $CHCl_3$). IR (ATR): ν = 2964, 1671, 1619, 1455, 1411, 1365, 1260, 1160, 1019 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.54–7.43 (m, 1H, aromatic *H*), 7.40–7.07 (m, 8H, aromatic *H*), 7.07–6.87 (m, 2H, N*H*Me and aromatic *H*), 6.74–6.59 (m, 3H, aromatic *H*), 5.26 (broad d, *J* = 9.9 Hz, 1H, H-5), 4.90, 4.24 (AB syst, *J* = 17.2 Hz, 2H, H-1), 4.90 (d, *J* = 12.1 Hz, 1H, H-3), 4.57 (broad d, *J* = 9.9 Hz, 1H, N*H*Boc), 3.59 (s, 3H, OCH_3), 3.13 (dd, *J* = 12.1, 10.4 Hz, 1H, H-4), 2.91 (d, *J* = 9.8 Hz, 3H, NHCH_3), 2.69 (broad d, *J* = 12.2 Hz, 1H, CH_2Ph), 2.54 (broad t, *J* = 12.2 Hz, 1H, CH_2Ph), 1.47 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 172.9, 169.7 (C=O), 159.2 (quat), 155.9 (C=O), 140.3, 139.4, 136.7, 135.5 (quat), 132.1, 129.7, 129.4, 128.4, 127.9, 127.5, 126.3, 119.5, 117.4, 111.9 (aromatic CH), 79.9 (quat), 58.3 (C-3), 55.1 (OCH_3), 52.9 (C-5), 50.7 (C-1), 43.5 (C-4), 35.7 (CH_2Ph), 28.4 (CH_3 of Boc), 26.4 (NHCH_3). HPLC–MS: see Supporting Information. HRMS (ESI+) *m*/*z*: $[M + H]^+$ calcd for $C_{32}H_{38}N_3O_5$ 544.2816, found 544.2811.

Ethyl 2-((3*R*,4*R*,5*S*)-2-Benzoyl-4-benzyl-8-bromo-5-((*tert*-butoxycarbonyl)amino)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]-azepine-3-carboxamido)acetate (45a). Compound **45a** was prepared from 310 mg of ureidosulfone **26** (0.63 mmol) through aldehyde **33**, following the typical procedure described above for **19a**. Hydrocinnamaldehyde was used for the Mannich reaction. The dr of this reaction was determined as 88:12 by ^1H NMR of the crude. The crude was purified by chromatography with 6:1 PE/EtOAc to give **33** (68%) as a pale yellow oil. Ethyl isocyanoacetate and benzoic acid were then used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 1:2 PE/Et_2O to give first pure **45a** (93 mg, 33% from **33**, 22% from **26**) as a pale yellow foam and then a mixture of **45b** and **45c** (37 mg, 13% from **33**, 9% from **26**) (foam). **45a**. R_f = 0.41 (PE/Et_2O 1:2). $[\alpha]^{20}_D$ −21.1 (*c* 1, $CHCl_3$). IR (ATR): ν = 2671, 1682, 1622, 1494, 1455, 1365, 1198, 1161, 1020 cm^{-1}. ^1H NMR ($CDCl_3$, 25 °C): δ = 7.53–7.11 (m, 14H, N*H*CH_2 and aromatic *H*), 6.77 (s, 1H, aromatic *H*), 5.22 (broad d, *J* = 10.1 Hz, 1H, H-5), 5.04 (broad d, *J* = 11.4 Hz, 1H, H-3), 4.75, 4.20 (AB syst, *J* = 17.4 Hz, 2H, H-1), 4.58 (broad d, *J* = 10.1 Hz, 1H, N*H*-Boc), 4.27 and 3.95 (AB part of a ABX syst, *J* = 17.9, 7.0, 4.9 Hz, 2H, NHCH_2), 4.23 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.07 (dd, *J* = 11.4, 10.7 Hz, 1H, H-4), 2.74 (broad d, *J* = 12.9 Hz, 1H, CH_2Ph), 2.58 (broad dd, *J* = 12.9, 10.7 Hz, 1H, CH_2Ph), 1.48 (s, 9H, Boc), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 173.6, 169.7, 169.3, 155.8 (C=O), 139.4, 139.2, 138.6, 134.1 (quat), 133.8, 131.1, 131.0, 130.1, 129.7, 128.6, 128.4, 127.3, 126.4 (aromatic CH), 80.2 (quat), 61.5 (CH_2CH_3), 57.8 (C-3), 52.3 (C-5), 50.0 (C-1), 43.2 (C-4), 41.4 (NHCH_2), 35.6 (CH_2Ph), 28.4 (CH_3 Boc), 14.2 (CH_3). HPLC–MS: see the

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Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{34}H_{39}BrN_3O_6$ 664.2029, found 664.2022.

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-Benzyl-3-(benzylcarbamoyl)-8-bromo-2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-acetyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (46a).** Compound **46a** was prepared from 310 mg of ureidosulfone **26** (0.63 mmol) through aldehyde **33**, following the typical procedure described above for **19a**. Hydrocinnamaldehyde was used for the Mannich reaction. The dr of this reaction was determined as 88:12 by ^{1}H NMR of the crude. The crude was purified by chromatography with 6:1 PE/EtOAc to give **33** (68%) as a pale yellow oil. Benzyl isocyanide and Fmoc-glycine were then used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 1:2 PE/Et_2O to give first **46a** (169 mg, 47% from **33**, 32% from **26**) as a pale yellow foam and a mixture of **46b** and **46c** (36 mg, 10% from **33**, 7% from **26**) (foam). **46a**. R_f = 0.36 (PE/Et_2O 1:2). $[\alpha]^{20}_D$ −41.8 (*c* 2, $CHCl_3$). IR (ATR): ν = 3323, 2931, 1704, 1651, 1496, 1450, 1391, 1365, 1231, 1159, 1104, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.76 (d, J = 7.5 Hz, 2H, aromatic *H*), 7.57 (d, J = 7.4 Hz, 2H, aromatic *H*), 7.47–7.16 (m, 17H, aromatic *H*), 6.65 (broad s, 1H, N*H*Fmoc), 5.55 (broad s, 1H, N*H*Bn), 5.17 (broad d, J = 10.0 Hz, 1H, H-5), 4.99, 4.21 (AB syst, J = 17.7 Hz, 2H, H-1), 4.88 (broad d, J = 10.4 Hz, 1H, H-3), 4.67–4.54 (m, 2H, N*H*-Boc and Hα), 4.41–4.15 (m, 5H, Hα, 1 H of CH_2Bn, C*H* and CH_2 of Fmoc), 3.69 (broad d, J = 14.1 Hz, 1H, 1 H of CH_2Bn), 3.05 (t, J = 10.4 Hz, 1H, H-4), 2.73–2.45 (m, 2H, CH_2Ph), 1.45 (s, 9H, Boc). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 169.2, 168.7, 156.2, 155.9 (C═O), 143.7, 143.6, 141.2, 139.0, 137.6, 136.4, 131.6 (quat), 133.9, 130.2, 129.7, 128.8, 128.5, 127.7, 127.6, 127.0, 126.5, 125.0, 121.4, 120.0 (aromatic *C*H), 80.1 (quat), 67.2 (CH_2 Fmoc), 57.7 (C-3), 52.3 (C-5), 46.9 (*C*H Fmoc), 46.8 (C-1), 43.7 (CH_2NHFmoc), 43.5 (C-4), 43.1 (NHCH_2Ph), 35.1 (CH_2Ph), 28.3 (CH_3 Boc). HPLC–MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{47}H_{48}BrN_4O_6$ 843.2775, found 843.2757.

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-Benzyl-7-bromo-3-(*tert*-butylcarbamoyl)-2-propionyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)-carbamate (47a).** Compound **47a** was prepared from 400 mg of ureidosulfone **27** (0.81 mmol) through aldehyde **34**, following the typical procedure described above for **19a**. Hydrocinnamaldehyde was used for the Mannich reaction. The dr of this reaction was determined as 87:13 by ^{1}H NMR of the crude. The crude was purified by chromatography with 6:1 PE/EtOAc to give **34** (76%) as a pale yellow oil. *tert*-Butyl isocyanide and propanoic acid were then used in the Ugi–Joullié reaction. The residue was eluted from a column of silica gel with 3:2:1 PE/CH_2Cl_2/Et_2O to give first **47a** (108 mg, 30% from **34**, 23% from **27**) as a pale yellow foam and a mixture of **47b** and **47c** (39 mg, 11% from **34**, 8% from **27**). **47a**. R_f = 0.48 (PE/CH_2Cl_2/Et_2O 2:2:1). $[\alpha]^{20}_D$ −52.7 (*c* 1, $CHCl_3$). IR (ATR): ν = 3317, 2971, 1709, 1676, 1632, 1489, 1455, 1391, 1365, 1224, 1162, 1050, 1019 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.92 (d, J = 8.1 Hz, 1H, aromatic *H*), 7.51–7.18 (m, 7H, aromatic *H*), 6.22 (broad s, 1H, N*H*tBu), 5.11 (broad d, J = 10.3 Hz, 1H, H-5), 4.90, 4.21 (AB syst, J = 17.4 Hz, 2H, H-1), 4.78 (broad d, J = 11.4 Hz, 1H, H-3), 4.41 (broad d, J = 10.3 Hz, 1H, N*H*-Boc), 2.96 (t, J = 10.5 Hz, 1H, H-4), 2.65, 2.50 (AB syst, J = 12.3 Hz, 2H, CH_2Ph), 2.51–2.37 (m, 1H, CH_2CH$_3$), 2.20–2.04 (m, 1H, CH_2CH$_3$), 1.49 (s, 9H, Boc), 1.37 (s, 9H, C(CH_3)$_3$), 1.09 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 174.3, 168.6, 155.7 (C═O), 142.5, 139.4, 134.6 (quat), 134.9, 130.4, 129.7, 128.9, 128.5, 126.4 (aromatic *C*H), 80.0 (quat), 57.5 (C-3), 52.3 (C-5), 51.5 (quat), 47.4 (C-1), 43.7 (C-4), 35.2 (CH_2Ph), 28.6 (CH_3 tBu), 28.3 (CH_3 Boc), 26.9 (CH_2CH$_3$), 9.3 (CH_2CH$_3$). HPLC–MS: see the Supporting Information. HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{30}H_{41}BrN_3O_4$ 586.2289, found 586.2280.

Determination of ee of Intermediate Aldehydes 32–34 and of Their Enantiomers. The crude aldehydes were prepared as described for the synthesis of **19a** either using L-proline or D-proline as catalyst. Then they were reduced to the corresponding alcohols with $NaBH_4$ (following the same procedure employed for the synthesis of **14**) and the crude alcohols were examined at HPLC using a chiral stationary phase. *Crude alcohols derived from* **32** *or* ***ent*-32**: Conditions: hexane/*i*PrOH 90:10. t_R = 15.45 min. (t_R of *ent*-**32**: 11.66 min); er > 99.5:0.5. *Crude alcohols derived from* **33** *or* ***ent*-33**: Conditions: hexane/*i*PrOH 90:10. t_R = 22.61 min. (t_R of *ent*-**33**: 11.62 min); er > 99.5:0.5. *Crude alcohols derived from* **34** *or* ***ent*-34**: in this case HPLC analysis was not feasible. Therefore the ee of **34** has been determined as 99% by comparison of the ^{1}H NMR spectra of the *S*-Mosher esters of the crude alcohols. For this purpose, a solution of the alcohols derived from **34** or *ent*-**34** (10 mg, 21 μmol) in dry CH_2Cl_2 (1 mL) was cooled to 0 °C and treated with 4,4-dimethylaminopyridine (10 mg, 84 μmol) and *R*-α-methoxy-α-trifluoromethylphenylacetyl chloride (6 μL, 31 μmol). The mixture was allowed to reach room temperature for 1 h, and then it was concentrated and directly purified by preparative TLC (PE/EtOAc 8:1) to give the Mosher esters which were examined at ^{1}H NMR (see the Supporting Information).

***tert*-Butyl ((3*R*,4*R*,5*S*)-4-Benzyl-3-(*tert*-butylcarbamoyl)-7-phenyl-2-propionyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl)carbamate (48).** To a solution of **47a** (50 mg, 85 μmol), phenylboronic acid (22 mg, 180 μmol), and triphenylphosphine (3.5 mg, 14 μmol) in dry THF (0.6 mL) under an argon atmosphere, Na_2CO_3 (29 mg solubilized in 60 μL of H_2O) and $Pd(OAc)_2$ (1 mg, 4.5 μmol) were added. The mixture was heated in the presence of microwaves for 2 h at 100 °C with magnetic stirring, treated with H_2O (10 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with PE/CH_2Cl_2/Et_2O (3:2:1) to give **48** (40 mg, 76%) as a pale yellow foam. R_f = 0.55 (PE/CH_2Cl_2/Et_2O 2:2:1). $[\alpha]^{20}_D$ −61.1 (*c* 1.3, $CHCl_3$). IR (ATR): ν = 3323, 2972, 2930, 1710, 1681, 1630, 1486, 1455, 1426, 1391, 1365, 1325, 1225, 1165, 1059, 1019 cm^{-1}. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 7.58 (s, 1H, aromatic *H*), 7.51–7.10 (m, 12H, aromatic *H*), 6.28 (broad s, 1H, N*H*tBu), 5.25 (d, J = 10.8 Hz, 1H, H-5), 4.99, 4.35 (AB syst, J = 17.4 Hz, 2H, H-1), 4.81 (d, J = 10.8 Hz, 1H, H-3), 4.45 (broad d, J = 10.8 Hz, 1H, N*H*-Boc), 3.05 (t, J = 10.8 Hz, 1H, H-4), 2.68, 2.52 (AB syst, J = 13.2 Hz, 2H, CH_2Ph), 2.57–2.42 (m, 1H, CH_2CH$_3$), 2.27–2.15 (m, 1H, CH_2CH$_3$), 1.38 (s, 9H, Boc), 1.38 (s, 9H, C(CH_3)$_3$), 1.11 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 174.4, 168.8, 155.9 (C═O), 141.1, 140.9, 139.9, 139.6, 134.5 (quat), 130.7, 129.7, 128.7, 128.4, 128.0, 127.5, 127.0, 126.3, 125.9 (aromatic *C*H), 79.7 (quat), 57.7 (C-3), 53.0 (C-5), 51.5 (quat), 47.7 (C-1), 43.7 (C-4), 35.3 (CH_2Ph), 28.7 (CH_3 tBu), 28.4 (CH_3 Boc), 27.0 (CH_2CH$_3$), 9.4 (CH_2CH$_3$). HRMS (ESI+) m/z: $[M + H]^+$ calcd for $C_{36}H_{46}N_3O_4$ 584.3494, found 584.3488.

■ ASSOCIATED CONTENT

Supporting Information

Details of the optimization of regioselective synthesis of **22** and **23**; discussion on the assignment of relative configuration to **19a–c**; rationalization of observed stereochemical course; HPLC–MS/UV data and chromatograms of **36–47**; copies of HPLC chromatograms (reversed-phase and on chiral stationary phases); ^{1}H NMR of Mosher esters and amides; copies of ^{1}H and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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