Organocatalytic Transannular Approach to Stereodefined Bicyclo[3.1.0]hexanes

Iker Riaño, Uxue Uria, Efraím Reyes, Luisa Carrillo, and Jose L. Vicario

The Journal of Organic Chemistry **2018** *83* (7), 4180-4189

DOI: 10.1021/acs.joc.8b00165

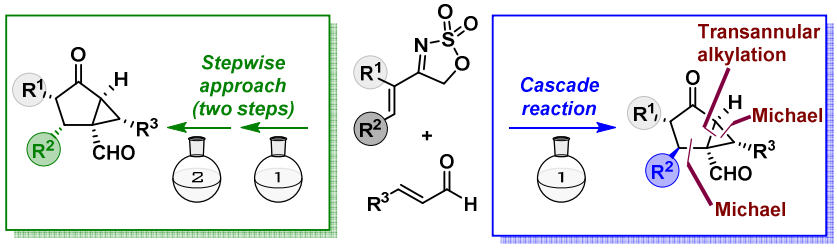
Organocatalytic Transannular Approach to Stereodefined Bicyclo[3.1.0]hexanes

Iker Riaño, Uxue Uria, Efraím Reyes, Luisa Carrillo and Jose L. Vicario,**

Department of Organic Chemistry II. University of the Basque Country (UPV/EHU). P.O. Box 644, 48080, Bilbao, Spain.

marisa.carrillo@ehu.es; joseluis.vicario@ehu.es

TOC GRAPHIC

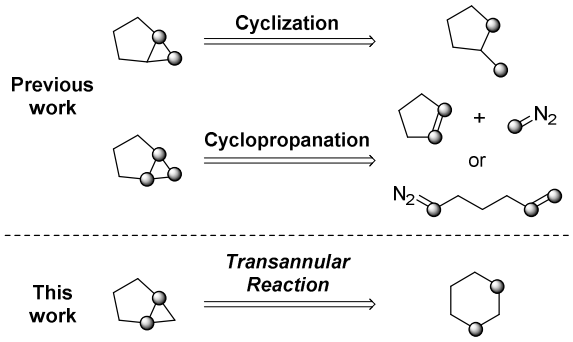


Abstract

A diastereodivergent approach to highly substituted bicyclo[3.1.0]hexanes has been developed through a transannular alkylation reaction that builds up the bicyclic core employing asymmetric organocatalysis as the tool for the installation of all stereocenters. On one hand, a Michael/Michael cascade process between enals and 4-alkenyl sulfamidate imines under the iminium/enamine activation manifold provides a oxathiazole-2,2-dioxide-fused cyclohexane adduct that, after isolation, is subsequently engaged in a transannular alkylation/hydrolysis through enamine activation by the use of a primary amine. On the other hand, the corresponding C-2 epimers are directly obtained from the same starting materials in a single operation through cascade Michael/Michael/transannular alkylation/hydrolysis sequence through sequential iminium/enamine/enamine combination of aminocatalytic activation manifolds.

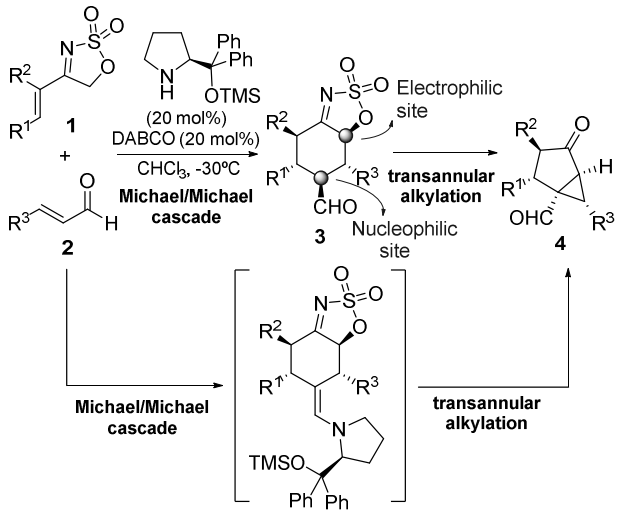
The bicyclo[3.1.0]hexane architecture is found as the main structural feature of the thujane family of monoterpenes[1] that display a variety of interesting biological activities.[2] Moreover, this scaffold possesses unique conformational features and therefore it has been used as a convenient platform for the survey of new types of lead structures in drug discovery programs.[3] Consequently, a major effort has been dedicated to the development of effective synthetic protocols for the construction of this scaffold, with a particular emphasis on the possibility of the stereocontrolled formation of derivatives incorporating different substitution patterns. In general, the enantioselective synthetic routes described up to date typically involve the formation of the cyclopropane ring from a conveniently functionalized cyclopentane substrate, either through a ring-closure event[4] or through a [2+1] cycloaddition process (See Scheme 1).[5,6] However, the possibility of constructing the bicyclo[3.1.0]hexane scaffold in a stereoselective manner by transannular C-C bond formation starting from a conveniently functionalized cyclohexane derivative has received very little attention up to date, despite the fact that some very early reports exist in which functionalized 4-chlorocyclohexanones,[7] 3-bromocyclohexyl esters[8] or 3-sulfonylcyclohexyl esters[9] are used as substrates undergoing ring contraction via transannular alkylation through enolate formation.

SCHEME 1. Different approaches to the bicyclo[3.1.0]hexane scaffold



In this sense, we recently reported the catalytic and enantioselective synthesis of highly functionalized oxathiazole-2,2-dioxide-fused cyclohexane scaffolds (**3**) through Michael/Michael cascade reaction between enals (**2**) and 4-alkenyl sulfamidate imines (**1**) in the presence of a chiral secondary amine catalyst (See Scheme 2).[10] These highly functionalized cyclohexanes incorporate a potentially nucleophilic site at the formyl-containing carbon atom, together with an electrophilic site by means of the good leaving-group ability of the sulfonate group, and both reactive points are located at an strategic 1,3-relative position. This made us to envision the potential of these substrates as starting materials for the construction of highly functionalized bicyclo[3.1.0]hexanes (**4**) via transannular reaction, also being able to obtain these adducts as single stereoisomers provided that the key transannular reaction proceeds in a diastereoselective manner under efficient substrate control. Moreover, and in view of the very simple and mild conditions required for the construction of these oxathiazole-2,2-dioxide-fused cyclohexane adducts, we also decided to target the one-pot or cascade approach that would eventually lead to the direct formation of bicyclo[3.1.0]hexanes from enals and 4-alkenyl sulfamidate imines through the combination of the initial catalytic and enantioselective cascade Michael/Michael reaction followed by the transannular process.

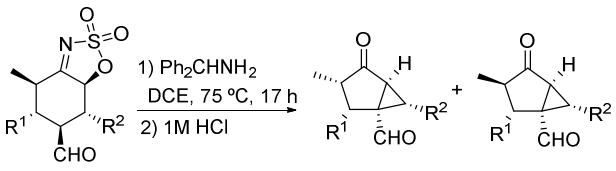
SCHEME 2. Stereodefined oxathiazole-2,2-dioxide-fused cyclohexanes (**3**) previously synthesized in our group as potential substrates for the transannular construction of bicyclo[3.1.0]hexanes



We initially tested the possibility of carrying out the transannular process through enolate intermediates using substrate **3a** and different bases for the deprotonation of the formyl α-proton but without any success. When the reaction was performed in the presence of mild amine bases (Et_3N, DABCO or DBU) the starting material was recovered unchanged and the use of stronger bases (LHMDS, NaH) led to extensive decomposition. At this point, we decided to use a primary amine such as benzhydrylamine in order to generate a nucleophilic enamine species upon condensation with the formyl group, observing the formation of a bicyclic imine product when the reaction was carried out using one equivalent of benzhydrylamine, which could be cleanly converted into bicyclo[3.1.0]hexane adduct **4a** after aqueous workup (See Scheme in Table 1).[11] After a set of different experiments directed towards the optimization of the reaction, it was found that the best conditions involved heating substrate **3a** with 1 equiv. of benzhydrylamine[12] in dichloroethane at 75 ºC for 17 hours, leading to the formation of bicyclic compound **4a** in 80% yield (combined yield for both diastereoisomers). It should also be noted that the reaction furnished adduct **4a** as a 86:14 mixture of epimers at the C3-position of the 4-oxobicyclo[3.1.0]hexane scaffold, which indicates that the transannular process had proceeded with complete stereochemical control on the configuration of the two stereocentres generated across the newly formed C-C bond and the

observation of two diastereomers **4**/**4'** was happening through isomerization of the enolizable α-H of the cyclopentanone moiety, being the major diastereoisomer the thermodynamic product. This epimerization process can take place either at the final product or at the corresponding oxathiazole precursor during the hydrolysis. With the best conditions in hands, we proceeded to extend the reaction to other substrates **3** (Table 1), which were synthesized in an enantioenriched fashion through our previously reported methodology.[10] As shown in Table 1, when a variety of starting products incorporating a methyl group at R^1 and aryl groups with different substitution pattern at the R^2 position were tested, the reaction proceeded with high yield and diastereoselectivity (entries 1-8), only observing that the reaction provided inferior yields and a somewhat lower degree of diastereoselectivity when a phenyl substituent were placed at R^1 (entry 9). On the other hand, the reaction did not take place when substrates incorporating other bulkier groups at this position like ethyl or *iso*-propyl were tested (entries 10-11). Reactions with substrates incorporating alkyl substitutents at R^2 of the starting materials (e.g. Me) were also tested, only detecting the formation of the imine intermediate arising from the initial condensation with the primary amine but without observing any evolution towards the transannular product.[13] Compound **4e** was isolated as a yellow solid that could be recrystallized and its stereostructure could also be determined by single crystal X-ray analysis.

TABLE 1. Transannular reaction for the conversion of cyclohexanes 3a-i into bicyclo[3.1.0]hexane adducts 4a-i



Entry	R^1	R^2	4	Yield (%)[a]	4/4' ratio[b]
1	Me	Ph	**4a**	80	86:14
2	Me	4-MeC_6H_4	**4b**	77	87:13
3	Me	4-AcO-3-$MeOC_6H_3$	**4c**	71	87:13
4	Me	4-ClC_6H_4	**4d**	71	86:14

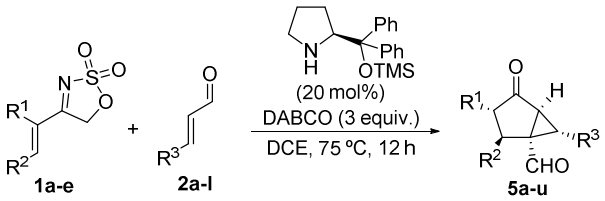
5	Me	4-BrC_6H_4	**4e**	72	85:15
6	Me	4-$NO_2C_6H_4$	**4f**	51	86:14
7	Me	4-CNC_6H_4	**4g**	58	86:14
8	Me	4-$CF_3C_6H_4$	**4h**	75	86:14
9	Ph	4-$NO_2C_6H_4$	**4i**	57	75:25
10	Et	Ph	-	<5	-
11	^{i}Pr	Ph	-	<5	-

[a] Yield of pure product after flash column chromatography purification. [b] Determined by NMR analysis of crude reaction mixture.

Having demonstrated the ability of compounds **3** to undergo transannular alkylation under the intermediacy of a nucleophilic enamine, we next decided to evaluate the possibility of accessing to bicyclo[3.1.0]hexane adducts **4** directly from 4-alkenyl sulfamidate imines **1** and enals **2** in a cascade Michael/Michael reaction that generates compounds **3**, followed by the transannular alkylation process (See Table 2). It should be highlighted that the inherent mechanistic profile of the Michael/Michael cascade reaction that leads to compounds **3** involves the participation of an α,β-unsaturated iminium ion species that, after the double Michael reaction cascade, still generates an iminium ion that, upon tautomeric equilibrium, has also the potential to form the same type of enamine intermediates than those required for the transannular process to occur (See scheme 3 for a full mechanistic picture). In this sense, when alkenylsulfamidate imine **1a** and cinnamaldehyde (**2a**) were reacted under the conditions previously optimized for the formation of compound **3a** (20 mol% of (*S*)-α,α-diphenylprolinol trimethylsilyl ether and 20 mol% of DABCO in 1,2-dichloroethane), but increasing the temperature to reflux, bicyclo[3.1.0]hexane derivative **5a** was obtained in 39% yield and as a single diastereoisomer, as determined by ^{1}H-NMR analysis of the non-purified reaction mixture. Remarkably, the reaction also proceeded with an outstanding level of enantiocontrol, isolating **5a** with a 95% e.e. Fine tuning of the reaction conditions led to an optimized protocol for the formation of the target bicyclo[3.1.0]hexane adduct **5a** that involved carrying out the reaction at 75ºC and using an excess of DABCO. Under these conditions, the reaction was found to be remarkably efficient, considering that it involves the formation of three new

C-C bonds through the combination of a two consecutive Michael reaction followed by transannular nucleophilic displacement and a final imine hydrolysis sequence. Moreover, five new stereogenic centres are formed with complete stereocontrol. It should be pointed out that, under these conditions, there was no epimerization observed at the enolizable α-H of the cyclopentanone moiety. With optimal conditions in hands, we next proceeded to evaluate the scope of the reaction, using enals (**2**) and alkenylsulfamidate imines (**1**) with different substitution patterns (Table 2).

TABLE 2. Cascade Michael/Michael/Transannular alkylation/Hydrolysis for the synthesis of bicyclo[3.1.0]hexane adducts 5a-u.[a]



Entry	R^1	R^2	R^3	5	Yield (%)[b]	e.e. (%)[c]
1	Me	Me	Ph	**5a**	53	94
2	Me	Me	4-MeC_6H_4	**5b**	55	93
3	Me	Me	2-$MeOC_6H_4$	**5c**	39	90
4	Me	Me	4-$MeOC_6H_4$	**5d**	43	94
5	Me	Me	4-AcO-3-$MeOC_6H_3$	**5e**	51	94
6	Me	Me	3,5-$(MeO)_2C_6H_3$	**5f**	42	92
7	Me	Me	4-ClC_6H_4	**5g**	52	92
8	Me	Me	4-BrC_6H_4	**5h**	46	90
9	Me	Me	2-$NO_2C_6H_4$	**5i**	47	92
10	Me	Me	4-$NO_2C_6H_4$	**5j**	32	86
11	Me	Me	4-CNC_6H_4	**5k**	41	89
12	Me	Me	4-$CF_3C_6H_4$	**5l**	54	90
13	Me	Me	Me	-	<5	-
14	Me	Et	Ph	**5m**	43	91
15	Me	Et	4-$MeOC_6H_4$	**5n**	41	90
16	Me	Et	4-BrC_6H_4	**5o**	30	86
17	Me	Ph	Ph	**5p**	49	93
18	Me	Ph	4-AcO-3-$MeOC_6H_3$	**5q**	51	90

19	$(CH_2)_4$		Ph	**5r**	46	98
20	$(CH_2)_4$		4-$MeOC_6H_4$	**5s**	34	96
21	$(CH_2)_4$		4-BrC_6H_4	**5t**	38	96
22[d]	H	Ph	2-$MeOC_6H_4$	**5u**	46	98
23[d]	H	Ph	4-$MeOC_6H_4$	**5v**	41	98

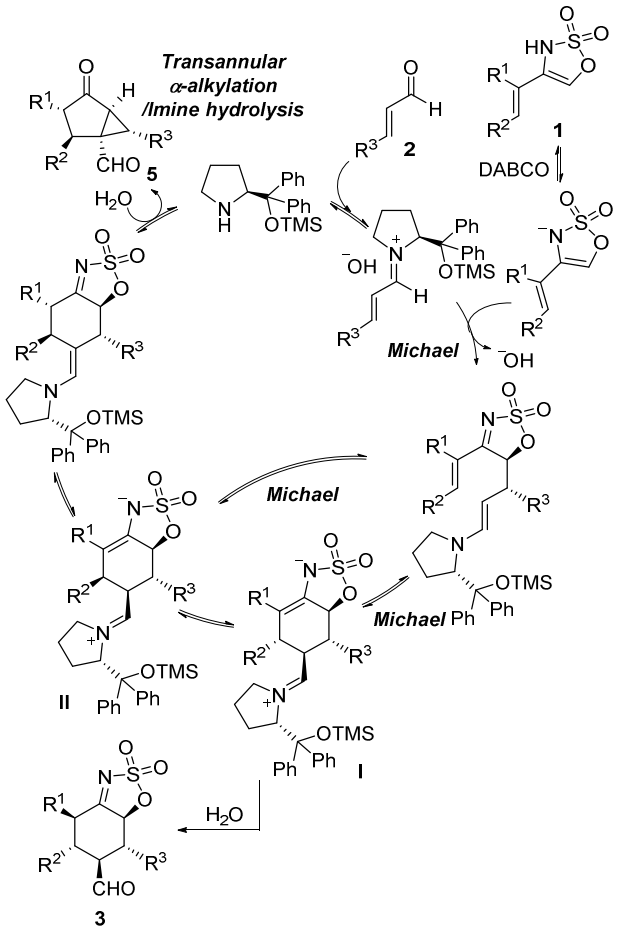
[a] The reaction was carried out on a 0.15 mmol scale of **1**, using 1.5 equiv. of **2** in 0.30 mL of solvent. [b] Yield of pure product **5** after flash column chromatography purification. [c] Determined by HPLC analysis on chiral stationary phase (See Supporting Information for details). [d] The reaction was carried out on a 0.15 mmol scale of **1**, using 1.5 equiv. of **2** and 20 mol% of DABCO at r.t. in 0.30 mL of solvent.

As it can be observed in Table 2, the reaction performed well with a variety of enals incorporating β-aryl substituents of different electronic features, including both electron-donating (entries 2-6) and electron-withdrawing groups (entries 7-12). Unfortunately, when crotonaldehyde (entry 13) was tested in the reaction, only products arising from the decomposition of the starting materials were observed.[14] In addition, the reaction using sulfamidate imines **1** with different β-substituents also proceeded efficiently, providing the corresponding adducts **5** with excellent diastereo- and enantiocontrol, albeit in somewhat lower overall yields (entries 14-18). Cyclohexenyl-substituted sulfamidate imine **1d** was also surveyed, providing cyclopropane-fused octahydroindenones **5r-t** as single diastereoisomers of very high enantiomeric purity in comparable yields as those obtained in the previous cases. Finally, alkenyl sulfamidate imine **1e** was also surveyed, leading to the formation of bicyclo[3.1.0]hexane adducts **5u** and **5v** that do not incorporate any α-substituent at the cyclopentanone core, also with good results in terms of yield and stereocontrol, although it has to be pointed out that in these cases the reaction provided directly the bicyclic adduct **5** when it was carried out at r.t. and using a substoichiometric amount of DABCO (20 mol%), without observing the presence of any cyclohexane intermediate of type **3** in the analysis of the crude reaction mixture. The absolute configuration of compound **5e** was determined by single crystal X-

ray analysis (See supporting information for details) and the stereostructure of all other compounds **5** was stablished based on mechanistic analogy.

It should be noted that adducts **5** resulted to be the C-2 epimers of compounds **4** obtained in the transannular reaction from functionalized cyclohexanes **3**. This issue behavior is explained by assuming a mechanistic picture such as the one depicted in Scheme 3. This would involve the initial activation of the enal through iminium ion followed by the subsequent Michael/Michael cascade reaction that follows the well established combination of iminium and enamine activation manifolds.[15,16] In this case, it is proposed that diastereomeric cyclohexane intermediates **I** and **II** would be in equilibrium by means of the potential reversible nature of the second intramolecular Michael reaction, being the transannular reaction a favoured process on intermediate **II** operating at high temperatures, while hydrolysis and catalyst turnover on intermediate **I** would be the preferred pathway when the reaction is carried out at lower temperatures and in the presence of substoichiometric amounts of DABCO. The more favoured arrangement of substituents on the cyclohexane moiety of the enamine intermediate derived from the intermediate **II** (R^1, R^2 and R^3 can take pseudoequatorial positions during the reaction) compared to the corresponding enamine formed from intermediate **I** might account for the kinetic preference for the former to undergo the transannular alkylation step.

SCHEME 3. Proposed mechanistic pathway for the cascade Michael/Michael/Transannular alkylation/Hydrolysis process



In conclusion, the diastereodivergent access to the two C-2 epimers of densely substituted bicyclo[3.1.0]hexanes in highly enantiopure form can be achieved by direct reaction between enals and 4-alkenyl sulfamidate imines through two different protocols that provide the final adducts in good yields and excellent enantioselectivities. In both processes, a Michael/Michael cascade reaction under the well-known combination of aminocatalytic iminium/enamine activation mechanisms is responsible of the installation of all stereocenters in the presence of a diarylprolinol derivative as catalyst, forming a oxathiazole-2,2-dioxide-fused cyclohexane adduct intermediate. This intermediate can continue the cascade process by undergoing a subsequent transannular alkylation reaction through an enamine intermediate. Alternatively, isolation of this cyclohexane intermediate followed by addition of

benzhydrylamine promotes the transannular alkylation process through activation *via* an enamine intermediate and gives rise to the other C-2 epimer of the target bicyclic adduct.

Experimental Section

General methods: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H-NMR and ^{13}C-NMR) were acquired at 25ºC on a 300MHzor 500MHz spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C or 500 MHz for ^{1}H and 125.7 MHz for ^{13}C respectively). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments for assigning different types of carbon environment. Selective n.O.e. NOESY, COSY and HSQC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals. Infrared spectra were measured in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case. High-resolution mass spectra were recorded using chemical ionization (CI) or using electrospray ionization (ESI). Analytical grade solvents and commercially available reagents were used without further purification. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated aluminium-backed plates. These were visualized by ultraviolet irradiation or $KMnO_4$-H_2SO_4 ethanolic solution dip. For flash chromatography Merck 60, 230-400 mesh silica gel was used. High performance liquid chromatography on chiral stationary phase was performed in a chromatograph coupled to a photodiode array detector, using Daicel Chiralpak AD-H and AS-H columns. Melting points were measured in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of bicyclo[3.1.0]hexanes 4a-i. To a solution of the corresponding cyclohexane **3a-i** (1.00 mmol) in $(CH_2Cl)_2$ (2 mL), benzhydrylamine (1.00 mmol) was added. The reaction was stirred at 75 ºC until it was completed. A solution of HCl 1 M (5.00 mmol) was added at 75 ºC, and the reaction was stirred for 20 minutes. Then, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL).

The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was isolated by flash column chromatography with the indicated eluent, obtaining the desired bicyclo[3.1.0]hexanes **4a-i**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases the racemic cyclohexane **(±)-3**.

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (4a). Following the general procedure, **4a** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cyclohexane **3a** (46 mg, 0.150 mmol) and benzhydrylamine (28 mg, 0.150 mmol) using $(CH_2Cl)_2$ (0.3 mL) as solvent. Yield: 80% (27 mg, 0.120 mmol). dr: 86:14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.35-7.23 (m, 5H), 3.38 (d, *J* = 4.2 Hz, 1H), 3.13 (d, *J* = 4.2 Hz, 1H), 3.10-2.97 (m, 1H), 2.74-2.60 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.3, 197.9, 132.6, 128.8, 128.8, 127.8, 49.3, 41.1, 37.8, 36.5, 34.6, 13.2, 8.5. IR (ATR): 1731, 1703 cm^{-1}. HRMS: Calculated for $[C_{15}H_{17}O_2]^+$: 229.1229 $[M+H]^+$; found: 229.1231. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.73 min, τ_{minor} = 21.14 min (99% ee). $[\alpha]_D^{20}$: +76.7 (*c* = 0.56, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(*p*-tolyl)bicyclo[3.1.0]hexane-1-carbaldehyde (4b). Following the general procedure, **4b** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cyclohexane **3b** (27 mg, 0.083 mmol) and benzhydrylamine (16 mg, 0.083 mmol) using $(CH_2Cl)_2$ (0.16 mL) as solvent. Yield: 77% (15 mg, 0.064 mmol). dr: 87:13. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.15-7.08 (m, 4H), 3.34 (d, *J* = 4.2 Hz, 1H), 3.10 (d, *J* = 4.2 Hz, 1H), 3.08-2.96 (m, 1H), 2.71-2.59 (m, 1H), 2.31 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.4, 198.1, 137.6, 129.5, 129.4, 128.7, 49.3, 41.1, 37.6, 36.7, 34.6, 21.0, 13.2, 8.5. IR (ATR): 1731, 1703 cm^{-1}. HRMS: Calculated for $[C_{16}H_{19}O_2]^+$: 243.1385 $[M+H]^+$; found: 243.1381. $[\alpha]_D^{20}$: +75.7 (*c* = 0.44, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (4c). Following the general procedure, **4c** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 17 hours, starting from cyclohexane **3c** (18 mg, 0.047 mmol) and benzhydrylamine (9 mg, 0.047 mmol) using $(CH_2Cl)_2$ (0.1 mL) as solvent. Yield: 71% (10 mg, 0.033 mmol). dr: 87:13. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 6.99-6.94 (m, 1H), 6.85-6.80 (m, 2H), 3.81 (s, 3H), 3.35 (d, *J* = 4.1 Hz, 1H), 3.10-2.97 (m, 2H), 2.71-2.56 (m, 1H), 2.29 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.1, 197.7, 168.8, 151.3, 139.3, 131.4, 123.1, 121.0, 113.0, 56.0, 49.2, 41.1, 37.4, 36.8, 34.5, 20.6, 13.2, 8.5. IR (ATR): 1764, 1731, 1703 cm^{-1}. HRMS: Calculated for $[C_{18}H_{21}O_5]^+$: 317.1389 $[M+H]^+$; found: 317.1397. $[\alpha]_D^{20}$: +48.1 (*c* = 1.00, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Chlorophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (4d). Following the general procedure, **4d** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cyclohexane **3d** (36 mg, 0.108 mmol) and benzhydrylamine (20 mg, 0.108 mmol) using $(CH_2Cl)_2$ (0.22 mL) as solvent. Yield: 71% (20 mg, 0.077 mmol). dr: 86:14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.31 (d, *J* = 4.2 Hz, 1H), 3.12-2.99 (m, 2H), 2.71-2.59 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.0, 197.3, 133.8, 131.1, 130.2, 129.0, 49.4, 41.1, 37.2, 36.5, 34.6, 13.4, 8.5. IR (ATR): 1731, 1700 cm^{-1}. HRMS: Calculated for $[C_{15}H_{14}O_2Cl]^-$: 261.0682 $[M-H]^-$; found: 261.0679. $[\alpha]_D^{20}$: +75.4 (*c* = 0.66, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (4e). Following the general procedure, **4e** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow solid after 17 hours, starting from cyclohexane **3e** (29 mg, 0.076 mmol) and benzhydrylamine (14 mg, 0.076 mmol) using $(CH_2Cl)_2$ (0.16 mL) as solvent. Yield: 72% (17 mg, 0.055 mmol). dr: 85:15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.28 (d, *J* = 4.1 Hz, 1H), 3.13-2.99 (m, 2H), 2.73-2.59 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.9, 197.2, 131.9, 131.6, 130.5, 121.8, 49.4,

41.1, 37.2, 36.4, 34.6, 13.4, 8.5. IR (ATR): 1732, 1704 cm^{-1}. HRMS: Calculated for $[C_{15}H_{14}O_2Br]^-$: 305.0177 $[M-H]^-$; found: 305.0171. $[\alpha]_D^{20}$: +68.0 (*c* = 0.49, CH_2Cl_2). M.p.: 102-104 ºC (hexanes/EtOAc).

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(4-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (4f). Following the general procedure, **4f** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 36 hours, starting from cyclohexane **3f** (35 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using $(CH_2Cl)_2$ (0.20 mL) as solvent. Yield: 51% (14 mg, 0.051 mmol). dr: 86:14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 3.36 (d, *J* = 4.4 Hz, 1H), 3.20-3.07 (m, 2H), 2.76-2.64 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.3, 196.2, 147.3, 140.2, 129.8, 123.9, 50.1, 41.1, 37.3, 36.5, 34.6, 13.6, 8.5. IR (ATR): 1733, 1703, 1519, 1345 cm^{-1}. HRMS: Calculated for $[C_{15}H_{14}NO_4]^-$: 272.0923 $[M-H]^-$; found: 272.0923. $[\alpha]_D^{20}$: +55.4 (*c* = 0.40, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Cyanophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (4g). Following the general procedure, **4g** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 36 hours, starting from cyclohexane **3g** (33 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using $(CH_2Cl)_2$ (0.20 mL) as solvent. Yield: 58% (15 mg, 0.058 mmol). dr: 86:14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 3.33 (d, *J* = 4.4 Hz, 1H), 3.17-3.04 (m, 2H), 2.75-2.61 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.4, 196.4, 138.2, 132.4, 129.6, 118.2, 111.7, 50.0, 41.1, 37.5, 36.3, 34.6, 13.5, 8.5. IR (ATR): 2227, 1732, 1704 cm^{-1}. HRMS: Calculated for $[C_{16}H_{16}NO_2]^+$: 254.1181 $[M+H]^+$; found: 254.1197. $[\alpha]_D^{20}$: +92.8 (*c* = 0.64, CH_2Cl_2).

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hexane-1-carbaldehyde (4h). Following the general procedure, **4h** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cyclohexane **3h** (38 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using $(CH_2Cl)_2$ (0.20 mL) as solvent. Yield: 75% (22 mg, 0.075 mmol). dr: 86:14. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 3.36 (d, *J* = 4.2 Hz, 1H), 3.16-3.04 (m, 2H), 2.75-2.61 (m, 1H), 1.10 (d, *J* = 7.0

Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.7, 196.8, 136.8, 130.0 (q, $^2J_{CF}$ = 32.8 Hz), 129.3, 125.7 (q, $^3J_{CF}$ = 3.7 Hz), 123.8 (q, $^1J_{CF}$ = 272.3 Hz), 49.6, 41.1, 37.3, 36.4, 34.6, 13.4, 8.5. IR (ATR): 1733, 1705 cm^{-1}. HRMS: Calculated for $[C_{16}H_{14}O_2F_3]^-$: 295.0946 $[M-H]^-$; found: 295.0935. $[\alpha]_D^{20}$: +54.1 (c = 0.58, CH_2Cl_2).

(1*R*,2*S*,3*S*,5*S*,6*R*)-3-Methyl-6-(4-nitrophenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (4i). Following the general procedure, **4i** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 36 hours, starting from cyclohexane **3i** (55 mg, 0.133 mmol) and benzhydrylamine (25 mg, 0.133 mmol) using $(CH_2Cl)_2$ (0.26 mL) as solvent. Yield: 57% (25 mg, 0.076 mmol). dr: 75:25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.18 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.36-7.25 (m, 3H), 7.18-6.90 (m, 2H), 4.22 (d, J = 8.4 Hz, 1H), 3.44 (d, J = 4.7 Hz, 1H), 3.37 (d, J = 4.7 Hz, 1H), 3.04-2.91 (m, 1H), 0.69 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.8, 195.6, 147.3, 140.0, 137.9, 130.0, 130.0, 129.3, 127.9, 123.7, 49.8, 46.9, 42.3, 38.4, 37.8, 9.8. IR (ATR): 1733, 1708, 1519, 1345 cm^{-1}. HRMS: Calculated for $[C_{20}H_{16}NO_4]^-$: 334.1079 $[M-H]^-$; found: 334.1077. $[\alpha]_D^{20}$: +121.5 (c = 0.82, CH_2Cl_2).

General Procedure for the Synthesis of bicyclo[3.1.0]hexanes 5a-q. The corresponding α,β-unsaturated aldehyde **2a-l** (1.50 mmol) was added to a solution of (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol), DABCO (3.00 mmol) and the corresponding 4-alkenyl-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a-c** (1.00 mmol) in $(CH_2Cl)_2$ (2 mL). The reaction was stirred at 75 ºC until it was completed. A saturated solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired bicyclo[3.1.0]hexanes **5a-q**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol) as catalyst.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (5a). Following the general procedure, **5a** was isolated by flash column chromatography (hexanes/EtOAc gradient from

9:1 to 8:2) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **2a** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 53% (18 mg, 0.079 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.40-7.27 (m, 5H), 3.29 (d, *J* = 4.4 Hz, 1H), 3.11 (d, *J* = 4.4 Hz, 1H), 2.59 (dq, *J* = 9.7, 6.5 Hz, 1H), 1.89 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.7, 197.4, 132.2, 129.0, 128.9, 128.0, 49.1, 45.1, 39.6, 36.5, 35.2, 16.2, 12.2. IR (ATR): 1731, 1697 cm^{-1}. HRMS: Calculated for $[C_{15}H_{15}O_2]^-$: 227.1072 $[M-H]^-$; found: 227.1080. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.43 min, τ_{minor} = 25.74 min (94% ee). $[\alpha]_D^{20}$: +34.4 (*c* = 1.00, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(*p*-tolyl)bicyclo[3.1.0]hexane-1-carbaldehyde (5b). Following the general procedure, **5b** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-methylcinnamaldehyde **2b** (33 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 55% (20 mg, 0.082 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.24-7.13 (m, 4H), 3.25 (d, *J* = 4.3 Hz, 1H), 3.08 (d, *J* = 4.3 Hz, 1H), 2.57 (dq, *J* = 9.7, 6.5 Hz, 1H), 2.34 (s, 3H), 1.87 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.9, 197.7, 137.8, 129.7, 129.1, 128.8, 49.1, 45.1, 39.7, 36.5, 35.0, 21.1, 16.2, 12.2. IR (ATR): 1732, 1698 cm^{-1}. HRMS: Calculated for $[C_{16}H_{17}O_2]^-$: 241.1229 $[M-H]^-$; found: 241.1226. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.13 min, τ_{minor} = 20.12 min (93% ee). $[\alpha]_D^{20}$: +27.7 (*c* = 0.50, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(2-Methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5c). Following the general procedure, **5c** was isolated by flash column chromatography (hexanes/EtOAc

gradient from 8:2 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-2-methoxycinnamaldehyde **2c** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 39% (15 mg, 0.058 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.34-7.27 (m, 2H), 6.99-6.91 (m, 1H), 6.88-6.83 (m, 1H), 3.82 (s, 3H), 3.13 (d, *J* = 4.5 Hz, 1H), 2.99 (d, *J* = 4.5 Hz, 1H), 2.60 (dq, *J* = 9.7, 6.5 Hz, 1H), 1.91 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.4, 197.7, 158.2, 129.5, 129.4, 121.1, 120.7, 110.2, 55.3, 48.1, 45.1, 39.7, 36.6, 31.2, 15.5, 12.2. IR (ATR): 1719, 1694 cm^{-1}. HRMS: Calculated for $[C_{16}H_{17}O_3]^-$: 257.1178 $[M-H]^-$; found: 257.1190. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.10 min, τ_{minor} = 40.71 min (90% ee). $[\alpha]_D^{20}$: -24.7 (*c* = 0.49, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5d). Following the general procedure, **5d** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **2d** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 43% (17 mg, 0.065 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.23 (d, *J* = 4.4 Hz, 1H), 3.05 (d, *J* = 4.4 Hz, 1H), 2.56 (dq, *J* = 9.7, 6.5 Hz, 1H), 1.86 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.9, 197.8, 159.2, 130.0, 124.0, 114.4, 55.3, 49.2, 45.2, 40.0, 36.5, 34.7, 16.2, 12.2. IR (ATR): 1732, 1698 cm^{-1}. HRMS: Calculated for $[C_{16}H_{17}O_3]^-$: 257.1178 $[M-H]^-$; found: 257.1188. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 22.05 min, τ_{minor} = 37.60 min (94% ee). $[\alpha]_D^{20}$: +30.8 (*c* = 0.50, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5e). Following the general procedure, **5e** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow solid after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-acetoxy-3-methoxycinnamaldehyde **2e** (52 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 51% (24 mg, 0.076 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.03-6.98 (m, 1H), 6.90-6.83 (m, 2H), 3.83 (s, 3H), 3.25 (d, *J* = 4.4 Hz, 1H), 3.05 (d, *J* = 4.4 Hz, 1H), 2.58 (dq, *J* = 9.7, 6.5 Hz, 1H), 2.30 (s, 3H), 1.87 (dq, *J* = 9.7, 6.9 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.6, 197.2, 168.8, 151.5, 139.5, 131.1, 123.3, 121.2, 113.0, 56.0, 49.1, 45.1, 39.8, 36.5, 35.0, 20.6, 16.2, 12.2. IR (ATR): 1763, 1731, 1697 cm^{-1}. HRMS: Calculated for $[C_{18}H_{19}O_5]^-$: 315.1233 $[M-H]^-$; found: 315.1259. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 27.99 min, τ_{minor} = 47.73 min (94% ee). $[\alpha]_D^{20}$: +18.3 (*c* = 0.89, CH_2Cl_2). M.p.: 99-101 ºC (hexanes/EtOAc).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(3,5-Dimethoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5f). Following the general procedure, **5f** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-3,5-dimethoxycinnamaldehyde **2f** (43 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 42% (18 mg, 0.063 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 6.43 (d, *J* = 2.1 Hz, 2H), 6.38 (t, *J* = 2.1 Hz, 1H), 3.78 (s, 6H), 3.22 (d, *J* = 4.4 Hz, 1H), 3.06 (d, *J* = 4.4 Hz, 1H), 2.57 (dq, *J* = 9.6, 6.5 Hz, 1H), 1.85 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.7, 197.4, 161.3, 134.4, 107.1, 99.6, 55.4, 49.0, 45.1, 39.6, 36.4, 35.2, 16.2, 12.2. IR (ATR): 1731, 1697 cm^{-1}. HRMS: Calculated for $[C_{17}H_{19}O_4]^-$: 287.1283 $[M-H]^-$; found: 287.1275. The enantiomeric

excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 25.08 min, τ_{minor} = 30.14 min (92% ee). $[\alpha]_D^{20}$: +6.7 (*c* = 0.74, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Chlorophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5g). Following the general procedure, **5g** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-chlorocinnamaldehyde **2g** (39 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 52% (21 mg, 0.078 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.37-7.30 (m, 2H), 7.27-7.21 (m, 2H), 3.22 (d, *J* = 4.4 Hz, 1H), 3.06 (d, *J* = 4.4 Hz, 1H), 2.58 (dq, *J* = 9.6, 6.5 Hz, 1H), 1.87 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.4, 196.9, 134.0, 130.8, 130.3, 129.3, 49.1, 45.1, 39.6, 36.5, 34.4, 16.3, 12.2. IR (ATR): 1732, 1698 cm^{-1}. HRMS: Calculated for $[C_{15}H_{14}O_2Cl]^-$: 261.0682 $[M-H]^-$; found: 261.0686. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 15.47 min, τ_{minor} = 25.23 min (92% ee). $[\alpha]_D^{20}$: +29.7 (*c* = 0.85, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5h). Following the general procedure, **5h** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **2h** (49 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 46% (21 mg, 0.069 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 3.20 (d, *J* = 4.5 Hz, 1H), 3.06 (d, *J* = 4.5 Hz, 1H), 2.58 (dq, *J* = 9.6, 6.5 Hz, 1H), 1.87 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.3, 196.8, 132.2, 131.4, 130.6, 122.0, 49.0, 45.1, 39.5, 36.5, 34.5, 16.2, 12.2. IR (ATR): 1732, 1698 cm^{-1}. HRMS: Calculated for $[C_{15}H_{14}O_2Br]^-$: 305.0177 $[M-H]^-$; found: 305.0172. The enantiomeric excess was determined by HPLC

using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.41 min, τ_{minor} = 26.38 min (90% ee). $[\alpha]_D^{20}$: +28.3 (*c* = 0.65, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(2-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5i). Following the general procedure, **5i** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-2-nitrocinnamaldehyde **2i** (41 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 47% (19 mg, 0.070 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.00 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.70-7.61 (m, 1H), 7.60-7.48 (m, 2H), 3.57 (d, *J* = 4.6 Hz, 1H), 3.04 (d, *J* = 4.6 Hz, 1H), 2.61 (dq, *J* = 9.9, 6.6 Hz, 1H), 1.97 (dq, *J* = 9.9, 6.9 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.2, 195.6, 150.1, 133.5, 131.5, 129.3, 127.8, 125.1, 48.9, 45.2, 39.7, 37.4, 32.8, 15.7, 12.1. IR (ATR): 1733, 1703, 1525, 1348 cm^{-1}. HRMS: Calculated for $[C_{15}H_{16}NO_4]^+$: 274.1079 $[M+H]^+$; found: 274.1077. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 25.73 min, τ_{minor} = 68.40 min (92% ee). $[\alpha]_D^{20}$: -66.8 (*c* = 0.54, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(4-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5j). Following the general procedure, **5j** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-nitrocinnamaldehyde **2j** (41 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 32% (13 mg, 0.048 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.24 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 3.28 (d, *J* = 4.6 Hz, 1H), 3.15 (d, *J* = 4.6 Hz, 1H), 2.62 (dq, *J* = 9.6, 6.5 Hz, 1H), 1.91 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.6, 195.8, 147.6, 139.9, 129.9, 124.2, 49.4, 45.1, 39.5, 36.7, 34.4, 16.3, 12.2. IR (ATR): 1733, 1699, 1519, 1344 cm^{-1}. HRMS:

Calculated for $[C_{15}H_{14}NO_4]^-$: 272.0923 $[M-H]^-$; found: 272.0927. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.55 min, τ_{minor} = 28.64 min (86% ee). $[\alpha]_D^{20}$: +32.9 (*c* = 0.57, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Cyanophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5k). Following the general procedure, **5k** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-cyanocinnamaldehyde **2k** (35 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 41% (16 mg, 0.062 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 3.25 (d, *J* = 4.5 Hz, 1H), 3.11 (d, *J* = 4.5 Hz, 1H), 2.61 (dq, *J* = 9.5, 6.5 Hz, 1H), 1.89 (dq, *J* = 9.5, 6.9 Hz, 1H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.8, 196.0, 137.9, 132.8, 129.7, 118.1, 112.1, 49.3, 45.1, 39.3, 36.7, 34.6, 16.3, 12.2. IR (ATR): 2228, 1732, 1701 cm^{-1}. HRMS: Calculated for $[C_{16}H_{14}NO_2]^-$: 252.1025 $[M-H]^-$; found: 252.1030. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 28.72 min, τ_{minor} = 64.64 min (89% ee). $[\alpha]_D^{20}$: +43.0 (*c* = 0.53, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hexane-1-carbaldehyde (5l). Following the general procedure, **5l** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1a** (26 mg, 0.150 mmol) and (*E*)-4-(trifluoromethyl)cinnamaldehyde **2l** (45 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 54% (24 mg, 0.081 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 3.28 (d, *J* = 4.5 Hz, 1H), 3.13 (d, *J* = 4.5 Hz, 1H), 2.61 (dq, *J* = 9.5, 6.5 Hz, 1H), 1.90 (dq, *J* = 9.5, 6.9 Hz, 1H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.1, 196.4, 136.5, 130.4 (q, $^2J_{CF}$ = 32.8 Hz), 129.4, 126.0 (q, $^3J_{CF}$ = 3.7 Hz),

123.8 (q, $^1J_{CF}$ = 272.3 Hz), 49.1, 45.1, 39.3, 36.6, 34.5, 16.3, 12.2. IR (ATR): 1734, 1699 cm^{-1}. HRMS: Calculated for $[C_{16}H_{14}O_2F_3]^-$: 295.0946 $[M-H]^-$; found: 295.0942. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.32 min, τ_{minor} = 17.87 min (90% ee). $[\alpha]_D^{20}$: +16.2 (*c* = 1.00, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2-Ethyl-3-methyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (5m). Following the general procedure, **5m** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1b** (28 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **2a** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 43% (16 mg, 0.065 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.40-7.28 (m, 5H), 3.30 (d, *J* = 4.5 Hz, 1H), 3.06 (d, *J* = 4.5 Hz, 1H), 2.65-2.53 (m, 1H), 2.04-1.90 (m, 1H), 1.81-1.69 (m, 2H), 1.19-1.08 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.0, 197.0, 132.3, 129.0, 128.9, 128.0, 48.5, 44.6, 42.4, 39.7, 35.1, 26.0, 14.1, 12.5. IR (ATR): 1732, 1698 cm^{-1}. HRMS: Calculated for $[C_{16}H_{17}O_2]^-$: 241.1229 $[M-H]^-$; found: 241.1225. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.74 min, τ_{minor} = 27.37 min (91% ee). $[\alpha]_D^{20}$: -10.0 (*c* = 0.92, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-2-Ethyl-6-(4-methoxyphenyl)-3-methyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5n). Following the general procedure, **5n** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1b** (28 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **2d** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 41% (17 mg, 0.062 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.24 (d, *J* = 4.5 Hz, 1H), 3.00 (d, *J* = 4.5 Hz, 1H), 2.62-2.50 (m, 1H), 2.01-1.88 (m, 1H), 1.80-1.67 (m, 2H), 1.16-1.06 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 210.2, 197.3, 159.2, 130.0,

124.0, 114.4, 55.3, 48.6, 44.6, 42.4, 40.0, 34.6, 26.0, 14.2, 12.5. IR (ATR): 1731, 1699 cm^{-1}. HRMS: Calculated for $[C_{17}H_{19}O_3]^-$: 271.1334 $[M-H]^-$; found: 271.1328. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 23.13 min, τ_{minor} = 21.83 min (90% ee). $[\alpha]_D^{20}$: +10.7 (*c* = 0.96, CH_2Cl_2).

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2-ethyl-3-methyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (5o). Following the general procedure, **5o** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1b** (28 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **2h** (49 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 30% (14 mg, 0.045 mmol) dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 3.20 (d, *J* = 4.6 Hz, 1H), 3.01 (d, *J* = 4.6 Hz, 1H), 2.63-2.41 (m, 1H), 2.02-1.89 (m, 1H), 1.80-1.67 (m, 2H), 1.17-1.07 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.6, 196.5, 132.2, 131.4, 130.5, 122.0, 48.4, 44.6, 42.5, 39.6, 34.4, 26.0, 14.2, 12.5. IR (ATR): 1731, 1701 cm^{-1}. HRMS: Calculated for $[C_{16}H_{16}O_2Br]^-$: 319.0334 $[M-H]^-$; found: 319.0335. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.25 min, τ_{minor} = 26.86 min (86% ee). $[\alpha]_D^{20}$: +15.8 (*c* = 1.00, CH_2Cl_2).

(1*R*,2*R*,3*S*,5*S*,6*R*)-3-Methyl-4-oxo-2,6-diphenylbicyclo[3.1.0]hexane-1-carbaldehyde (5p). Following the general procedure, **5p** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1c** (36 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **2a** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 49% (21 mg, 0.073 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.55-7.50 (m, 2H), 7.46-7.39 (m, 2H), 7.37-7.23 (m, 6H), 3.81 (d, *J* = 10.1 Hz, 1H), 3.68 (d, *J* = 4.5 Hz, 1H), 3.16 (d, *J* = 4.5 Hz, 1H), 2.58 (dq, *J* = 10.1, 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.4, 196.4, 139.7, 131.9, 129.0, 128.9, 128.8, 128.1,

127.5, 127.5, 48.7, 46.4, 44.2, 38.7, 36.0, 13.0. IR (ATR): 1732, 1699 cm^{-1}. HRMS: Calculated for $[C_{20}H_{17}O_2]^-$: 289.1229 $[M-H]^-$; found: 289.1236. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.61 min, τ_{minor} = 29.31 min (93% ee). $[\alpha]_D^{20}$: +25.7 (*c* = 0.83, CH_2Cl_2).

(1*R*,2*R*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-3-methyl-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (5q). Following the general procedure, **5q** was isolated by flash column chromatography (hexanes/EtOAc gradient from 7:3 to 1:1) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1c** (36 mg, 0.150 mmol) and (*E*)-4-acetoxy-3-methoxycinnamaldehyde **2e** (52 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 51% (29 mg, 0.077 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.53-7.46 (m, 2H), 7.45-7.29 (m, 3H), 7.01-6.95 (m, 1H), 6.84-6.78 (m, 2H), 3.86-3.76 (m, 4H), 3.63 (d, *J* = 4.5 Hz, 1H), 3.10 (d, *J* = 4.5 Hz, 1H), 2.57 (dq, *J* = 10.0, 6.9 Hz, 1H), 2.30 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.3, 196.2, 168.8, 151.5, 139.6, 139.6, 130.7, 128.9, 127.5, 127.5, 123.3, 121.0, 112.8, 55.9, 48.8, 46.3, 44.2, 38.9, 35.8, 20.6, 13.0. IR (ATR): 1764, 1732, 1699 cm^{-1}. HRMS: Calculated for $[C_{23}H_{21}O_5]^-$: 377.1389 $[M-H]^-$; found: 377.1392. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 26.85 min, τ_{minor} = 38.87 min (90% ee). $[\alpha]_D^{20}$: +19.1 (*c* = 0.81, CH_2Cl_2).

General Procedure for the Synthesis of cyclopropane-fused octahydroindenones 5r-t. The corresponding α,β-unsaturated aldehyde **2a**, **2d** or **2h** (1.00 mmol) was added to a solution of (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol), DABCO (5.00 mmol) and 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1d** (1.50 mmol) in $(CH_2Cl)_2$ (2 mL). The reaction was stirred at 75 ºC until it was completed. A saturated solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired cyclopropane-fused

octahydroindenones **5r-t**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol) as catalyst.

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-6-oxo-1-phenyldecahydrocyclopropa[*a*]indene-1a-carbaldehyde (5r). Following the general procedure, **5r** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1d** (45 mg, 0.225 mmol) and (*E*)-cinnamaldehyde **2a** (19 μL, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 46% (18 mg, 0.069 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.42-7.23 (m, 5H), 3.60 (d, *J* = 4.3 Hz, 1H), 2.91 (d, *J* = 4.3 Hz, 1H), 2.43-2.30 (m, 1H), 2.29-2.21 (m, 1H), 2.09-2.01 (m, 1H), 1.93-1.80 (m, 3H), 1.45-1.33 (m, 2H), 1.27-1.18 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.5, 197.8, 132.5, 129.0, 128.9, 128.0, 47.5, 47.0, 41.5, 37.6, 36.8, 29.2, 25.9, 25.8, 24.7. IR (ATR): 1731, 1698 cm^{-1}. HRMS: Calculated for $[C_{17}H_{19}O_2]^+$: 255.1385 $[M+H]^+$; found: 255.1387. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 19.87 min, τ_{minor} = 41.63 min (98% ee). $[\alpha]_D^{20}$: +49.7 (*c* = 0.69, CH_2Cl_2).

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-1-(4-Methoxyphenyl)-6-oxodecahydrocyclopropa[*a*]indene-1a-carbaldehyde (5s). Following the general procedure, **5s** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1d** (45 mg, 0.225 mmol) and (*E*)-4-methoxycinnamaldehyde **2d** (25 mg, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 34% (14 mg, 0.051 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.55 (d, *J* = 4.2 Hz, 1H), 2.85 (d, *J* = 4.2 Hz, 1H), 2.41-2.29 (m, 1H), 2.29-2.19 (m, 1H), 2.08-2.00 (m, 1H), 1.93-1.77 (m, 3H), 1.45-1.32 (m, 2H), 1.27-1.17 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.7, 198.1, 159.2, 130.0, 124.4, 114.4, 55.3, 47.6, 47.1, 41.5, 38.0, 36.4, 29.2, 25.9, 25.8, 24.8. IR (ATR): 1728,

1695 cm^{-1}. HRMS: Calculated for $[C_{18}H_{21}O_3]^+$: 285.1491 $[M+H]^+$; found: 285.1494. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 18.36 min, τ_{minor} = 42.20 min (96% ee). $[\alpha]_D^{20}$: +74.0 (*c* = 0.75, CH_2Cl_2).

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-1-(4-Bromophenyl)-6-oxodecahydrocyclopropa[*a*]indene-1a-carbaldehyde (5t). Following the general procedure, **5t** was isolated by flash column chromatography (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole-2,2-dioxide **1d** (45 mg, 0.225 mmol) and (*E*)-4-bromocinnamaldehyde **2h** (32 mg, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using $(CH_2Cl)_2$ (0.30 mL) as solvent. Yield: 38% (19 mg, 0.057 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.52 (d, *J* = 4.3 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H), 2.42-2.29 (m, 1H), 2.29-2.21 (m, 1H), 2.11-2.01 (m, 1H), 1.95-1.79 (m, 3H), 1.44-1.31 (m, 2H), 1.27-1.17 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.0, 197.2, 132.2, 131.7, 130.6, 122.0, 47.5, 46.9, 41.5, 37.4, 36.0, 29.2, 25.8, 25.8, 24.7. IR (ATR): 1732, 1697 cm^{-1}. HRMS: Calculated for $[C_{17}H_{16}O_2Br]^-$: 331.0334 $[M-H]^-$; found: 331.0321. The enantiomeric excess was determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 17.70 min, τ_{minor} = 47.53 min (96% ee). $[\alpha]_D^{20}$: +54.8 (*c* = 0.66, CH_2Cl_2).

General Procedure for the Synthesis of bicyclo[3.1.0]hexanes 5u-v. The corresponding α,β-unsaturated aldehyde **2c-d** (1.50 mmol) was added to a solution of (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol), DABCO (0.20 mmol) and (*E*)-4-styryl-5*H*-1,2,3-oxathiazole-2,2-dioxide **1e** (1.00 mmol) in dry $CHCl_3$ (2 mL) under inert atmosphere. The reaction was stirred at room temperature until it was completed. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired bicyclo[3.1.0]hexanes **5u-v**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-α,α-diphenylprolinol trimethylsilyl ether (0.20 mmol) as catalyst.

(1*S*,2*R*,5*S*,6*R*)-6-(2-Methoxyphenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (5u). Following the general procedure, **5u** was isolated by flash column chromatography (hexanes/EtOAc

gradient from 8:2 to 6:4) as a yellow oil after 24 hours, starting from (*E*)-4-styryl-5*H*-1,2,3-oxathiazole-2,2-dioxide **1e** (33 mg, 0.150 mmol) and (*E*)-2-methoxycinnamaldehyde **2c** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.30 mL) as solvent. Yield: 46% (21 mg, 0.069 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.59-7.48 (m, 2H), 7.42-7.33 (m, 2H), 7.32-7.26 (m, 3H), 7.01-6.90 (m, 1H), 6.83-6.74 (m, 1H), 4.44 (app t, *J* = 10.0 Hz, 1H), 3.52 (s, 3H), 3.43 (d, *J* = 4.6 Hz, 1H), 3.04 (d, *J* = 4.6 Hz, 1H), 2.78 (dd, *J* = 18.5, 9.8 Hz, 1H), 2.65 (dd, *J* = 18.5, 10.3 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.3, 196.7, 158.2, 139.6, 129.7, 129.5, 128.2, 128.0, 127.0, 120.6, 120.4, 110.3, 54.7, 49.2, 40.2, 40.1, 37.9, 31.0. IR (ATR): 1732, 1702 cm^{-1}. HRMS: Calculated for $[C_{20}H_{17}O_3]^-$: 305.1178 $[M-H]^-$; found: 305.1175. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 10.73 min, τ_{minor} = 12.04 min (98% ee). $[\alpha]_D^{20}$: +40.7 (*c* = 0.66, CH_2Cl_2).

(1*S*,2*R*,5*S*,6*R*)-6-(4-Methoxyphenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (5v). Following the general procedure, **5v** was isolated by flash column chromatography (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 24 hours, starting from (*E*)-4-styryl-5*H*-1,2,3-oxathiazole-2,2-dioxide **1e** (33 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **2d** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), (*S*)-α,α-diphenylprolinol trimethylsilyl ether (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.30 mL) as solvent. Yield: 41% (19 mg, 0.062 mmol). dr: >20:1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.41-7.28 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.42 (app t, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.39 (d, *J* = 4.6 Hz, 1H), 3.15 (d, *J* = 4.6 Hz, 1H), 2.86 (dd, *J* = 18.6, 9.9 Hz, 1H), 2.56 (dd, *J* = 18.6, 10.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.9, 196.8, 159.3, 140.2, 129.7, 128.8, 127.3, 127.1, 123.4, 114.5, 55.3, 50.2, 40.5, 40.5, 37.3, 34.7. IR (ATR): 1737, 1699 cm^{-1}. HRMS: Calculated for $[C_{20}H_{17}O_3]^-$: 305.1178 $[M-H]^-$; found: 305.1176. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 13.40 min, τ_{minor} = 11.95 min (98% ee). $[\alpha]_D^{20}$: +45.5 (*c* = 0.27, CH_2Cl_2).

Acknowledgments. The authors thank the Spanish MINECO (FEDER- CTQ2017-83633-P), the Basque Government (IT908-16) and UPV/EHU (EHUA15/24, EHUA16/10 and a fellowship to I. R.) for financial support. Membership in the COST Action CM1407 is also acknowledged.

Supporting Information Available. ^{1}H- and ^{13}C-NMR spectra of all compounds prepared and HPLC traces for racemic standards and enantioenriched samples. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

1 Whittaker, D.; Banthorpe, D. V. *Chem. Rev.*, **1972**, *72*, 305.

2 See for example: (a) Deiml, T.; Haseneder, R.; Zieglgansberger, W.; Rammes, G.; Eisensamer, B.; Rupprecht, R.; Hapfelmeier, G. *Neuropharmacology*, **2004**, *46*, 192. (b) Hold, K. M.; Sirisoma, N. S.; Ikeda, T.; Narahashi, T.; Casida, J. E. *Proc. Natl. Acad. Sci. USA*, **2000**, *97*, 3826. (c) Lee, S.; Tsao, R.; Peterson, C.; Coats, J. R. *J. Econ. Entomol.*, **1997**, *90*, 883. (d) Bonkovsky, H. L.; Cable, E. E.; Cable J. W.; Donohue, S. E.; White, E. C.; Greene, Y. J.; Lambrecht, R. W.; Srivastava, K. K.; Arnold, W. N. *Biochem. Pharmacol.*, **1992**, *43*, 2359. (e) Millet, Y.; Jouglard, J.; Steinmetz, M. D.; Tognetti, P.; Joanny, P.; Arditti, J. *Clin. Toxicol.* **1981**, *18*, 1485. (f) Rice, K. C.; Wilson, R. S. *J. Med. Chem.*, **1976**, *19*, 1054.

3 See for example: (a) Dressman, B. A.; Tromiczak, E. G.; Chappell, M. D.; Tripp, A. E.; Quimby, S. J.; Vetman, T.; Fivush, A. M.; Matt, J.; Jaramillo, C.; Li, R.; Khilevich, A.; Blanco, M. J.; Smith, S. C.; Carpintero, M.; de Diego, J. E.; Barberis, M.; García-Cerrada, S.; Soriano, J. F.; Schkeryantz, J. M.; Witkin, J. M.; Wafford, K. A.; Seidel, W.; Britton, T.; Overshiner, C. D.; Li, X.; Wang, X. S.; Heinz, B. A.; Catlow, J. T.; Swanson, S.; Bedwell, D.; Ornstein, P. L.; Mitch, C. H. *Bioorg. Med. Chem. Lett.*, **2016**, *26*, 5663. (b) Chappell, M. D.; Li R.; Smith, S. C.; Dressman, B. A.; Tromiczak, E. G.; Tripp, A. E.; Blanco, M. J.; Vetman, T.; Quimby, S. J.; Matt, J.; Britton, T. C.; Fivush, A. M.; Schkeryantz, J.

M.; Mayhugh, D.; Erickson, J. A.; Bures, M. G.; Jaramillo, C.; Carpintero, M.; Diego, J. E.; Barberis, M.; Garcia-Cerrada, S.; Soriano, J. F.; Antonysamy, S.; Atwell, S.; MacEwan, I.; Condon, B.; Sougias, C.; Wang, J.; Zhang, A.; Conners, K.; Groshong, C.; Wasserman, S. R.; Koss, J. W.; Witkin, J. M.; Li, X.; Overshiner, C.; Wafford, K. A.; Seidel, W.; Wang, X. S.; Heinz, B. A.; Swanson, S.; Catlow, J. T.; Bedwell, D. W.; Monn, J. A.; Mitch, C. H.; Ornstein, P. L. *J. Med. Chem.*, **2016**, *59*, 10874. (c) Kobayashi, T.; Suemasa, A.; Igawa, A.; Ide, S.; Fukuda, H.; Abe, H.; Arisawa, M.; Minami, M.; Shuto, S. *ACS Med. Chem. Lett.*, **2014**, *5*, 889. (d) Comin, M. J.; Agbaria, R.; Ben-Kasus, T.; Huleihel, M.; Liao, C.; Sun, G.; Nicklaus, M. C.; Deschamps, J. R.; Parrish, D. A.; Marquez, V. E. *J. Am. Chem. Soc.* **2007**, *129*, 6216. (e) Tchilibon, S.; Joshi, B. V.; Kim, S. K.; Duong, H. T.; Gao, Z. G.; Jacobson, K. A. *J. Med. Chem.*, **2005**, *48*, 1745. (f) Shuto, S.; Ono, S.; Hase, Y.; Kamiyama, N.; Takada, H.; Yamashita, K.; Matsuda, A. *J. Org. Chem.*, **1996**, *61*, 915.

4 Recent examples: (a) Zhang, Z.-D.; Song, J.; Gao, N.; Guan, Z.; He, Y.-H. *J. Mol. Cat. B: Enzymatic*, **2016**, *134*, 1. (b) Luo, C.; Wang, Z.; Huang, Y. *Nat. Commun.*, **2015**, *6*, 10041. (c) Krysiak, J.; Midura, W. H.; Wieczorek, W.; Sieron, L.; Mikolajczyk, M. *Tetrahedron: Asymmetry*, **2010**, *21*, 1486. (d) Piovesana, S.; Schietroma, D. M. S.; Tulli, L. G.; Monaco, M. R.; Bella, M. *Chem. Commun.*, **2010**, *46*, 5160. (e) Dong, L.-t.; Du, Q.-s.;- Lou, C.-l.; Zhang, J.-m.; Lu, R.-j.; Yan, M. *Synlett*, **2010**, 266. (f) Lv, J.; Zhang, J.; Lin, Z.; Wang, Y. *Chem. Eur. J.*, **2009**, *15*, 972. (g) Wascholowski, V.; Hanse, H. M.; Longbottom, D. A.; Ley, S. V. *Synthesis*, **2008**, 1269. (h) Aggarwal, V. K.; Grange, A. *Chem. Eur. J.*, **2006**, *12*, 568. (i) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.*, **1999**, *40*, 4215.

5 For some selected recent examples see: (a) Marichev, K. O.; Ramey, J. T.; Arman, H.; Doyle, M. P. *Org. Lett.*, **2017**, *19*, 1306. (b) Nagatani, K.; Hoshino, Y.; Tezuda, H.; Nakda, M. *Tetrahedron Lett.*, **2017**, *58*, 959. (c) Trost, B. M.; Ryan, M. C.; Rao, M. *Beilstein J. Org. Chem.*, **2016**, *12*, 1136. (d) Torres, O.; Roglans, A.; Pla-Quintanta, A. *Adv. Synth. Catal.*, **2016**, *358*, 3512. (e) Sawada, T.; Nakada, M. *Org. Lett.*, **2013**, *15*, 1004. (f) Trost, B. M.; Malhotra, S.; Ellerbrock, P. *Org. Lett.*, **2013**, *15*, 440. (g) Abu-elfotoh, A.-M.; Nguyen, D. P. T.; Chanthamath, S.; Phomkeona, K.; Shibatomi, K.; Iwasa, S.

Adv. Synth. Catal., **2012**, *354*, 3435. (h) Deng, C.; Wang, L.-L.; Zhu, J.; Tang, Y. *Angew. Chem. Int. Ed.*, **2012**, *51*, 11620.

6 Other methodologies have been used recently for the enantioselective preparation of the bicyclo[3.1.0]hexane scaffolds using a cycloisomerization reactions: (a) Wu, Z.; Retailleau, P.; Gandon, V.; Voituriez, A.; Marinetti, A. *Eur. J. Org. Chem.*, **2016**, 70. (b) Qian, D.; Hu, H.; Liu, F.; Tang, B.; Ye, W.; Wang, Y.; Zhang, J. *Angew. Chem. Int. Ed.*, **2014**, *53*, 13751. (c) Masutomi, K.; Noguchi, K.; Tanaka, K. *J. Am. Chem. Soc.*, **2014**, *136*, 7627. (d) Trost, B. M.; Ryan, M. C.; Rao, M.; Markovic, T. Z. *J. Am. Chem. Soc.*, **2014**, *136*, 17422.

7.- Recent examples: (a) Krief, A.; Jeanmart, S.; Gondal, H. Y.; Kremer, A. *Helv. Chim. Acta.*, **2012**, *95*, 2123. (b) Krief, A.; Gondal, H. Y.; Kremer, A. *Chem. Commun.*, **2008**, 4753. For a related example using an epoxide ring opening reaction, see: (c) Li, J.; Lowary, T. L. *Org. Lett.* **2008**, *10*, 881.

8 McDonald, R. N.; Reitz, R. R. *J. Org. Chem.* **1970**, *35*, 2666.

9 (a) Huang, P.-Q.; Sabbe, K.; Pottie, M., Vandevalle, M. *Tetrahedron Lett.* **1995**, *36*, 8299. (b) Zhao, Y.-R.; Guang, B.; Bouillon, R.; Verstuyf, A.; De Clercq, P.; Vandevalle, M. *Eur. J. Org. Chem.* **2005**, 4414.

10 Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.*, **2015**, *2*, 206.

11 Attempts to use catalytic ammount of the primary amine gave lower conversions.

12 Other primary amines were tested using the same reaction conditions: Benzylamine (yield 68%), 1-adamantylamine (yield 66%), cyclohexylamine (yield 65%), isopropylamine (yield 59%), propyl-1-amine (yield 55%) and anisidine (yield 33%).

13 When crotonaldehyde was employed, mixture of compounds were observed arising from Diels-Alder-type reactivity of between the dienamine tautomer of the correspoding iminium ion and crotonaldehyde itself. This behavior has been previously observed. See for example Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459

14 Other β-alkyl substituted enals were also evaluated without success.

15 For some reviews focused in iminium/enamine cascade reactions, see: (a) Volla, C.; Atodiresei, I.; Rueping, M. *Chem. Rev.*, **2014**, *114*, 2390. (b) Chen Y.-C.; Cui, H.-L. Organocatalytic Cascade Reactions in *Science of Synthesis, Asymmetric Organocatalysis*, ed. B. List and K. Maruoka, Thieme: Stuttgart, 2012, vol. 2, p. 787. (c) Bonne, D.; Constantieux, T.; Coquerel Y.; Rodriguez, J. *Org. Biomol. Chem.*, **2012**, *10*, 3969. (d) Pellissier, H. *Adv. Synth. Catal.*, **2012**, *354*, 237. (e) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.*, **2012**, *51*, 314. (f) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem. Int. Ed.*, **2010**, *49*, 846. (g) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.*, **2010**, *2*, 167.

16 For some selected reviews specifically focused on aminocatalysis, see: (a) Paz, B. M.; Jiang H.; Jørgensen, K. A. *Chem. Eur. J.*, **2015**, *21*, 1846. (b) Holland, M. C.; Gilmour, R. *Angew. Chem. Int. Ed.*, **2015**, *54*, 3862. (c) Melchiorre, P. *Angew. Chem. Int. Ed.*, **2012**, *51*, 9748. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6138. (e) List, B. *Chem. Commun.*, **2006**, 819.