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Enantioselective synthesis of 4-alkenoic acids via Pd-catalyzed allylic alkylation: stereocontrolled construction of γ and δ -lactones

Isabel Alvarado-Beltrán^{a,*}, Eddy Maerten^b, R. Alfredo Toscano^a, José G. López-Cortés^a, Antoine Baceiredo^b, Cecilio Álvarez-Toledano^{a,*}

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ABSTRACT

An enantioselective and diastereoselective synthesis of γ,δ -unsaturated carboxylic acids by palladium-catalyzed carbon alkylation of bis(trimethylsilyl)ketene acetals with (*E*)-1,3-diphenylpropenyl acetate was developed. These acids could be efficiently turned into new γ - or δ -halolactones containing multiple stereocenters using a halolactonization protocol. The stereochemistry of these acids was established by X-ray analysis after derivatization to the corresponding amide with (*R*)-(+)-1-phenylethylamine.

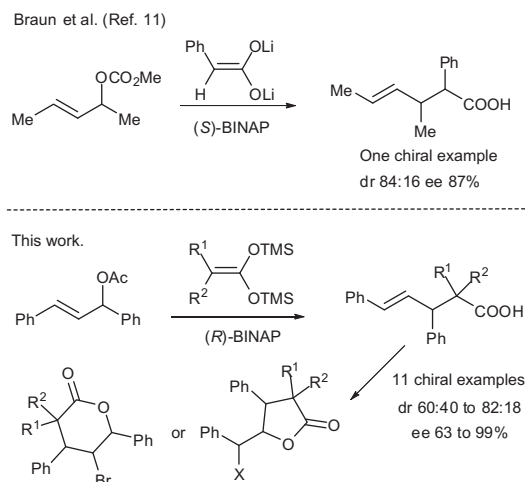
1. Introduction

The γ - and δ -lactone skeleton appears as an important moiety in several natural products that exhibit a wide range of biological activities.¹ Some of these lactones contain multiple contiguous stereocenters,² which means that their asymmetric synthesis can represent a significant challenge. Consequently, the development of new methods for the synthesis of lactones, particularly in a stereocontrolled fashion, has received considerable attention; however, their synthesis involves several steps and low overall yields.³ Asymmetric halolactonization is a common method for the formation of highly substituted stereocontrolled lactones. Nevertheless, the procedure is relatively complicated because it requires a long multi-step catalytic synthesis, the use of a catalyst and involves several steps in their synthesis.⁴ A straightforward precursor for chiral γ - and δ -lactones could be the corresponding chiral 4-alkenoic acids, but to date, their enantioselective synthesis has not been broadly studied.

On the other hand, palladium-catalyzed asymmetric allylic alkylation is a powerful synthetic tool in modern organic synthesis for the construction of quaternary carbon centers. Using this method, different types of bonds can be formed (C–C, C–heteroatom), under mild conditions, with a wide functional group tolerance, and with the possibility to control the regio- and the stereoselectivity.⁵ Asymmetric allylic alkylation using symmetric nucleophiles such as dialkyl malonates can be performed in good yields and with high enantioselectivities,⁶ however, asymmetric alkylations involving prochiral nucleophiles are less common.

Only a few examples, including β -ketoesters,⁷ β -diketones,⁸ azalactones,⁹ oxindoles,¹⁰ and more recently carboxylic acids as nucleophiles have been reported so far.¹¹

Recently, Braun¹¹ et al. reported the stereocontrolled synthesis of one 4-alkenoic acid using two-fold deprotonated carboxylic acid in the presence of (*S*)-BINAP as the ligand (Scheme 1). Although these systems can be useful for the synthesis of γ,δ -unsaturated acids, one limitation is the manipulation of the highly reactive doubly-lithiated species that require low temperatures and inert



Scheme 1. Synthesis of 4-alkenoic acids.

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atmosphere conditions. Alternatively, bis(TMS)ketene acetals have emerged as very convenient 1,3-dinucleophiles,¹² noteworthy for the synthesis of lactones¹³ among a variety of substrates.¹⁴ Indeed these bis(TMS)ketene acetals can be easily prepared and are very convenient to manipulate. Moreover their high thermal stability allows their storage under inert atmosphere for months. The use of ketene acetals in allylic substitution reactions has been poorly explored to date.¹⁵

Herein we report the use of bis(TMS)ketene acetals as nucleophiles in asymmetric allylic alkylations to prepare 4-alkenoic acids in good yields and with high enantioselectivities. The scope of the reaction was studied using symmetric and prochiral ketene acetals, affording several unsaturated acids with one or two consecutive stereogenic centers, respectively. Finally, one of these acids was converted into functionalized halolactones containing three contiguous stereocenters with an excellent level of stereocontrol (Scheme 1).

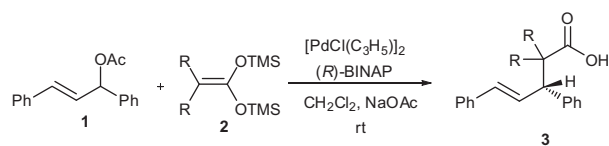
2. Results and discussion

Exploratory experiments were carried out using (*E*)-1,3-diphenylpropenyl acetate **1** with the bis(trimethylsilyl)ketene acetal **2a** to give carboxylic acid **3a** (Table 1). Initially, we decided to examine the influence of the solvent. The desired reaction took place at room temperature in Et₂O and CH₂Cl₂ (Table 1, entries 1–3) in moderate yield, while no reaction was observed in toluene, probably due to the low solubility of the catalyst in this solvent. Dichloromethane appeared to be the more promising solvent in terms of enantioselectivity (75% ee vs 0%). In order to improve the conversion, TBAF was added as an activating agent, but no reaction was observed after 72 h at room temperature (Table 1, entry 4). In contrast, in the presence of NaOAc as activating agent,¹⁶ a considerable increase in the conversion, 99% after 31 h, was observed (Table 1, entry 5). Lowering the reaction temperature to 0 °C resulted in a significant increase in enantioselectivity from 76% to 84% ee (Table 1, entry 6). It is noteworthy that no subsequent improvement in the ee was encountered when performing the reaction at –20 °C (Table 1, entry 7).

Previous reports have indicated that the isomerization of π -allyl complex intermediates can occur in substrates of type **1** through a η^3 - η^1 - η^3 mechanism.¹⁷ As a result, the stereochemical information can be lost during the ionization step. In several cases, this phenomenon was observed with high catalyst loadings.¹⁸ Therefore, the best results (ee > 99%, quantitative conversion) were

Table 2

Synthesis of 4-alkenoic acids with one stereogenic center^a



Entry	Ketene acetal	R	Time (h)	Conv. ^b	ee ^b
1	2a	–(CH ₂) ₅ –	20	>99	99
2	2b	–(CH ₂) ₄ –	72	>99	53(62) ^c
3	2c	–(CH ₂) ₃ –	24	>99	99
4	2d	Me	23	>99	48(82) ^c
5	2e	Ph	26	>99	62(69) ^c

^a All reactions were carried out on a 7.9 mmol reaction scale of **1** using 1 mol % [PdCl(C₃H₅)₂] with 2 mol % (*R*)-BINAP and 1 equiv NaOAc.

^b The enantiomeric excess and conversion of the carboxylic acid, based on **1** were determined by capillary HPLC analysis with CHIRALPAK-IA column on the crude reaction mixtures.

^c Values in parentheses indicate the ee obtained for the reaction performed at 0 °C.

obtained by decreasing the catalyst loading from 3% to 1% and (*R*)-BINAP from 6% to 2% (Table 1, entry 8).

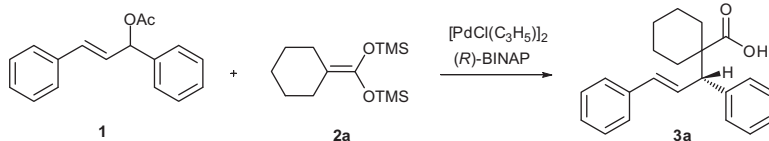
With these optimized conditions in hand, a large variety of symmetric bis(trimethylsilyl)ketene acetals **2a–2e**, derived from α substituted saturated carboxylic acids were examined, and the results are summarized in Table 2.

The Pd-catalyzed allylic substitution was not affected by the substituents of the ketene acetals in terms of conversion. Ketene acetals **2a** and **2c** afforded carboxylic acids **3a** and **3c** in 99% ee (Table 2, entries 1 and 3). In contrast, a significant loss of enantiocontrol was observed in the case of products **3b**, **3d**, and **3e**. A slight increase of enantioselectivity was obtained by lowering the reaction temperature to 0 °C (Table 2, entries 2, 4, and 5).

We evaluated the use of prochiral ketene acetal **4a** with (*E*)-1,3-diphenylpropenyl acetate **1**. In this case, two contiguous stereogenic centers were formed simultaneously. Using the previously optimized conditions in the presence of (*R*)-BINAP as a chiral ligand led to complete conversion after 24 h and 84% ee with a moderate diastereomeric ratio (dr) (65:35) (Table 3, entry 1). A similar result was obtained using the other enantiomer of BINAP (Table 3, entry 2). We also tested other phosphorus-based chiral ligands to improve both the enantio- and diastereoselectivities

Table 1

Optimization experiments of the Pd-catalyzed allylic alkylation of bis(trimethylsilyl)ketene acetals^a

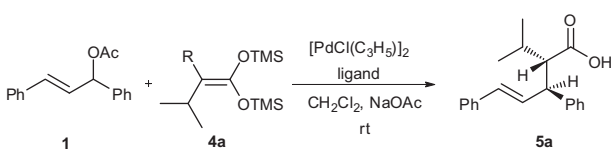


Entry	Pd (mol %)	(<i>R</i>)-BINAP (mol %)	Solvent	Temperature	Additive	Time (h)	Conversion ^b	ee ^b
1	3	6	CH ₂ Cl ₂	rt	—	30	68	75
2	3	6	Toluene	rt	—	72	0	—
3	3	6	Et ₂ O	rt	—	72	50	0
4	3	6	CH ₂ Cl ₂	rt	TBAF	72	0	—
5	3	6	CH ₂ Cl ₂	rt	NaOAc	31	99	76
6	3	6	CH ₂ Cl ₂	0	NaOAc	48	80	84
7	3	6	CH ₂ Cl ₂	–20	NaOAc	48	50	84
8	1	2	CH ₂ Cl ₂	rt	NaOAc	30	99	99

^a Reaction conditions: **1** (1 mmol), **2a** (2 mmol), additive (NaOAc or TBAF, 1 mmol), 1 mol % [PdCl(C₃H₅)₂] with 2 mol % (*R*)-BINAP, dry CH₂Cl₂ (4 mL), rt, argon.

^b Enantiomeric excess and conversion of the carboxylic acid, based on **1** were determined by capillary HPLC analysis with a CHIRALPAK-IA column on the crude reaction mixture.

Table 3
Synthesis of 4-alkenoic acid **5a** with two stereogenic centers^a



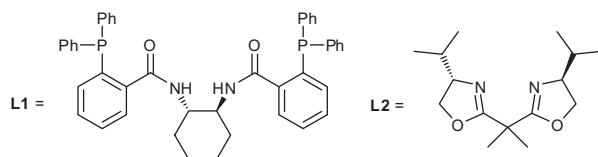
Entry	Ligand	Time (h)	Conv. ^b	ee ^b	dr ^b
1	(<i>R</i>)-BINAP	24	>99	88	65:35
2	(<i>S</i>)-BINAP	26	>99	88 ^c	40:60
3	(<i>S</i>)-DM-BINAP	24	>99	54 ^c	62:38
4	(<i>R</i>)-SEGPPOS	120	62	16	5:95
5	(<i>R</i>)-DUPHOS	120	80	92	63:37
6	L1	120	0	—	—
7	L2	120	Traces	—	—

^a All reactions were carried out on a 1 mmol reaction scale using 1 mol % [PdCl(C₃H₅)₂] with 2 mol % (*R*)-BINAP and 1 equiv NaOAc.

^b The enantiomeric excess, diastereomeric ratio, and conversion of the carboxylic acid, based on **1** were determined by capillary HPLC analysis with CHIRALPAK-IA column on the crude reaction mixtures.

^c The major enantiomer is the opposite from entry 1.

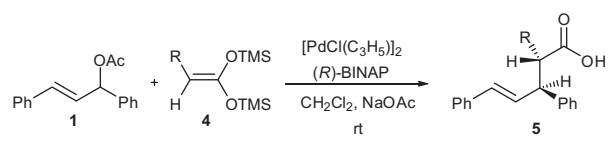
(Table 3, entries 3–6). Unfortunately, none of the tested ligands satisfied both criteria. (*R*)-SEGPPOS gave a poor enantioselectivity but with a high dr whereas (*R*)-DUPHOS gave a slightly improved ee but with a dr similar to that obtained with BINAP (Table 3, entries 4 and 5). The use of a bulkier ligand (*S*)-DM-BINAP than BINAP (Table 3, entry 3) did not lead to better stereinduction.



Other chiral ligands such as diphosphinodiamido ligand **L1** or oxazoline **L2** were completely ineffective under identical conditions (Table 3, entries 6 and 7). In order to evaluate the scope of the reaction, we prepared a series of 4-alkenoic acids **5** from different prochiral bis(trimethylsilyl)ketene acetals **4** using the previously established reaction conditions.

As shown in Table 4, alkyl or aryl substituted bis(trimethylsilyl)ketene acetals gave satisfying results in terms of conversion.

Table 4
Synthesis of 4-alkenoic acids **5** with two stereogenic centers^a



Entry	Ketene acetal	R	Time (h)	Conv. ^b	ee ^b	dr ^b
1	4a	<i>i</i> -Pr	24	>99	88	65:35
2	4b	<i>t</i> -Bu	10	>99	86	65:35
3	4c	Et	48	>99	93 ^c	72:28
4	4d	Me	48	80	40	70:30
5	4e	Ph	3.5	>99	70	86:14
6	4f	4-OMePh	8	80	72	75:25

^a All reactions were carried out on a 1 mmol reaction scale of **1** using 1 mol % [PdCl(C₃H₅)₂] with 2 mol % (*R*)-BINAP and 1 equiv NaOAc.

^b The enantiomeric excess, diastereomeric ratio, and conversion of the carboxylic acid, based on **1** were determined by capillary HPLC analysis with a CHIRALPAK-IA column on the crude reaction mixture.

^c Enantiomeric excess was determined from the isolated compound.

It is important to note that the enantioselectivity is highly dependent on the substituent size, and good ee values with *i*Pr, *t*-Bu, or Et (Table 4, entries 1–3). With planar substituents such as phenyl, the enantiomeric excess drops dramatically to 70% (Table 4, entry 5). Smaller substituent such as Me led to moderate stereoselection (Table 4, entry 4). The diastereoselectivities of the reaction were relatively modest for most of the substrates (~65:35) (Table 4, entries 1–4), and improved in the case of ketene acetals bearing planar substituents (Table 4, entries 5 and 6).

The molecular structure and relative configuration of the acid **5a** were established by X-ray diffraction analysis (Fig. 1).

Figure 1 clearly shows a *trans*-configuration at carbons C-4 and C-5; and an (*S*)-relative configuration at the carbons C-2 and C-3. In addition, the absolute configuration of the acid **5a** was unequivocally established after derivatization with (*R*)-(+)-1-phenylethylamine leading to the corresponding amide **10** (Scheme 2). The (*S,S*)-absolute configurations of **5a** were unambiguously determined from the X-ray structure of the amide **10** (Fig. 2).

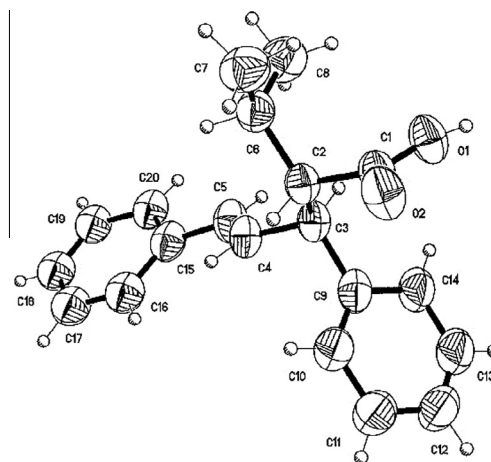


Figure 1. ORTEP representation of 4-alkenoic acid **5a**. Ellipsoids are shown at the 30% probability level. Selected bond lengths [Å] and angles [°]: O(1)–C(1) 1.260(4), O(2)–C(1) 1.252(5), C(1)–C(2) 1.512(5), C(2)–C(3) 1.525(5), C(2)–C(6) 1.552(6), C(3)–C(4) 1.511(5), C(4)–C(5) 1.289(5); O(2)–C(1)–O(1) 123.1(4), O(2)–C(1)–C(2) 117.3(4), O(1)–C(1)–C(2) 119.6(4), C(1)–C(2)–C(3) 111.3(3), C(1)–C(2)–C(6) 111.8(3), C(3)–C(2)–C(6) 114.6(3), C(4)–C(3)–C(9a) 106.7(7), C(4)–C(3)–C(9Bb) 109.3(5), C(4)–C(3)–C(2) 111.5(3), C(9a)–C(3)–C(2) 114.6(11), C(9Bb)–C(3)–C(2) 113.3(11), C(5)–C(4)–C(3) 127.4(4), C(4)–C(5)–C(15Bb) 131(2), C(4)–C(5)–C(15a) 122.9(17), C(8)–C(6)–C(2) 114.7(3).

Finally, the enantiomerically enriched mixture of the carboxylic acid **3d** (ee 82%) was transformed into γ -lactone **11** and δ -lactone **12** using traditional halolactonization methods.¹⁹ It is important to note that the regioselectivity is highly dependent on the halolactonization conditions; however, high diastereoselectivity was observed. Several bromolactonization conditions were tested, providing the desired lactones as a mixture of regioisomers in moderate to good yields (Table 5, entries 1–4). Bromolactonization of **3d** with NBS in THF and CH₂Cl₂ gave good regioselectivity, that is, 76:24 and 90:10, respectively (Table 5, entries 1 and 2). The yield of the reaction was improved if the reaction was performed in CH₃CN however a loss of regioselectivity was observed (Table 5, entry 3), whereas the use of Br₂ led to no regioselectivity. Iodolactonization conditions afforded the desired lactone in good yields and more importantly almost exclusively the γ -lactone (Table 5, entries 5–7). The best conditions were found when a mixture of I₂ and KI was used (Table 5, entry 7).

The configuration of the major regioisomer **11a** from entry 3, was determined in the following manner: the pure regioisomer

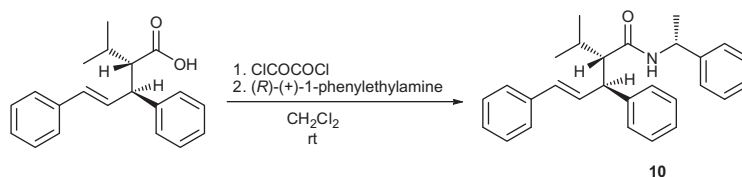
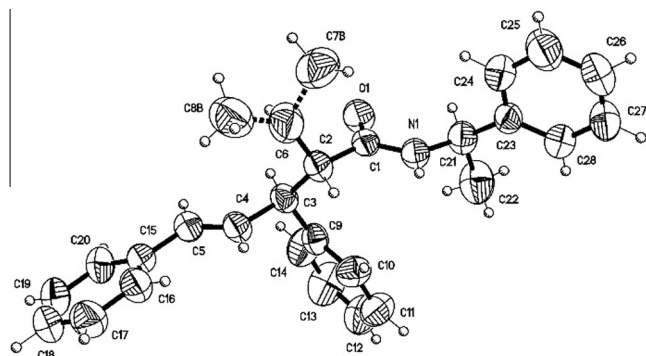
Scheme 2. Synthesis of amide **10**.

Figure 2. ORTEP representation of amide **10**. Ellipsoids are shown at the 30% probability level. Selected bond lengths [Å] and angles [°]: O(1)–C(1) 1.237(5), N(1)–C(1) 1.333(5), N(1)–C(21) 1.451(5), C(1)–C(2) 1.512(6), C(2)–C(6) 1.524(7), C(2)–C(3) 1.539(6), C(3)–C(4) 1.502(6), C(4)–C(5) 1.313(6); C(1)–N(1)–C(21) 123.0(4), C(1)–N(1)–H(1) 118(3), C(21)–N(1)–H(1) 118(3), O(1)–C(1)–N(1) 121.7(4), O(1)–C(1)–C(2) 122.0(4), N(1)–C(1)–C(2) 116.4(4), C(1)–C(2)–C(6) 113.0(4), C(1)–C(2)–C(3) 108.9(4), C(6)–C(2)–C(3) 115.0(4), C(1)–C(2)–H(2) 106.4, C(4)–C(3)–C(9) 106.8(3), C(4)–C(3)–C(2) 112.2(4), C(9)–C(3)–C(2) 114.2(3), C(5)–C(4)–C(3) 125.5(4).

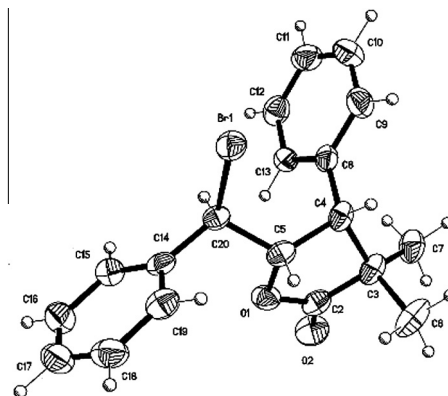
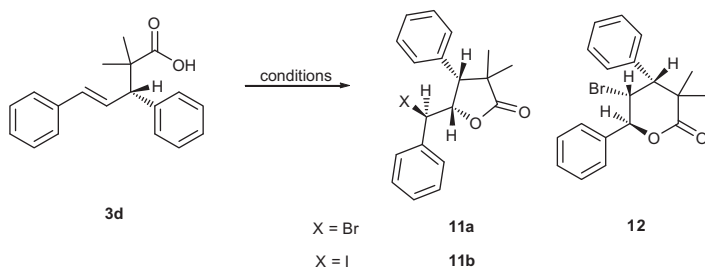


Figure 3. ORTEP representation of γ -lactone **11a**. Ellipsoids are shown at the 30% probability level. Selected bond lengths [Å] and angles [°]: Br(1)–C(20) 1.978(4), O(1)–C(2) 1.366(5), O(1)–C(5) 1.460(6), O(2)–C(2) 1.200(6), C(2)–C(3) 1.502(7), C(3)–C(4) 1.561(6), C(4)–C(5) 1.544(6), C(5)–C(20) 1.524(6), C(2)–O(1)–C(5) 109.3(4), O(2)–C(2)–O(1) 120.2(5), O(2)–C(2)–C(3) 129.3(4), O(1)–C(2)–C(3) 110.5(4), C(2)–C(3)–C(4) 101.5(3), C(5)–C(4)–C(3) 100.0(4), O(1)–C(5)–C(20) 104.1(4), O(1)–C(5)–C(4) 105.5(3), C(5)–C(20)–Br(1) 107.5(3).

Table 5
Synthesis of γ -halolactones from **3d**^a



Entry	X	Conditions	Time (h)	Yield	11 : 12 ^b
1	Br	NBS, NaHCO ₃ , THF, rt	4	84	76:24
2	Br	NBS, NaHCO ₃ , CH ₂ Cl ₂ , rt	9	74	90:10
3	Br	NBS, NaHCO ₃ , CH ₃ CN, rt	1.5	99	60:40
4	Br	Br ₂ , CH ₃ CN	2	80	50:50
5	I	NIS, NaHCO ₃ , CH ₃ CN, rt	2	79	94:6
6	I	I ₂ , CH ₃ CN	24	75	92:8
7	I	I ₂ , KI, NaHCO ₃ , CH ₃ CN	24	76	99:1

^a All reactions were carried out on a 0.36 mmol reaction scale 1.1 equiv of electrophile and 1.2 equiv of NaHCO₃, NaOAc.

^b The regioisomer proportions of the lactone **11** and **12** by HPLC analysis with a Zorbax Eclipse Plus column on the crude reaction mixture, (CH₃CN–H₂O), $t_R = 29.46$ min (*S,S,R*)-**11a**, $t_R = 30.99$ min **12**, $t_R = 27.29$ min **11b**.

was isolated by silica gel chromatography; the compound was highly crystalline, which allowed X-ray crystallographic analysis. The ORTEP structure of **11a** indicates that C-4 had an (*R*)-configuration. The rest of the centers were resolved by X-ray crystallography, which unambiguously indicated an (*R,S,R*)-configuration at carbons C-4, C-5, and C-20, as shown in Figure 3.

3. Conclusion

In conclusion, bis(trimethylsilyl)ketene acetals have been shown for the first time to be suitable nucleophiles in palladium-catalyzed allylic asymmetric alkylations. A highly enantioselective reaction could be obtained with sterically demanding ketene acetals using commercially available BINAP ligands as the chiral promoter. The diastereoselectivity with prochiral ketene acetals still needs to be improved, but the developed method offers, from a synthetic point of view, a direct two-step alternative for the synthesis of enantioenriched γ - and δ -lactones. Additionally, the absolute configuration of acid **5a** was deduced from the X-ray structure of amide **10**. This result indicates the stereochemistry of the center generated during the allylic substitution. Finally, we established an appropriate diastereoselective iodolactonization protocol for the synthesis of a new iodolactone with three contiguous stereocenters. Similarly, the bromolactonization procedure led to the analogous bromolactone, whose absolute configuration was determined by X-ray crystallography.

4. Experimental

4.1. General

All reactions were performed under an inert atmosphere of nitrogen or argon using standard Schlenk techniques. Solvents were distilled from sodium/benzophenone ketyl (diethyl ether, tetrahydrofuran), phosphorus pentoxide (dichloromethane), and saturated with argon. Merck silica gel (type 60, 0.063–0.200 mm) was used for column chromatography. All reagents were obtained from commercial suppliers and used without further purification. All compounds were characterized by IR spectra, recorded on a

Perkin-Elmer 283B or 1420 spectrophotometer, by means of film and KBr techniques, and all data are expressed as wavenumbers (cm^{-1}). Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance III at 300 MHz (^1H NMR) and 75 MHz (^{13}C NMR) in chloroform-*d*. Chemical shifts are given in ppm with TMS as the reference. The MS-DART data were obtained on a Jeol AccuTOF; the values of the signals are expressed as mass/charge units (m/z), followed by the relative intensity with reference to a 100% base peak. Elemental analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 2400 elemental analyzer using cysteine as a standard. Optical rotations were measured on a Perkin Elmer model 343 polarimeter at 589 nm and 25 °C, using a 1 dm path length. The enantioselectivity was determined by chiral HPLC (CHIRALPAK-IA, *i*PrOH/Hexanes/TFA 95:5:0.1, flow rate 1 mL min^{-1} , $\lambda = 254$ nm).

4.2. Structure determination by X-ray crystallography

Suitable X-ray quality crystals of **5a**, **10**, and **11a** were grown by slow evaporation of a *n*-hexane-dichloromethane mixture at -5 °C and chloroform at room temperature, respectively. The crystals of each compound were mounted on a glass fiber at room temperature, and then placed on a Bruker Smart Apex CCD diffractometer, equipped with Mo $K\alpha$ radiation; decay was negligible in both cases. Details of the crystallographic data collected for compounds **5a**, **10**, and **11a** are provided in Table 6. Systematic absences and intensity statistics were used in the space group determination. The structure was solved using direct methods. Anisotropic structure refinements were achieved using a full matrix, least-squares technique on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times the value of the attached atom. Structure solutions and refinements were performed using SHELXTL V6.10. Full crystallographic data for these structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 1038483 for **5a**, CCDC number 1038484 for **10**, and CCDC number 1038485 for **11b**. These data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 (1223)336033; or e-mail: deposit@ccdc.cam.ac.uk.

4.3. Synthesis of bis(trimethylsilyl)ketene acetals

The saturated and conjugated ketene acetals were prepared in two steps (via trimethylsilyl esters) from the corresponding acids using reported procedures.²⁰

4.4. General procedure for palladium-catalyzed allylic alkylation

Bis-(trimethylsilyl)ketene acetal was added at room temperature to a suspension of NaOAc in anhydrous CH_2Cl_2 . After stirring at room temperature for 5 min, the anion was charged with a pre-stirred solution (rt, 5 min) of electrophile (0.2 g, 0.79 mmol), palladium dimer (1%), and *R*-BINAP (2%) in anhydrous CH_2Cl_2 . After completion of the reaction, the resulting mixture was quenched with water and CH_2Cl_2 . The organic phase was dried over Na_2SO_4 . After evaporation of the solvent, the crude product was purified by column chromatography (hexane/AcOEt).

4.4.1. (E)-1-(1,3-Diphenylallyl)cyclohexanecarboxylic acid 3a

Colorless oil; $[\alpha]_{\text{D}}^{25} = +32.7$ (c 0.0066, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 1.37$ – 2.32 (m, 10H, CH_2), 3.54 (d, 1H, $J = 9.9$ Hz, $-\text{CH}-\text{Ph}$), 6.44 (d, 1H, $J = 15.6$ Hz, $\text{Ph}-\text{CH}=\text{CH}$), 6.68 (dd, 1H, $J = 9.9$, 15.6 Hz, $\text{CH}-\text{CH}=\text{CH}$), 7.18–7.36 (m, 10H, H_{arom}); ^{13}C NMR

(75 MHz, CDCl_3 , 25 °C): $\delta = 23.4$ (CH_2), 23.6 (CH_2), 28.8 (CH_2), 31.8 (C_{qt}), 58.7 ($\text{CH}-\text{Ph}$), 126.4 (C_{arom}), 126.9 (C_{arom}), 127.3 (C_{arom}), 128.1 (C_{arom}), 128.4 ($\text{CH}-\text{CH}=\text{CH}$), 128.5 (C_{arom}), 129.1 (C_{arom}), 132.6 ($\text{Ph}-\text{CH}=\text{CH}$), 137.4 (C_{arom}), 140.0 (C_{arom}), 183.0 ($\text{C}=\text{O}$) ppm; IR (KBr) $\nu = 2934$, 1700 cm^{-1} ; MS (DART): m/z : 321.16 [M^+], 276.16 [$\text{M}^+ - \text{CO}_2$]; HRMS (DART): calcd for $\text{C}_{22}\text{H}_{25}\text{O}_2$ [M^+] 321.18545; found 321.18541.

4.4.2. (E)-1-(1,3-Diphenylallyl)cyclopentanecarboxylic acid 3b

Colorless oil, $[\alpha]_{\text{D}}^{25} = +12.0$ (c 0.0102, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 1.59$ – 1.93 (m, 8H, CH_2), 3.90 (d, 1H, $J = 9.3$ Hz, $\text{CH}-\text{Ph}$), 6.50 (d, 1H, $J = 15.6$ Hz, $\text{Ph}-\text{CH}=\text{CH}$), 6.66 (dd, 1H, $J = 9.3$, 15.6 Hz, $\text{CH}-\text{CH}=\text{CH}$), 7.23–7.41 (m, 10H, H_{arom}); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 24.3$ (CH_2), 24.6 (CH_2), 33.3 (CH_2), 34.0 (CH_2), 55.3 (C_{qt}), 59.2 ($\text{CH}-\text{Ph}$), 126.3 (C_{arom}), 126.7 (C_{arom}), 127.3 (C_{arom}), 128.2 (C_{arom}), 128.4 ($\text{CH}-\text{CH}=\text{CH}$), 128.8 (C_{arom}), 129.4 (C_{arom}), 132.4 ($\text{Ph}-\text{CH}=\text{CH}$), 137.3 (C_{arom}), 141.1 (C_{arom}), 183.2 ($\text{C}=\text{O}$); IR (KBr) $\nu = 2956$, 1696 cm^{-1} ; MS (DART): m/z : 307.16 [M^+], 289.15 [$\text{M}^+ - \text{HO}$]; HRMS (DART): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_2$ [M^+] 307.16980; found 307.16954.

4.4.3. (E)-1-(1,3-Diphenylallyl)cyclobutanecarboxylic acid 3c

Colorless oil, $[\alpha]_{\text{D}}^{25} = -1.8$ (c 0.0112, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 1.55$ – 2.37 (m, 6H, CH_2), 3.74 (d, 1H, $J = 8.4$ Hz, $\text{CH}-\text{Ph}$), 6.41 (d, 1H, $J = 15.6$ Hz, $\text{Ph}-\text{CH}=\text{CH}$), 6.51 (dd, 1H, $J = 8.4$, 15.6 Hz, $\text{CH}-\text{CH}=\text{CH}$), 7.09–7.29 (m 10H, H_{arom}); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 15.8$ (CH_2), 27.9 (CH_2), 28.9 (CH_2), 52.05 (C_{qt}), 54.30 ($\text{CH}-\text{Ph}$), 126.5 (C_{arom}), 126.9 (C_{arom}), 127.5 (C_{arom}), 128.5 ($\text{CH}-\text{CH}=\text{CH}$), 128.6 (C_{arom}), 128.9 (C_{arom}), 132.8 ($\text{Ph}-\text{CH}=\text{CH}$), 137.4 (C_{arom}), 140.7 (C_{arom}), 183.4 ($\text{C}=\text{O}$); IR (KBr) $\nu = 2990$, 1695 cm^{-1} ; MS (DART): m/z : 293.15 [M^+], 275.14 [$\text{M}^+ - \text{HO}$]; HRMS (DART): calcd for $\text{C}_{20}\text{H}_{20}\text{O}_2$ [M^+] 293.15415; found 293.15433.

4.4.4. (E)-2,2-Dimethyl-3,5-diphenylpent-4-enoic acid 3d

White powder; mp 90–92 °C; $[\alpha]_{\text{D}}^{25} = +45$ (c 0.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 1.16$ (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 3.76 (d, 1H, $J = 9.3$ Hz, $\text{CH}-\text{Ph}$), 6.48 (d, 1H, $J = 15.6$ Hz, $\text{Ph}-\text{CH}=\text{CH}$), 6.61 (dd, 1H, $J = 9.3$, 15.6 Hz, $\text{CH}-\text{CH}=\text{CH}$), 6.45–7.36 (m, 10H, H_{arom}); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 22.5$ (CH_3), 23.4 (CH_3), 47.3 (C_{qt}), 56.7 ($\text{CH}-\text{Ph}$), 126.5 (C_{arom}), 127.0 (C_{arom}), 127.5 (C_{arom}), 128.3 (C_{arom}), 128.4 (C_{arom}), 128.5 ($\text{CH}-\text{CH}=\text{CH}$), 128.6 (C_{arom}), 129.4 (C_{arom}), 133.0 ($\text{Ph}-\text{CH}=\text{CH}$), 137.5 (C_{arom}), 140.3 (C_{arom}), 184.0 ppm ($\text{C}=\text{O}$); IR (KBr) $\nu = 2982$, 1691 cm^{-1} ; MS (DART): m/z : 281.15 [M^+], 235.14 [$\text{M}^+ - \text{CO}_2$]; HRMS (DART): calcd for $\text{C}_{19}\text{H}_{20}\text{O}_2$ [M^+] 281.15234; found 281.15234.

4.4.5. (E)-2,2,3,5-Tetraphenylpent-4-enoic acid 3e

Colorless oil, $[\alpha]_{\text{D}}^{25} = +64.09$ (c 0.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 5.27$ (d, 1H, $J = 7.5$ Hz, $\text{CH}-\text{Ph}$), 6.38 (dd, 1H, $J = 7.8$, 15.9 Hz, $\text{Ph}-\text{CH}=\text{CH}$), 6.48 (d, 1H, $J = 15.9$ Hz, $\text{CH}-\text{CH}=\text{CH}$), 7.0–7.49 (m, 20H, H_{arom}); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 51.9$ (C_{qt}), 57.1 ($\text{CH}-\text{Ph}$), 126.3 (C_{arom}), 126.8 (C_{arom}), 126.9 (C_{arom}), 127.4 (C_{arom}), 127.5 (C_{arom}), 127.6 (C_{arom}), 127.9 (C_{arom}), 128.5 (C_{arom}), 128.5 ($\text{CH}-\text{CH}=\text{CH}$), 128.8 (C_{arom}), 130.1 (C_{arom}), 130.9 (C_{arom}), 131.2 (C_{arom}), 131.9 ($\text{Ph}-\text{CH}=\text{CH}$), 133.2 (C_{arom}), 137.6 (C_{arom}), 137.9 (C_{arom}), 140.8 (C_{arom}), 140.8 (C_{arom}), 179.5 ($\text{C}=\text{O}$); IR (KBr) $\nu = 3027$, 1698 cm^{-1} ; MS (DART): m/z : 405.14 [M^+], 361.14 [$\text{M}^+ - \text{CO}_2$]; HRMS (DART): calcd for $\text{C}_{29}\text{H}_{25}\text{O}_2$ [M^+] 405.18545; found 405.18466.

4.4.6. (E)-2-Isopropyl-3,5-diphenylpent-4-enoic acid 5a

White powder; mp 134–136 °C, $[\alpha]_{\text{D}}^{25} = -13.3$ (c 0.01, CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 0.98$ (d, 3H, $J = 6$ Hz, CH_3), 1.01 (d, 3H, $J = 6$ Hz, CH_3), 2.06–2.17 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.84 (dd, 1H, $J = 3$, 12 Hz, $\text{CH}-\text{COOH}$), 3.75 (dd, 1H, $J = 9.9$, 10.9 Hz,

Table 6
Crystal data and structure refinement for **5a**, **10**, and **11a**

	5a	10	11a
Empirical formula	C ₂₀ H ₂₂ O ₂	C ₂₈ H ₃₁ NO	C ₁₉ H ₁₉ BrO ₂
Formula weight (g mol ⁻¹)	294.37	397.54	359.25
Crystal size (mm)	0.480 × 0.451 × 0.185	0.494 × 0.056 × 0.046	0.318 × 0.208 × 0.094
Color	Colorless	Colorless	Colorless
Crystal system	Trigonal	Orthorhombic	Monoclinic
Space group	<i>P</i> 3 ₂ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁
<i>a</i> (Å)	8.9537(9)	9.7252(14)	11.7617 (4)
<i>b</i> (Å)	8.9537(9)	15.474(2)	6.0733 (2)
<i>c</i> (Å)	38.060(4)	15.678 (2)	12.0729 (4)
α (°)	90	90	90
β (°)	90	90	98.3036 (18)
γ (°)	120	90	90
<i>V</i> (Å ³)	2642.5(6)	2359.4(6)	853.35(5)
<i>Z</i>	6	4	2
<i>D</i> _{calcd} (g cm ⁻³)	1.110 Mg/m ³	1.119 Mg/m ³	1.398 Mg/m ³
Number of collected reflections	21,429	24,250	15,005
Number of independent reflections (<i>R</i> _{int})	3245 [<i>R</i> (int) = 0.0597]	5420 [<i>R</i> (int) = 0.0885]	3337 [<i>R</i> (int) = 0.0427]
Maximum and minimum transmission	0.9876 and 0.9618	0.9969 and 0.9678	0.7460 and 0.4190
Data/restraints/parameters	3245/394/315	5420/24/298	3337/1/201
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)]	<i>R</i> ₁ = 0.0493, <i>wR</i> ₂ = 0.1183	<i>R</i> ₁ = 0.0582, <i>wR</i> ₂ = 0.1163	<i>R</i> ₁ = 0.0340, <i>wR</i> ₂ = 0.0727
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0998, <i>wR</i> ₂ = 0.1467	<i>R</i> ₁ = 0.1846, <i>wR</i> ₂ = 0.1666	<i>R</i> ₁ = 0.0391, <i>wR</i> ₂ = 0.0765
GOF (<i>F</i> ²)	1.029	0.965	1.128
Absorption correction method	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents

CH–Ph), 6.18 (dd, 1H, *J* = 9.6, 15.6 Hz, *CH*–*CH*=*CH*), 6.48 (d, 1H, *J* = 15.6 Hz, Ph–*CH*=*CH*), 7.15–7.33 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 16.5 (CH₃), 22.0 (CH₃), 28.1 (*CH*(CH₃)₂), 49.6 (*CH*–COOH), 56.2 (*CH*–Ph), 126.3 (C_{arom}), 126.7 (C_{arom}), 127.4 (C_{arom}), 127.7 (C_{arom}), 128.6 (C_{arom}), 130.9 (C_{arom}), 131.1 (C_{arom}), 137.1 (*CH*–*CH*=*CH*), 142.3 (Ph–*CH*=*CH*), 178.9 (C=O); IR (KBr) ν = 2955, 1700 cm⁻¹; MS (DART): *m/z*: 295.17 [*M*⁺], 235.14 [*M*⁺–HO]; HRMS (DART): calcd for C₂₀H₂₂O₂ [*M*⁺] 295.16980; found 295.17066; Anal. calcd for C₂₀H₂₂O₂: C, 81.6; H, 7.53; found: C, 81.69; H, 7.44.

4.4.7. (*E*)-2-(*tert*-Butyl)-3,5-diphenylpent-4-enoic acid **5b**

White powder, mp 116–118 °C, [α]_D²⁵ = –42.6 (*c* 0.0053, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.06 (s, 9H, CH₃), 2.77 (d, 1H, *J* = 11.1 Hz, *CH*–COOH), 3.83 (t, 1H, *J* = 10.8 Hz, *CH*–Ph), 6.25 (dd, 1H, *J* = 10.2, 15.7 Hz, *CH*–*CH*=*CH*), 6.42 (d, 1H, *J* = 15.6 Hz, Ph–*CH*=*CH*), 7.11–7.30 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 28.7 (CH₃), 33.3 (CH_q), 50.6 (*CH*–COOH), 60.7 (*CH*–Ph), 126.1 (C_{arom}), 127.7 (C_{arom}), 128.5 (C_{arom}), 128.6 (C_{arom}), 129.3 (C_{arom}), 133.2 (C_{arom}), 137.2 (*CH*–*CH*=*CH*), 142.6 (Ph–*CH*=*CH*), 179.6 (C=O); IR (KBr) ν = 2952, 1708 cm⁻¹; MS (DART) *m/z*: 309.17 [*M*⁺], 292.17 [*M*⁺–HO]; HRMS (DART): calcd for C₂₁H₂₄O₂ [*M*⁺] 309.18545; found: 309.18515.

4.4.8. (*E*)-2-Ethyl-3,5-diphenylpent-4-enoic acid **5c**

White powder; mp 146–148 °C, [α]_D²⁵ = +4.8 (*c* 0.01, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.91 (t, 3H, *J* = 6 Hz, CH₃), 1.56–1.84 (m, 2H, CH₂), 2.72 (td, 1H, *J* = 3 Hz, 9 Hz, *CH*–COOH), 3.61 (t, 1H, *J* = 9 Hz, *CH*–Ph), 6.22 (dd, 1H, *J* = 9, 15 Hz, *CH*–*CH*=*CH*), 6.45 (d, 1H, *J* = 15 Hz, Ph–*CH*=*CH*), 7.17–7.34 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 11.8 (CH₃), 24.2 (CH₂), 52.0 (*CH*–COOH), 52.8 (*CH*–Ph), 126.3 (C_{arom}), 126.8 (C_{arom}), 127.5 (C_{arom}), 127.7 (C_{arom}), 128.5 (C_{arom}), 128.6 (C_{arom}), 130.5 (C_{arom}), 131.7 (C_{arom}), 137.0 (*CH*–*CH*=*CH*), 141.9 (Ph–*CH*=*CH*), 180.6 (C=O); IR (KBr) ν = 2930, 1696 cm⁻¹; MS (DART) *m/z*: 281.15 [*M*⁺], 235.14 [*M*⁺–CO₂]; HRMS (DART): calcd for C₁₉H₂₁O₂ [*M*⁺] 281.15415; found 281.15352.

4.4.9. (*E*)-2,3,5-Triphenylpent-4-enoic acid **5e**

White powder, mp 60–62 °C; [α]_D²⁵ = –78.9 (*c* 0.0053, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 4.03 (d, 1H, *J* = 11.4 Hz,

CH–COOH), 4.18 (dd, 1H, *J* = 7.8, 11.2 Hz, *CH*–Ph), 6.44 (dd, 1H, *J* = 7.8, 15.7 Hz, *CH*–*CH*=*CH*), 6.55 (d, 1H, *J* = 15.9, Ph–*CH*=*CH*), 7.04–7.31 (m, 15H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 51.8 (*CH*–COOH), 57.1 (*CH*–Ph), 126.2 (C_{arom}), 126.9 (C_{arom}), 127.4 (C_{arom}), 127.6 (C_{arom}), 127.9 (C_{arom}), 128.5 (C_{arom}), 130.0 (C_{arom}), 130.9 (C_{arom}), 131.2 (C_{arom}), 131.9 (C_{arom}), 133.1 (C_{arom}), 137.6 (C_{arom}), 138.4 (*CH*–*CH*=*CH*), 140.7 (Ph–*CH*=*CH*), 178.9 (C=O); IR (KBr) ν = 2990, 1696 cm⁻¹; MS (DART): *m/z* (%): 329.12 [*M*⁺], 283.12 [*M*⁺–CO₂]; HRMS (DART): calcd for C₂₃H₂₁O₂ [*M*⁺] 329.15415; found 329.15362.

4.4.10. (*E*)-2-(4-Methoxyphenyl)-3,5-diphenylpent-4-enoic acid **5f**

Colorless oil, [α]_D²⁵ = –41.1 (*c* 0.0053, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 3.78 (s, 3H, OCH₃), 3.99 (d, 1H, *J* = 12.0 Hz, *CH*–COOH), 4.15 (dd, 1H, *J* = 6.0, 10.5 Hz, *CH*–Ph), 6.42 (dd, 1H, *J* = 9, 15.0 Hz, *CH*–*CH*=*CH*), 6.54 (d, 1H, *J* = 15.0, Ph–*CH*=*CH*), 7.04–7.32 (m, 14H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 51.8 (*CH*–COOH), 57.1 (*CH*–Ph), 126.2 (C_{arom}), 126.9 (C_{arom}), 127.4 (C_{arom}), 127.6 (C_{arom}), 127.9 (C_{arom}), 128.5 (C_{arom}), 130.0 (C_{arom}), 130.9 (C_{arom}), 131.2 (C_{arom}), 131.9 (C_{arom}), 133.1 (C_{arom}), 137.6 (C_{arom}), 138.4 (*CH*–*CH*=*CH*), 140.7 (Ph–*CH*=*CH*), 178.9 (C=O); IR (KBr) ν = 2903, 1691 cm⁻¹; MS (DART): *m/z* (%): 359.12 [*M*⁺], 313.12 [*M*⁺–CO₂]; HRMS (DART): calcd for C₂₄H₂₃O₃ [*M*⁺] 359.16472; found 359.16382.

4.5. Synthesis of (*E*)-2-isopropyl-3,5-diphenyl-*N*-((*R*)-1-phenylethyl)pent-4-enamide **10**

Acid **5a** (0.68 mmol) was dissolved in anhydrous CH₂Cl₂ under a nitrogen atmosphere and oxalyl chloride (0.06 mL, 2.5 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, and then the solvent was removed with a vacuum line. After removing all of the solvent, a mixture of triethylamine (0.4 mL, 2.5 mmol) and (*R*)-(+)-1-phenylethylamine (0.1 mL, 1.2 mmol) in anhydrous CH₂Cl₂ was added. The reaction mixture was stirred for 1 h at room temperature, and then the reaction was quenched by adding 30 mL of water. The mixture was extracted with dichloromethane, and the organic layers were dried over Na₂SO₄. After evaporation of the solvent, the crude product was purified by column chromatography (Hexane/ACoEt). White

powder, mp 204 °C. $[\alpha]_D^{25} = +51.9$ (c 0.0053, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.92 (d, 3H, J = 6.9 Hz, CH₃–CH–NH), 0.98 (d, 3H, J = 6.9 Hz, CH₃–CH–CH₃), 1.10 (d, 3H, J = 6.6 Hz, CH₃–CH–CH₃), 2.04–2.12 (m, 1H, CH–(CH₃)₂), 2.37 (dd, 1H, J = 4.5, 11.2 Hz, CH–CONHR), 3.89 (dd, 1H, J = 9.9, 9.6 Hz, CH–Ph), 4.86 (q, 1H, J = 6.9, 7.5 Hz, CH–NH), 5.18 (d, 1H, J = 8.1 Hz, N–H), 6.32 (dd, 1H, J = 9.6, 15.9 Hz, CH–CH=CH), 6.53 (d, 1H, J = 15.9 Hz, Ph–CH=CH), 7.13–7.36 (m, 15H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 16.8 (CH₃–CH–NH), 20.6 (CH₃–CH–CH₃), 22.2 (CH₃–CH–CH₃), 28.6 (CH–(CH₃)₂), 47.9 (CH–NH), 50.3 (CH–COOH), 59.3 (CH–Ph), 126.2 (C_{arom}), 126.5 (C_{arom}), 127.1 (C_{arom}), 127.3 (C_{arom}), 127.9 (C_{arom}), 128.4 (C_{arom}), 128.5 (C_{arom}), 131.1 (C_{arom}), 131.1 (C_{arom}), 137.3 (C_{arom}), 143.1 (CH–CH=CH), 143.2 (Ph–CH=CH), 171.1 (C=O); IR (KBr) ν = 3294, 1632 cm⁻¹; MS (DART): m/z: 399.23 [M⁺], 398.33 [M]; HRMS (DART): calcd for C₂₈H₃₂N₂O₁ [M⁺] 398.24839; found 398.24740.

4.6. General procedure for the synthesis of γ and δ-halolactone 11a, 11b, and 12

A 100 mL round-bottom flask was charged with the carboxylic acid **3d** (0.1 g, 0.36 mmol), sodium bicarbonate (1.2 equiv), and an electrophile (1.1 equiv) in dry dichloromethane (30 mL). The mixture was stirred at room temperature and protected from light. The reaction progress was monitored by TLC until completion then the crude mixture was washed with water (3 × 30 mL). The organic phase was dried over Na₂SO₄ and evaporated under reduced pressure. The obtained γ-halolactone was purified by silica gel column chromatography (Hexane/AcOEt).

4.6.1. 5-(Bromo(phenyl)methyl)-3,3-dimethyl-4-phenyldihydrofuran-2(3H)-one **11a**

white powder, mp 118–120 °C; $[\alpha]_D^{25} = +61.6$ (c 0.01, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.92 (s, 3H, CH₃); 1.53 (s, 3H, CH₃); 3.57 (d, 1H, J = 4.8 Hz, CH–Ph); 4.58 (d, 1H, J = 11.2 Hz, CH–Br), 5.34 (dd, 1H, J = 4.8, 10.8 Hz, CH–O), 7.18–7.39 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 21.2 (CH₃), 25.3 (CH₃), 45.7 (CH–Br), 50.9 (CH–Ph), 56.9 (C_{qt}), 81.4 (CH–O), 127.9 (C_{arom}), 128.2 (C_{arom}), 128.6 (C_{arom}), 128.7 (C_{arom}), 129.0 (C_{arom}), 135.0 (C_{arom}), 137.9 (C_{arom}), 180.9 (C_{arom}) ppm; IR (KBr) ν = 1770 cm⁻¹; MS (DART): m/z: 359.01 [M⁺], 279.10 [M⁺–Br]; HRMS (DART): calcd for C₁₉H₂₀BrO₂ [M⁺] 359.06467; found 359.06435.

4.6.2. 5-(Iodo(phenyl)methyl)-3,3-dimethyl-4-phenyldihydrofuran-2(3H)-one **11b**

white powder, mp 122–124 °C; $[\alpha]_D^{25} = +17.3$ (c 0.04, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 0.90 (s, 3H, CH₃), 1.55 (s, 3H, CH₃), 3.62 (d, 1H, J = 4.8 Hz, CH–Ph), 4.71 (d, 1H, J = 11.4 Hz, CH–I), 5.54 (dd, 1H, J = 4.8, 11.4 Hz, CH–O), 7.21–7.38 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 21.4 (CH₃), 25.4 (CH₃), 30.4 (CH–I), 46.2 (CH–Ph), 57.8 (C_{qt}), 82.2 (CH–O), 128.0 (C_{arom}), 128.6 (C_{arom}), 128.7 (C_{arom}), 128.8 (C_{arom}), 134.7 (C_{arom}), 139.9 (C_{arom}), 181.4 (C=O); IR (KBr) ν = 1767 cm⁻¹; MS (DART): m/z: 407.00 [M⁺], 279.10 [M⁺–I]; HRMS (DART): calcd for C₁₉H₂₀I₂O₂ [M⁺] 407.05080; found 407.05041.

4.6.3. 5-Bromo-3,3-dimethyl-4,6-diphenyltetrahydro-2H-pyran-2-one **12**

white powder, mp °C; $[\alpha]_D^{25} = +55.3$ (c 0.01, CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.35 (s, 3H, CH₃); 1.37 (s, 3H, CH₃); 3.51 (d, 1H, J = 12 Hz, CH–Ph); 4.75 (t, 1H, J = 12 Hz, CH–Br), 5.54 (d, 1H, J = 12 Hz, CH–O), 7.21–7.50 (m, 10H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 23.2 (CH₃), 25.9 (CH₃), 44.6 (C_{qt}), 51.9 (CH–Br), 56.9 (CH–Ph), 85.6 (CH–O), 127.6 (C_{arom}), 127.8 (C_{arom}),

128.1 (C_{arom}), 128.6 (C_{arom}), 129.4 (C_{arom}), 136.8 (C_{arom}), 137.3 (C_{arom}), 175.5 (C_{arom}) ppm; IR (KBr) ν = 1770 cm⁻¹; MS (DART): m/z: 359.01 [M⁺], 279.10 [M⁺–Br]; HRMS (DART): calcd for C₁₉H₂₀BrO₂ [M⁺] 359.06467; found 359.06435.

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