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Stereoselective Synthesis of Tetrahydroisoquinolines from Chiral 4-Azaocta-1,7-diynes and 4-Azaocta-1,7-enynes

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Keywords: Chiral sulfinyl imines · Diastereoselective propargylation · Diastereoselective allylation · Tetrahydroisoquinolines · Cyclotrimerization of alkynes · Ring-closing enyne metathesis

The *N*-propargylation of enantioenriched homopropargylic amine derivatives **3** proceeds in high yields under basic conditions. The resulting 4-azaocta-1,7-dynes **5** were transformed into 1,2,3,4-tetrahydrosioquinolines **7** bearing substituents at 3-, 6- and 7-positions, upon reaction with symmetrical alkynes, through a [2+2+2] cyclotrimerization promoted by Wilkinson catalyst. Ruthenium-catalyzed ring closing metathesis of azaocta-1,7-enynes **9a** and **15a** gave 1,3-dienes **10a** and **16a**, respectively, in high yields. Tetrahydroisoquinolines **12a** and **18a**, with a substitution pattern in the aromatic ring different to that of compounds **7**, were prepared by a [4+2] cycloaddition of dimethyl acetylenedicarboxylate with dienes **10a** and **16a**, respectively.

Introduction

Benzo-fused nitrogen-containing heterocycles have attracted much attention to synthetic organic chemists, especially, 1,2,3,4-tetrahydroisoquinolines. Many compounds with this structural motif bearing substituents at 1-position display a wide range of biological activities.[1] Some of them are available from natural sources, such as, for instance, alkaloids (−)-salsolidine,[2] first isolated from a subshrub of *Salsola* genus, tetracyclic (−)-xylopinine, a member of protoberberines isolated from *Xylopia discrete*,[3] (+)-reticuline, a dopamine receptor antagonist,[4] which is also a biosynthetic precursor of many isoquinoline alkaloids, and (+)-crispine A, a pyrroloisoquinoline tricyclic derivative isolated from *Carduus crispus*, which has been proved to show significant cytotoxic activity against different cancer cell lines (Scheme 1).[5] Aminoacids phenylalanine and tyrosine were found to be the biosynthetic precursors of this type of alkaloids.[6] Another numerous group of pharmacologically active 1,2,3,4-tetrahydroisoquinolines are synthetic analogs of these natural products, which have been prepared in many cases from 2-arylethylamine derivatives, following a biomimetic approach, involving intramolecular cyclizations. Among these methodologies to access to both natural and synthetic 1-substituted heterocycles, Pictet-Spengler[7] and Bichler-Napieralsky[8] reactions are the most commonly used (Scheme 1). Recently, there has been increasing interest in performing the benzylic C-H bond functionalization in 1,2,3,4-tetrahydro-

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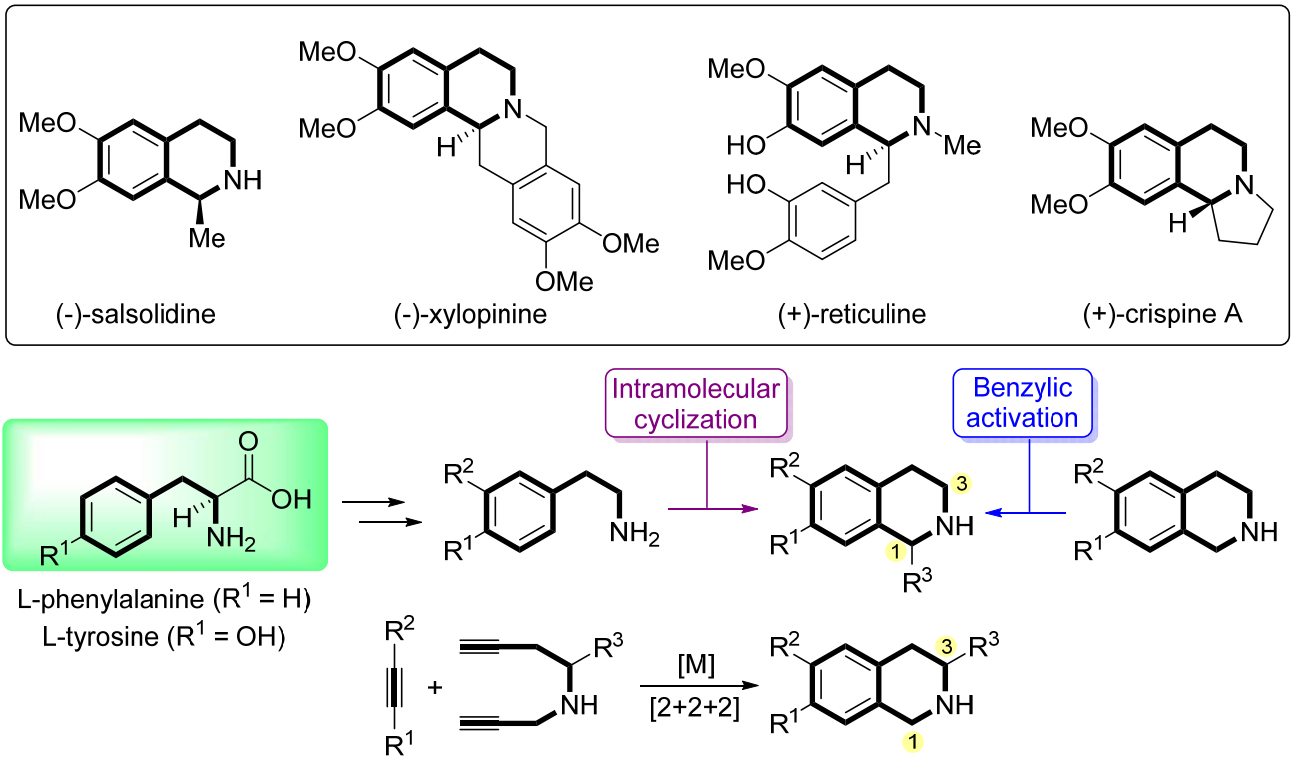
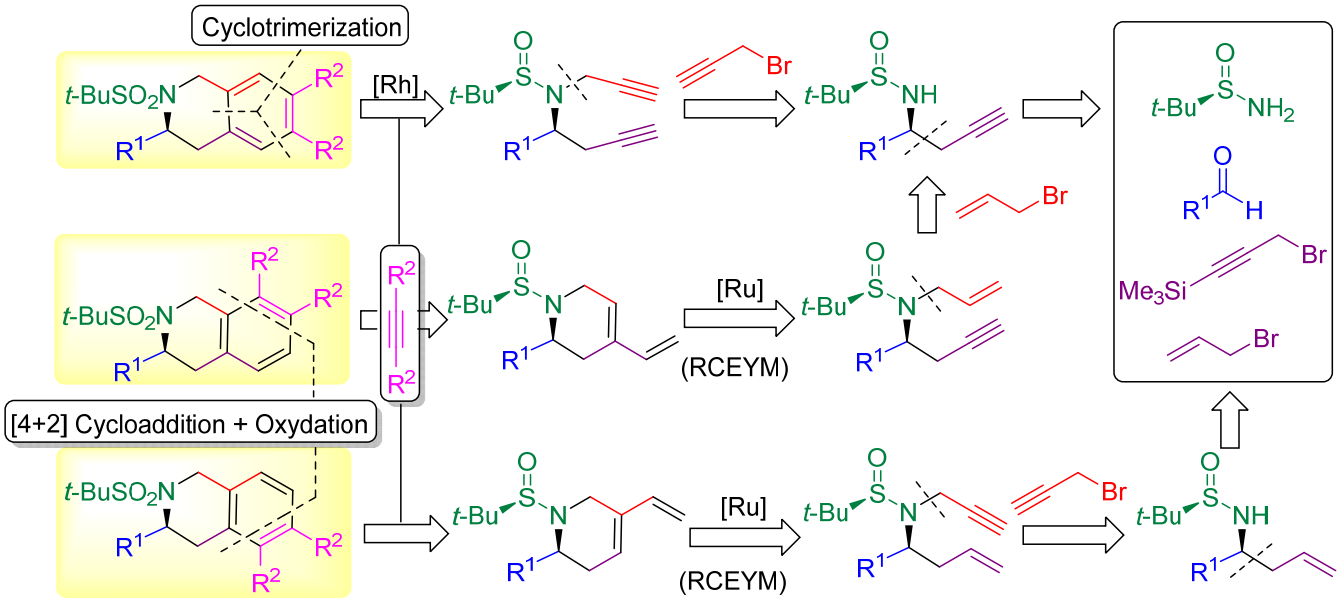
isoquinolines by oxidative or photoredox activation.[9] Compounds bearing substituents at 3-position are less represented in nature, and 3-carboxylic acid derivatives, which are constrained analogs of phenylalanine, were used in peptide synthesis replacing the aminoacid, promoting changes in the activity and selectivity of the peptide.[10] Interestingly, cyclotrimerization of alkynes under ruthenium, cobalt or rhodium catalysis allowed the formation of these bicyclic heterocyclic scaffolds with substituents at 3-position in a single step (Scheme 1).[11]



Scheme 1. Selected substituted tetrahydroisoquinoline alkaloids and general strategies to synthesized 1- and 3-substituted derivatives.

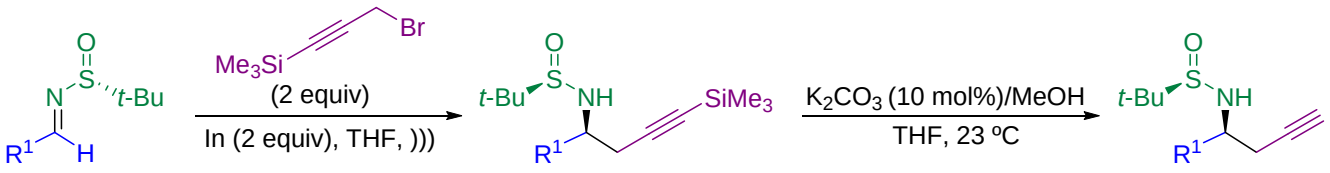
Continuing our interest in the development of new methodologies involving chiral *N-tert*-butanesulfinyl imines for the stereoselective synthesis of nitrogen containing heterocyclic systems,[12] we decided to explore new synthetic pathways to access to 3-substituted 1,2,3,4-tetrahydroisoquinoline derivatives in an enantioenriched form. These chiral imines have found great applicability in synthesis due to the easy accessibility of both enantiomers from commercially available (*R*) and (*S*)-*tert*-butanesulfinamide.[13] In addition, the *tert*-butanesulfinyl group can be removed easily under mild reaction conditions to produce free amines, and different synthetic procedures have also been reported to perform the recycling of the chiral auxiliary.[14] Regarding our research in this area, we have reported the stereoselective synthesis of homoallyl and homopropargyl amine derivatives, through an indium promoted coupling of *N-tert*-butanesulfinyl imines with allylic bromides or alcohols,[15] and also with trimethylsilyl propargyl bromide,[16] respectively. Diastereoselective allylation and propargylation of chiral *N-tert*-butanesulfinyl imine, ruthenium-catalyzed ring-closing enyne metathesis (RCEYM), and rhodium-catalyzed cyclotrimerization are key steps in the synthetic strategy we have envisioned for the synthesis of these heterocycles (Scheme 2).



Scheme 2. Retrosynthetic analysis for 3-substituted 1,2,3,4-tetrahydroisoquinoline derivatives.

Results and Discussion

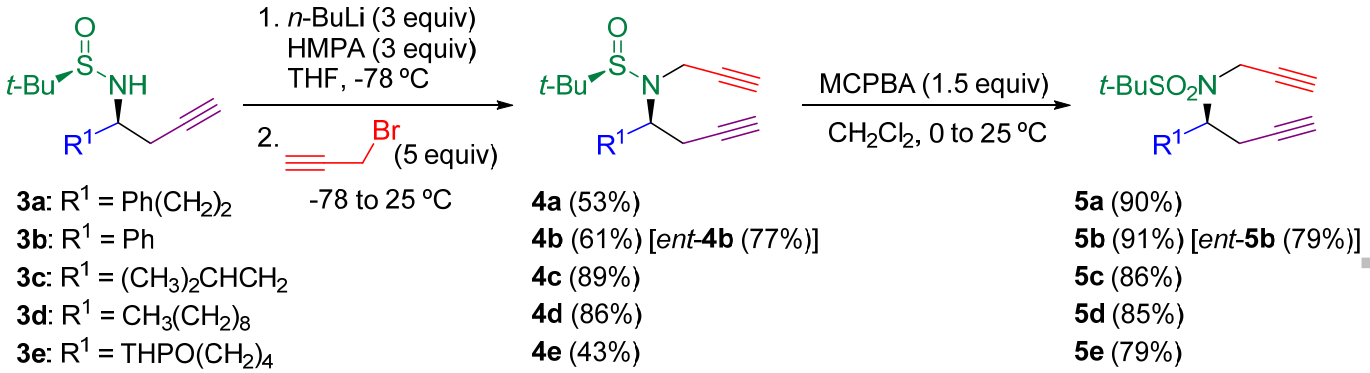
Our synthesis of the 3-substituted 1,2,3,4-tetrahydroisoquinolines started with homopropargyl amine derivatives **3**. We had already reported the diastereoselective propargylation of chiral *N*-*tert*-butanesulfinyl aldimines **1** using trimethylsilylpropargyl bromide in the presence of indium metal, and under sonication.[12g,16] The corresponding silylated homopropargyl amine derivatives **2** were obtained in good yields and excellent diastereomeric ratios, being isolated in an almost enantiopure form after column chromatography purification (>95:5 dr). The configuration of the stereogenic centre in compounds **2** was established at this point, and we observed that the nucleophilic attack took always place in a larger extension to the *Si*-face of imines **1** with R_S configuration. Further removal of the silicon unit in compounds **2** under mild basic conditions led to the expected terminal alkynes **3** (Scheme 3).



1a: R^1 = $Ph(CH_2)_2$	**2a** (80%)	**3a** (93%)
1b: R^1 = Ph	**2b** (73%)	**3b** (76%)
1c: R^1 = $(CH_3)_2CHCH_2$	**2c** (87%)	**3c** (81%)
1d: R^1 = $CH_3(CH_2)_8$	**2d** (85%)	**3d** (80%)
1e: R^1 = $THPO(CH_2)_4$	**2e** (88%)	**3e** (80%)

Scheme 3. Diastereoselective synthesis of homopropargyl amine derivatives **3**.

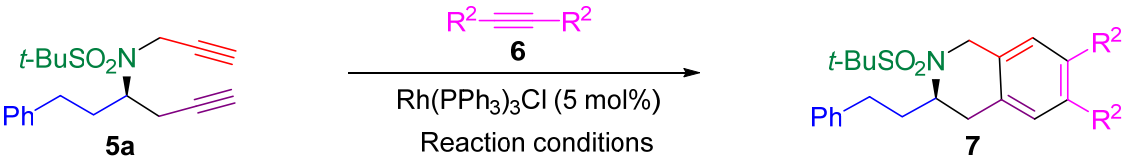
Selective *N*-propargylation of compounds **3** was achieved by performing first deprotonation with *n*-BuLi in THF, followed by reaction with an excess of propargyl bromide in the presence of 3 equivalents of HMPA.[17] The corresponding *N*-propargylated compounds **4** were obtained in fair to good yields. Final oxidation of the sulfinyl group led to sulfonamides **5** (Scheme 4). The sulfonyl group usually performs better than the sulfinyl in most of transition metal-catalyzed reactions.



Scheme 4. Synthesis of 4-azaocta-1,7-diyne derivatives **5**.

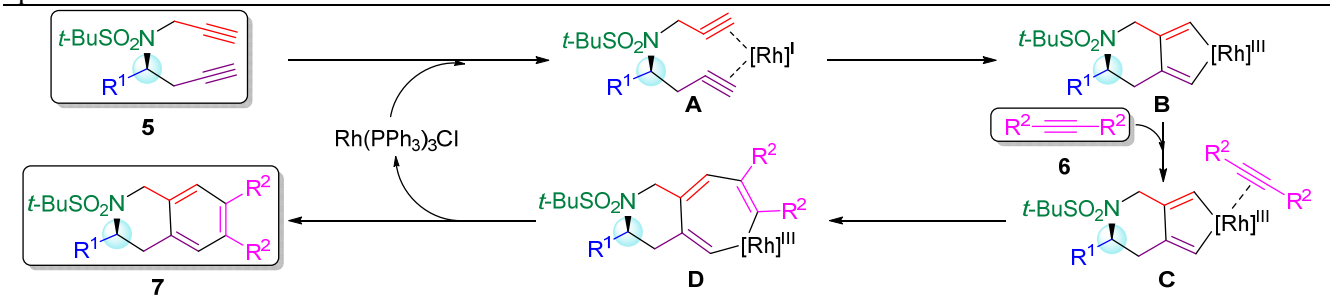
All the attempts to carry out a cyclotrimerization involving diyne derivative **5a** and 3-hexyne (**6a**) with $CpCo(CO)_2$[18] failed. Better results were obtained working with Wilkinson catalyst. The reaction of a 0.1 M solution of diyne **5a** in toluene, with 2 equivalents of 3-hexyne (**6a**), in the presence of 5 mol% of $Rh(PPh_3)_3Cl$, at 100 ºC for 15 h, produced tetrahydroisoquinoline **7a** in only 14% yield (Table 1, entry 1). Fortunately, there was a greatly increased yield (54%) when the reaction was performed in a ten-times less concentrated solution, and with a larger excess of symmetrical alkyne **6a** (10 equivalents), maintaining the same solvent, temperature and reaction time (Table 1, entry 2). Cyclotrimerization occurred also under the same reaction conditions in polar protic solvents, such as ethanol, although the yield was in this case a little bit lower (Table 1, entry 3). When 2-butyne-1,4-diol (**6b**) was taken as a model compound for the cyclotrimerization with diyne **5a**, the expected product **7b** was not produced in any extension, under the optimal reaction conditions found for 3-hexyne (**6a**) in toluene, and also the same happened working in dichloromethane as solvent (Table 1, entries 4 and 5). Fortunately, we were please to find that switching from apolar solvents to ethanol, the cyclotrimerization with the rhodium catalyst occurred even in higher yield (68%) than for **6a** in toluene (Table 1, entry 6). Concerning the mechanism,[11] the process begins with the coordination of the triple bonds of diyne **5** to Rh(I) to give complex **A**, followed by reductive coupling of the acetylenic units with concomitant oxidation of the metal, leading to rhodiacyclopentadiene **B**. Coordination of an external alkyne **6** gives complex **C**, and subsequent insertion produces rhodiacyclohepatriene **D**. The final reductive elimination provides the expected tetrahydroisoquinoline **7** and regenerates the Rh (I) catalyst (Table 1). Since the stereogenic center is not involved in the catalytic cycle, we assume that the enantiomeric purity of the starting diynes **5** (>95:5) is maintained throughout the process and is reflected in the reaction products **7**.

Table 1. Optimization of the rhodium-catalyzed cyclotrimerization of diyne **5a** and symmetrical alkynes **6a** and **6b**[a]



	Alkyne		Reaction conditions			
Entry	Nº.	R^2 (equiv)	Solvent	Temperature	Time	Yield (%)[b]
1	**6a**	Et (2 equiv)	PhMe (0.1 M)	100 ºC	15 h	14
2	**6a**	Et (10 equiv)	PhMe (0.01 M)	100 ºC	15 h	54
3	**6a**	Et (10 equiv)	EtOH (0.01 M)	75 ºC	15 h	45
4	**6b**	CH_2OH (10 equiv)	PhMe (0.01 M)	100 ºC	15 h	0
5	**6b**	CH_2OH (10 equiv)	CH_2Cl_2 (0.01 M)	40 ºC	15 h	0
6	**6b**	CH_2OH (10 equiv)	EtOH (0.01 M)	75 ºC	15 h	68

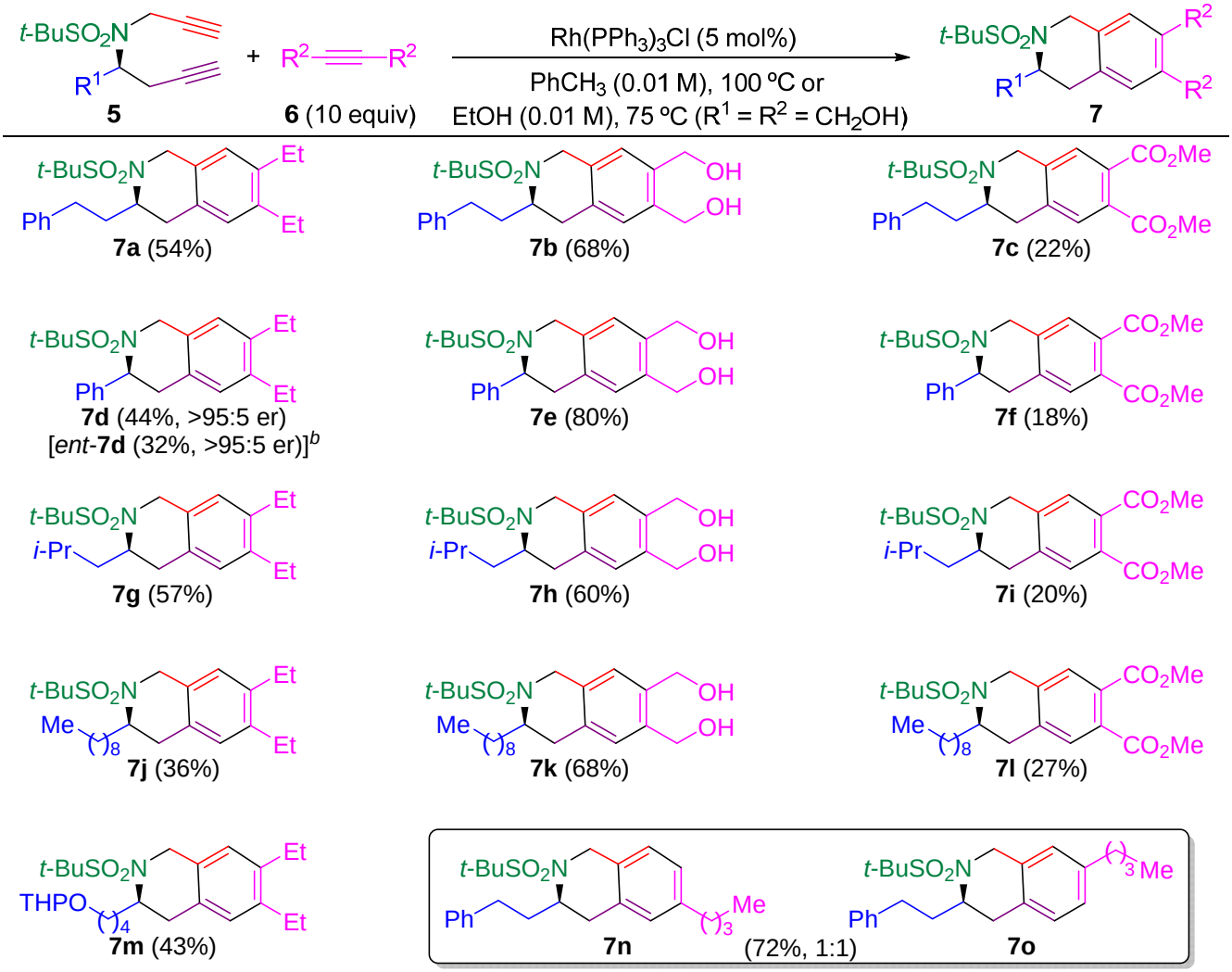
[a] All the reactions were carried out with 0.1 mmol of **5a**. [b] Isolated yield after column chromatography purification.



We studied next the scope of the reaction under the optimized conditions shown in entry 2 of Table 1 for 3-hexyne (**6a**), dimethyl acetylenedicarboxylate (**6c**) and 1-henxyne (**6d**). Meanwhile, for 2-butyne-1,4-diol (**6b**), the reaction conditions were those shown in entry 6 of Table 1. The expected tetrahydroisoquinolines **7** were obtained in variable yields, these yields depending mainly on the alkyne **6** used. Yields were higher for compounds **7b**, **7e**, **7h** and **7k**, all of them derived from 2-butyne-1,4-diol (**6b**) (Table 2). Slightly lower yields were obtained for tetrahydroisoquinolines derived from 3-hexyne (**6a**), with values ranging between 36% (**7j**) and 57% (**7g**) (Table 2). It is worth mentioning that compound **7m** (43%) with an alcohol function protected as a tetrahydropyranyl ether, could be transformed into a tricyclic compound through known reactions, such as the removal of the sulfinyl group, the transformation of the alcohol functionality in a leaving group, and a final intramolecular *N*-alkylation. Unfortunately, tetrahydroisoquinolines **7c**, **7f**, **7i** and **7l**, derived from dimethyl acetylenedicarboxylate (**6c**), were obtained in low yields in a range of about 20-30% (Table 2). On the other hand, the reaction of diyne **5a** with unsymmetrical alkyne 1-hexyne (**6d**) took place with lack of regioselectivity, leading to a mixture of regioisomers **7n** and **7o**, in a 1:1 ratio, in a fairly good yield (72%) (Table 2). Through this methodology it is also possible to access to the corresponding enantiomers *ent*-**7** starting from the (S_S)-*N*-*tert*-butanesulfinyl imine *ent*-**1** (Scheme 3). This was exemplified in the synthesis of compound *ent*-**7d**, and the stereochemical integrity of compounds **7d** and its enantiomer *ent*-**7d** was determined by HPLC with

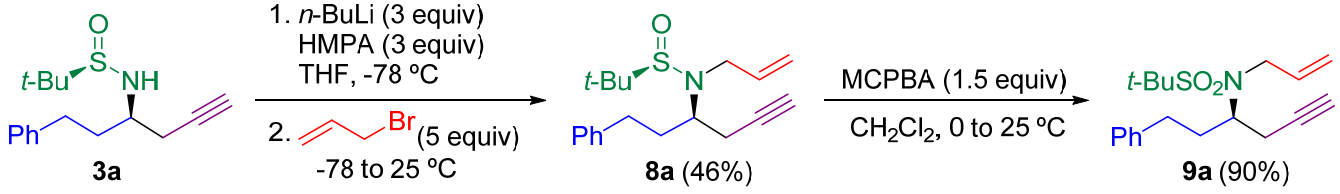
columns with chiral stationary phases, exhibiting high enantiomeric ratios (>95:5 er). The rest of compounds **7** should be of similar enantiomeric purity, since all of them were prepared following the same synthetic strategy.

Table 2. Scope of the rhodium-catalyzed cyclotrimerization involving diynes **5** and alkynes **6**[a]



[a] All the reactions were carried out with 0.1 mmol of **5**. Isolated yield after column chromatography purification is given in parenthesis. [b] Diyne *ent*-**5b** was used as starting material.

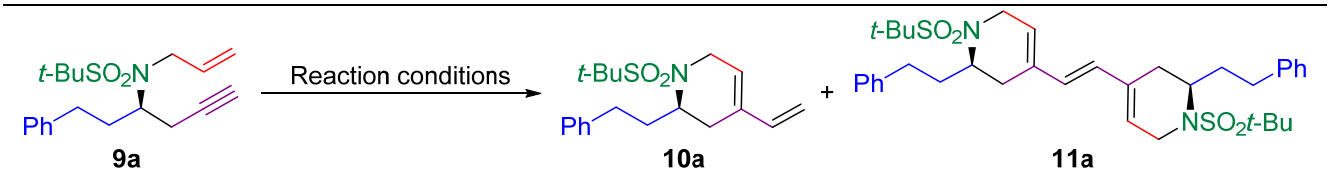
It was also possible to achieve the synthesis of chiral tetrahydroisoquinolines with a different substitution pattern at the aromatic ring to that of compounds **7**, starting from the same precursors **3**, but following a different strategy, being a [4+2] cycloaddion the key step in the formation of the aromatic ring of the tetrahydroisoquinolinic system. For instance, *N*-allylation of **3a** under the same reaction conditions led to **8a** in 46% yield. Further oxidation produced the more robust sulfonamide derivative **9a** (Scheme 5).



Scheme 5. Synthesis of 4-azaoct-1-en-7-yne derivative **9a** from *N*-*tert*-butanesulfinylhomopropargyl amine **3a**.

Intramolecular ruthenium-catalyzed ring-closing enyne metathesis of compound **9a** was explored next with the aim of synthesizing diene **10a**.[11b] Total consumption of the starting material was observed using Grubbs second generation catalyst in toluene at 120 ºC for 1 h. However, along with the expected diene **10a**, a significant amount of triene **11a**, resulting from **10a** through a homo cross metathesis, was also formed (Table 3, entry 1). Working with Grubbs first generation catalyst under milder reaction conditions did not give better results. In this case, both diene **10a** and triene **11a** were also formed, although most of the starting material remained unaltered (Table 3, entry 2). Similar results were also obtained performing the ring-closing metathesis with the same catalyst in the presence of four equivalents of 1,7-octadiene,[19] which has been found to be a useful ethylene surrogate in ring-closing metathesis, facilitating the regeneration of the ruthenium catalyst species (Table 3, entry 3). Fortunately, Hoveyda-Grubbs second generation catalyst produced total conversion of enyne **9a** into cyclic diene **10a** in a highly selective manner (Table 3, entry 4). It has been proposed that a ruthenacyclobutane **E** is formed in the initial step of enyne metathesis, followed by elimination of a styrene, giving a new carbene complex **F**. Intramolecular cycloaddition involving the triple bond leads to a ruthenacyclobutene **G**, which undergoes an electrocyclic opening to give a new carbene **H**. The reaction of this carbene with starting enyne **9** leads to expected 1,3-diene **10** and carbene **F**, which makes it possible to continue the catalytic cycle (Table 3).[20] In the same way, enantiopurity of diene **10a** must be similar to that of starting enyne **9a** (>95:5 er), since the stereogenic center was not involved in these reactions.

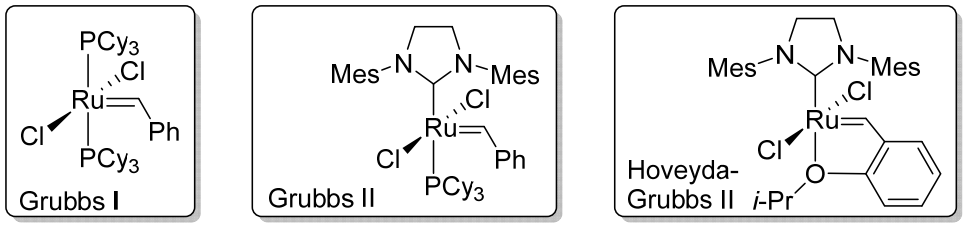
Table 3. Optimization of the ruthenium-catalyzed intramolecular enyne metathesis of compound **9a**[a]

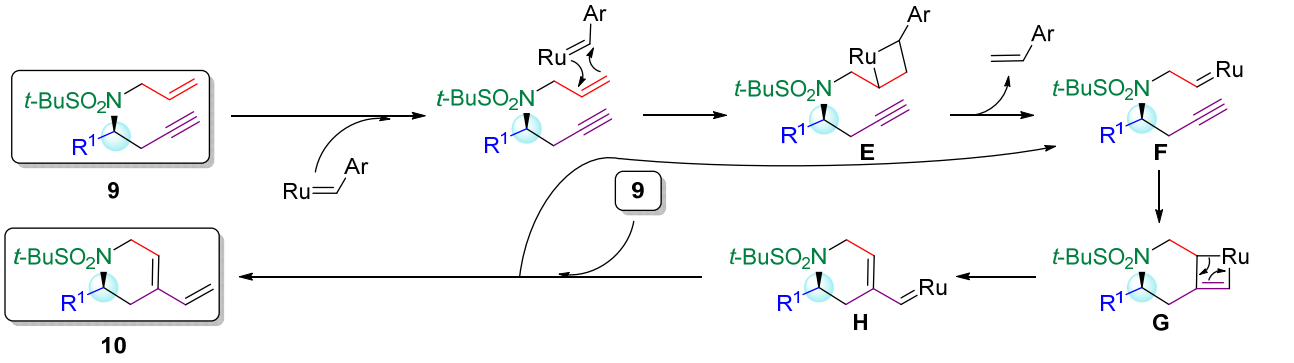


9a **10a** **11a**

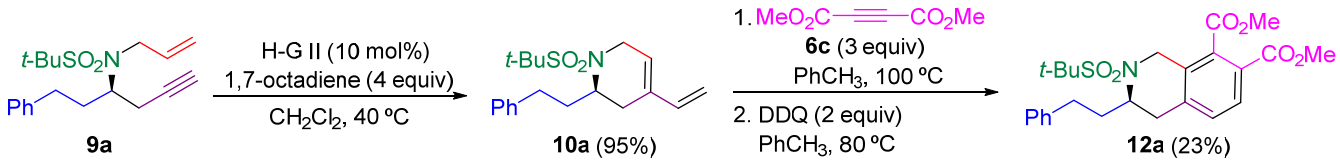
Entry	Reaction conditions	**9a**:**10a**:**11a**[b]
1	Grubbs II (10 mol%), $PhCH_3$ (0.01 M), 120 ºC, 1 h	--:80:20
2	Grubbs I (20 mol%), CH_2Cl_2 (0.005 M), 40 ºC, 17 h	64:32:4
3	Grubbs I (10 mol%), 1,7-octadiene (4 equiv), CH_2Cl_2 (0.005 M), 40 ºC, 17 h	45:55:--
4	Hoveyda-Grubbs II (10 mol%), 1,7-octadiene (4 equiv), CH_2Cl_2 (0.01 M), 40 ºC, 12 h	--:98:2

[a] All the reactions were carried out with 0.2 mmol of **9a**. [b] Reaction products ratio was determined by ^{1}H-NMR analysis of the crude reaction mixtures.



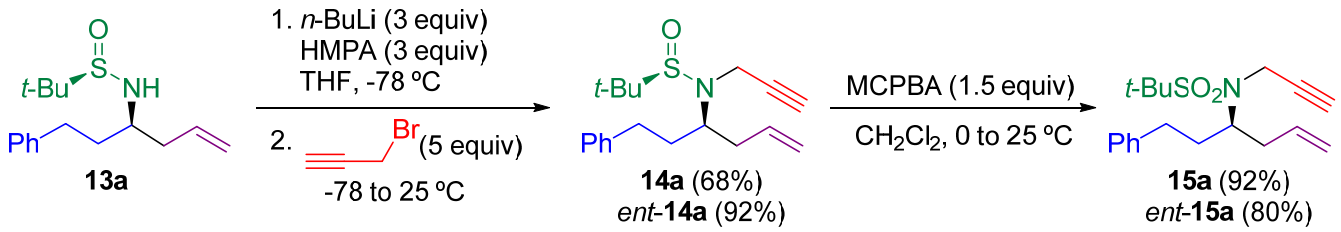


Cyclic diene **10a** was obtained from **9a** in 95% isolated yield. The reaction of **10a** with dimethyl acetylenedicarboxylate (**6c**), followed by oxidation of the resulting cycloadduct with DDQ gave tetrahydroisoquinoline derivative **12a** with substituents at 7 and 8 positions of the aromatic ring in low yield, although the yield of this two-step process could be improved after appropriate optimization (Scheme 6).



Scheme 6. Synthesis of tetrahydroisoquinoline **12a** from 4-azaoct-1-en-7-yne derivative **9a**.

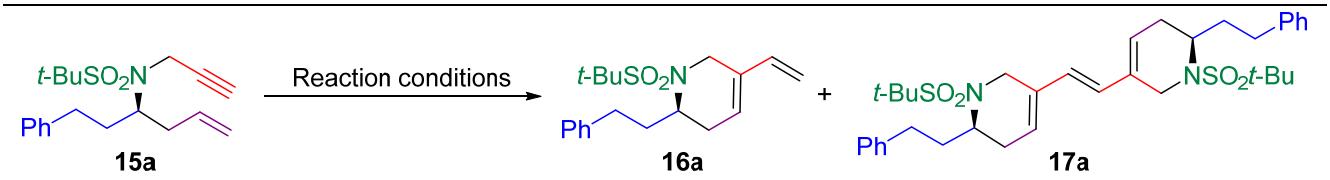
On the other hand, starting from *N*-*tert*-butanesulfinylhomoallyl amine **13a**, which was easily prepared by an indium promoted diastereoselective allylation of chiral imine **1a**,[15a] 5-azaoct-1-en-7-yne derivative **15a** was prepared by *N*-propargylation, leading to **14a** first, followed by oxidation of the sulfinyl group (Scheme 7).



Scheme 7. Synthesis of 5-azaoct-1-en-7-yne derivatives **15a** and *ent*-**15a** from *N*-*tert*-butanesulfinylhomoallyl amines **13**.

Similarly to enyne **9a**, the intramolecular ruthenium-catalyzed ring-closing metathesis of compound **15a** showed to be strongly catalyst-dependent. For instance, a 1:1 mixture of cyclic diene **16a** and triene **17a** was obtained with Grubbs second generation catalyst in toluene at temperatures ranging from 40 to 80 ºC, and different reaction times (Table 4, entries 1 to 4). It was not possible to transform selectively enyne **15a** into cyclic diene **16a**, because triene **17a** was always formed, even working under high dilution conditions at room temperature, and short reaction times, in order to avoid cross metathesis of diene **16a** leading to **17a** (Table 4, entry 5). Grubbs first generation catalyst showed to be more selective in this transformation, always giving rise to desired product **16a** and in a lesser extension of triene **17a**, although total conversion was not achieved in dichloromethane at 40 ºC (Table 4, entries 6 and 7). However, this ruthenium catalyst led exclusively to cyclic diene **16** when the ring-closing metathesis was carried out in the presence of four equivalents of 1,7-octadiene, performing the reaction under high dilution conditions or at higher concentrations (Table 4, entries 8 and 10, respectively). On the other hand, Hoveyda-Grubbs second generation catalyst, the most efficient catalyst in the ring closing metathesis of enyne **9a**, was less efficient for the selective transformation of enyne **15a** (Table 4, entry 9).

Table 4. Optimization of the intramolecular ruthenium-catalyzed enyne metathesis of compound **15a**[a]

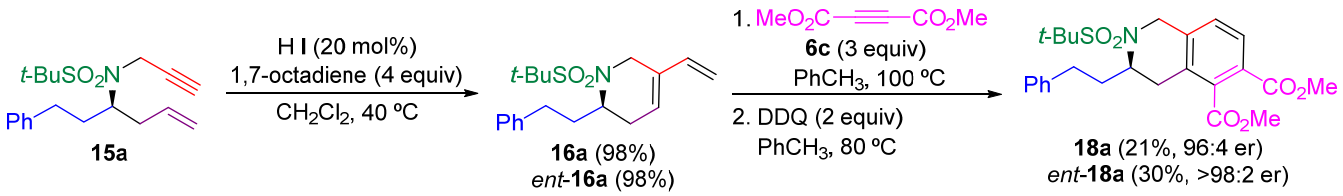


Entry	Reaction conditions	**15a**:**16a**:**17a**[b]
1	Grubbs II (10 mol%), $PhCH_3$ (0.01 M), 80 ºC, 17 h	--:50:50
2	Grubbs II (10 mol%), $PhCH_3$ (0.01 M), 80 ºC, 3 h	--:50:50
3	Grubbs II (10 mol%), $PhCH_3$ (0.005 M), 60 ºC, 2 h	--:50:50
4	Grubbs II (10 mol%), $PhCH_3$ (0.004 M), 40 ºC, 0.5 h	--:50:50
5	Grubbs II (10 mol%), $PhCH_3$ (0.00025 M), 25 ºC, 1 h	70:20:10
6	Grubbs I (10 mol%), CH_2Cl_2 (0.005 M), 40 ºC, 2.5 h	71:28:1
7	Grubbs I (10 mol%), CH_2Cl_2 (0.005 M), 40 ºC, 18 h	40:54:6
8	Grubbs I (20 mol%), 1,7-octadiene (4 equiv), CH_2Cl_2 (0.005 M), 40 ºC, 17 h	--:100:--
9	Hoveyda-Grubbs II (10 mol%), 1,7-octadiene (4 equiv), CH_2Cl_2 (0.005 M), 40 ºC, 17 h	--:90:10
10	Grubbs I (20 mol%), 1,7-octadiene (4 equiv), CH_2Cl_2 (0.01 M), 40 ºC, 20 h	--:100:--

[a] All the reactions were carried out with 0.2 mmol of **15a**. [b] Reaction products ratio was determined by ^{1}H-NMR analysis of the crude reaction mixtures.

The intramolecular ring-closing enyne metathesis of compound **15a** under the reaction conditions shown in entry 10 of Table 4 led to cyclic dine **16a** in 98% isolated yield. Finally, tetrahydroisoquinoline derivative **18a** with

substituents at 5 and 6 positions of the aromatic ring was obtained from **16a** and dimethyl acetylenedicarboxylate (**6c**) in 21% overall yield, considering the [4+2] cyclization and the oxidation steps. The synthesis of *ent*-**18a** was also carried out from *ent*-**16a**, with the aim of proving that stereochemical integrity of compound **15a** (>95:5 er) was maintained after the intramolecular ruthenium-catalyzed enyne metathesis process. Enantiomeric ratios in compounds **18a** and *ent*-**18a** were determined by HPLC with chiral columns, and values were 96:4 and >98:2, respectively (Scheme 8).



Scheme 8. Synthesis of tetrahydroisoquinolines **18a** and *ent*-**18a** from 5-azaoct-1-en-7-yne derivatives **15**.

Conclusions

In summary, 1,2,3,4-tetrahydrosioquinolines bearing substituents at 3-, 6- and 7-positions were prepared in a highly enantioselective fashion starting from chiral *N*-*tert*-butanesulfinyl imines. Diastereoselective indium-promoted propargylation of the sulfinyl imine, selective *N*-propargylation of the resulting homopropargylamine derivative, and [2+2+2] cyclotrimerization involving the azadiyne system and a symmetrical alkyne, are key steps of the here presented methodology. Sulfinyl imines could be also precursors of tetrahydroisoquinolines with substituents at different positions of the aromatic ring, by combining allylation and propargylation processes as the first steps of this new strategy. The resulting azaenynes were efficiently transformed by a ruthenium-catalyzed ring-closing metathesis into cyclic 1,3-dienes. A subsequent [4+2] cycloaddition with dimethyl acetylenedicarboxylate, and final oxidation, led to 5,6- or 7,8-bis(methoxycarbonyl)substituted 1,2,3,4-tetrahydrosioquinolines.

Experimental Section

General: (R_S)-*tert*-Butanesulfinamide was a gift of MEDALCHEMY SL (> 99% ee by chiral HPLC on a Chiracel AS column, 90:10 n-hexane/*i*-PrOH, 1.2 mL/min, λ=222 nm). TLC was performed on silica gel 60 F_{254}, using aluminium plates and visualized with phosphomolybdic acid (PMA) stain. Flash chromatography was carried out on hand packed columns of silica gel 60 (230- 400 mesh). Gas chromatographic analyses (GC) were carried out in a Agilent Technologies 6890N instrument equipped with a flame ionization detector and a 30.0 m capillary column (0.25 mm diam, 0.25 μm film thickness), using nitrogen (1.4 ml/min) as carrier gas, $T_{injector}$ = 275°C, T_{column} = 60 °C (3 min) and 60-270 °C (15 °C/min). Melting points are uncorrected. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 23 ºC and concentrations (*c*) are given in g/100 mL. Infrared analyses were performed with a spectrophotometer equipped with an ATR component; wave numbers are given in cm^{-1}. Low-resolution mass spectra (EI) were obtained at 70 eV; and fragment ions in *m/z* with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were also

carried out in the electron impact mode (EI) at 70 eV and on an apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatography (UPLC) model. ^{1}H NMR spectra were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm). The data is being reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad signal, coupling constant(s) in Hz, integration. ^{13}C NMR spectra were recorded with ^{1}H-decoupling at 100 MHz and referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. Microwave-assisted synthesis was performed using microwave oven CEM Discover Intellivent Explorer in sealed reaction vessels, and the temperature was monitored using a vertically focused IR temperature sensor. All reactions requiring anhydrous conditions were performed in oven dried glassware under argon. Otherwise indicated, all commercially available chemicals were purchased from Acros or Sigma-Aldrich and used without purification. Compounds **1a**,[21] **1b**,[22] **1c**,[23] **1d**[24] and **1e**[25] were prepared from the corresponding aldehyde and (R_S)-*tert*-butanesulfinamide in THF in the presence of two equivalents of titanium tetraethoxide.

General Procedure for the Propargylation of *N*-*tert*-Butanesulfinylimines 1. Synthesis of Homopropargylamine Derivatives 2: A mixture of *N*-*tert*-butanesulfinyl imine **1** (1.5 mmol), 3-bromo-1-trimethylsilyl-1-propyne (600 mg, 0.51 mL, 3.0 mmol), and indium (360 mg, 3.0 mmol) was sonicated in dry THF (6.0 mL) for 3 h. Then the resulting mixture was hydrolyzed with H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The organic phase was washed with brine (3 × 10 mL), dried with anhydrous $MgSO_4$, and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **2**. Yields are given in Scheme 3. Compounds **2a**,[16] **2b**[16] and **2c**[12g] were characterized by comparison of their physical and spectroscopic data with those reported in the literature. The corresponding physical, spectroscopic, and analytical data for new compounds **2d** and **2e** follow.

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-1-(trimethylsilyl)tridec-1-yn-4-amine (2d): Yellow oil; R_F 0.26 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ –6.2 (*c* 1.10, CH_2Cl_2); IR (film) *v* 3212, 2953, 2924, 2855, 2175, 1248, 1027, 839, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.15 [9H, s, $Si(CH_3)_3$], 0.85-0.90 (3H, m, CH_3), 1.23 [9H, s, $C(CH_3)_3$], 1.26 (14H, s, 7 x CH_2), 1.56-1.62 (2H, m, CH_2), 2.48 (1H, dd, *J* = 16.8, 5.0 Hz, CH*H*), 2.65 (1H, dd, *J* = 16.8, 5.4 Hz, CH*H*), 3.30-3.38 (1H, m, NC*H*), 3.61 (1H, d, *J* = 7.7 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 0.16 (CH_3), 14.2 (CH_3), 22.7 (CH_2), 22.8 (CH_3), 25.7 (CH_2), 28.0 (CH_2), 29.4 (2 CH_2), 29.6 (2 CH_2), 32.0 (CH_2), 34.9 (CH_2), 54.6 (CH), 56.0 (C), 88.3 (C), 102.9 (C); LRMS (EI) *m/z* 371 (M^+, 0.09%), 315 (25), 299 (17), 268 (16), 267 (72), 260 (19), 204 (29), 203 (53), 188 (12), 157 (11), 156 (100), 154 (16), 140 (31), 83 (17), 75 (19), 73 (81), 70 (21), 57 (75), 43 (21), 41 (24); HRMS (ESI-TOF) Calcd for $C_{16}H_{33}NOSSi$ [$M^+ - C_4H_8$] 315.2052, found 315.2052.

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-8-[(tetrahydro-2H-pyran-2-yl)oxy]-1-(trimethylsilyl)oct-1-yn-4-amine (2e): Yellow oil (1:1 mixture of diastereoisomers); R_F 0.43 (hexane/EtOAc 1:1); IR (film) *v* 2942, 2868, 2174, 1248, 1024, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.15 [9H, s, $Si(CH_3)_3$], 1.23 [9H, s, $C(CH_3)_3$], 1.41-1.85 (12H,

m, 6 x CH_2), 2.49 (1H, ddd, *J* = 16.8, 4.9, 0.8 Hz, CH*H*), 2.68 (1H, dd, *J* = 16.8, 5.7 Hz, CH*H*), 3.33-3.44 (2H, m, NC*H* + CH*H*), 3.44-3.58 (1H, m, CH*H*), 3.62 (1H, d, *J* = 7.9 Hz, NH), 3.67-3.80 (1H, m, CH*H*), 3.82-3.89 (1H, m, CH*H*), 4.53-4.60 (1H, m, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 0.17 (CH_3), 19.7 (CH_2), 19.8 (CH_2), 22.6 (2 CH_2), 22.8 (CH_3), 25.6 (CH_2), 28.1 (CH_2), 29.6 (CH_2), 30.9 (CH_2), 34.7, 34.8 (CH_2), 54.6 (CH), 56.1 (C), 62.4, 62.5 (CH_2), 67.4 (CH_2), 88.4 (C), 98.9 (CH), 99.0 (CH), 102.8 (CH); LRMS (EI) *m/z* 401 (M^+, 0.02%), 261 (18), 213 (13), 85 (100), 73 (15), 57 (18); HRMS (ESI-TOF) Calcd for $C_{16}H_{31}NO_3SSi$ [$M^+ - C_4H_8$] 345.1794, found 345.1795.

General Procedure for the Desilylation of Compounds 2. Synthesis of Terminal Alkynes 3: A suspension of K_2CO_3 (40 mg, 0.24 mmol) in methanol (15.0 mL) was added dropwise to a solution of the corresponding silylated homopropargyl amine derivative **2** (0.5 mmol) in THF (15.0 mL). The reaction mixture was stirred for 15 h at 23 ºC, and then it was hydrolyzed with a 1 N NH_4Cl aqueous solution (5.0 mL), and extracted with methyl *tert*-butyl ether (3 × 15 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc, 2:1) to yield products **3**. Yields are given in Scheme 3. Compounds **3a**,[16] **3b**[12g] and **3c**[12g] were characterized by comparison of their physical and spectroscopic data with those reported in the literature. The corresponding physical, spectroscopic, and analytical data for new compounds **3d** and **3e** follow.

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)tridec-1-yn-4-amine (3d): Yellow oil; R_F 0.14 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ –17.5 (*c* 0.99, CH_2Cl_2); IR (film) *v* 3316, 3212, 2238, 2117, 1465, 1363, 1055, 909, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84-0.91 (3H, m, CH_3), 1.23 [9H, s, $C(CH_3)_3$], 1.26 (14H, s, 7 x CH_2), 1.54-1.65 (2H, m, CH_2), 2.06 (1H, t, *J* = 2.6 Hz, CC*H*), 2.48 (1H, ddd, *J* = 16.6, 4.5, 2.6 Hz, CH*H*), 2.65 (1H, ddd, *J* = 16.7, 5.6, 2.6 Hz, CH*H*), 3.28-3.40 (1H, m, NC*H*), 3.49 (1H, d, *J* = 8.4 Hz, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.7 (CH_2), 22.8 (CH_3), 25.8 (CH_2), 26.8 (CH_2), 29.4 (2 CH_2), 29.6 (2 CH_2), 32.0 (CH_2), 34.9 (CH_2), 54.9 (CH), 56.1 (C), 71.6 (CH), 80.3 (C); LRMS (EI) *m/z* 299 (M^+, 0.29%), 243 (10), 204 (31), 203 (100), 188 (11), 156 (52), 154 (12), 116 (39), 70 (18), 57 (74), 43 (19), 41 (27); HRMS (ESI-TOF) Calcd for $C_{13}H_{25}NOS$ [$M^+ - C_4H_8$] 243.1657, found 243.1661.

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-8-[(tetrahydro-2H-pyran-2-yl)oxy]oct-1-yn-4-amine (3e): Yellow oil (1:1 mixture of diastereoisomers); R_F 0.27 (hexane/EtOAc 1:1); IR (film) *v* 2940, 2867, 1363, 1058, 1030, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23 [9H, s, $C(CH_3)_3$], 1.36-1.85 (12H, m, 6 x CH_2), 2.06 (1H, t, *J* = 2.6 Hz, CC*H*), 2.50 (1H, ddd, *J* = 16.7, 4.4, 2.6 Hz, CH*H*), 2.67 (1H, dd, *J* = 16.7, 5.7, 2.7 Hz, CH*H*), 3.34-3.41 (2H, m, NC*H* + CH*H*), 3.47-3.53 (2H, m, NH + CH*H*), 3.71-3.87 (1H, m, CH*H*), 3.83-3.88 (1H, m, CH*H*), 4.55-4.59 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.7 (CH_2), 19.8 (CH_2), 22.6 (CH_2), 22.7 (CH_2), 22.8 (CH_3), 25.6 (CH_2), 26.8 (CH_2), 29.5 (2 CH_2), 30.8 (CH_2), 34.7 (CH_2), 34.8 (CH_2), 54.9 (CH), 56.1 (C), 62.4 (2 CH_2), 67.4 (CH_2), 71.7 (CH), 80.2 (C), 98.9 (CH), 99.0 (CH); LRMS (EI) *m/z* 329 (M^+, 0.01%), 189 (26), 85 (100), 84 (12), 57 (21); HRMS (ESI-TOF) Calcd for $C_{13}H_{23}NO_3S$ [$M^+ - C_4H_8$] 273.1399, found 273.1393.

General Procedure for the *N*-Propargylation of Compounds 3 and 13a. Synthesis of Diynes 4 and Enyne 14a: To a solution of the corresponding homopropargylamine derivative **3** or the homoallylamine derivatives **13a** or *ent*-**13a** (1.1 mmol) in dry THF (10.0 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 1.4 mL, 3.3 mmol) at –78 ºC. After 20 min, HMPA (0.60 g, 0.42 mL, 3.3 mmol) was also added, and the resulting solution was stirred for 10 min, followed by addition of propargyl bromide (80 wt% in $PhCH_3$, 0.84 g, 0.57 mL, 5.5 mmol). The reaction mixture was stirred at –78 °C for 1 h, and then was allowed to reach room temperature for 15 h. The reaction mixture was hydrolyzed with saturated aq. NH_4Cl (5 mL) and extracted with EtOAc (3 x 15 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **4**, **14a** and *ent*-**14a**. Yields are given in Schemes 4 and 7. Physical, spectroscopic, and analytical data follow.

(3*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-1-phenylhex-5-yn-3-amine (4a): Brown oil; R_F 0.32 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +97.1 (*c* 0.90, CH_2Cl_2); IR (film) *v* 3297, 3225, 3025, 2952, 2916, 2861, 2117, 1600, 1454, 1066, 843, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.28 [9H, s, $C(CH_3)_3$], 2.07 (1H, t, *J* = 2.7 Hz, CC*H*), 2.14-2.23 (2H, m, CH_2), 2.26 (1H, t, *J* = 2.5 Hz, CC*H*), 2.49-2.55 (2H, m, CH_2), 2.62-2.72 (1H, m, CH*H*), 2.93-3.06 (1H, m, CH*H*), 3.34 (1H, dd, *J* = 19.0, 2.4 Hz, CH*H*), 3.43-3.55 (1H, m, NC*H*), 4.18 (1H, dd, *J* = 19.0, 2.6 Hz, CH*H*), 7.19-7.32 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.5 (CH_3), 24.1 (CH_2), 28.9 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 58.9 (C), 63.4 (CH), 71.4 (CH), 71.9 (CH), 80.9 (C), 81.6 (C), 126.1 (CH), 128.4 (CH), 128.5 (CH), 141.6 (C); LRMS (EI) *m/z* 315 (M^+, 0.08%), 259 (30), 220 (22), 219 (51), 172 (28), 154 (35), 129 (13), 118 (11), 117 (82), 115 (10), 91 (100), 57 (37), 41 (14); HRMS (ESI-TOF) Calcd for $C_{15}H_{17}NOS$ [M^+ - C_4H_8] 259.1031, found 259.1045.

(1*S*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-1-phenylbut-3-yn-1-amine (4b): Brown wax; R_F 0.35 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +14.6 (*c* 1.02, CH_2Cl_2); IR (film) *v* 3297, 3231, 2952, 2922, 2861, 2117, 1455, 1068, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.29 [9H, s, $C(CH_3)_3$], 1.96 (1H, t, *J* = 2.6 Hz, CC*H*), 2.21 (1H, t, *J* = 2.5 Hz, CC*H*), 2.88-3.06 (2H, m, CH_2), 3.16 (1H, dd, *J* = 18.7, 2.4 Hz, CH*H*), 4.00 (1H, dd, *J* = 18.7, 2.6 Hz, CH*H*), 4.62 (1H, dd, *J* = 9.3, 6.1 Hz, NC*H*), 7.32-7.48 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.7 (CH_3), 24.8 (CH_2), 32.3 (CH_2), 59.1 (C), 64.1 (CH), 71.2 (CH), 72.4 (CH), 80.4 (C), 80.8 (C), 128.4 (CH), 128.5 (CH), 128.7 (CH), 137.8 (C); LRMS (EI) *m/z* 287 (M^+, 0.37%), 231 (16), 192 (23), 191 (50), 152 (16), 149 (13), 144 (27), 130 (13), 129 (100), 128 (62), 127 (26), 115 (17), 104 (14), 91 (12), 77 (16), 57 (44), 55 (10), 43 (38), 41 (18); HRMS (ESI-TOF) Calcd for $C_{13}H_{13}NOS$ [$M^+ - C_4H_8$] 231.0718, found 231.0723.

(1*R*,*S*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-1-phenylbut-3-yn-1-amine (*ent*-4b): Physical and spectroscopic data were found to be same than for **4b**. $[\alpha]_D^{20} = -17.8$ (*c* = 1.01, CH_2Cl_2).

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-2-methylhept-6-yn-4-amine (4c): Brown oil; R_F 0.46 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +102.2 (*c* 1.05, CH_2Cl_2); IR (film) *v* 3310, 3225, 2956, 2864, 2117, 1363, 1070, 897, 828, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.93 (3H, d, *J* = 6.6 Hz, CH_3), 0.94 (3H, d, *J* = 6.6 Hz, CH_3),

1.27 [9H, s, $C(CH_3)_3$], 1.72-1.85 (2H, m, CH_2), 1.87-1.98 (1H, m, CH), 2.07 (1H, t, *J* = 2.7 Hz, CC*H*), 2.22 (1H, t, *J* = 2.5 Hz, CC*H*), 2.44-2.50 (2H, m, CH_2), 3.28 (1H, dd, *J* = 19.0, 2.4 Hz, CH*H*), 3.45-3.59 (1H, m, NC*H*), 4.12 (1H, dd, *J* = 19.0, 2.5 Hz, CH*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.1 (CH_3), 22.8 (CH_3), 23.4 (CH_3), 24.0 (CH_2), 24.6 (CH), 28.4 (CH_2), 41.6 (CH_2), 58.7 (C), 61.5 (CH), 71.2 (CH), 71.6 (CH), 81.2 (C), 81.6 (C); LRMS (EI) *m/z* 267 (M^+, 0.74%), 211 (14), 172 (56), 171 (82), 154 (24), 149 (14), 129 (17), 128 (10), 124 (30), 73 (16), 69 (18), 57 (47), 43 (100), 41 (28); HRMS (ESI-TOF) Calcd for $C_{15}H_{25}NOS$ [M^+] 267.1657, found 267.1653.

(4*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)tridec-1-yn-4-amine (4d): Brown oil; R_F 0.53 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +90.8 (*c* 1.05, CH_2Cl_2); IR (film) *v* 3310, 3231, 2923, 2855, 2117, 1457, 1362, 1072, 871, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.85-0.91 (3H, m, CH_3), 1.26 [25H, s, 7 x CH_2 + $C(CH_3)_3$], 1.79-1.87 (2H, m, CH_2), 2.06 (1H, t, *J* = 2.7 Hz, CC*H*), 2.21 (1H, t, *J* = 2.5 Hz, CC*H*), 2.46-2.49 (2H, m, CH_2), 3.31 (1H, dd, *J* = 18.9, 2.4 Hz, CH*H*), 3.37-3.44 (1H, m, NC*H*), 4.13 (1H, dd, *J* = 18.9, 2.6 Hz, CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.8 (CH_2), 23.5 (CH_3), 24.0 (CH_2), 27.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.6 (CH_2), 58.8 (C), 63.5 (CH), 71.1 (CH), 71.6 (CH), 81.3 (C), 81.6 (C); LRMS (EI) *m/z* 337 (M^+, 0.07%), 281 (7), 243 (13), 242 (63), 241 (100), 154 (35), 57 (22), 41 (13); HRMS (ESI-TOF) Calcd for $C_{11}H_{16}NOS$ [$M^+ - C_9H_{19}$] 210.0953, found 210.0947.

(4*R*)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-1-yn-4-amine (4e): Brown oil (1:1 mixture of diastereoisomers); R_F 0.20 (hexane/EtOAc 4:1); IR (film) *v* 3303, 2943, 2866, 1266, 1120, 1073, 1030, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 [9H, s, $C(CH_3)_3$], 1.45-1.64 (10H, m, 5 x CH_2), 1.81-1.91 (2H, m, CH_2), 2.06 (1H, t, *J* = 2.7 Hz, CC*H*), 2.22 (1H, t, *J* = 2.5 Hz, CC*H*), 2.47-2.50 (2H, m, CH_2), 3.31 (1H, dd, *J* = 18.9, 2.4 Hz, CH*H*), 3.35-3.46 (2H, m, NC*H* + CH*H*), 3.46-3.54 (1H, m, CH*H*), 3.71-3.79 (1H, m, CH*H*), 3.81-3.89 (1H, m, CH*H*), 4.13 (1H, dd, *J* = 18.9, 2.6 Hz, CH*H*), 4.57-4.59 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.7 (CH_2), 23.5 (CH_3), 23.8 (2 CH_2), 24.0 (2 CH_2), 25.6 (CH_2), 28.9 (CH_2), 29.7 (CH_2), 30.9 (CH_2), 32.4 (CH_2), 58.9 (C), 62.4 (CH_2), 63.5 (C), 67.4 (CH_2), 67.5 (CH_2), 71.2 (CH), 71.7 (CH), 81.1 (C), 81.4 (C), 98.9 (CH), 99.0 (CH); LRMS (EI) *m/z* 367 (M^+, 0.01%), 227 (41), 122 (10), 85 (100), 57 (19); HRMS (ESI-TOF) Calcd for $C_{11}H_{16}NOS$ [$M^+ - C_9H_{17}O_2$] 210.0953, found 210.0962.

(3*R*,*R*$_S$)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-1-phenylhex-5-en-3-amine (14a): $C_{19}H_{27}NOS$; Orange wax; R_F 0.47 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +104.9 (*c* 1.08, CH_2Cl_2); IR (film) *v* 3304, 3219, 3025, 2928, 2861, 1639, 1454, 1361, 1068, 915, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 [9H, s, $C(CH_3)_3$], 1.88-1.97 (1H, m, CH*H*), 2.05-2.14 (1H, m, CH*H*), 2.26 (1H, t, *J* = 2.5 Hz, CC*H*), 2.29-2.35 (1H, m, CH*H*), 2.40-2.47 (1H, m, CH*H*), 2.60 (1H, ddd, *J* = 13.6, 10.7, 5.4 Hz, CH*H*), 3.03 (1H, ddd, *J* = 13.6, 10.9, 5.5 Hz, CH*H*), 3.23 (1H, dd, *J* = 19.0, 2.4 Hz, CH*H*), 3.30-3.36 (1H, m, NC*H*), 4.18 (1H, dd, *J* = 19.0, 2.6 Hz, CH*H*), 5.04-5.14 (2H, m, CH_2), 5.72-5.86 (1H, m, CH), 7.14-7.28 (3H, m, ArH), 7.23-7.32 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.6 (CH_3), 28.2 (CH_2), 33.6 (CH_2), 34.9 (CH_2), 38.2 (CH_2), 58.9 (C), 65.3 (CH), 71.6 (CH), 82.1 (C), 117.8 (CH_2), 126.0 (CH), 128.4 (CH), 128.5 (CH), 134.9 (CH), 142.0 (C); LRMS (EI) *m/z* 317 (M^+, 0.33%), 261 (32), 220 (58), 219

(26), 172 (10), 117 (92), 91 (100), 57 (27), 41 (14); HRMS (ESI-TOF) Calcd for $C_{15}H_{19}NOS$ [$M^+ - C_4H_8$] 261.1187, found 261.1191.

(3*S*,S_S)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propyl)-1-phenylhex-5-en-3-amine (*ent*-14a): Physical and spectroscopic data were found to be same than for **14a**. $[\alpha]_D^{20} = -70.0$ (*c* = 1.18, CH_2Cl_2).

Synthesis of Enamine Derivative 8a by *N*-Allylation of 3a: To a solution of homopropargylamine derivative **3a** (304,7 mg, 1.1 mmol) in dry THF (10.0 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 1.4 mL, 3.3 mmol) at –78 ºC. After 20 min, HMPA (0.60 g, 0.42 mL, 3.3 mmol) was also added, and the resulting solution was stirred for 10 min, followed by addition of allyl bromide (0.66 g, 0.48 mL, 5.5 mmol). The reaction mixture was stirred at –78 °C for 1 h, and then was allowed to reach room temperature for 15 h. The reaction mixture was hydrolyzed with saturated aq. solution of NH_4Cl (5 mL) and extracted with EtOAc (3 x 15 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated (15 Torr). Purification by column chromatography (silica gel, hexane/EtOAc) yielded **8a** (160.4 mg, 0.50 mmol, 46%). Physical, spectroscopic, and analytical data follow.

(3*R*,R_S)-*N*-(*tert*-Butanesulfinyl)-*N*-(2-propenyl)-1-phenylhex-5-yn-3-amine (8a): Orange wax; R_F 0.40 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +40.6 (*c* 1.05, CH_2Cl_2); IR (film) *v* 3297, 3219, 3025, 2916, 2117, 1455, 1066, 920, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.23 [9H, s, $C(CH_3)_3$], 1.83-1.98 (1H, m, CH*H*), 2.03 (1H, t, *J* = 2.7 Hz, CC*H*), 2.09-2.23 (1H, m, CH*H*), 2.45-2.86 (4H, m, 2 x CH_2), 3.16-3.33 (2H, m, CH*H* + NC*H*), 3.98-4.09 (1H, m, CH*H*), 5.08-5.27 (2H, m, CH_2), 5.77-5.93 (1H, m, CH), 7.18-7.21 (3H, m, ArH), 7.27-7.33 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.6 (CH_2), 23.8 (CH_3), 32.9 (CH_2), 34.9 (CH_2), 45.4 (CH_2), 58.3 (C), 61.1 (CH), 70.6 (CH), 81.9 (C), 118.0 (CH_2), 126.1 (CH), 128.4 (CH), 128.5 (CH), 135.7 (CH), 141.4 (C); LRMS (EI) *m/z* 317 (M^+, 0.07%), 261 (32), 222 (47), 221 (66), 174 (23), 157 (11), 156 (36), 117 (80), 91 (100), 57 (30), 41 (26); HRMS (ESI-TOF) Calcd for $C_{15}H_{19}NOS$ [$M^+ - C_4H_8$] 261.1187, found 261.1191.

General Procedure for the Selective *S*-Oxydation of Compounds 4, 8a and 14. Synthesis of Sulfonamides 5, 9a and 15a: To a solution of the corresponding sulfinyl imine **4**, **8a** or **14a** (0.5 mmol) in CH_2Cl_2 (7 mL) was added at 0 ºC *m*CPBA (0.14 g, 0.75 mmol) in portions every 5 min. The reaction was stirred at 0 °C for 20 additional min, and after that, was allowed to warm to 23 °C for 1 h. A diluted aq. solution of $Na_2S_2O_3$ (3.0 mL) was added, followed by the addition of a saturated aq. solution of $NaHCO_3$ (3.0 mL). The mixture was stirred at 23 °C for 1 h, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried with anhydrous $MgSO_4$ and the solvent was evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **5**, **9a** and **15a**. Yields are given in Schemes 4, 5 and 7. Physical, spectroscopic, and analytical data follow.

(3*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-1-phenylhex-5-yn-3-amine (5a): Orange solid; mp 102-103 °C (hexane/ CH_2Cl_2); R_F 0.51 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ –0.8 (*c* 1.03, CH_2Cl_2); IR (film) *v* 3291, 3267, 2983, 2916,

2124, 1361, 1312, 1127, 996, 889, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.43 [9H, s, $C(CH_3)_3$], 2.10-2.20 (2H, m, CC*H* + CH*H*), 2.24-2.35 (2H, m, CC*H* + CH*H*), 2.71-2.78 (4H, m, 2 x CH_2), 3.99-4.04 (1H, m, NC*H*), 4.20-4.32 (2H, m, CH_2), 7.17-7.32 (5H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.6 (CH_2), 24.7 (CH_3), 33.3 (CH_2), 33.6 (CH_2), 34.7 (CH_2), 58.5 (C), 62.0 (CH), 71.9 (CH), 72.9 (CH), 81.0 (C), 81.2 (C), 126.2 (CH), 128.4 (CH), 128.6 (CH), 141.3 (C); LRMS (EI) *m/z* 331 (M^+, 0.03%), 292 (13), 173 (13), 172 (100), 106 (11), 91 (24), 57 (23); HRMS (ESI-TOF) Calcd for $C_{19}H_{25}NO_2S$ [M^+] 331.1606, found 331.1614.

(1*S*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-1-phenylbut-3-yn-1-amine (5b): Yellow solid; mp 72-74 °C (hexane/ CH_2Cl_2); R_F 0.54 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ +14.2 (*c* 0.96, CH_2Cl_2); IR (film) *v* 3304, 3279, 2987, 1978, 1478, 1300, 1132, 1016, 774, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.49 (9H, s, $C(CH_3)_3$), 1.98 (1H, t, *J* = 2.7 Hz, CC*H*), 2.29 (1H, t, *J* = 2.5 Hz, CC*H*), 3.04-3.12 (1H, m, CH*H*), 3.46 (1H, ddd, *J* = 17.0, 10.7, 2.6 Hz, CH*H*), 3.57 (1H, d, *J* = 19.0 Hz, CH*H*), 4.17 (1H, d, *J* = 18.3 Hz, CH*H*), 5.34 (1H, dd, *J* = 10.7, 4.8 Hz, NC*H*), 7.32-7.34 (1H, m, ArH), 7.38-7.43 (2H, m, ArH), 7.55-7.60 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.3 (CH_2), 24.9 (CH_3), 34.4 (CH_2), 61.4 (CH), 62.2 (C), 71.6 (CH), 73.1 (CH), 81.0 (C), 81.1 (C), 128.5 (CH), 128.8 (2 CH), 136.6 (C); LRMS (EI) *m/z* 303 (M^+, 0.04%), 264 (15), 145 (12), 144 (100), 57 (27), 43 (28); HRMS (ESI-TOF) Calcd for $C_{17}H_{21}NO_2S$ [M^+] 303.1293, found 303.1288.

(1*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-1-phenylbut-3-yn-1-amine (*ent*-5b): Physical and spectroscopic data were found to be same than for **5b**. $[\alpha]_D^{20} = -17.9$ (*c* = 0.97, CH_2Cl_2).

(4*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-2-methylhept-6-yn-4-amine (5c): Yellow oil; R_F 0.58 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ +3.8 (*c* 0.96, CH_2Cl_2); IR (film) *v* 3289, 2956, 2932, 2871, 2117, 1715, 1315, 1158, 1053, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.95 (3H, d, *J* = 6.2 Hz, CH_3), 0.97 (3H, d, *J* = 6.2 Hz, CH_3), 1.45 [9H, s, $C(CH_3)_3$], 1.70-1.75 (2H, m, CH_2), 1.77-1.83 (1H, m, CH), 2.09 (1H, t, *J* = 2.7 Hz, CC*H*), 2.29 (1H, t, *J* = 2.5 Hz, CC*H*), 2.59-2.71 (2H, m, CH_2), 3.99-4.07 (1H, m, NC*H*), 4.13-4.26 (2H, m, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.4 (CH_3), 22.9 (CH_3), 24.7 (CH_2), 24.8 (CH_3), 24.9 (CH), 33.7 (CH_2), 41.9 (CH_2), 56.7 (CH), 61.9 (C), 71.6 (CH), 72.6 (CH), 81.3 (2 C); LRMS (EI) *m/z* 283 (M^+, 0.15%), 244 (10), 144 (19), 125 (10), 124 (100), 106 (12), 70 (13), 61 (13), 57 (42), 45 (12), 43 (82), 41 (16); HRMS (ESI-TOF) Calcd for $C_{15}H_{25}NO_2S$ [M^+] 283.1606, found 283.1602.

(4*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)tridec-1-yn-4-amine (5d): Yellow oil; R_F 0.67 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ +6.1 (*c* 1.02, CH_2Cl_2); IR (film) *v* 3307, 2925, 2853, 2120, 1457, 1317, 1140, 880, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.83-0.92 (3H, m, CH_3), 1.26 (14H, s, 7 x CH_2), 1.44 [9H, s, $C(CH_3)_3$], 1.72-2.01 (2H, m, CH_2), 2.08 (1H, t, *J* = 2.7 Hz, CC*H*), 2.28 (1H, t, *J* = 2.5 Hz, CC*H*), 2.62-2.74 (2H, m, CH_2), 3.89-3.60 (1H, m, NC*H*), 4.09 (1H, d, *J* = 19.2 Hz, CH*H*), 4.23 (1H, dd, *J* = 18.9, 2.5 Hz, CH*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.8 (CH_2), 24.7 (CH_2), 24.8 (CH_3), 27.0 (CH_2), 29.4 (CH_2), 29.6 (2 CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.9 (CH_2), 33.5 (CH_2), 58.9 (CH), 62.0 (C), 71.5 (CH), 72.6 (CH), 81.2 (C), 81.4 (C); LRMS (EI) *m/z* 353 (M^+,

0.01%), 258 (15), 195 (35), 194 (100), 106 (21), 57 (37); HRMS (ESI-TOF) Calcd for $C_{20}H_{35}NO_2S$ [M^+] 353.2389, found 353.2372.

(4*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-1-yn-4-amine (5e): Brown oil (1:1 mixture of diastereoisomers); R_F 0.31 (hexane/EtOAc 5:1); IR (film) *v* 3269, 2940, 2869, 1316, 1122, 1031, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.44 [9H, s, $C(CH_3)_3$], 1.50-1.90 (12H, m, 6 x CH_2), 2.08 (1H, t, *J* = 2.7 Hz, CC*H*), 2.29 (1H, t, *J* = 2.5 Hz, CC*H*), 2.61-2.79 (2H, m, CH_2), 3.37-3.43 (1H, m, NC*H*), 3.46-3.55 (1H, m, CH*H*), 3.70-3.82 (1H, m, CH*H*), 3.84-3.88 (1H, m, CH*H*), 3.89-3.96 (1H, m, CH*H*), 4.08-4.13 (1H, m, CH*H*), 4.23 (1H, dd, *J* = 19.0, 2.5 Hz, CH*H*), 4.55-4.58 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.8 (2 CH_2), 24.7 (CH_2), 24.8 (CH_3), 29.6 (2 CH_2), 30.9 (CH_2), 32.6 (CH_2), 33.5 (CH_2), 58.9 (CH), 62.0 (C), 62.4 (2 CH_2), 67.3 (CH_2), 71.4 (CH), 72.6 (CH), 81.2 (C), 81.3 (C), 98.9 (CH), 99.0 (CH); LRMS (EI) *m/z* 383 (M^+, 0.01%), 260 (41), 224 (11), 178 (11), 140 (100), 122 (22), 106 (26), 85 (94), 57 (51), 56 (11), 43 (11), 41 (17); HRMS (ESI-TOF) Calcd for $C_{16}H_{24}NO_4S$ [$M^+ - C_4H_9$] 326.1426, found 326.1422.

(3*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propenyl)-1-phenylhex-5-yn-3-amine (9a): White solid; mp 63-64 °C (hexane/ CH_2Cl_2); R_F 0.54 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ –3.1 (*c* 0.40, CH_2Cl_2); IR (film) *v* 3265, 2975, 2861, 2117, 1602, 1452, 1310, 1125, 989, 891, 737, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.41 (9H, s, $C(CH_3)_3$), 2.02-2.10 (2H, m, CH_2), 2.10 (1H, t, *J* = 2.7 Hz, CC*H*), 2.60-2.64 (2H, m, CH_2), 2.68-2.74 (2H, m, CH_2), 3.90-4.00 (3H, m, CH_2 + NC*H*), 5.08-5.25 (2H, m, CH_2), 5.93-6.10 (1H, m, CH), 7.15-7.23 (3H, m, ArH), 7.25-7.33 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 24.7 (CH_2), 25.0 (CH_3), 33.5 (CH_2), 36.6 (CH_2), 48.7 (CH_2), 58.7 (CH), 62.2 (CH), 71.6 (CH), 81.4 (C), 117.4 (CH_2), 126.2 (CH), 128.4 (CH), 128.6 (CH), 137.8 (CH), 141.4 (C); LRMS (EI) *m/z* 333 (M^+, 0.01%), 294 (17), 238 (19), 175 (13), 174 (100), 108 (12), 91 (21), 57 (27); HRMS (ESI-TOF) Calcd for $C_{16}H_{24}NO_2S$ [$M^+ - C_3H_3$] 294.1528, found 294.1537.

(3*R*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-1-phenylhex-5-en-3-amine (15a): Orange solid; mp 61-63 °C (hexane/ CH_2Cl_2); R_F 0.62 (hexane/EtOAc 5:1); $[\alpha]^{20}_D$ –4.5 (*c* 1.05, CH_2Cl_2); IR (film) *v* 3262, 2987, 2930, 2117, 1639, 1312, 1124, 1051, 884, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.43 [9H, s, $C(CH_3)_3$], 1.98-2.05 (2H, m, CH_2), 2.29 (1H, t, *J* = 2.5 Hz, CC*H*), 2.45-2.62 (2H, m, CH_2), 2.62-2.73 (1H, m, CH*H*), 2.75-2.85 (1H, m, CH*H*), 3.86-3.96 (1H, m, NC*H*), 4.05-4.20 (2H, m, CH_2), 5.06-5.15 (2H, m, CH_2), 5.77-5.90 (1H, m, CH), 7.16-7.21 (3H, m, ArH), 7.26-7.30 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.8 (CH_3), 33.2 (CH_2), 33.6 (CH_2), 35.2 (CH_2), 39.3 (CH_2), 60.0 (CH), 61.8 (C), 72.6 (CH), 81.4 (C), 117.8 (CH_2), 126.1 (CH), 128.4 (CH), 128.5 (CH), 135.1 (CH), 141.8 (C); LRMS (EI) *m/z* 333 (M^+, 0.01%), 292 (11), 173 (13), 172 (100), 108 (11), 91 (23), 57 (21); HRMS (ESI-TOF) Calcd for $C_{19}H_{27}NO_2S$ [M^+] 333.1762, found 333.1765.

(3*S*)-*N*-(*tert*-Butanesulfonyl)-*N*-(2-propyl)-1-phenylhex-5-en-3-amine (*ent*-15a): Physical and spectroscopic data were found to be same than for **15a**. $[\alpha]_D^{20}$ = +3.1 (*c* = 1.12, CH_2Cl_2).

General Procedure for the Cyclotrimerization of Diynes 5 and Alkynes 6a, 6c and 6d. Synthesis of Tetrahydroisoquinolines 7: To a solution of the corresponding diyne **5** (0.1 mmol) in degasified and dry toluene (10.0 mL) was added Wilkinson's catalyst (4.6 mg, 0.005 mmol) and the corresponding alkyne **6a**, **6c** or **6d** (1.0 mmol). The reaction mixture was stirred at 100 °C for 17 h. Then the solvent was evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **7**. Yields are given in Table 2. Physical, spectroscopic, and analytical data follow.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-phenethyl-1,2,3,4-tetrahydroisoquinoline (7a): Yellow wax; R_F 0.55 (hexane/EtOAc 6:1); $[\alpha]^{20}_D$ +0.7 (*c* 0.58, CH_2Cl_2); IR (film) *v* 3055, 2970, 2874, 2856, 1452, 1311, 1265, 1128, 734, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.20 (3H, t, *J* = 7.5 Hz, CH_3), 1.21 (3H, t, *J* = 7.5 Hz, CH_3), 1.35 [9H, s, $C(CH_3)_3$], 1.67-2.15 (2H, m, CH_2), 2.60 (4H, q, *J* = 7.6 Hz, 2 x CH_2), 2.65-2.76 (3H, m, CH*H* + CH_2), 3.23 (1H, dd, *J* = 16.9, 6.0 Hz, CH*H*), 4.16-4.22 (1H, m, NC*H*), 4.35 (1H, d, *J* = 16.9 Hz, CH*H*), 4.61 (1H, d, *J* = 16.9 Hz, CH*H*), 6.83 (1H, s, ArH), 6.90 (1H, s, ArH), 7.14-7.17 (3H, m, ArH), 7.21-7.25 (2H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.3 (2 CH_3), 24.6 (CH_3), 25.2 (2 CH_2), 29.8 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 44.4 (CH_2), 53.2 (CH), 61.4 (C), 125.6 (CH), 126.0 (CH), 128.5 (2 CH), 129.2 (C), 129.3 (C), 129.6 (CH), 139.9 (C), 140.6 (C), 141.7 (C); LRMS (EI) *m/z* 413 (M^+, 1.71%), 356 (11), 292 (39), 252 (12), 189 (14), 188 (100), 187 (14), 186 (18), 160 (19), 57 (17); HRMS (ESI-TOF) Calcd for $C_{25}H_{35}NO_2S$ [M^+] 413.2389, found 413.2409.

Dimethyl (3*R*)-2-(*tert*-butanesulfonyl)-3-phenethyl-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (7c): Yellow solid; mp 38-39 °C (hexane/ CH_2Cl_2); R_F 0.33 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ +11.4 (*c* 0.90, CH_2Cl_2); IR (film) *v* 3061, 2922, 2850, 1725, 1310, 1266, 1126, 1058, 734, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 [9H, s, $C(CH_3)_3$], 1.66-2.00 (2H, m, CH_2), 2.63-2.76 (2H, m, CH_2), 2.81 (1H, d, *J* = 17.2 Hz, CH*H*), 3.30 (1H, dd, *J* = 17.0, 6.1 Hz, CH*H*), 3.90 (3H, s, CH_3), 3.90 (3H, s, CH_3), 4.20-4.27 (1H, m, NC*H*), 4.38 (1H, d, *J* = 17.8 Hz, CH*H*), 4.74 (1H, d, *J* = 17.9 Hz, CH*H*), 7.09-7.21 (3H, m, ArH), 7.23-7.26 (2H, m, ArH), 7.46 (1H, s, ArH), 7.50 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.6 (CH_3), 29.8 (CH_2), 32.8 (CH_2), 33.1 (CH_2), 33.7 (CH_2), 44.3 (CH_2), 52.6 (CH), 52.8 (CH_3), 61.7 (C), 126.3 (CH), 126.9 (CH), 128.4 (2 CH), 128.7 (2 CH), 130.0 (C), 130.8 (CH), 130.9 (C), 135.5 (C), 136.1 (C), 141.0 (C), 167.7 (C), 167.9 (C); LRMS (EI) *m/z* 473 (M^+, 0.12%), 353 (15), 352 (52), 321 (12), 249 (15), 248 (100), 246 (11), 235 (11), 217 (10), 216 (46), 189 (22), 91 (10), 57 (32); HRMS (ESI-TOF) Calcd for $C_{21}H_{22}NO_6S$ [$M^+ - C_4H_9$] 416.1168, found 416.1172.

(3*S*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (7d): Yellow wax; R_F 0.53 (hexane/EtOAc 6:1); 95.5:4.5 er [HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 98/2, 1.0 mL/min, 210 nm): t_{major} = 9.09 min, t_{minor} = 16.53 min]; $[\alpha]^{20}_D$ +34.6 (*c* 0.81, CH_2Cl_2); IR (film) *v* 3061, 2965, 2927, 2856, 1724, 1452, 1312, 1265, 1128, 948, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.18-1.25 (6H, m, 2 x CH_3), 1.39 [9H, s, $C(CH_3)_3$], 2.54-2.68 (4H, m, 2 x CH_2), 3.25 (1H, d, *J* = 16.8 Hz, CH*H*), 3.51 (1H, dd, *J* = 16.8, 6.7 Hz, CH*H*), 4.06 (1H, d, *J* = 16.7 Hz, CH*H*), 4.51 (1H, d, *J* = 16.7 Hz, CH*H*), 5.36 (1H, d, *J* = 6.4 Hz, NC*H*), 6.76 (1H, s, ArH), 7.02 (1H, s, ArH), 7.21-7.29 (3H, m, ArH), 7.36-7.41 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$)

δ = 15.1 (CH_3), 15.2 (CH_3), 24.8 (CH_3), 25.2 (CH_2), 25.3 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 55.4 (CH), 61.7 (C), 125.5 (CH), 127.6 (CH), 127.9 (CH), 128.6 (CH), 129.9 (C), 130.1 (C), 132.4 (CH), 139.5 (C), 140.0 (C), 140.7 (C); LRMS (EI) *m/z* 385 (M^+, 0.92%), 328 (10), 265 (20), 264 (96), 263 (33), 161 (17), 160 (100), 57 (20); HRMS (ESI-TOF) Calcd for $C_{23}H_{31}NO_2S$ [M^+] 385.2075, found 385.2083.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (*ent*-7d): Physical and spectroscopic data were found to be same than for **7d**. 4.6:95.4 er [HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 98/2, 1.0 mL/min, 210 nm): t_{minor} = 9.24 min, t_{major} = 17.05 min]; $[\alpha]_D^{20}$ = −52.0 (*c* = 0.70, CH_2Cl_2).

Dimethyl (3*S*)-2-(*tert*-butanesulfonyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (7f): Yellow solid; mp 37-38 °C (hexane/ CH_2Cl_2); R_F 0.31 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ +62.2 (*c* 0.51, CH_2Cl_2); IR (film) *v* 3061, 2983, 2952, 2922, 1726, 1433, 1265, 1127, 732, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.41 (9H, s, $C(CH_3)_3$), 3.40 (1H, d, *J* = 17.4 Hz, CH*H*), 3.60 (1H, dd, *J* = 17.4, 6.7 Hz, CH*H*), 3.88 (3H, s, CH_3), 3.92 (3H, s, CH_3), 4.08 (1H, d, *J* = 17.7 Hz, CH*H*), 4.62 (1H, d, *J* = 17.6 Hz, CH*H*), 5.43 (1H, d, *J* = 6.4 Hz, NC*H*), 7.22-7.34 (5H, m, ArH), 7.39 (1H, s, ArH), 7.64 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.8 (CH_3), 29.8 (CH_2), 45.0 (CH_2), 52.8 (CH_3), 52.9 (CH_3), 55.0 (CH), 62.0 (C), 126.9 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 129.9 (CH), 130.0 (C), 131.0 (C), 136.3 (C), 136.8 (C), 138.2 (C), 167.7 (C), 168.0 (C); LRMS (EI) *m/z* 445 (M^+, 1.54%), 414 (11), 325 (39), 324 (100), 310 (15), 293 (17), 292 (13), 278 (21), 248 (15), 220 (31), 208 (11), 207 (62), 190 (10), 189 (40), 91 (11), 57 (42); HRMS (ESI-TOF) Calcd for $C_{23}H_{27}NO_6S$ [M^+] 445.1559, found 445.1571.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-(*sec*-butyl)-1,2,3,4-tetrahydroisoquinoline (7g): Yellow oil; R_F 0.63 (hexane/EtOAc 6:1); $[\alpha]^{20}_D$ +4.9 (*c* 0.60, CH_2Cl_2); IR (film) *v* 2960, 2926, 2871, 1730, 1464, 1365, 1315, 1129, 1052, 939, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.92 (3H, d, *J* = 6.5 Hz, CH_3), 0.95 (3H, d, *J* = 6.6 Hz, CH_3), 1.21 (3H, t, *J* = 7.6 Hz, CH_3), 1.22 (3H, t, *J* = 7.6 Hz, CH_3), 1.36 [9H, s, $C(CH_3)_3$], 1.42-1.50 (2H, m, CH_2), 1.62-1.68 (1H, m, CH), 2.58-2.64 (5H, m, CH*H* + 2 x CH_2), 3.19 (1H, dd, *J* = 16.4, 6.1 Hz, CH*H*), 4.16-4.21 (1H, m, NC*H*), 4.30 (1H, d, *J* = 16.8 Hz, CH*H*), 4.57 (1H, d, *J* = 16.8 Hz, CH*H*), 6.83 (1H, s, ArH), 6.90 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.2 (2 CH_3), 22.4 (CH_3), 23.4 (CH_3), 24.7 (CH_3), 25.2 (CH_2), 25.2 (CH), 25.25 (CH_2), 29.9 (CH_2), 40.7 (CH_2), 44.3 (CH_2), 51.4 (CH), 61.3 (C), 125.5 (CH), 129.4 (C), 129.5 (C), 129.6 (CH), 139.8 (C), 140.5 (C); LRMS (EI) *m/z* 365 (M^+, 0.51%), 308 (18), 252 (15), 244 (29), 189 (15), 188 (100), 186 (31), 160 (24), 57 (23); HRMS (ESI-TOF) Calcd for $C_{17}H_{26}NO_2S$ [M^+ - C_4H_9] 308.1684, found 308.1685.

Dimethyl (3*R*)-2-(*tert*-butanesulfonyl)-3-(*sec*-butyl)-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (7i): Yellow wax; R_F 0.38 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ +17.0 (*c* 0.90, CH_2Cl_2); IR (film) *v* 3049, 2959, 2928, 2874, 1728, 1265, 1129, 733, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.90-0.96 (6H, m, 2 x CH_3), 1.37 (9H, s, $C(CH_3)_3$), 1.54-1.65 (3H, m, CH_2 + CH), 2.74 (1H, d, *J* = 17.0 Hz, CH*H*), 3.26 (1H, dd, *J* = 16.9, 6.1 Hz, CH*H*), 3.90 (3H, s, CH_3), 3.90 (3H, s, CH_3), 4.20-4.27 (1H, m, NC*H*), 4.34 (1H, d, *J* = 17.9 Hz, CH*H*), 4.72 (1H, d, *J* =

17.8 Hz, CH*H*), 7.45 (1H, s, ArH), 7.50 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.4 (CH_3), 24.6 (CH_3), 25.1 (CH), 32.7 (CH_2), 40.7 (CH_2), 44.3 (CH_2), 50.9 (CH), 52.9 (2 CH_3), 61.6 (C), 126.8 (CH), 129.8 (C), 130.7 (C), 130.8 (CH), 135.8 (C), 136.4 (C), 167.8 (C), 168.1 (C); LRMS (EI) *m/z* 425 (M^+, 0.35%), 368 (19), 304 (15), 262 (20), 249 (15), 248 (100), 246 (11), 216 (46), 189 (17), 187 (10), 57 (34); HRMS (ESI-TOF) Calcd for $C_{21}H_{31}NO_6S$ [M^+] 425.1872, found 425.1845.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-nonanyl-1,2,3,4-tetrahydroisoquinoline (7j): Colorless oil; R_F 0.68 (hexane/EtOAc 6:1); $[\alpha]^{20}_D$ –6.1 (*c* 0.62, CH_2Cl_2); IR (film) *v* 2961, 2924, 2854, 1733, 1462, 1316, 1130, 1013, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.83-0.89 (3H, m, CH_3), 1.19-1.27 (20H, m, 2 x CH_3 + 7 x CH_2), 1.36 (9H, s, $C(CH_3)_3$), 1.55-1.68 (2H, m, CH_2), 2.58-2.66 (5H, m, CH*H* + 2 x CH_2), 3.18 (1H, dd, *J* = 16.4, 6.0 Hz, CH*H*), 4.05-4.10 (1H, m, NC*H*), 4.30 (1H, d, *J* = 16.8 Hz, CH*H*), 4.56 (1H, d, *J* = 16.8 Hz, CH*H*), 6.83 (1H, s, ArH), 6.91 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 15.2 (2 CH_3), 22.8 (CH_2), 24.6 (CH_3), 25.2 (2 CH_2), 26.9 (CH_2), 29.4 (CH_2), 29.7 (2 CH_2), 29.8 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 53.4 (CH), 61.4 (C), 125.5 (CH), 129.5 (2 C), 129.6 (CH), 139.8 (C), 140.5 (C); LRMS (EI) *m/z* 435 (M^+, 0.15%), 378 (10), 314 (23), 252 (20), 202 (23), 189 (15), 188 (100), 186 (34), 160 (20), 57 (22); HRMS (ESI-TOF) Calcd for $C_{22}H_{36}NO_2S$ [$M^+ - C_4H_9$] 378.2467, found 378.2464.

Dimethyl (3*R*)-2-(*tert*-butanesulfonyl)-3-nonanyl-1,2,3,4-tetrahydroisoquinoline-6,7-dicarboxylate (7l): Yellow oil; R_F 0.49 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ +3.9 (*c* 1.35, CH_2Cl_2); IR (film) *v* 2952, 2923, 2856, 1728, 1434, 1270, 1128, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.84-0.92 (3H, m, CH_3), 1.22-1.28 (14H, m, 7 x CH_2), 1.36 (9H, s, $C(CH_3)_3$), 1.50-1.58 (2H, m, CH_2), 2.76 (1H, d, *J* = 17.0 Hz, CH*H*), 3.26 (1H, dd, *J* = 17.0, 6.0 Hz, CH*H*), 3.90 (3H, s, CH_3), 3.90 (3H, s, CH_3), 4.10-4.16 (1H, m, NC*H*), 4.34 (1H, d, *J* = 17.6 Hz, CH*H*), 4.70 (1H, d, *J* = 17.6 Hz, CH*H*), 7.45 (1H, s, ArH), 7.50 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.8 (CH_2), 24.6 (CH_3), 26.8 (CH_2), 29.4 (CH_2), 29.6 (2 CH_2), 29.8 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 32.8 (CH_2), 44.3 (CH_2), 52.8 (CH), 52.8 (2 CH_3), 61.6 (C), 126.8 (CH), 129.8 (C), 130.7 (C), 130.8 (CH), 135.7 (C), 136.4 (C), 167.8 (C), 168.1 (C); LRMS (EI) *m/z* 495 (M^+, 0.33%), 374 (16), 368 (15), 264 (13), 262 (43), 249 (15), 248 (100), 246 (15), 216 (39), 189 (14), 156 (16), 57 (34); HRMS (ESI-TOF) Calcd for $C_{26}H_{41}NO_6S$ [M^+] 495.2655, found 495.2652.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-diethyl-3-[4-((tetrahydro-2*H*-pyran-2-yl)oxy)butyl]-1,2,3,4-tetrahydroisoquinoline (7m): Colorless wax (1:1 mixture of diastereoisomers); R_F 0.31 (hexane/EtOAc 6:1); IR (film) *v* 2937, 2872, 1456, 1312, 1265, 1129, 1031, 1021, 733, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.20 (3H, t, *J* = 7.5 Hz, CH_3), 1.21 (1H, t, *J* = 7.5 Hz, CH_3), 1.36 (9H, s, $C(CH_3)_3$), 1.40-1.70 (12H, m, 6 x CH_2), 2.56-2.69 (5H, m, CH*H* + 2 x CH_2), 3.18 (1H, dd, *J* = 16.3, 6.1 Hz, CH*H*), 3.31-3.40 (1H, m, NC*H*), 3.41-3.52 (1H, m, CH*H*), 3.66-3.76 (1H, m, CH*H*), 3.76-3.87 (1H, m, CH*H*), 4.04-4.13 (1H, m, CH*H*), 4.31 (1H, d, *J* = 16.7 Hz, CH*H*), 4.50-4.61 (2H, m, CH*H* + CH), 6.83 (1H, s, ArH), 6.91 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.2 (CH_3), 19.7 (CH_2), 19.8 (CH_2), 23.7 (CH_2), 24.5 (CH_3), 25.1 (CH_2), 25.3 (CH_2), 25.6 (CH_2), 29.6 (CH_2), 30.6 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 44.4 (CH_2), 53.2 (CH), 61.4 (C), 62.4 (2 CH_2), 67.4 (CH_2), 67.5 (CH_2), 98.8 (CH), 98.9

(CH), 125.5 (CH), 129.4 (2 C), 129.6 (CH), 139.8 (C), 140.5 (C); LRMS (EI) *m/z* 465 (M^+, 0.03%), 380 (17), 344 (21), 261 (19), 260 (100), 258 (16), 252 (11), 242 (21), 189 (13), 188 (94), 186 (22), 160 (21), 85 (20), 57 (24); HRMS (ESI-TOF) Calcd for $C_{22}H_{34}NO_2$ [$M^+ - C_4H_9O_2S$] 344.2590, found 344.2588.

(3*R*)-2-(*tert*-Butanesulfonyl)-6-butyl-3-phenethyl-1,2,3,4-tetrahydroisoquinoline (7n) and (3*R*)-2-(*tert*-Butanesulfonyl)-7-butyl-3-phenethyl-1,2,3,4-tetrahydroisoquinoline (7o): Orange wax (1:1 mixture of regioisomers); R_F 0.55 (hexane/EtOAc 6:1); IR (film) *v* 3061, 2959, 2929, 2856, 1455, 1314, 1130, 1045, 938, 735, 700, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.92 (3H, t, *J* = 7.3 Hz, CH_3), 0.93 (3H, t, *J* = 7.3 Hz, CH_3), 1.35 [18H, s, 2 x $C(CH_3)_3$], 1.41-1.63 (8H, m, 4 x CH_2), 1.75-2.00 (4H, m, 2 x CH_2), 2.51-2.60 (4H, m, 2 x CH_2), 2.61-2.81 (6H, m, 2 x CH_2 + 2 x CH*H*), 3.20-3.29 (2H, m, 2 x CH*H*), 4.16-4.23 (2H, m, 2 x NC*H*), 4.36 (2H, d, *J* = 17.0 Hz, 2 x CH*H*), 4.62 (2H, d, *J* = 16.9 Hz, 2 x CH*H*), 6.85 (1H, s, ArH), 6.93-7.01 (5H, m, ArH), 7.13-7.17 (6H, m, ArH), 7.21-7.25 (4H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.9 (CH_3), 22.6 (CH_2), 24.6 (CH_3), 29.8 (CH_2), 33.2 (CH_2), 33.6 (CH_2), 33.7 (CH_2), 33.8 (CH_2), 35.4 (CH_2), 35.45 (CH_2), 44.5 (CH_2), 44.6 (CH_2), 53.0 (CH), 53.1 (CH), 61.4 (C), 125.8 (CH), 125.9 (CH), 126.1 (CH), 126.6 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 129.1 (C), 129.15 (C), 129.8 (CH), 129.85 (CH), 131.7 (C), 141.1 (C), 141.6 (C), 141.7 (C); LRMS (EI) *m/z* 413 (M^+, 0.62%), 356 (9), 292 (36), 252 (11), 189 (15), 188 (100), 186 (13), 57 (20); HRMS (ESI-TOF) Calcd for $C_{25}H_{35}NO_2S$ [M^+] 413.2389, found 413.2391.

General Procedure for the Cyclotrimerization of Diynes 5 and 2-Butyne-1,4-diol (6b). Synthesis of Tetrahydroisoquinolines 7: To a solution of the corresponding diyne **5** (0.1 mmol) in degasified and HPLC quality ethanol (10.0 mL) was added Wilkinson's catalyst (4.6 mg, 0.005 mmol) and alkyne **6b** (86.0 mg,77.5 µL, 1.0 mmol). The reaction mixture was stirred at 75 °C for 17 h. Then the solvent was evaporated (15 Torr) and CH_2Cl_2 (5.0 mL) was added to the crude of the reaction and washed with H_2O (3 x 10 mL) in order to remove the excess of 2-butyne-1,4-diol (**6b**). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **7**. Yields are given in Table 2. Physical, spectroscopic, and analytical data follow.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-di(hydroxymethyl)-3-phenethyl-1,2,3,4-tetrahydroisoquinoline (7b): Orange solid; mp 56-58 °C (hexane/ CH_2Cl_2); R_F 0.30 (hexane/EtOAc 1:2); $[\alpha]^{20}_D$ +10.7 (*c* 0.75, CH_2Cl_2); IR (film) *v* 3376, 2922, 2856, 1457, 1433, 1308, 1124, 1013, 722, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.36 [9H, s, $C(CH_3)_3$], 1.72-2.07 (2H, m, CH_2), 2.71-2.77 (3H, m, CH*H* + CH_2), 2.84 (2H, s, 2 x OH), 3.26 (1H, dd, *J* = 16.7, 6.0 Hz, CH*H*), 4.19-4.27 (1H, m, NC*H*), 4.36 (1H, d, *J* = 17.3 Hz, CH*H*), 4.64-4.70 (5H, m, 2 x CH_2 + CH*H*), 7.05 (1H, s, ArH), 7.14-7.28 (7H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.6 (CH_3), 29.8 (CH_2), 33.1 (CH_2), 33.6 (CH_2), 44.3 (CH_2), 52.9 (CH), 61.5 (C), 63.9 (2 CH_2), 126.1 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 131.4 (CH), 132.1 (C), 132.7 (C), 137.6 (C), 138.3 (C), 141.3 (C); LRMS (EI) *m/z* 417 (M^+, 0.55%), 360 (11), 296 (42), 294 (13), 278 (10), 193 (12), 192 (100), 190 (32), 188 (20), 175 (14), 174 (41), 172 (16), 144 (12), 91 (18), 57 (48), 41 (11); HRMS (ESI-TOF) Calcd for $C_{19}H_{22}NO_4S$ [$M^+ - C_4H_9$] 360.1270, found 360.1259.

(3*S*)-2-(*tert*-Butanesulfonyl)-6,7-di(hydroxymethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (7e): Yellow solid; mp 63-64 °C (hexane/ CH_2Cl_2); R_F 0.28 (hexane/EtOAc 1:2); $[\alpha]^{20}_D$ +61.9 (*c* 0.63, CH_2Cl_2); IR (film) *v* 3352, 2952, 2922, 2861, 1308, 1124, 947, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.39 [9H, s, $C(CH_3)_3$], 2.77 (2H, s, 2 x OH), 3.30 (1H, d, *J* = 17.0 Hz, CH*H*), 3.54 (1H, dd, *J* = 17.1, 6.7 Hz, CH*H*), 4.05 (1H, d, *J* = 17.1 Hz, CH*H*), 4.55 (1H, d, *J* = 17.0 Hz, CH*H*), 4.66 (2H, s, CH_2), 4.71 (2H, s, CH_2), 5.38 (1H, d, *J* = 6.1 Hz, NC*H*), 6.96 (1H, s, ArH), 7.20-7.27 (4H, m, ArH), 7.30-7.37 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.7 (CH_3), 29.8 (CH_2), 45.0 (CH_2), 55.2 (CH), 61.8 (C), 63.9 (CH_2), 64.0 (CH_2), 127.3 (CH), 127.8 (CH), 128.7 (CH), 128.9 (CH), 130.5 (CH), 132.3 (CH), 132.5 (CH), 132.9 (C), 133.0 (C), 137.6 (C), 138.4 (C), 138.9 (C); LRMS (EI) *m/z* 389 (M^+, 1.13%), 332 (10), 269 (21), 268 (100), 267 (14), 266 (12), 251 (19), 250 (16), 164 (48), 146 (17), 118 (13), 117 (14), 91 (14), 57 (33); HRMS (ESI-TOF) Calcd for $C_{21}H_{27}NO_4S$ [M^+] 389.1661, found 389.1651.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-di(hydroxymethyl)-3-(*sec*-butyl)-1,2,3,4-tetrahydroisoquinoline (7h): Orange solid; mp 61-63 °C (hexane/ CH_2Cl_2); R_F 0.33 (hexane/EtOAc 1:2); $[\alpha]^{20}_D$ +7.1 (*c* 1.30, CH_2Cl_2); IR (film) *v* 3382, 2952, 2924, 2850, 1433, 1310, 1122, 1014, 734, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.88-0.95 (6H, m, 2 x CH_3), 1.36 [9H, s, $C(CH_3)_3$], 1.54-1.68 (3H, m, CH_2 + CH), 2.66 (1H, d, *J* = 16.7 Hz, CH*H*), 3.20 (1H, dd, *J* = 16.7, 5.8 Hz, CH*H*), 3.22-3.50 (2H, bs, 2 x OH), 4.17-4.24 (1H, m, NC*H*), 4.30 (1H, d, *J* = 17.3 Hz, CH*H*), 4.60-4.68 (5H, m, 2 x CH_2 + CH*H*), 7.03 (1H, s, ArH), 7.12 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.8 (CH_3), 24.5 (CH_3), 25.1 (CH), 32.3 (CH_2), 40.6 (CH_2), 44.2 (CH_2), 51.1 (CH), 61.4 (C), 64.0 (2 CH_2), 127.3 (CH), 131.5 (CH), 132.3 (C), 132.6 (C), 137.4 (C), 138.1 (C); LRMS (EI) *m/z* 369 (M^+, 0.41%), 312 (24), 277 (13), 248 (22), 206 (14), 202 (10), 193 (12), 192 (100), 190 (38), 188 (34), 175 (10), 174 (42), 172 (12), 144 (11), 57 (58), 43 (25), 41 (16); HRMS (ESI-TOF) Calcd for $C_{15}H_{22}NO_4S$ [$M^+ - C_4H_9$] 312.1270, found 312.1269.

(3*R*)-2-(*tert*-Butanesulfonyl)-6,7-di(hydroxymethyl)-3-nonanyl-1,2,3,4-tetrahydroisoquinoline (7k): Yellow solid; mp 39-40 °C; R_F 0.38 (hexane/EtOAc 1:2); $[\alpha]^{20}_D$ –1.2 (*c* 1.01, CH_2Cl_2); IR (film) *v* 3364, 2959, 2922, 2856, 1463, 1312, 1128, 1011, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.82-0.91 (3H, m, CH_3), 1.21-1.28 (14H, m, 7 x CH_2), 1.36 [9H, s, $C(CH_3)_3$], 1.49-1.64 (2H, m, CH_2), 2.69 (1H, d, *J* = 16.7 Hz, CH*H*), 3.20 (1H, dd, *J* = 16.5, 6.0 Hz, CH*H*), 4.07-4.13 (1H, m, NC*H*), 4.30 (1H, d, *J* = 17.0 Hz, CH*H*), 4.61 (1H, d, *J* = 16.6 Hz, CH*H*), 4.68 (4H, s, 2 x CH_2), 7.03 (1H, s, ArH), 7.12 (1H, s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2 (CH_3), 22.8 (CH_2), 24.6 (CH_3), 26.8 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 32.4 (CH_2), 44.2 (CH_2), 53.2 (CH), 61.5 (C), 64.0 (2 CH_2), 127.3 (CH), 131.5 (CH), 132.3 (C), 132.6 (C), 137.4 (C), 138.1 (C); LRMS (EI) *m/z* 439 (M^+, 0.01%), 330 (12), 316 (13), 314 (14), 206 (31), 204 (49), 203 (17), 202 (100), 192 (35), 190 (52), 188 (74), 186 (31), 174 (28), 172 (17), 158 (16), 156 (26), 57 (63), 43 (30), 41 (29); HRMS (ESI-TOF) Calcd for $C_{20}H_{32}NO_4S$ [$M^+ - C_4H_9$] 382.2052, found 382.2055.

Ruthenium-Catalyzed Ring Closing Metathesis of Enyne 9a. Synthesis of Cyclic 1,3-Diene 10a: A mixture of enyne **9a** (66.6 g, 0.2 mmol), Hoveyda-Grubbs second generation ruthenium catalyst (12.4 mg, 0.02 mmol),

and 1,7-octadiene (0.088 g, 0.116 mL, 0.8 mmol) in dry CH_2Cl_2 (20 mL) was stirred at 40 °C for 12 h. Then the solvent was evaporated (15 Torr). Purification by column chromatography (silica gel, hexane/EtOAc) yielded **10a** (63.3 mg, 0.19 mmol, 95%). Physical, spectroscopic, and analytical data follow.

(2*R*)-1-(*tert*-Butanesulfonyl)-2-phenethyl-4-vinyl-1,2,3,6-tetrahydropyridine (10a): Colorless wax; R_F 0.54 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ +10.1 (*c* 0.95, CH_2Cl_2); IR (film) *v* 3061, 2977, 2935, 2904, 2861, 2837, 1713, 1312, 1128, 950, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.35 [9H, s, $C(CH_3)_3$], 1.73-2.00 (2H, m, CH_2), 2.27 (1H, d, *J* = 16.6 Hz, CH*H*), 2.51-2.62 (1H, m, CH*H*), 2.65-2.77 (2H, m, CH_2), 3.83 (1H, d, *J* = 19.5 Hz, CC*H*), 4.06-4.18 (2H, m, NC*H* + CH*H*), 4.99-5.30 (2H, m, CH_2), 5.67-5.73 (1H, m, CH), 6.39 (1H, dd, *J* = 17.5, 10.7 Hz, CH), 7.15-7.20 (3H, m, ArH), 7.24-7.30 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.5 (CH_3), 29.8 (CH_2), 33.3 (CH_2), 34.1 (CH_2), 42.6 (CH_2), 52.2 (CH), 61.5 (C), 112.1 (CH_2), 119.9 (CH), 123.9 (CH), 126.1 (CH), 128.4 (CH), 128.5 (CH), 133.0 (C), 136.6 (CH), 138.6 (CH), 141.7 (C); LRMS (EI) *m/z* 333 (M^+, 0.41%), 276 (17), 252 (32), 213 (30), 212 (95), 148 (34), 109 (14), 108 (100), 106 (19), 105 (11), 91 (40), 79 (16), 77 (11), 57 (69), 41 (14); HRMS (ESI-TOF) Calcd for $C_{19}H_{27}NO_2S$ [M^+] 333.1762, found 333.1776.

Ruthenium-Catalyzed Ring Closing Metathesis of Enynes 15a and *ent*-15a. Synthesis of Cyclic 1,3-Diene 16a: A mixture of enyne **15a** or *ent*-**15a** (66.6 g, 0.2 mmol), Grubbs first generation ruthenium catalyst (32.8 mg, 0.04 mmol), and 1,7-octadiene (0.088 g, 0.116 mL, 0.8 mmol) in dry CH_2Cl_2 (20 mL) was stirred at 40 °C for 20 h. Then the solvent was evaporated (15 Torr). Purification by column chromatography (silica gel, hexane/EtOAc) yielded **16a** (65.3 mg, 0.195 mmol, 98%) or *jent*-**16a** (66.0 mg, 0.195 mmol, 98%). Triene **17a** was isolated and characterized as a side reaction product working under different reaction conditions (see table 4). Physical, spectroscopic, and analytical data follow.

(2*R*)-1-(*tert*-Butanesulfonyl)-2-phenethyl-5-vinyl-1,2,3,6-tetrahydropyridine (16a): Colorless wax; R_F 0.51 (hexane/EtOAc 4:1); $[\alpha]^{20}_D$ –11.0 (*c* 0.40, CH_2Cl_2); IR (film) *v* 3057, 2975, 2935, 2868, 1603, 1313, 1265, 1129, 733, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 [9H, s, $C(CH_3)_3$], 1.69-2.04 (2H, m, CH_2), 2.15 (1H, dd, *J* = 19.0, 5.7 Hz, CH*H*), 2.62-2.76 (3H, m, CH*H* + CH_2), 3.77 (1H, d, *J* = 17.8 Hz, CH*H*), 4.00-4.07 (1H, m, NC*H*), 4.20 (1H, d, *J* = 17.4 Hz, CH*H*), 4.95-5.11 (2H, m, CH_2), 5.80 (1H, d, *J* = 5.7 Hz, CH), 6.29 (1H, dd, *J* = 17.8, 11.0 Hz, CH), 7.13-7.22 (3H, m, ArH), 7.23-7.32 (2H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.6 (CH_3), 29.8 (CH_2), 33.2 (CH_2), 34.1 (CH_2), 41.5 (CH_2), 52.1 (CH), 61.4 (C), 111.5 (CH_2), 125.4 (CH), 126.1 (CH), 126.4 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 132.7 (C), 136.5 (CH), 141.7 (C); LRMS (EI) *m/z* 333 (M^+, 1.13%), 213 (20), 212 (29), 172 (12), 108 (100), 91 (17), 79 (13), 57 (38); HRMS (ESI-TOF) Calcd for $C_{19}H_{27}NO_2S$ [M^+] 333.1762, found 333.1769.

(2*S*)-1-(*tert*-Butanesulfonyl)-2-phenethyl-5-vinyl-1,2,3,6-tetrahydropyridine (*ent*-16a): Physical and spectroscopic data were found to be same than for **16a**. $[\alpha]_D^{20}$ = +8.6 (*c* = 0.84, CH_2Cl_2).

(*E*)-1,2-bis[(2*R*)-1-(*tert*-Butanesulfonyl)-6-phenethyl-1,2,3,6-tetrahydropyridin-3-yl]ethane (17a): Orange solid; mp 72-74 °C (hexane/ CH_2Cl_2); R_F 0.39 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ –12.1 (*c* 0.45, CH_2Cl_2); IR (film) *v* 3027, 2933, 1454, 1312, 1266, 1127, 733, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.35 [18H, s, 2 x $C(CH_3)_3$], 1.74-1.98 (4H, m, 2 x CH_2), 2.14-2.22 (2H, m, 2 x CC*H*), 2.67-2.75 (6H, m, 2 x CH*H* + 2 x CH_2), 3.79 (2H, d, *J* = 17.5 Hz, 2 x CC*H*), 4.00-4.07 (2H, m, 2 x NC*H*), 4.19 (2H, d, *J* = 17.5 Hz, 2 x CC*H*), 5.82 (1H, d, *J* = 4.7 Hz, CH), 6.01 (1H, s, CH), 7.13-7.30 (10H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.6 (CH_3), 29.8 (CH_2), 33.2 (CH_2), 34.0 (CH_2), 41.8 (CH_2), 52.2 (CH), 61.5 (C), 125.7 (CH), 125.8 (CH), 126.1 (CH), 128.4 (CH), 128.5 (CH), 132.2 (C), 141.7 (C); LRMS (EI) *m/z* 638 (M^+, 0.84%), 427 (11), 413 (14), 397 (18), 293 (11), 264 (30), 214 (11), 159 (11), 134 (15), 132 (18), 117 (20), 105 (19), 91 (53), 57 (100), 41 (24); HRMS (ESI-TOF) Calcd for $C_{36}H_{50}N_2O_4S_2$ [M^+] 638.3212, found 638.3217.

General Procedure for the Diels-Alder Reaction of Cyclic Dienes 10a, 16a and *ent*-16a with Dimethyl Acetylenedicarboxylate (6c), and Further Oxidation with DDQ. Synthesis of Tetrahydroisoquinolines 12a, 18a and *ent*-18a: To a solution of the corresponding diene **10a**, **16a** or *ent*-**16a** (0.2 mmol) in dry toluene (3.0 mL) was added freshly distilled dimethyl acetylenedicarboxylate (**6c**, 0.084 g, 0.072 mL, 0.6 mmol). The reaction mixture was stirred at 100 °C for 40 h. After that, it was cooled down, and the solvent was evaporated (15 Torr). The crude of the reaction and freshly recrystalized DDQ (0.091 g, 0.4 mmol) were dissolved in dry toluene (10.0 mL) in a pressure tube, and the reaction mixture was stirred at 80 °C for 20 h. After that, it was filtered through a pad of celite with EtOAc (30 mL), and was evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield products **12a**, **18a** and *ent*-**18a**. Yields are given in Schemes 6 and 8. Physical, spectroscopic, and analytical data follow.

Dimethyl (3*R*)-2-(*tert*-butanesulfonyl)-3-phenethyl-1,2,3,4-tetrahydroisoquinoline-7,8-dicarboxylate (12a): Orange wax; R_F 0.36 (hexane/EtOAc 3:1); $[\alpha]^{20}_D$ +3.1 (*c* 0.74, CH_2Cl_2); IR (film) *v* 2952, 2922, 2850, 1725, 1433, 1266, 1125, 1005, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.34 [9H, s, $C(CH_3)_3$], 1.73-1.98 (2H, m, CH_2), 2.69-2.71 (2H, m, CH_2), 2.81 (1H, d, *J* = 17.2 Hz, CH*H*), 3.33 (1H, dd, *J* = 17.0, 6.1 Hz, CH*H*), 3.88 (3H, s, CH_3), 3.95 (3H, s, CH_3), 4.21-4.26 (1H, m, NC*H*), 4.32 (1H, d, *J* = 17.6 Hz, CH*H*), 4.70 (1H, d, *J* = 17.7 Hz, CH*H*), 7.11-7.20 (4H, m, ArH), 7.23-7.27 (2H, m, ArH), 7.83 (1H, d, *J* = 8.1 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.6 (CH_3), 29.8 (CH_2), 33.0 (CH_2), 33.6 (CH_2), 41.9 (CH_2), 52.1 (CH), 52.7 (CH_3), 53.0 (CH_3), 61.7 (C), 126.3 (CH), 126.4 (C), 128.4 (CH), 128.6 (2 CH), 129.4 (CH), 129.9 (C), 131.3 (CH), 135.2 (CH), 136.6 (C), 138.1 (C), 141.0 (C), 166.1 (C), 168.7 (C); LRMS (EI) *m/z* 473 (M^+, 0.10%), 352 (35), 321 (25), 320 (100), 248 (29), 235 (11), 216 (47), 91 (15), 57 (31); HRMS (ESI-TOF) Calcd for $C_{24}H_{28}NO_5S$ [M^+ - OCH_3] 442.1695, found 416.1688.

Dimethyl (3*R*)-2-(*tert*-butanesulfonyl)-3-phenethyl-1,2,3,4-tetrahydroisoquinoline-5,6-dicarboxylate (18a): Orange solid; mp 36-37 °C (hexane/CH_2Cl_2); R_F 0.33 (hexane/EtOAc 3:1); 4.0:96.0 er [HPLC (Chiralpak AD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm): t_{minor} = 19.70 min, t_{major} = 37.62 min]; $[\alpha]^{20}_D$ +23.5 (*c* 0.92, CH_2Cl_2); IR (film) *v* 3061, 2994, 2946, 1726, 1439, 1265, 732, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ =

1.35 [9H, s, $C(CH_3)_3$], 1.69-1.97 (2H, m, CH_2), 2.66-2.71 (2H, m, CH_2), 2.77 (1H, d, *J* = 17.9 Hz, CH*H*), 3.18 (1H, dd, *J* = 16.6, 6.3 Hz, CH*H*), 3.90 (3H, s, CH_3), 3.96 (3H, s, CH_3), 4.18-4.25 (1H, m, NC*H*), 4.43 (1H, d, *J* = 17.9 Hz, CH*H*), 4.74 (1H, d, *J* = 17.7 Hz, CH*H*), 7.12-7.26 (6H, m, ArH), 7.85 (1H, d, *J* = 7.8 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.5 (CH_3), 29.8 (CH_2), 33.0 (CH_2), 33.7 (CH_2), 44.7 (CH_2), 52.3 (CH), 52.7 (CH_3), 52.9 (CH_3), 61.7 (C), 126.1 (CH), 126.2 (CH), 127.1 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 130.0 (C), 134.5 (C), 136.8 (C), 137.6 (C), 141.1 (C), 165.9 (C), 169.4 (C); LRMS (EI) *m/z* 473 (M^+, 0.20%), 352 (26), 320 (21), 248 (18), 230 (19), 217 (17), 216 (100), 57 (28); HRMS (ESI-TOF) Calcd for $C_{25}H_{31}NO_6S$ [M^+] 473.1872, found 473.1858.

Dimethyl (3*S*)-2-(*tert*-butanesulfonyl)-3-phenethyl-1,2,3,4-tetrahydroisoquinoline-5,6-dicarboxylate (*ent*-18a): Physical and spectroscopic data were found to be same than for **18a**. 98:7 er [HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 90/10, 1.0 mL/min, 220 nm): t_{major} = 19.33 min, t_{minor} = 1.3 min]; $[\alpha]_D^{20}$ = −16.5 (*c* = 0.37, CH_2Cl_2).

Supporting Information (see footnote on the first page of this article): Copies of ^1H, ^{13}C NMR and DEPT spectra for new compounds **1e**, **2d**, **2e**, **3d**, **3e**, **4**, **5**, **7**, **8a-10a**, **12a**, **14a-18a**. Copies of chiral HPLC chromatograms for compounds **7d**, *ent*-**7d**, **18a** and *ent*-**18a**.

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Table of Contents

3,6,7-Trisubstituted 1,2,3,4-tetrahydroisoquinolines were prepared through a [2+2+2] cyclotrimerization of chiral 4-azaocta-1,7-dienys promoted by Wilkinson catalyst. Regioisomeric 5,6- and 7,8-disubstituted tetrahydroisoquinolines were synthesized by [4+2] cycloaddition of dimethyl acetylenedicarboxylate and chiral cyclic dienes.

Key Topic: Synthesis of Tetrahydroisoquinolines by Cyclotrimerization of 4-Azaocta-1,7-diynes and Alkynes, and by [4+2] Cycloaddition of Alkynes and Cyclic 1,3-Dienes Resulting from Ring Closing Metathesis of 4-Azaocta-1,7-enynes