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Practical Syntheses of Enantiomerically Pure *N*-Acetylbenzhydrylamines

Daniele Castagnolo,[a] Gianluca Giorgi,[b] Raffaella Spinosa,[a] Federico Corelli,[a] and Maurizio Botta*[a]

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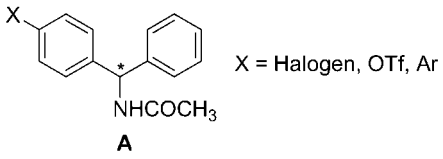
Two practical routes for the synthesis of benzhydrylamine derivatives in enantiomerically pure form have been developed. *N*-Acetylbenzhydrylamines can be synthesised in few steps and good yields starting from 1-aryl-1-propargylamines. The key steps are represented by the alkene-alkyne cross metathesis reaction and alkyne–diene methylene-free tandem-metathesis reaction; these reactions have been performed under microwave irradiation in a few minutes and high yields. *N*-Acetylbenzhydrylamines have been also converted in both enantiomers of the antifungal agent bifonazole, emphasizing the importance of these compounds as scaffolds for the synthesis of biologically active compounds in enatiopure form.

Introduction

Benzhydrylamine (diarylmethylamine) and its substituted derivatives are an important class of compounds in organic synthesis because of their use as protecting groups.[1] Moreover the benzhydryl structural motif is an important substitution pattern in many pharmaceuticals and biologically active molecules.[2] Specifically, drugs containing the benzhydryl motif either in preclinical testing or in clinical applications include antihypertensives, anti-allergics, hypolipidemics, anti-Parkinson agents, opioid agonists, antifungal agents,[3] aromatase inhibitors and others.[4] A wide array of syntheses of benzhydrylamines are known, based on transformations of the corresponding benzhydrols, reduction of oxime derivatives, reductive amination of benzophenone precursors, and addition of organometallic reagents to either aldimines, *N*-boryl imines, quaternary hydrazonium salts or nitriles.[5] Otherwise only few methods are available for the synthesis of diarylmethylamines in optically pure form. Resolution using (+)- or (–)-tartaric acid salts has previously been used by our group.[3c,6] In recent years many efforts have been made and great progress has been achieved in the catalytic enantioselective arylation of imines. Nevertheless, the use of toxic, moisture-sensitive, or non-commercially available organometallic reagents and sometimes the need of sterically tuned substrates or expensive chiral auxiliaries for high enantioselectivity may limit their application.[7] Thus, the development of an efficient and versatile method for the synthesis of optically active diarylmethylamines is still highly desiderable.

In the last decade our group has been involved in the synthesis of enantiomerically pure azole derivatives as antifungal agents and aromatase inhibitors which contain the benzhydrylamino motif.[3b–3e] In this work we described two routes for the synthesis of enantiomerically pure *N*-acetylbenzhydrylamines with the general structure **A** which could be easily converted into chiral biologically active compounds. The two retrosynthetic approaches are illustrated in Scheme 1.



A

N-Protected benzhydrylamines **A** could be obtained by aromatization from cyclohexenes **B** synthesised by Diels–Alder reaction from dienes **C**; dienes could be obtained via alkene–alkyne cross-metathesis from *N*-acetyl-1-aryl-1-propargylamines **E** whose synthesis in enantiomerically pure form was described previously by our group.[8] Alternatively, *N*-protected benzhydrylamines **A** could be prepared by aromatization from cyclohexadienes **D**, in turn synthesised via alkyne–diene methylene-free tandem-metathesis reaction from *N*-acetyl-1-aryl-1-propargylamines **E**. In both cases the starting material is represented by the *N*-acetyl-1-aryl-1-propargylamines which can be synthesised in enantiomerically pure form in few steps and high and reproducible yields via kinetic enzymatic resolution of the corresponding racemic amines.

[a] Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena,
Via Alcide de Gasperi 2, 53100 Siena, Italy
Fax: +39-0577-234333
E-mail: botta@unisi.it
[b] Dipartimento di Chimica, Università degli Studi di Siena,
Via A. Moro, 53100 Siena, Italy
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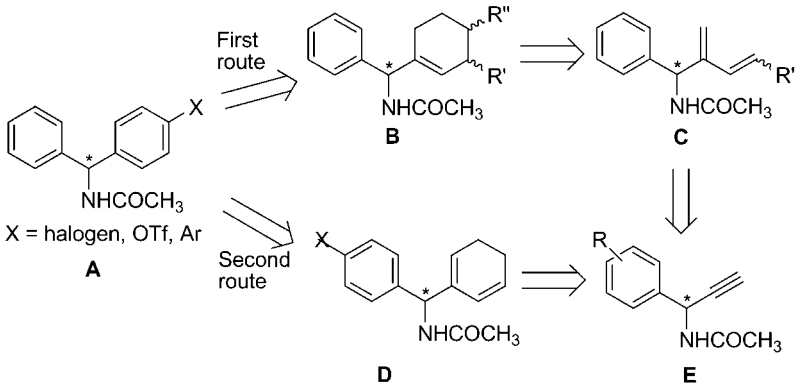
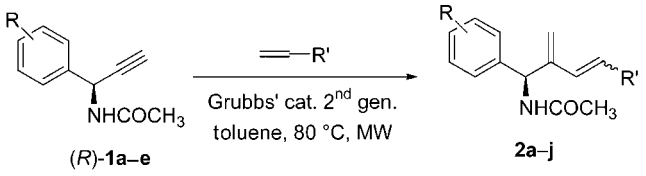


Scheme 1.

Furthermore, the reactivity of 1,3-butadienes of type **C** with different dienophiles in Diels–Alder cycloaddition reactions was also investigated. Finally, *N*-acetylbenzhydrylamines were converted into both enantiomers of antifungal agent bifonazole, which were previously synthesised by us via resolution of diastereomeric salts of (4-bromophenyl)phenylmethylamine with (+)- and (–)-tartrate,[3c] thus confirming the initial configuration assignment.



Scheme 2.

Results and Discussion

First Route. Alkyne–Alkene Cross-Metathesis Reaction

N-Acetyl-1-aryl-1-propargylamines **1a**–**e** were synthesised in enantiomerically pure form according to our procedure via enzymatic kinetic resolution of the corresponding racemate using *Candida antarctica* Lipase B.[8a] In our previous communication we reported the cross metathesis reaction of these substrates with ethylene under microwave irradiation; under these conditions 1,3-dienes **2a**–**e** have been obtained in good yields and in a few minutes.[8b] Herein we decided to extend our methodology and to evaluate the efficacy of the microwave-assisted cross-metathesis reaction; compound (*R*)-**1a** was treated with different alkenes in the presence of Grubbs' 2nd generation catalyst (10 mol-%) in toluene at 80 °C and under microwave irradiation, affording dienes **2f**–**j** after only 20 minutes (2 runs of 10 min) (Scheme 2). Yields and *ee* values are reported in Table 1. Compounds **2f** and **2i** were obtained in high yields, while **2g** and **2j** were isolated in lower yields. Vinyltrimethylsilane did not undergo cross metathesis under these conditions and compound **2h** was not obtained even with higher catalyst loading and longer reaction times. In every instance, dienes were obtained as a mixture of *E*/*Z* isomers (1.0:0.5 *E*/*Z* ratio), and the ratios were determined by ^{1}H-NMR spectroscopy.

Table 1. Yields and *ee* values for dienes **2a**–**j**.

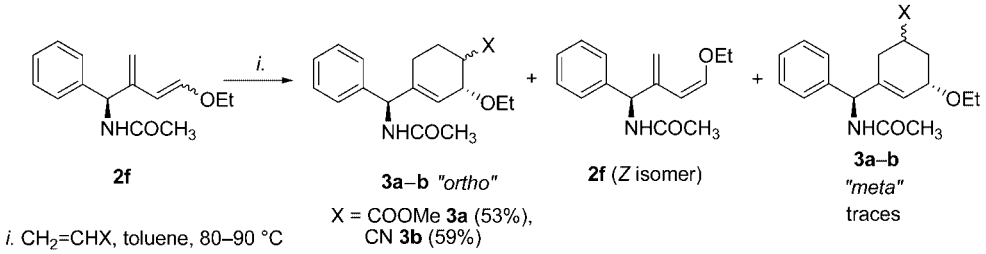
	R	R′	*ee*[a]	Yield (%)[b]	Ratio *E*/*Z*[c]
2a	H	H	96	45	
2b	4-F	H	97	64	
2c	4-Cl	H	95	70	
2d	3-F	H	96	55	
2e	3-Me	H	95	48	
2f	H	OEt	97	88	1.0:0.5
2g	H	OAc	96	53	1.0:0.5
2h	H	TMS	0	0	
2i	H	CN	97	79	1.0:0.5
2j	H	3-MeOC$_6$H$_4$	94	58	1.0:0.5

[a] Determined by chiral HPLC-MS using an S,S-Whelk-O1 column. (50% water/methanol, 0.8 mL/min, UV-254). [b] Referred to isolated and purified materials. [c] Determined by ^{1}H-NMR intergration.

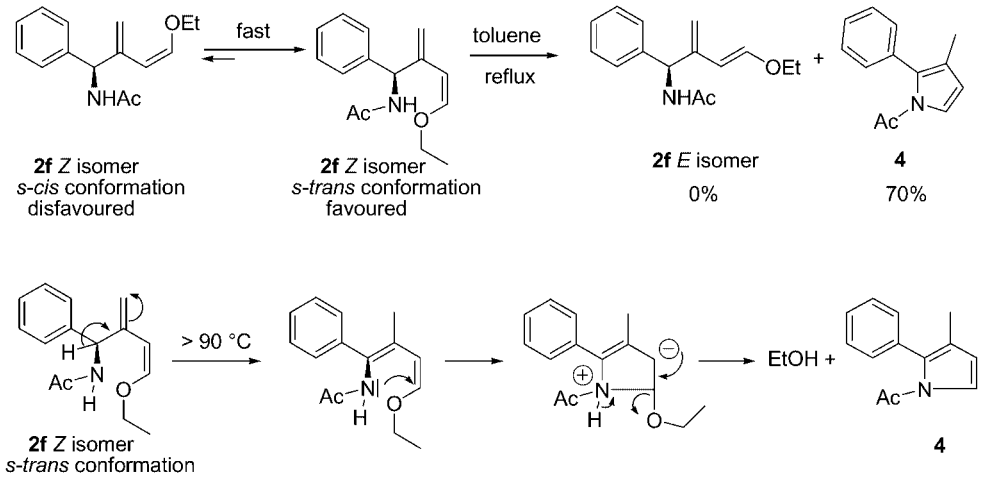
First Route. Diels–Alder Reactions

Product **2f** has been chosen to explore the reactivity of these dienes toward the Diels–Alder cycloaddiction since it is an electron-rich diene due to electron-donating ethoxy group. Compound **2f** was treated with different dienophiles with the aim to obtain an appropriate cyclohexene synthon to be further transformed into benzhydrylamines.

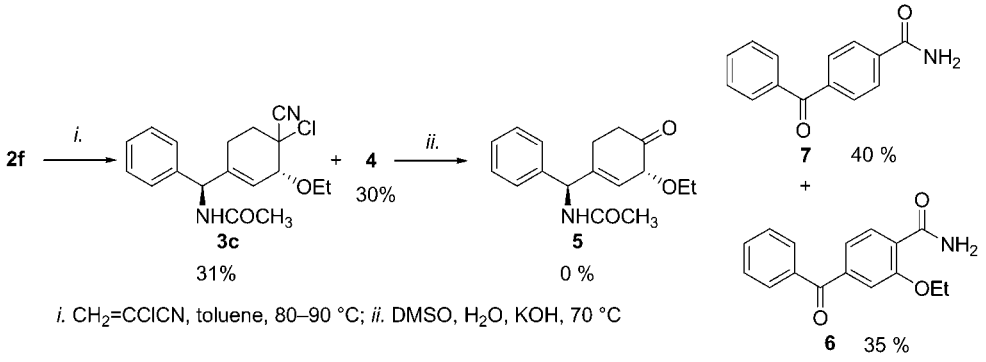
At first, compound **2f** (*E*/*Z* mixture) was reacted under thermal conditions: methylacrylate and acrylonitrile were selected as dienophiles (Scheme 3). In both cases, after 24 hours, diastereoisomeric mixtures of cyclohexenes **3a**–**b** were detected in 53% and 59% yield respectively, together



Scheme 3.



Scheme 4.



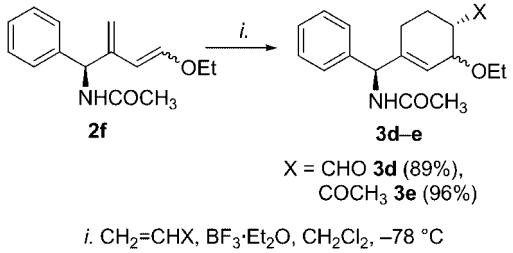
Scheme 5.

with traces of the *"meta"* isomers and the unreacted *Z* isomer of **2f**.[9–10]

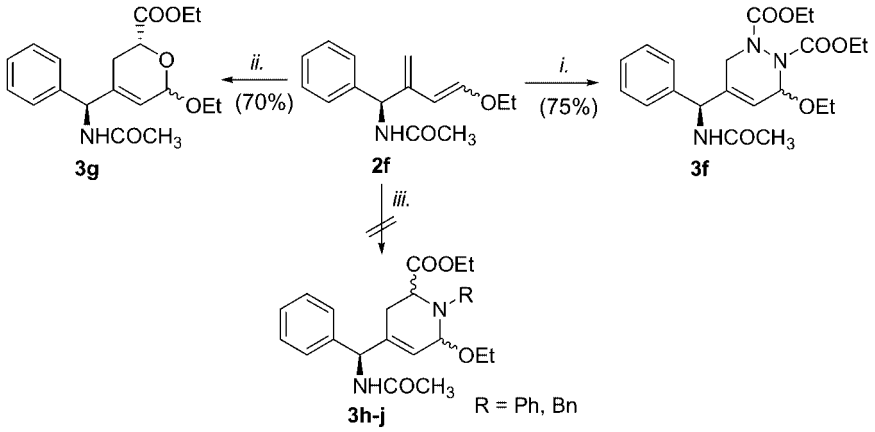
The resistance of *Z* isomer to undergo cycloaddition can be explained on the basis of the favoured *s-trans* conformation assumed by *Z* isomer (Scheme 4). Efforts to convert the recovered **2f** (*Z* isomer) into the corresponding *E* isomer were made according to the literature;[11] **2f** (*Z* isomer) was heated in toluene at reflux for 24 hours (Scheme 4) but no traces of *E* isomer were detected and only a small amount of **2f** (*Z* isomer) was recovered. Compound **4** was isolated as major product (70% yield).

In the Scheme 4 the proposed mechanism is reported. We can assume that above 90 °C the cyclization of **2f** (*Z* isomer) leading to the stable pyrrole **4** with elimination of ethanol is faster than the *Z*→*E* isomerization.

The reactivity of **2f** with chloroacrylonitrile (Corey's masked ketene) under thermal condition was also examined; only a small amount of the desired cycloadduct **3c**



Scheme 6.



i. DEAD, toluene, r.t.; *ii.* CHOCOOEt, CH_2Cl_2, r.t.; *iii.* RN=CHCOOEt, CH_2Cl_2, r.t.⟶ reflux.

Scheme 7.

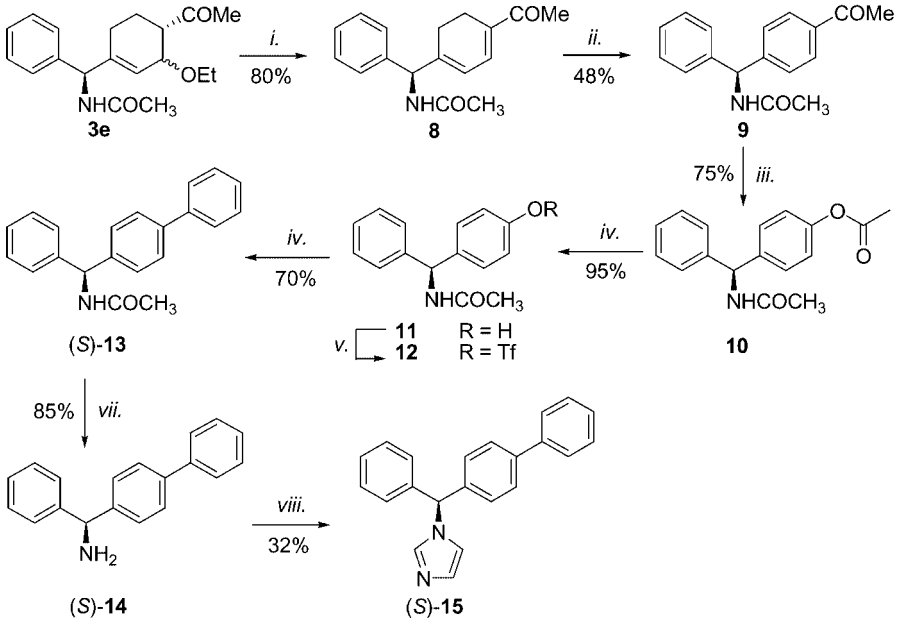
was recovered in 31% yield as a mixture of diastereoisomers together with pyrrole **4** in 30% yield. (Scheme 5). We hypothesised that during the course of the reaction some HCl could have been formed and the acidic conditions as well as the high temperature could have catalyzed and accelerated the formation of the pyrrole. It is known that chloroacrylonitrile represents the equivalent of a ketene and that chloronitrile functionality can be hydrolyzed to a carbonyl group. Hence, adduct **3c** was treated with DMSO and KOH following standard procedures[12] in order to obtain ketone **5**; unfortunately we were unable to isolate from the reaction mixture the desired compound **5** whereas derivatives **6** and **7** were obtained. The structure of **7** was confirmed by X-ray analysis. A possible explanation for the formation of **7** could be that under basic conditions, aromatization of cyclohexane by elimination of hydrochloric acid and ethanol may occur with the concomitant formation of the amide by hydrolysis of CN group. Under the same conditions also hydrolisis of acetamide may occurs. The acidic benzylic proton could be then removed under basic conditions leading to an imine, which could be then hydrolysed to give the ketone **7** (Scheme 5).

In order to overcome the shortcomings of the thermal cycloaddition, compound **2f** was reacted under acid-catalyzed conditions using either acrolein or methyl vinyl ketone as dienophiles; in both cases compounds **3d**–**e** were obtained as a mixture of two major diastereoisomers in high yields (89 and 96%, respectively) as "*ortho*" and *endo* adducts[9,10] (Scheme 6). It is well known that most of the Diels–Alder reactions are accelerated by the presence of a Lewis acid and that their regio- and stereoselectivities are often increased over the uncatalyzed reactions. Both *Z* and *E* dienes turned out to be reactive under catalyzed conditions. In fact, under acidic conditions the *Z* isomer readily isomerizes to the *E* isomer, which again can readily adapt the *s-cis* conformation.

The reactivity of diene **2f** in hetero [4+2] cycloaddiction was also investigated. Diene **2f** underwent cycloaddition with either ethyl glyoxalate and DEAD to afford respectively dihydropyran **3f** and dihydropyridazine **3g** as mixture of diasteroisomers.[13] Compound **2f** was also tried to be react with different imines under several conditions but in no one case the desired cycloadducts **3h**–**j** were obtained (Scheme 7).

First Route. From *N*-Acetylbenzhydrylamines to (*S*)-Bifonazole

Starting from cycloadduct **3e** a synthesis of *N*-acetylbenzhydrylamines with general structure **A** has been developed. The alkoxy group of cyclohexenes could be eliminated under acidic or basic condition.[10,14] Treatment of **3e** with K_2CO_3 in refluxing methanol afforded the elimination product cyclohexadiene **8**; under these conditions racemization was observed and compound **8** showed to have an enantiomeric excess of 22% as revealed by HPLC-MS analysis. When **3e** was submitted to acidic elimination with H_2SO_4 20%, **8** could be obtained in high yield and in enantiomerically pure form. Subsequent oxidation of **8** with DDQ[15] led to the benzhydrylamide **9** which was then converted into the acetyl phenol **10** by Baeyer–Villiger oxidation. After removal of acetyl ester of **10** under mild basic conditions, phenol **11** was obtained and then converted into the corresponding triflate **12**. This latter compound is one of the targets of our synthesis since it represents an important enantiomerically pure building block containing a benzhydrylamino motif and a triflate group which can be coupled through Suzuki reaction with different boronic acids. Since compound **12** is unstable, it was immediately converted into the biary derivative (*S*)-**13**, which showed a 95% *ee* according to HPLC analysis. Compound (*S*)-**13** was then transformed in two steps[16] into the enantiopure bifonazole (*S*)-**15**, whose configuration assignment reported in our previous work was confirmed[3c] (Scheme 8).

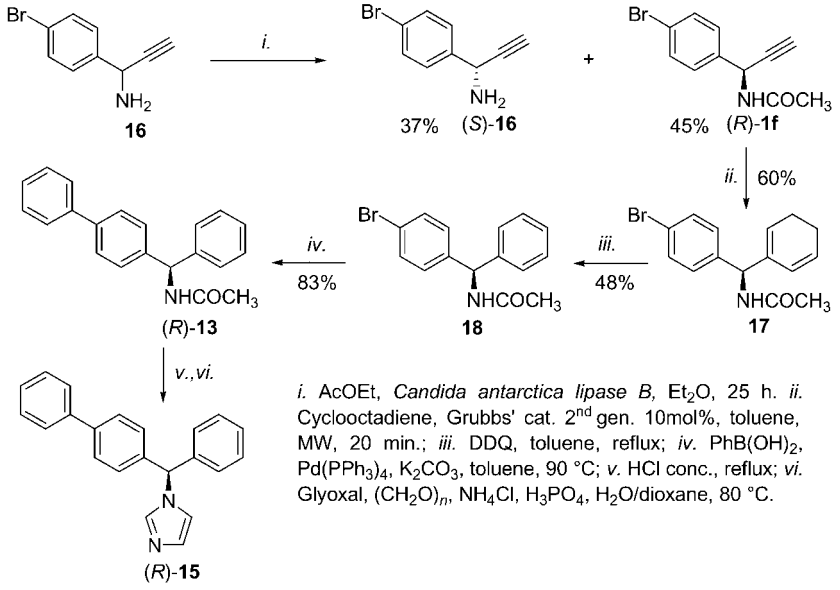


i. H_2SO_4 20%, THF, r.t.; *ii.* DDQ, toluene, reflux; *iii.* m-CPBA, CH_2Cl_2, reflux; *iv.* $NaHCO_3$, H_2O/MeOH, r.t.; *v.* $(TfO)_2O$, pyridine, CH_2Cl_2, r.t.; *vi.* $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 90 °C; *vii.* HCl conc., reflux; *viii.* Glyoxal, $(CH_2O)_n$, NH_4Cl, H_3PO_4, H_2O/dioxane, 80 °C.

Scheme 8.

Second Route. From *N*-Acetyl-bromo-benzhydrylamine to (*R*)-Bifonazole

With the aim to develop a shorter and faster synthesis of benzhydrylamines with general structure **A**, another interesting approach has been developed and examined: the methylene-free tandem-metathesis reaction. Tandem metathesis between alkynes and dienes provides an useful and efficient way for ring synthesis. Diver and co-workers recently reported the synthesis of cyclohexadienes via tandem metathesis starting from different alkynes and using cyclooctadiene.[17] We reasoned that tandem metathesis could be a shorter and elegant approach for the synthesis of enantiopure benzhydrylamines starting from bromo-propargylamide (*R*)-**1f** which was not reported in our previous work.[8] The racemic amine **16** was submitted to enzymatic kinetic resolution using AcOEt as acylating agent and lipase B from *Candida antarctica*, affording enantiopure amide (*R*)-**1f** and amine (*S*)-**16**. Bromo-propargyl amide (*R*)-**1f**[18] was treated with cyclooctadiene in the presence of Grubbs' 2nd generation catalyst (10 mol-%), following our microwave-assisted method.[8b] Under these conditions cy-



i. AcOEt, *Candida antarctica lipase B,* Et_2O, 25 h. *ii.* Cyclooctadiene, Grubbs' cat. 2nd gen. 10mol%, toluene, MW, 20 min.; *iii.* DDQ, toluene, reflux; *iv.* $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, 90 °C; *v.* HCl conc., reflux; *vi.* Glyoxal, $(CH_2O)_n$, NH_4Cl, H_3PO_4, H_2O/dioxane, 80 °C.

Scheme 9.

clohexene **17** was obtained in 60% yield and the unreacted starting material was recovered. Prolonged reaction times and higher catalyst loading (15 mol-%) did not afford any improvement into the yield. Compound **17** was then oxidised with DDQ into **18** which results to be an interesting synthon containing a benzhydrylamino motif.[19] **18** was submitted to Suzuki coupling with phenylboronic acid affording (*R*)-**13** which presented an 97% *ee* according to HPLC analysis. Transformation of (*R*)-**13** into (*R*)-bifonazole (*R*)-**15** was accomplished in two steps without loss of enantiomeric purity[16,3c] (Scheme 9).

Conclusions

In conlusion in this work two approaches for the synthesis of *N*-acetylbenzhydrylamines **12**, **13** and **18** in enantiomerically pure form were developed. Both synthetic procedures revealed to be very efficient and reproducible for the synthesis of biarylmethylamines of type **A**. The alkene-alkyne metathesis reaction between enantiopure 1-aryl-1-propargylamides (*R*)-**1a**–**e** and different alkenes under microwave irradiation as well as the reactivity of resulting dienes toward Diels–Alder cycloaddition were extensively investigated. The feasibility of methylene-free tandem metathesis between alkyne (*R*)-**1f** and cyclooctadiene was also been explored. Finally both enantiomers of antifungal agent bifonazole **15** were synthesised starting from enantiomerically pure *N*-acetylbenzhydrylamines **12** and **18**.

Experimental Section

General: Reagents were obtained from commercial suppliers and used without further purification. Toluene was dried with Na/benzophenone prior to use. Anydrous reactions were run under a positive pressure of dry N_2 or Ar. Merck silica gel 60 was used for flash chromatography (23–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 200 MHz on a Bruker AC200F spectrometer and at 400 MHz on a Bruker Avance DPX400. Chemical shifts are reported relative to $CDCl_3$ at δ = 7.24 ppm and tetramethylsilane at δ = 0.00 ppm. Elemental analyses (C,H,N) were performed in-house.

HPLC and MS Analysis: The purity of compounds was assessed by reverse-phase liquid chromatography and a mass spectrometer (Agilent series 1100 LC/MSD) with a UV detector at λ = 254 nm and an electrospray ionization source (ESI). All the solvents were HPLC grade (Fluka). Mass spectral (MS) data were obtained using an Agilent 1100 LC/MSD VL system (G1946C) with a 0.4 mL/min flow rate using a binary solvent system of 95:5 methyl alcohol/water. UV detection was monitored at 254 nm. Mass spectra were acquired by using electrospray ionization in positive mode scanning over the mass range of 50–1500. The following ion source parameters were used: drying gas flow: 9 mL/min, nebulize pressure: 40 psi, drying gas temperature: 350 °C.

Microwave Irradiation Experiments: Microwave irradiations were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continous focused microwave source with operator-selectable power output from 0 to 300 W. The temperature of the content of a vessel was monitored by using a calibrated infrared-based thermometer mounted under the reaction vessel. All the experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stirbar in the vessel.

Synthesis of (*R*)- [(*R*)-1f] and (*S*)-*N*-Acetyl-1-(4-bromophenyl)prop-2-ynylamine [(*S*)-16]: Compounds (*R*)-**1f** and (*S*)-**1g** such as (*R*)-**1a**–**e** were synthesised starting from **16** (2 g, 7.93 mmol) as reported in the literature.[8]

(*R*)-*N*-Acetyl-1-(4-bromophenyl)prop-2-ynylamine [(*R*)-1f]: Time: 25 h. Yield: 900 mg (45%). ^{1}H NMR ($CDCl_3$): δ = 7.46 (d, *J* = 8.7 Hz, 2 H, Ph), 7.35 (d, *J* = 8.7 Hz, 2 H, Ph), 5.91 (s, 1 H, C*H*N), 2.43 (s, 1 H, CC*H*), 1.95 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1, 44.0, 73.5, 80.0, 122.3, 128.8, 131.8, 137.4, 168.8 ppm. IR (KBr): $\tilde{\nu}$ = 1669, 1486 cm^{-1}. MS: *m*/*z* = 274/276 [M + Na]. $[\alpha]_D^{20}$ = +50.1 (*c* = 0.6, $CHCl_3$). $C_{11}H_{10}BrNO$ (252.11): calcd. C 52.41, H 4.00, N 5.56; found C 52.30, H 4.29, N 5.89.

(*S*)-1-(4-Bromophenyl)prop-2-ynylamine [(*S*)-16]: Time: 25 h. Yield: 615 mg (37%). ^{1}H NMR ($CDCl_3$): δ = 7.28 (d, *J* = 8.4 Hz, 2 H, Ph), 7.22 (d, *J* = 8.4 Hz, 2 H, Ph), 4.51 (s, 1 H, C*H*N), 2.41 (s, 1 H, CC*H*), 1.75 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 46.0, 72.4, 85.3, 121.0, 128.0, 131.0, 140.1 ppm. IR (KBr): $\tilde{\nu}$ = 3295, 1661, 1534 cm^{-1}. MS: *m*/*z* = 232/234 [M + Na]. $[\alpha]_D^{20}$ = +20.0 (*c* = 2.4, $CHCl_3$). C_9H_8BrN (210.07): calcd. C 51.46, H 3.84, N 6.67; found C 51.72, H 4.02, N 6.70.

Synthesis of (*R*)- and (*S*)-2-[(Acetylamino)arylmethyl]-1,3-butadiene [(*R*)-2a–e]. General Procedure: Into an oven-dried pressure vial equipped with magnetic stirbar and under argon, (*R*)-**1a**–**e** (0.6 mmol) was dissolved in 4 mL of degassed toluene. Grubbs' 2nd generation catalyst (10 mol-%) was then added and the mixture was submitted to ethylene atmosphere whilst stirring. The vessel was introduced into the microwave oven and heated at 80 °C twice for 10 minutes under microwave irradiation. Dimethyl sulfoxide (DMSO) (50 equiv.) was added and the reaction mixture was left whilst stirring for 12 h; the solvent was then removed in vacuo to afford a dark brown oil that was purified by flash chromatography (Et_2O/petroleum ether, 2:1) to give (*R*)-**2a**–**e** as a clear oil.

(*R*)-2-[(Acetylamino)phenylmethyl]-1,3-butadiene (2a): Yield: 54 mg (45%). Oil. ^{1}H NMR ($CDCl_3$): δ = 7.47–7.26 (m, 5 H, Ph), 6.39–6.24 (dd, *J* = 17.6, *J* = 11.2 Hz, 1 H, CC*H*CH_2), 5.89 (d, *J* = 7.9 Hz, 1 H, C*H*N), 5.81 (br. d, *J* = 7.9 Hz, 1 H, N*H*), 5.31 (s, 1 H, CCH_2), 5.19 (d, *J* = 17.7 Hz, 1 H, CCHCH_2), 5.09 (s, 1 H, CCH_2), 5.05 (d, *J* = 12.0 Hz, 1 H, CCHCH_2), 2.00 (s, 3 H, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1676, 1497 cm^{-1}. MS: *m*/*z* = 202 [M + 1], 224 [M + Na]. $[\alpha]_D^{20}$ = +34.0 (*c* = 0.8, $CHCl_3$). $C_{13}H_{15}NO$ (201.26): calcd. C 77.58, H 7.51, N 6.96; found C 77.66, H 7.73, N 7.05.

(*R*)-2-[(Acetylamino)(4-fluorophenyl)methyl]-1,3-butadiene (2b): Yield: 81.4 mg (62%). Oil. ^{1}H NMR ($CDCl_3$): δ = 7.27–7.19 (m, 2 H, Ph), 7.09–7.02 (m, 2 H, Ph), 6.36–6.29 (dd, *J* = 17.8, *J* = 10.8 Hz, 1 H, CC*H*CH_2), 5.85 (d, *J* = 7.8 Hz, 1 H, C*H*N), 5.70 (br. d, *J* = 7.9 Hz, 1 H, N*H*), 5.31 (s, 1 H, CCH_2), 5.18 (d, *J* = 17.8 Hz, 1 H, CCHCH_2), 5.08 (d, *J* = 10.7 Hz, 1 H, CCHCH_2), 5.06 (s, 1 H, CCH_2), 2.01 (s, 3 H, CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1676, 1497 cm^{-1}. MS: *m*/*z* = 220 [M + 1], 242 [M + Na]. $[\alpha]_D^{20}$ = +36.0 (*c* = 1.0, $CHCl_3$). $C_{13}H_{14}FNO$ (219.25): calcd. C 71.21, H 6.44, N 6.39; found C 71.33, H 6.54, N 6.20.

(*R*)-2-[(Acetylamino)(4-chlorophenyl)methyl]-1,3-butadiene (2c): Yield: 96.2 mg (68%). Oil. ^{1}H NMR ($CDCl_3$): δ = 7.30–7.17 (m, 4 H, Ph), 6.38–6.24 (dd, *J* = 17.7, *J* = 10.9 Hz, 1 H, CC*H*CH_2), 5.86 (d, *J* = 7.9 Hz, 1 H, C*H*N), 5.76 (br. d, *J* = 7.9 Hz, 1 H, N*H*), 5.31 (s, 1 H, CCH_2), 5.18 (d, *J* = 17.8 Hz, 1 H, CCHCH_2), 5.08 (d, *J* = 10.9 Hz, 1 H, CCHCH_2), 5.05 (s, 1 H, CCH_2), 2.02 (s, 3 H, CH_3)

ppm. IR (KBr): ṽ = 1676, 1497 cm^{-1}. MS: *m*/*z* (%) = 238 [M + 1], 258/260 [M + Na]. $[\alpha]_D^{20}$ = +69.0 (*c* = 1.0, $CHCl_3$). $C_{13}H_{14}ClNO$ (235.71): calcd. C 66.24, H 5.99, N 5.94; found C 66.40, H 6.10, N 6.08.

(*R*)-2-[(Acetylamino)(3-fluorophenyl)methyl]-1,3-butadiene (2d): Yield: 71.0 mg (54%). Oil. ^{1}H NMR ($CDCl_3$): δ = 7.38–7.28 (m, 1 H, Ph), 7.26–6.89 (m, 3 H, Ph), 6.38–6.23 (dd, *J* = 17.3, *J* = 10.8 Hz, 1 H, CC*H*CH_2), 5.88 (d, *J* = 7.7 Hz, 1 H, C*H*N), 5.73 (br. d, *J* = 7.7 Hz, 1 H, N*H*), 5.32 (s, 1 H, CCH_2), 5.20 (d, *J* = 17.7 Hz, 1 H, CCHCH_2), 5.10 (d, *J* = 10.8 Hz, 1 H, CCHCH_2), 5.06 (s, 1 H, CCH_2), 2.03 (s, 3 H, CH_3) ppm. IR (KBr): ṽ = 1676, 1497 cm^{-1}. MS: *m*/*z* (%) = 220 [M + 1], 242 [M + Na]. $[\alpha]_D^{20}$ = +20.0 (*c* = 0.6, $CHCl_3$). $C_{13}H_{14}FNO$ (219.25): calcd. C 71.21, H 6.44, N 6.39; found C 71.39, H 6.60, N 6.46.

(*R*)-2-[(Acetylamino)(3-methylphenyl)methyl]-1,3-butadiene (2e): Yield: 63.2 mg (49%). Oil. ^{1}H NMR ($CDCl_3$): δ = 7.28–7.04 (m, 4 H, Ph), 6.37–6.23 (dd, *J* = 17.6, *J* = 11.0 Hz, 1 H, CC*H*CH_2), 5.94 (br. d, *J* = 7.7 Hz, 1 H, N*H*), 5.84 (d, *J* = 7.9 Hz, 1 H, C*H*N), 5.30 (s, 1 H, CCH_2), 5.19 (d, *J* = 17.7 Hz, 1 H, CCHCH_2), 5.10 (s, 1 H, CCH_2), 5.05 (d, *J* = 11.1 Hz, 1 H, CCHCH_2), 2.31 (s, 3 H, PhCH_3), 2.00 (s, 3 H, CH_3) ppm. IR (KBr): ṽ = 1676, 1497 cm^{-1}. MS: *m*/*z* = 216 [M + 1], 238 [M + Na]. $[\alpha]_D^{20}$ = +35.0 (*c* = 0.7, $CHCl_3$). $C_{14}H_{17}NO$ (215.29): calcd. C 78.10, H 7.96, N 6.51; found C 78.23, H 8.04, N 6.69.

Synthesis of (*R*)-*N*-[(*E*/*Z*)-2-Methylene-1-phenylbut-3-enyl]acetamides 2f–j. General Procedure: Into an oven-dried pressure vial equipped with magnetic stirbar and under argon, (*R*)-**1a** (1.15 mmol) was dissolved in 3 mL of degassed toluene. Grubbs' 2nd generation catalyst (10 mol-%) and the appropriate vinyl compound (9 equiv/mol) were then added. The vessel was introduced into the microwave oven and heated at 80 °C twice for 10 minutes under microwave irradiation. After cooling, the solvent was removed in vacuo to afford a dark brown oil that was purified by flash chromatography (Et_2O/petroleum ether, 2:1) to give **2f–j** as a *E*/*Z* mixture (proton NMR indicates a 1.0:0.5 *E*/*Z* ratio).

(*R*)-*N*-[(*E*/*Z*)-4-Ethoxy-2-methylene-1-phenylbut-3-enyl]acetamide (2f): Yield: 247.9 mg (88%). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.18 (m, 10 H, Ph), 6.49 (d, *J* = 12.9 Hz, 1 H, CHC*H*OEt, *E*), 6.44 (d, *J* = 8.0 Hz, 1 H, CN*H*, *Z*), 6.14 (d, *J* = 8.0 Hz, 1 H, CN*H*, *E*), 5.85 (d, *J* = 7.0 Hz, 1 H, CHC*H*OEt, *Z*), 5.80 (d, *J* = 8.0 Hz, 1 H, C*H*N, *Z*), 5.70 (d, *J* = 8.0 Hz, 1 H, C*H*N, *E*), 5.42 (d, *J* = 12.9 Hz, 1 H, C*H*CHOEt, *E*), 5.39 (s, 1 H, C=C*H*H, *Z*), 5.12 (s, 1 H, C=CH*H*, *Z*), 5.02 (s, 1 H, C=C*H*H, *E*), 4.78 (s, 1 H, C=CH*H*, *E*), 4.70 (d, *J* = 7.0 Hz, 1 H, C*H*CHOEt, *Z*), 3.67 (q, *J* = 7.0 Hz, 4 H, OCH_2CH$_3$, *E*/*Z*), 1.98 (s, 3 H, CH_3, *Z*), 1.96 (s, 3 H, CH_3, *E*), 1.17 (t, *J* = 7.0 Hz, 3 H, OCH$_2$CH_3, *E*), 1.05 (t, *J* = 7.0 Hz, 3 H, OCH$_2$CH_3, *Z*) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 15.0, 23.1, 23.4, 55.0, 57.3, 65.4, 68.8, 104.1, 105.8, 111.1, 115.5, 126.9, 127.1, 127.3, 127.9, 128.1, 128.4, 140.3, 140.7, 141.7, 143.4, 145.9, 148.7, 169.1 ppm. IR (KBr): ṽ = 1667, 1496 cm^{-1}. MS: *m*/*z* = 246 [M + 1], 268 [M + Na]. $C_{15}H_{19}NO_2$ (245.32): calcd. C 73.44, H 7.81, N 5.71; found C 73.55, H 7.93, N 5.88.

(*R*)-*N*-[(*E*/*Z*)-4-Acetoxy-2-methylene-1-phenylbut-3-enyl]acetamide (2g): Yield: 157.8 mg (53%). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.23 (m, 11 H, Ph, CHC*H*OAc, *E*), 6.97 (d, *J* = 7.4 Hz, 1 H, CHC*H*OAc, *Z*), 6.93 (br. s, 1 H, CN*H*, *E*), 6.21 (br. s, 1 H, CN*H*, *Z*), 5.94 (d, *J* = 12.3 Hz, 1 H, C*H*CHOAc, *E*), 5.90 (d, *J* = 8.2 Hz, 1 H, C*H*N, *Z*), 5.72 (d, *J* = 8.0 Hz, 1 H, C*H*N, *E*), 5.54 (s, 2 H, C=C*H*H, *Z*/*E*), 5.26 (s, 1 H, C=CH*H*, *Z*), 5.08 (s, 1 H, C=C*H*H, *E*), 4.19 (d, *J* = 7.4 Hz, 1 H, C*H*CHOAc, *Z*), 2.04 (s, 3 H, OCOCH_3, *E*), 2.01 (s, 3 H, OCOCH_3, *Z*), 2.00 (s, 6 H, NCOCH_3, *Z*/*E*) ppm. IR (KBr): ṽ = 3442, 1759, 1673, 1496 cm^{-1}. MS: *m*/*z* = 260 [M + 1], 282 [M + Na]. $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 69.60, H 6.84, N 5.67.

(*R*)-*N*-[(*E*/*Z*)-4-Cyano-2-methylene-1-phenylbut-3-enyl]acetamide (2i): Yield: 205.3 mg (79%). ^{1}H NMR ($CDCl_3$): δ = 7.32–7.00 (m, 11 H, Ph, C*H*CHCN, *Z*), 6.81 (d, *J* = 10.2 Hz, 1 H, CHC*H*CN, *E*), 6.30 (d, *J* = 10.2 Hz, 1 H, C*H*CHCN, *E*), 6.33 (d, *J* = 8.0 Hz, 1 H, C*H*N, *Z*), 6.00 (s, 1 H, C=C*H*H, *E*), 5.75 (s, 1 H, C=C*H*H, *Z*), 5.73 (d, *J* = 8.2 Hz, 1 H, C*H*N, *E*), 5.53 (s, 1 H, C=CH*H*, *E*), 5.36 (s, 1 H, C=C*H*H, *Z*), 5.22 (m, 1 H, CHC*H*CN, *Z*), 2.02 (s, 3 H, NCOCH_3, *Z*), 2.00 (s, 3 H, NCOCH_3, *E*) ppm. IR (KBr): ṽ = 2238, 1661, 1494 cm^{-1}. MS: *m*/*z* = 227 [M + 1], 249 [M + Na]. $C_{14}H_{14}N_2O$ (226.27): calcd. C 74.31, H 6.24, N 12.38; found C 74.56, H 6.54, N 12.56.

(*R*)-*N*-[(*E*/*Z*)-4-(3-Methoxyphenyl)-2-methylene-1-phenylbut-3-enyl]acetamide (2j): Yield: 204.7 mg (58%). ^{1}H NMR ($CDCl_3$): δ = 7.42–7.02 (m, 19 H, Ph, C*H*CHPhOMe, *Z*), 6.75 (d, *J* = 11.2 Hz, 1 H, C*H*CHPhOMe, *E*), 6.62–6.56 (m, 2 H, CHC*H*PhOMe, *Z*/*E*), 5.99 (s, 1 H, C=C*H*H, *Z*), 5.96 (d, *J* = 8.6 Hz, 1 H, C*H*N, *Z*), 5.42 (s, 2 H, C=CH*H*, *Z*/*E*), 5.24 (m, 1 H, C*H*N, *E*), 5.14 (s, 1 H, C=C*H*H, *E*), 3.77 (s, 3 H, OCH_3, *E*), 3.73 (s, 3 H, OCH_3, *Z*), 2.02 (s, 6 H, NCOCH_3, *Z*/*E*) ppm. IR (KBr): ṽ = 1664, 1494 cm^{-1}. MS: *m*/*z* = 308 [M + 1], 330 [M + Na]. $C_{20}H_{21}NO_2$ (307.39): calcd. C 78.15, H 6.89, N 4.56; found C 78.34, H 6.99, N 4.78.

Synthesis of Cyclohexenes 3a–c. General Procedure: Into an oven-dried baloon equipped with a condenser, **2f** (200 mg, 0.8 mmol) was dissolved in dry toluene (5.6 mL). The appropriate dienophile (2 equiv/mol) was then added and the mixture stirred at 80–90 °C for 24 hours. After this time, the solution was cooled, water was added and the mixture left stirring for 30 min. The mixture was then extracted with AcOEt two times. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **3a–c**. The crude products were purified by flash chromatography on silica gel, using Et_2O/petroleum ether (2:1) as eluant. After purification *Z*-dienes isomers were recovered. Compounds **3a–c** were obtained as a mixture of diastereoismers. Proton NMR indicate two major diastereoisomers (*endo* and *exo*) in 1:2.5 ratio.

Methyl 4-[(Acetylamino)(phenyl)methyl]-2-ethoxycyclohex-3-ene-1-carboxylate (3a, "*ortho*"): Yield: 140.3 mg (53%). ^{1}H NMR ($CDCl_3$): δ = 7.27–7.20 (m, 10 H, Ph), 6.15 (d, *J* = 8.5 Hz, 1 H, N*H*), 6.10 (d, *J* = 8.6 Hz, 1 H, N*H*), 5.86 (d, *J* = 3.7 Hz, 1 H, C=C*H*), 5.78 (d, *J* = 4.3 Hz, 1 H, C=C*H*), 5.50 (d, *J* = 8.6 Hz, 1 H, C*H*N), 5.42 (d, *J* = 8.5 Hz, 1 H, C*H*N), 4.12–4.01 (m, 2 H, 2 C*H*OEt), 3.65 (s, 6 H, 2 COOCH_3), 3.62–3.42 (m, 4 H, 2 OCH_2CH$_3$), 2.55–2.47 (m, 2 H, 2 C*H*COOCH$_3$), 2.08–1.81 (m, 8 H, 2 CCH_2CH_2CH), 2.02 (s, 3 H, NCOCH_3), 2.01 (s, 3 H, NCOCH_3), 1.24–1.02 (m, 6 H, 2 OCH$_2$CH_3) ppm. IR (KBr): ṽ = 1725, 1671, 1496 cm^{-1}. MS: *m*/*z* = 332 [M + 1], 354 [M + Na]. $C_{19}H_{25}NO_4$ (331.41): calcd. C 68.86, H 7.60, N 4.23; found C 68.59, H 7.69, N 4.36.

***N*-[(4-Cyano-3-ethoxycyclohex-1-enyl)(phenyl)methyl]acetamide (3b):** Yield: 140.6 mg (59%). ^{1}H NMR ($CDCl_3$): δ = 7.32–7.12 (m, 10 H, Ph), 5.87 (d, *J* = 7.6 Hz, 1 H, N*H*), 5.83 (d, *J* = 7.5 Hz, 1 H, N*H*), 5.72 (d, *J* = 1.8 Hz, 1 H, C=C*H*), 5.68 (m, 1 H, C=C*H*), 5.48 (d, *J* = 7.6 Hz, 1 H, C*H*N), 5.45 (d, *J* = 7.5 Hz, 1 H, C*H*N), 4.06 (m, 2 H, 2 C*H*OEt), 3.72–3.43 (dq, *J* = 7.3 Hz, 4 H, 2 OCH_2CH$_3$), 2.83–2.69 (m, 2 H, 2 C*H*CN), 2.05–1.76 (m, 8 H, 2 CCH_2CH_2CH), 1.98 (s, 6 H, 2 NCOCH_3), 1.25–1.16 (dt, *J* = 7.3 Hz, 6 H, 2 OCH$_2$CH_3) ppm. IR (KBr): ṽ = 2239, 1667, 1496 cm^{-1}. MS: *m*/*z* = 299 [M + 1], 321 [M + Na]. $C_{18}H_{22}N_2O_2$ (298.38): calcd. C 72.46, H 7.43, N 9.39; found C 72.59, H 7.65, N 9.57.

***N*-[(4-Chloro-4-cyano-3-ethoxycyclohex-1-enyl)(phenyl)methyl]acetamide (3c):** Yield: 82.3 mg (31%). ^{1}H NMR ($CDCl_3$): δ = 7.35–7.19 (m, 10 H, Ph), 5.94 (d, J = 8.5 Hz, 1 H, N*H*), 5.89 (d, J = 7.9 Hz, 1 H, N*H*), 5.67 (m, 1 H, C=C*H*), 5.61 (d, J = 3.1 Hz, 1 H, C=C*H*), 5.53 (d, J = 8.6 Hz, 1 H, C*H*N), 5.43 (d, J = 7.9 Hz, 1 H, C*H*N), 4.14–4.02 (m, 2 H, 2 C*H*OEt), 3.88–3.70 (m, 4 H, 2 OCH_2CH$_3$), 2.49–2.33 (m, 2 H, 2 C*H*ClCN), 2.28–1.78 (m, 8 H, 2 CCH_2CH_2CH), 1.99 (s, 6 H, 2 NCOCH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2240, 1667, 1496 cm^{-1}. MS: *m*/*z* = 333/335 [M + 1], 355/357 [M + Na]. $C_{18}H_{21}ClN_2O_2$ (332.82): calcd. C 64.96, H 6.36, N 8.42; found C 64.78, H 6.53, N 8.74.

Synthesis of Cyclohexenes 3d–e. General Procedure: A solution of BF_3·Et_2O (1.1 mmol) and dienophile (1.1 mmol) in CH_2Cl_2 (3 mL) was stirred at –30 °C under argon for 20 min. To the mixture cooled to –78 °C was added a solution of the diene (1 mmol) in CH_2Cl_2 (3 mL) and stirring was continued for an additional 60 min. The mixture was quenched with $NaHCO_3$ (10 mL) and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **3d**–**e**. The crude products were purified by flash chromatography on silica gel, using Et_2O/petroleum ether (2:1) as eluant. Compounds **3d**–**e** were obtained as a mixture of diastereoisomers. Proton NMR indicate two major diastereoisomers in 1:0.5 ratio.

***N*-[(3-Ethoxy-4-formylcyclohex-1-enyl)(phenyl)methyl]acetamide (3d):** Yield: 267.9 mg (89%). ^{1}H NMR ($CDCl_3$): δ = 9.73 (s, 1 H, C*H*O), 9.42 (s, 1 H, C*H*O), 7.31–7.15 (m, 10 H, Ph), 6.33 (d, J = 7.6 Hz, 1 H, N*H*), 6.05 (d, J = 8.0 Hz, 1 H, N*H*), 5.91 (d, J = 2.1 Hz, 1 H, C=C*H*), 5.75 (d, J = 4.3 Hz, 1 H, C=C*H*), 5.58 (d, J = 8.0 Hz, 1 H, C*H*N), 5.48 (d, J = 7.6 Hz, 1 H, C*H*N), 4.26–4.19 (m, 2 H, 2 C*H*OEt), 3.67–3.40 (m, 4 H, 2 OCH_2CH$_3$), 2.55–2.45 (m, 2 H, 2 C*H*COH), 2.40–1.75 (m, 8 H, 2 CCH_2CH_2CH), 1.97 (s, 3 H, NCOCH_3), 1.96 (s, 3 H, NCOCH_3), 1.24–1.06 (m, 6 H, 2 OCH$_2$CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1729, 1665, 1496 cm^{-1}. MS: *m*/*z* = 302 [M + 1], 324 [M + Na]. $C_{18}H_{23}NO_3$ (301.38): calcd. C 71.73, H 7.69, N 4.65; found C 71.91, H 7.84, N 4.79.

***N*-[(4-Acetyl-3-ethoxycyclohex-1-enyl)(phenyl)methyl]acetamide (3e):** Yield: 302.4 mg (96%). ^{1}H NMR ($CDCl_3$): δ = 7.24–7.08 (m, 10 H, Ph), 6.84 (d, J = 8.3 Hz, 1 H, N*H*), 5.85 (d, J = 4.5 Hz, 1 H, C=C*H*), 5.79 (d, J = 4.5 Hz, 1 H, C=C*H*), 5.41 (d, J = 8.3 Hz, 1 H, C*H*N), 5.35 (d, J = 8.2 Hz, 1 H, C*H*N), 4.10–4.03 (m, 2 H, 2 C*H*OEt), 3.47 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 3.27 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 2.58–2.28 (m, 2 H, 2 C*H*COCH$_3$), 2.18–1.43 (m, 8 H, 2 CCH_2CH_2CH), 2.05 (s, 3 H, COCH_3), 2.01 (s, 3 H, COCH_3), 1.86 (s, 3 H, NCOCH_3), 1.82 (s, 3 H, NCOCH_3), 1.02–0.93 (dt, J = 7.1 Hz, 6 H, 2 OCH$_2$CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1740, 1661, 1494 cm^{-1}. MS: *m*/*z* = 316 [M + 1], 338 [M + Na]. $C_{19}H_{25}NO_3$ (315.41): calcd. C 72.35, H 7.99, N 4.44; found C 72.54, H 8.09, N 4.73.

Synthesis of *N*-Acetyl-3-methyl-2-phenyl-1*H*-pyrrole (4): Diene **2f** (*Z* isomer, 2 mmol) was dissolved in dry toluene (14 mL) and the mixture was refluxed for 24 hours. After cooling, the solvent was removed in vacuo to afford a dark brown oil that was purified by flash chromatography (Et_2O/petroleum ether, 2:1) to give **4** as a dark red oil. Yield: 278.6 mg (70%). ^{1}H NMR ($CDCl_3$): δ = 7.22–7.08 (m, 6 H, Ph and C*H*N), 6.01 (d, J = 3.4 Hz, 1 H, CHC*H*C), 1.99 (s, 3 H, NCOCH_3), 1.77 (s, 3 H, CCH$_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.8, 25.0, 114.2, 120.7, 123.6, 127.8, 128.4, 130.5, 130.7, 134.0, 168.9 ppm. IR (KBr): $\tilde{\nu}$ = 1661, 1494 cm^{-1}. MS: *m*/*z* = 200 [M + 1], 222 [M + Na]. $C_{13}H_{13}NO$ (199.25): calcd. C 78.36, H 6.58, N 7.03; found C 78.56, H 6.76, N 6.89.

Synthesis of Diethyl 5-[(Acetylamino)(phenyl)methyl]-3-ethoxy-3,6-dihydropyridazine-1,2-dicarboxylate (3f): Into an oven-dried balloon (*R*)-**2f** (0.12 mmol) was dissolved in dry toluene (2 mL). DEAD (1.2 equiv/mol) was then added and the mixture stirred at room temperature for 1 hour. The solvent was then removed under reduced pressure to give the crude **3f** which was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Compound **3f** was obtained as a mixture of two diastereoisomers in 1:0.6 ratio. Yield: 37.71 mg (75%). ^{1}H NMR ($CDCl_3$): δ = 7.27–7.15 (m, 10 H, Ph), 6.13 (d, J = 7.9 Hz, 1 H, C*H*OEt), 6.03 (d, J = 7.3 Hz, 1 H, C*H*OEt), 5.77 (m, 1 H, C*H*N), 5.59–5.55 (m, 2 H, C*H*N and C=C*H*), 5.50 (d, J = 8.0 Hz, 1 H, C=C*H*), 4.47–4.07 (m, 8 H, 2 COOCH_2CH$_3$), 3.80–3.49 (m, 4 H, 2 OCH_2CH$_3$), 1.95 (s, 3 H, NCOCH_3), 1.94 (s, 3 H, NCOCH_3), 1.25–1.14 (m, 18 H, 2 COOCH$_2$CH_3 and 2 OCH$_2$CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1740, 1660 cm^{-1}. MS: *m*/*z* = 420 [M + 1], 442 [M + Na]. $C_{21}H_{29}N_3O_6$ (419.47): calcd. C 60.13, H 6.97, N 10.02; found C 60.35, H 7.09, N 10.27.

Synthesis of Ethyl 5-[(Acetylamino)(phenyl)methyl]-6-ethoxy-3,6-dihydro-2*H*-pyran-2-carboxylate (3g): Into an oven-dried balloon (*R*)-**2f** (0.24 mmol) was dissolved in dry CH_2Cl_2 (2 mL) and the mixture was cooled to –30 °C. Ethyl glyoxalate (2 equiv./mol) was then added and the mixture stirred at room temperature for 24 hours. After this time, the solution was cooled, $NaHCO_3$ was added and the mixture left stirring for 30 min. The mixture was then extracted with AcOEt two times. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **3g**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Compound **3g** was obtained as a mixture of diastereoisomers. Proton NMR indicate two major diastereoisomers (*endo* and *exo*) in 1:0.5 ratio. Yield: 52.3 mg (70%). ^{1}H NMR ($CDCl_3$): δ = 7.27–7.20 (m, 10 H, Ph), 6.00–5.96 (m, 2 H, 2 C=C*H*), 5.63–5.55 (m, 2 H, 2 C*H*N), 5.15 (m, 2 H, 2 C*H*OEt), 4.50–4.26 (m, 2 H, 2 C*H*COOEt), 4.16 (dq, J = 7.1 Hz, 4 H, 2 COOCH_2CH$_3$), 3.86–3.51 (m, 4 H, 2 OCH_2CH$_3$), 2.25–1.87 (m, 4 H, 2 CCH_2CH), 1.99 (s, 3 H, NCOCH_3), 1.95 (s, 3 H, NCOCH_3), 1.29–1.13 (m, 12 H, 2 COOCH$_2$CH_3 and 2 OCH$_2$CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 1743, 1653 cm^{-1}. MS: *m*/*z* = 348 [M + 1], 370 [M + Na]. $C_{19}H_{25}NO_5$ (347.41): calcd. C 65.69, H 7.25, N 4.03; found C 65.89, H 7.43, N 4.32.

Synthesis of Ketones 6 and 7: KOH (47 mg, 0.84 mmol) was dissolved in DMSO (4 mL) and H_2O (1.5 mL) and heated at 50 °C for 10 min. After cooling to room temperature, a solution of **3c** (140 mg, 0.42 mmol) in DMSO (1 mL) was added dropwise and the mixture was stirred at 70 °C for 24 hours. The solution was cooled and water was added. The mixture was stirred for an additional 10 min. and then extracted with AcOEt. The combined organic layers were washed with brine once more, dried (Na_2SO_4), filtered and evaporated to give the crude mixture of **6** and **7**. The crude products were purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. **Ketone 7:** Yield: 41.6 mg (44%). ^{1}H NMR ($CDCl_3$): δ = 7.88–7.72 (m, 6 H, Ph), 7.59–7.41 (m, 3 H, Ph), 6.26 (br. s, 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 127.5, 128.7, 130.3, 130.4, 133.2, 136.7, 137.2, 140.8, 168.6, 195.8 ppm. IR (KBr): $\tilde{\nu}$ = 1731, 1661, 1598 cm^{-1}. MS: *m*/*z* = 226 [M + 1], 248 [M + Na]. $C_{14}H_{11}NO_2$ (225.24): calcd. C 74.65, H 4.92, N 6.22; found C 74.76, H 5.10, N 6.35.

Synthesis of Acetamide (*S*)-8: To a stirred solution of **3e** (3.8 mmol) in THF (50 mL) at 0 °C, H_2SO_4 20% (38 mL) was added and the resulting solution was stirred at room temperature for 24 hours. The reaction mixture was poured into AcOEt/brine and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **8**. The crude product was purified by flash chromatography on silica gel,

using AcOEt/petroleum ether (4:1) as eluant. Yield: 817.7 mg (80%). ^{1}H NMR ($CDCl_3$): δ = 7.33–7.24 (m, 5 H, Ph), 6.92 (d, J = 5.0 Hz, 1 H, CHC*H*), 6.06 (d, J = 5.0 Hz, 1 H, C*H*CH), 5.86 (d, J = 7.3 Hz, 1 H, N*H*), 5.59 (d, J = 7.7 Hz, 1 H, C*H*N), 2.45–1.94 (m, 4 H, CH_2CH_2), 2.28 (s, 3 H, COCH_3), 1.98 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.3, 23.3, 25.1, 25.3, 58.0, 119.2, 127.6, 128.2, 129.0, 141.7, 141.9, 146.3, 133.9, 171.9, 198.4 ppm. IR (KBr): $\tilde{\nu}$ = 1740, 1661, 1494 cm^{-1}. MS: m/z = 270 [M + 1], 292 [M + Na]. $[\alpha]_D^{20}$ = –12.0 (c = 1.0, $CHCl_3$). $C_{17}H_{19}NO_2$ (269.34): calcd. C 75.81, H 7.11, N 5.20; found C 75.99, H 7.32, N 5.44.

Synthesis of *N*-[(*S*)-(4-Acetylphenyl)(phenyl)methyl]acetamide (9): Compound **8** (2.97 mmol) was dissolved in toluene (100 mL). DDQ (5.94 mmol) was added and the reaction was refluxed and stirred for 3 hours. The reaction mixture was quenched with water (50 mL) and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **9**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (4:1) as eluant. Yield: 380 mg (48%). ^{1}H NMR ($CDCl_3$): δ = 7.84 (d, J = 8.4 Hz, 2 H, Ph), 7.30–7.04 (m, 7 H, Ph), 6.66 (d, J = 7.7 Hz, 1 H, N*H*), 6.19 (d, J = 7.7 Hz, 1 H, C*H*N), 2.51 (s, 3 H, COCH_3), 2.01 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1, 26.6, 56.9, 121.7, 127.6, 127.4, 128.6, 128.8, 136.1, 140.7, 146.8, 169.5, 197.7 ppm. IR (KBr): $\tilde{\nu}$ = 1701, 1664, 1494 cm^{-1}. MS: m/z = 268 [M + 1], 290 [M + Na]. $[\alpha]_D^{20}$ = +16.4 (c = 1.5, $CHCl_3$). $C_{17}H_{17}NO_2$ (267.32): calcd. C 76.38, H 6.41, N 5.24; found C 76.45, H 6.67, N 5.39.

Synthesis of (*S*)-*N*-[(4-Acetoxyphenyl)(phenyl)methyl]acetamide (10): Compound **9** (1 mmol) was dissolved in CH_2Cl_2 (10 mL). *m*-Choroperbenzoic acid (*m*-CPBA) (3 mmol) was added in portions and the reaction was refluxed and stirred for 8 hours. The reaction was quenched with $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with Na_2SO_3, brine and finally dried (Na_2SO_4), filtered and evaporated to give the crude **10**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (4:1) as eluant. Yield: 212.2 mg (75%). ^{1}H NMR ($CDCl_3$): δ = 7.85 (d, J = 7.9 Hz, 2 H, Ph), 7.31–7.01 (m, 7 H, Ph), 6.73 (d, J = 7.8 Hz, 1 H, N*H*), 6.17 (d, J = 7.8 Hz, 1 H, C*H*N), 2.25 (s, 3 H, OCOCH_3), 2.01 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.4, 21.1, 56.4, 121.7, 127.6, 127.9, 128.0, 128.7, 133.1, 139.1, 146.7, 169.2, 169.4 ppm. IR (KBr): $\tilde{\nu}$ = 1661, 1454 cm^{-1}. MS: m/z = 284 [M + 1], 306 [M + Na]. $[\alpha]_D^{20}$ = .13.2 (c — 0.7, CH_2Cl_2). $C_{17}H_{17}NO_3$ (283.32): calcd. C 72.07, H 6.05, N 4.94; found C 72.34, H 6.29, N 5.09.

Synthesis of (*S*)-*N*-[(4-Hydroxyphenyl)(phenyl)methyl]acetamide (11): Compound **10** (1 mmol) was dissolved in a mixture of H_2O/MeOH (15:30 mL) and then a saturated solution of $NaHCO_3$ (20 mL) was added dropwise. The reaction was stirred at room temperature for 1.5 hours. The reaction was quenched with HCl 2 N and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **11**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (4:1) as eluant. Yield: 228.9 mg (95%). ^{1}H NMR ($CDCl_3$): δ = 7.59–7.21 (m, 7 H, Ph), 7.03 (m, 2 H, Ph), 6.15 (d, J = 7.9 Hz, 1 H, N*H*), 6.10 (br. s, 1 H, O*H*), 5.28 (s, 1 H, C*H*N), 2.10 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.4, 56.5, 115.5, 127.2, 127.4, 128.6, 128.7, 133.4, 141.7, 155.4, 169.4 ppm. IR (KBr): $\tilde{\nu}$ = 3598, 1673, 1496 cm^{-1}. MS: m/z = 242 [M + 1], 264 [M + Na]. $[\alpha]_D^{20}$ = –38.0 (c = 0.5, MeOH). $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.86, H 6.45, N 5.98.

Synthesis of 4-[(Acetylamino)(phenyl)methyl]phenyl (*S*)-Trifluoromethanesulfonate (12): Phenol **11** (0.2 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to –20 °C. Pyridine (1.0 mmol) was added dropwise and the mixture stirred at this temperature for 10 min. Then $(TfO)_2O$ (0.26 mmol) was added and the resulting solution was stirred at room temperature for 2 hours. The reaction was quenched with HCl 2 N and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **12** which was used in the next step without any further purification. ^{1}H NMR ($CDCl_3$): δ = 7.91 (m, 2 H, Ph), 7.53–7.21 (m, 7 H, Ph), 6.24 (d, J = 7.7 Hz, 1 H, C*H*N), 2.09 (s, 3 H, NCOCH_3) ppm. MS: m/z = 394/396 [M + Na].

Synthesis of (*S*)-*N*-[(Biphenyl-4-yl)(phenyl)methyl]acetamide [(*S*)-13]: Triflate **12** was dissolved in toluene (4 mL) and K_2CO_3 (0.24 mmol) and phenylboronic acid (0.32 mmol) were added. The mixture was stirred at room temperature for 15 min. Then a catalytic amount of $Pd(PPh_3)_4$ was added and the resulting solution was stirred at 90 °C for 12 hours. The reaction was quenched with $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude (*S*)-**13**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Yield: 42.1 mg (70%, for two steps). ^{1}H NMR ($CDCl_3$): δ = 7.56–7.18 (m, 14 H, Ph), 6.28 (d, J = 7.8 Hz, 1 H, C*H*N), 6.07 (d, J = 7.8 Hz, 1 H, N*H*), 1.99 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.2, 56.4, 121.4, 127.4, 127.7, 127.9, 128.0, 128.5, 128.7, 129.1, 134.1, 140.5, 142.0, 148.6, 169.2 ppm. IR (KBr): $\tilde{\nu}$ = 1665, 1450 cm^{-1}. MS: m/z = 302 [M + 1], 324 [M + Na]. $[\alpha]_D^{20}$ = –30.2 (c = 0.8, $CHCl_3$). $C_{21}H_{19}NO$ (301.38): calcd. C 83.69, H 6.35, N 4.65; found C 83.92, H 6.54, N 4.81.

Synthesis of (*S*)-[(Biphenyl-4-yl)(phenyl)methyl]amine [(*S*)-14]: Acetamide (*S*)-**13** (0.1 mmol) was dissolved in HCl conc. (5 mL) and the mixture was stirred at 80 °C for 12 hours. The mixture containing (*S*)-**14** hydrochloride was cooled and alkalinized with solid $NaHCO_3$ to pH 7–8 and extracted three times with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude (*S*)-**14**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Spectroscopic data are identical to those reported in the literature. Yield: 22.0 mg (85%). ^{1}H NMR ($CDCl_3$): δ = 7.65–7.54 (m, 4 H, Ph), 7.42–7.26 (m, 10 H, Ph), 5.63 (s, 1 H, C*H*N) ppm. IR (KBr): $\tilde{\nu}$ = 3320, 1640 cm^{-1}. MS: m/z = 260 [M + 1], 282 [M + Na], 243 [M – 16]. $[\alpha]_D^{20}$ = –11.2 (c = 1.2, $CHCl_3$). $C_{19}H_{17}N$ (259.35): calcd. C 87.99, H 6.61, N 5.40; found C 88.12, H 6.92, N 5.65.

Synthesis of (*S*)-Bifonazole [(*S*)-15]: Amine (*S*)-**14** (0.38 mmol) was dissolved into a solution of H_2O/dioxane (3:1 mL) and H_3PO_4 was added until pH 2. Then solid paraformaldehyde (15 mg) and glyoxal sol. 40% in water (0.1 mL) were added and the mixture stirred at 80 °C for 10 min. NH_4Cl saturated solution (0.5 mL) was added at this temperature and the resulting solution was refluxed for 12 hours. The mixture was then cooled to 0 °C and NaOH was added until pH 12. The alkaline solution was extracted with AcOEt two times. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude (*S*)-**15**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Spectroscopic data are identical to those reported in the literature. Yield: 37.6 mg (32%). ^{1}H NMR ($CDCl_3$): δ = 7.65–7.54 (m, 4 H, Ph), 7.42–7.26 (m, 10 H, Ph), 5.63 (s, 1 H, C*H*N) ppm. MS: m/z = 311 [M + 1], 333 [M + Na]. $[\alpha]_D^{20}$ = +3.2 (c = 0.9, $CHCl_3$). $C_{22}H_{18}N_2$ (310.39): calcd. C 85.13, H 5.85, N 9.03; found C 85.42, H 5.98, N 9.32.

Synthesis of (*R*)-*N*-[(4-Bromophenyl)(cyclohexa-1,5-dienyl)methyl]-acetamide (17): Into an oven-dried pressure vial equipped with

magnetic stirbar and under argon, (*R*)-**1f** (3.4 mmol) was dissolved in 40 mL of degassed toluene. Grubbs' 2nd generation catalyst (10 mol-%) and cyclooctadiene (9 equiv./mol) were then added. The vessel was introduced into the microwave oven and heated at 80 °C twice for 10 minutes under microwave irradiation. After cooling, the solvent was removed in vacuo to afford a dark brown oil that was purified by flash chromatography (Et_2O/petroleum ether, 1:1) to give **17**. Yield: 624 mg (60%). ^{1}H NMR ($CDCl_3$): δ = 7.31 (d, J = 8.4 Hz, 2 H, Ph), 7.03 (d, J = 8.4 Hz, 2 H, Ph), 6.53 (d, J = 7.0 Hz, 1 H, CN*H*), 5.65 (m, 1 H, CC*H*CH_2), 5.55 (m, 1 H, C*H*$CHCH_2$), 5.40 (m, 1 H, CHC*H*CH_2), 5.36 (d, J = 7.0 Hz, 1 H, C*H*N), 2.13–1.97 (m, 4 H, CH_2CH_2), 1.99 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.1, 22.2, 23.1, 55.9, 121.2, 122.9, 124.4, 128.2, 129.1, 131.9, 134.9, 139.4, 169.5 ppm. IR (KBr): $\tilde{\nu}$ = 1661, 1445 cm^{-1}. MS: m/z = 306/308 [M + 1], 328/330 [M + Na]. $[\alpha]_D^{20}$ = +57.8, (c 1.7 MeOH). $C_{15}H_{16}BrNO$ (306.20): calcd. C 58.84, H 5.27, N 4.57; found C 58.97, H 5.46, N 4.76.

Synthesis of (*R*)-*N*-[(4-Bromophenyl)(phenyl)methyl]acetamide (18): Compound **17** (1.0 mmol) was dissolved in toluene (30 mL). DDQ (2.0 mmol) was added and the reaction was refluxed and stirred for 3 hours. The reaction was quenched with water (20 mL) and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude **18**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (4:1) as eluant. Yield: 145.9 mg (48%). ^{1}H NMR ($CDCl_3$): δ = 7.40–7.08 (m, 9 H, Ph), 6.60 (d, J = 7.8 Hz, 1 H, N*H*), 6.03 (d, J = 7.8 Hz, 1 H, C*H*N), 1.90 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.0, 56.6, 121.3, 127.7, 128.8, 129.7, 131.7, 132.5, 140.5, 140.8, 169.7 ppm. IR (KBr): $\tilde{\nu}$ = 1661, 1446 cm^{-1}. MS: m/z = 304/306 [M + 1], 326/328 [M + Na]. $[\alpha]_D^{20}$ = +22.0 (c = 1.4, MeOH). $C_{15}H_{14}BrNO$ (304.18): calcd. C 59.23, H 4.64, N 4.60; found C 59.53, H 4.87, N 4.81.

Synthesis of (*R*)-*N*-[(Biphenyl-4-yl)(phenyl)methyl]acetamide [(*R*)-13]: Compound **18** (0.33 mmol) was dissolved in toluene (10 mL) and K_2CO_3 (0.49 mmol) and phenylboronic acid (0.66 mmol) were added. The mixture was stirred at room temperature for 15 min. Then a catalytic amount of $Pd(PPh_3)_4$ was added and the resulting solution was stirred at 90 °C for 12 hours. The reaction was quenched with $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated to give the crude (*R*)-**13**. The crude product was purified by flash chromatography on silica gel, using AcOEt/petroleum ether (1:1) as eluant. Yield: 82.4 mg (83%). ^{1}H NMR ($CDCl_3$): δ = 7.56–7.18 (m, 14 H, Ph), 6.28 (d, J = 7.8 Hz, 1 H, C*H*N), 6.07 (d, J = 7.8 Hz, 1 H, N*H*), 1.99 (s, 3 H, NCOCH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.2, 56.4, 121.4, 127.4, 127.7, 127.9, 128.0, 128.5, 128.7, 129.1, 134.1, 140.5, 142.0, 148.6, 169.2 ppm. IR (KBr): $\tilde{\nu}$ = 1665, 1450 cm^{-1}. MS: m/z = 302 [M + 1], 324 [M + Na]. $[\alpha]_D^{20}$ = +32.2 (c = 1.0, $CHCl_3$). $C_{21}H_{19}NO$ (301.38): calcd. C 83.69, H 6.35, N 4.65; found C 83.92, H 6.54, N 4.81.

Synthesis of (*R*)-[(Biphenyl-4-yl)(phenyl)methyl]amine [(*R*)-14]: The same procedure used for (*S*)-**14** was followed. All the spectroscopic data are identical to those of (*S*)-**14**. $[\alpha]_D^{20}$ = +7.4, (c = 0.5 $CHCl_3$).

Synthesis of (*R*)-Bifonazole [(*R*)-15]: The same procedure used for (*S*)-**15** was followed. All the spectroscopic data are identical to those of (*S*)-**15**. $[\alpha]_D^{20}$ = –2.9 (c = 1.5, $CHCl_3$).

X-ray Crystal Structure Determination of 7: Single-crystals of **7** suitable for X-ray data collections were obtained by dissolving 50 mg of powder in 25 mL of ethyl acetate and allowing the solution to concentrate at room temperature. Data collection was carried out by using a Siemens P4 four-circle diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by the direct methods, while structure refinement was carried out by full-matrix anisotropic least-squares on F^2 for all reflections for all non-H atoms. The hydrogen atoms were located on Fourier difference maps and were included in the structure-factor calculations without any constraint for both the structures. Structure solution and refinement were carried out by using the SHELX-97 package.[20] Molcular graphics was performed by using WinGX package.[21]

CCDC-638969 (for **7**) contains the complete set of crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Copies of HPLC chromatograms for (*R*,*S*)-**13**, (*R*)-**13** and (*S*)-**13**. Selected crystal data and Ortep view of **7**.

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