Metal-dependant stereoselectivity in the Pauson-Khand cyclization of *N*-propargyl-γ-amino vinyl sulfones

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Dedicated to Prof. Joan Bosch on the occasion of his 60th birthday

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Abstract

An efficient enantioselective route to *N*-propargyl-γ-amino vinyl sulfones has been developed, and their Pauson-Khand cyclization has been investigated. The stereoselectivity of the reaction depends both on the structure of the substrate and on the nature of the metal-carbonyl promoter.

Keywords: γ-Amino vinyl sulfones, azabicyclo[3.3.0]octenones, Pauson-Khand reaction


Introduction

The intramolecular version of the Pauson-Khand (PK) reaction,[1] a metal-mediated [2+2+1] formal cycloaddition of an alkyne, an alkene and carbon monoxide to give a 2-cyclopentenone unit, has been widely utilized in the direct construction of carbo- and heterobicyclic systems, often with high degrees of stereocontrol.[2] While the presence of electron-deficient substituents in the alkene moiety leads in most instances to low yields and/or to the formation of conjugated 1,3-dienes,[3] Carretero and co-workers have demonstrated that 1-phenylsulfonyl-3-oxygenated enynes are excellent substrates for the reaction.[4] Moreover, contrary to the standard selectivity of allyl substituted enynes in PK cyclizations, in which the allylic substituent is located preferentially in the less hindered *exo* face of the bicyclic product,[1,5] the intramolecular PK reaction of several γ-alkoxy vinyl sulfones takes place with high *endo* selectivities.

   In the context of our long-standing interest in the synthetic applications of scalemic 2-(1-aminoalkyl)oxiranes,[6] we have recently developed a general, high-yielding and enantioselective route to γ-amino vinyl sulfones.[7] In spite of their high biomedical relevance as key components of potent and selective cysteine protease inhibitors,[8] practically nothing is known about the chemistry of these compounds. We decided therefore to investigate the PK cyclization of *N*-propargyl-γ-amino vinyl sulfones, paying special attention to the stereochemical outcome of the

process. Herein, we report the results of these studies, which have disclosed an unusual dependence of the *exo/endo* selectivity of the reaction on the nature of the metal promoter.


Results and Discussion

In order to develop a general and efficient process for the synthesis of *N*-propargyl-γ-amino vinyl sulfones, our initial goal was the preparation of the specific enyne **2a** starting from the *N*-Boc protected γ-amino vinyl sulfone **1a**, which we had previously synthesized in our laboratory.[7] This transformation, however, proved to be more challenging than anticipated. In effect, the attempted *N*-propargylation of **1a** by treatment with sodium hydride and propargyl bromide in anhydrous tetrahydrofuran resulted in the irreversible elimination of the phenylsulfinate anion, and the diene **3a** was the sole product isolated from the reaction mixture (Scheme 1). Likewise, all attempts to effect the *N*-propargylation of the epoxide **4a** (a synthetic precursor of **1a**)[7] were unsuccessful. Better results were obtained by trifluoroacetic acid-mediated cleavage of the Boc group in **1a**, followed by reaction of the intermediate trifluoroacetate salt with propargyl bromide in the presence of potassium carbonate. In this way, the unprotected enyne **2'a** was obtained in an overall 60% yield after chromatographic purification. We were disappointed to find that this yield dropped dramatically during the scaling up of this process, and we devoted considerable effort to develop a more practical alternative.
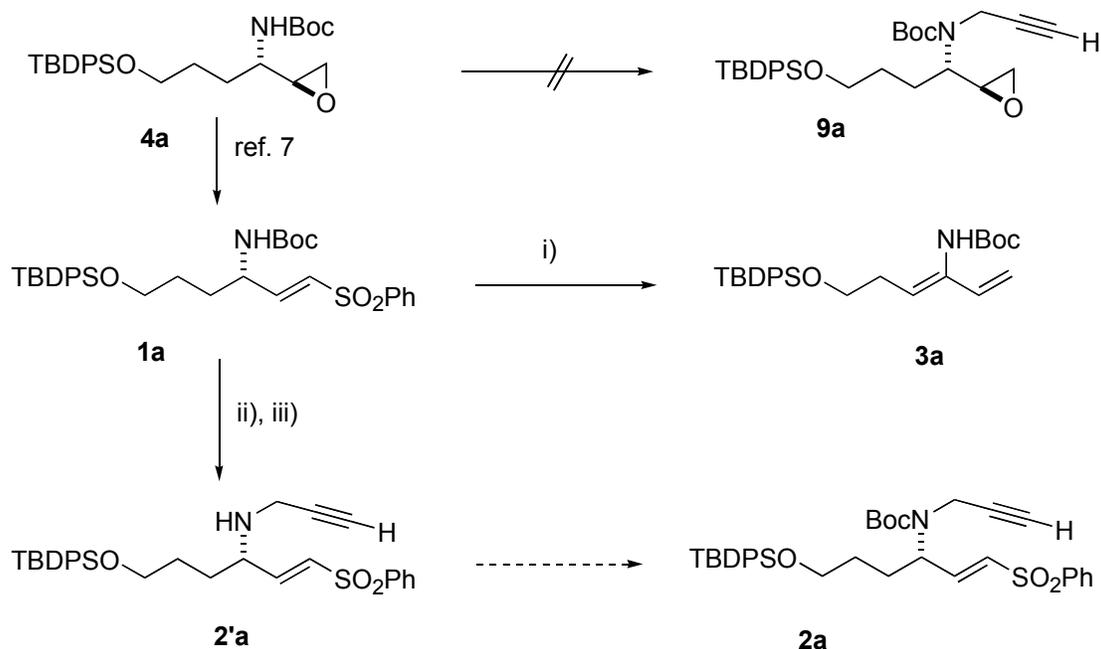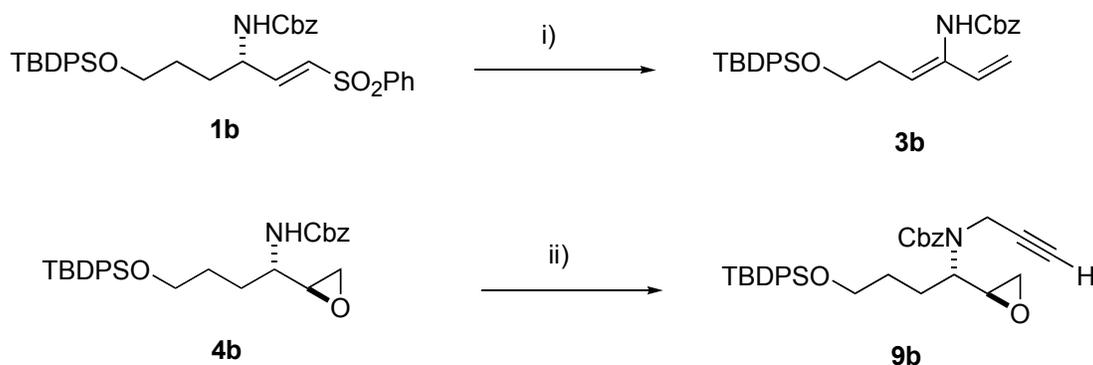

Scheme 1. i) NaH, propargyl bromide, THF, Δ (66% yield); ii) TFA, CH$_2$Cl$_2$, rt; iii) propargyl bromide, K$_2$CO$_3$, DMF, rt (60% yield from **1a**).

After some experimentation, we decided to replace the Boc protecting group by a Cbz one, taking into account some observations previously made by Jeong *et al.*[9] In this way, we prepared the *N*-Cbz epoxide **4b** and the corresponding γ-amino vinyl sulfone **1b**, starting from the known[7] azido diol **5**, by the synthetic route depicted in Scheme 2, that takes place with good overall yield.
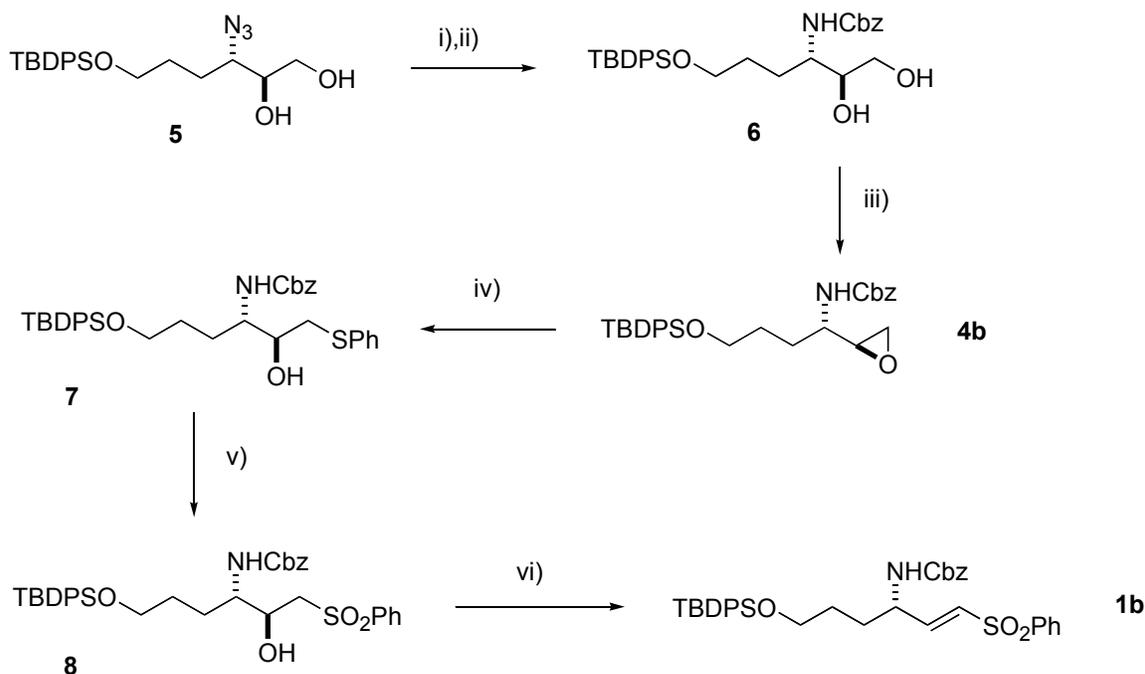

Scheme 2. i) H$_2$, cat. 10% Pd/C, MeOH, rt; ii) PhCH$_2$OCOCl, Et$_3$N, 4-DMAP, THF, rt (65% yield, two steps); iii) Ph$_3$P, DIAD, CH$_2$Cl$_2$, reflux (89% yield); iv) PhSH, Et$_3$N, MeOH, reflux (91% yield); v) *m*-CPBA, CH$_2$Cl$_2$, rt (95% yield); vi) MsCl, 4-DMAP, CH$_2$Cl$_2$, rt (75% yield).

As it happened in the case of **1a**, the base-mediated *N*-propargylation of **1b** was unsuccessful, leading to the formation of the diene **3b**. We were however pleased to find that, contrary to the case of **4a** (see Scheme 1), epoxide **4b** could be *N*-propargylated in good yield (Scheme 3).

Scheme 3. i) NaH, propargyl bromide, THF or DMF, Δ (50% yield); ii) NaH, propargyl bromide, THF-HMPA, Δ (82% yield).

Starting from **9b**, the target enyne **2b** could now be accessed in excellent overall yield, as shown in Scheme 4.
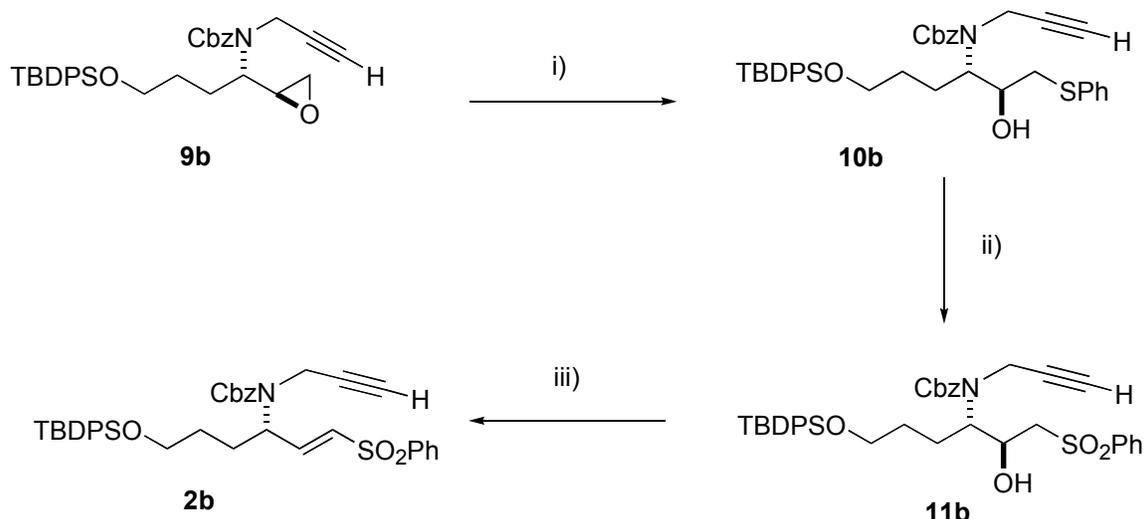
Scheme 4. i) PhSH, Et$_3$N, MeOH, reflux (93% yield); ii) *m*-CPBA, CH$_2$Cl$_2$, rt (95% yield); iii) *N*-cyclohexyl-(*N'*-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho-CDI), cat. CuCl$_2$, CH$_3$CN, rt (100% yield).

The generality of this synthetic sequence was next demonstrated by the preparation of the *N*-Cbz-*N*-propargyl-γ-amino vinyl sulfones **2c** and **2d**. According to the synthetic strategy previously developed by us,[7] the epoxide precursors **4c** and **4d** were first obtained from *trans*-cinnamyl and from *trans*-crotyl alcohols, respectively, by catalytic Sharpless epoxidation,[10] regioselective opening with azide anion,[11] and Mitsunobu cyclization[6a] (Scheme 5).
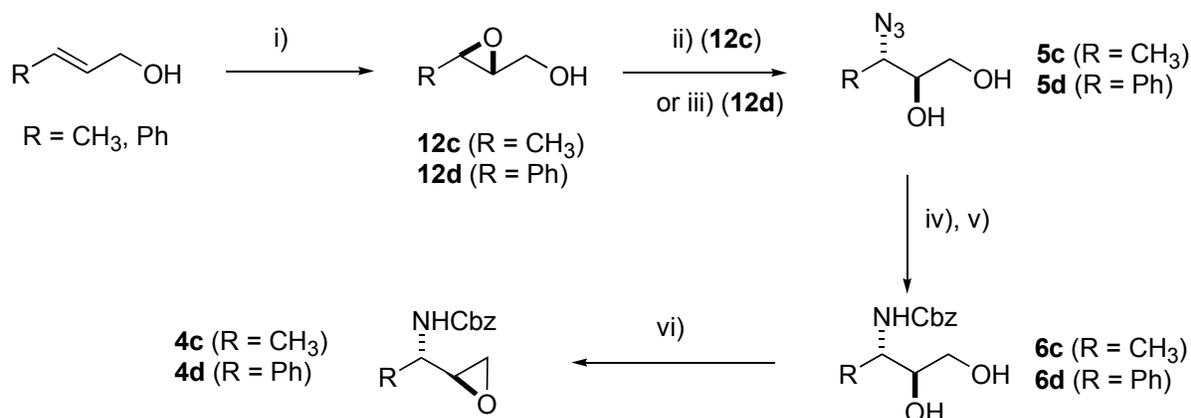
Scheme 5. i) cat. Ti(O^{i}Pr)$_4$, cat. D-(-)-DIPT, TBHP, CH$_2$Cl$_2$, -20ºC (**12c**: 53% yield, 93% ee; **12d**: 84% yield, >98% ee); ii) Ti(O^{i}Pr)$_2$(N$_3$)$_2$, toluene, 75ºC (75% yield); iii) LiClO$_4$, NaN$_3$, acetonitrile, 65ºC (94% yield); iv) cat. 10% Pd/C, H$_2$, MeOH, rt; v) PhCH$_2$OCOCl, Et$_3$N, 4-DMAP, THF, rt (**6c**: 55% yield; **6d**: 53% yield, three steps); vi) Ph$_3$P, DIAD, CH$_2$Cl$_2$, reflux (**4c**: 72% yield; **4d**: 93% yield).

Both **4c** and **4d** were then submitted to the same synthetic sequence that had allowed the efficient preparation of **2b** from **4b**: *N*-propargylation, oxirane ring-opening with thiophenol, oxidation to the hydroxysulfone stage and carbodiimide-mediated dehydration,[7] to provide the target enynes **2c** and **2d** (Scheme 6).

With the highly enantiopure enynes **2b**, **2c** and **2d** in our hands, we proceeded to investigate their Pauson-Khand cyclization. This reaction has lately received much attention with regard to reaction conditions using transition metal carbonyl complexes other than dicobalt octacarbonyl.[1c,12] Thus, a number of procedures using Co,[13] Ti,[14] Zr,[15] Ru,[16] Rh[17] and Ir[18] have been described. In particular, the molybdenum-promoted Pauson-Khand type cyclizations, first described by Hanaoka in 1992,[19] constitute a useful alternative to the standard cobalt-mediated process,[20] especially in the case of the intramolecular cyclocarbonylation of allenynes.[21] To the best of our knowledge, however, the stereoselectivity of molybdenum-Pauson-Khand type reactions has been scarcely addressed in the literature. A few years ago, we demonstrated that an unprecedented *endo*-selective and regioselective intermolecular cycloaddition takes place when heterobimetallic (Mo-Co) complexes derived from *N*-(2-alkynoyl)oxazolidinones or sultams are heated in the presence of norbornadiene;[22] more recently, Adrio and Carretero have studied the Mo(CO)$_3$(DMF)$_3$-mediated intramolecular reaction of electron-deficient alkenes,[23] and they have found that in the case of γ-hydroxy enynes the Pauson-Khand cyclization occurs with a relatively high *endo*-stereoselectivity, while the reaction of the bulky triisopropylsilyloxy derivatives is always *exo*-selective. In this last type of substrates, the cobalt-promoted cyclization is predominantly *endo*-selective.[24] Bearing these considerations in mind, three different experimental protocols were used for the reaction:

Scheme 6. i) NaH, propargyl bromide, THF-HMPA, Δ (**9c**: 54% yield; **9d**: 72% yield); ii) PhSH, Et$_3$N, MeOH, reflux (**10c**: 94% yield; **10d**: 91% yield); iii) *m*-CPBA, CH$_2$Cl$_2$, rt (**11c**: 100% yield; **11d**: 91% yield); iv) *N*-cyclohexyl-(*N'*-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho-CDI), cat. CuCl$_2$, CH$_3$CN, rt (**2c**: 98% yield; **2d**: 100% yield).
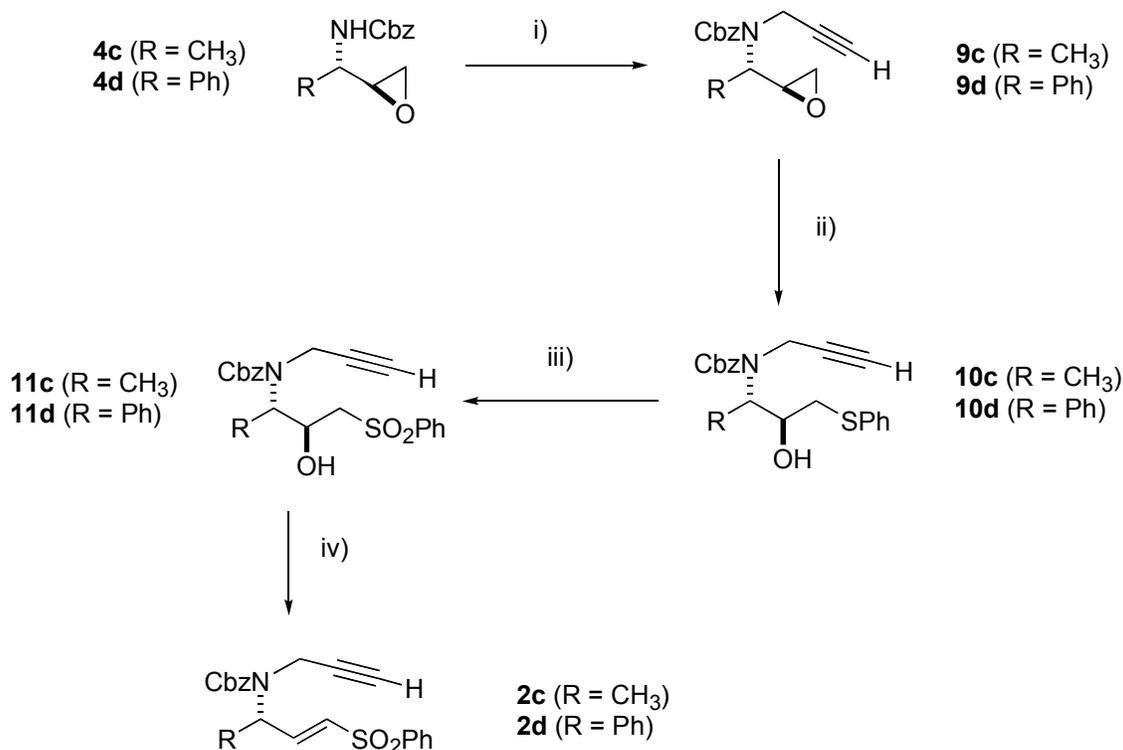
Conditions A: *In situ* formation of the alkyne-dicobalt hexacarbonyl complex by treatment of the enyne with a slight excess of dicobalt octacarbonyl in toluene, followed by mild (60ºC) thermal decomposition.[25]

Conditions B: *In situ* formation of the alkyne-dicobalt hexacarbonyl complex by treatment of the enyne with a slight excess of dicobalt octacarbonyl in toluene, followed by tertiary amine *N*-oxide (7.7 molar equivs.) oxidative decomposition.[26]

Conditions C: Molybdenum hexacarbonyl-promoted cycloaddition, according to the procedure of Jeong *et al.* (1.2 molar equivs. Mo(CO)$_6$, 5 molar equivs. DMSO, toluene, 100ºC).[20]

The results obtained in the Pauson-Khand cyclization of enynes **2b-d** are summarized in Table 1.

Table 1. Pauson-Khand cyclization of enynes **2b-d**

entry	enyne	conditions[a]	global yield (%)[b]	products (dr)
1	**2b**	A	41	**12b**,**13b** (65:35)
	(R = (CH$_2$)$_3$OTBDPS)			
2	**2b**	B (NMO)	22	**12b**
3	**2b**	B (TMANO)	24	**12b**
4	**2b**	C	70	**12b**,**13b** (20:80)
5	**2c** (R = CH$_3$)	A	12	**12c**,**13c** (50:50)
6	**2c**	B (NMO)	0	–
7	**2c**	C	77	**12c**,**13c** (33:67)
8	**2d** (R = Ph)	A	46	**12d**,**14d** (58:42)
9	**2d**	B (TMANO)	16	**12d**,**14d** (50:50)
10	**2d**	C	65	**12d**

[a] See text, [b] After chromatographic purification.

The behaviour of substrate **2b** was investigated on the first place (entries 1-4 in Table 1). When the reaction was performed under thermal, Co-promoted conditions A, a 65:35 mixture (separable by column chromatography) of two diastereomeric Pauson-Khand adducts **12b** and **13b** was obtained in a global 41% yield (entry 1). A careful NMR spectroscopic analysis of the two compounds readily established that the major one **12b** had both the side alkyl chain and the phenylsulfonyl group in the *exo* (or convex) face of the 3-azabicyclo[3.3.0]oct-5-ene-7-one framework, while the minor component **13b** had the opposite stereochemistry at C$_2$ (alkyl chain in the *endo* or concave face). Diagnostic signals for the stereochemical assignment were the different chemical shifts for H$_2$ (3.71 ppm in **12b** and 4.39 ppm in **13b**), the presence of NOE between H$_2$ and H$_8$ in the case of **12b**, and a 4.2 Hz coupling constant between H$_1$ and H$_2$ (indicative of a *cis* relationship) in **13b**. Moreover, both compounds had very similar chemical shift values for H$_8$ (3.84-3.85 ppm); see Figure 1 for the numbering of compounds **12-14**.

Figure 1. Atom numbering for Pauson-Khand cycloadducts **12b-d**, **13b-c,** and **14d**

When the cyclization was initiated by tertiary amine N-oxide decomposition of the intermediate alkyne-dicobalt hexacarbonyl complex (conditions B, entries 2 and 3 in Table 1), the *exo,exo* adduct **12b** was the sole compound isolated, albeit in low yield. Interestingly enough, when molybdenum hexacarbonyl (conditions C, entry 4 in Table 1) the *endo,exo* adduct **13b** was the predominant one (1:4 *exo,exo*/*endo,exo* mixture, 70% global yield). This contrasts the results of Adrio and Carretero, which pointed towards a high *exo*-selectivity for molybdenum-promoted Pauson-Khand intramolecular cycloadditions.[23]

A similar behaviour was observed for the methyl-substituted enyne **2c** (entries 5-7 in Table 1). In this case, the cobalt-mediated cycloaddition was very inefficient, either under thermal (entry 5) or N-oxide-mediated conditions (entry 6); on the other hand, the molybdenum-promoted reaction again resulted in the predominant formation of the *endo,exo* isomer **13c**, in good global yield (entry 7).[27] The stereochemistry of the adducts **12c** and **13c** was also established by NMR spectroscopy, and is consistent with the following observations: chemical shifts of the H_2 (3.63 ppm for **12c**, 4.37 ppm for **13c**) and of the H_8 (3.87 ppm for **12c**, 3.84 ppm for **13c**) protons, and NOE enhancements (**12c**: NOE between H_2 and H_8, and between the CH_3 group and H_1; **13c**: NOE between the CH_3 and H_8).

When we performed the cyclization of the phenyl-substituted enyne **2d**, we found that under conditions C (entry 10), a single product was obtained in good yield. The diagnostic $J_{H1,H2}$ value of 8.8 Hz (indicative of a *trans* stereochemistry), together with the observation of NOE between H_2 and H_8, established the stereochemistry of this compound as *exo,exo* (**12d**). The cobalt-mediated, thermal reaction (conditions A, entry 8) afforded a 58:42 mixture of the same compound with a diastereisomer **14d** in 46% global yield. The stereochemistry of **14d** was tentatively assigned as *exo,endo*, according to the 8.8 Hz value of the coupling constant between H_1 and H_2, and to the lack of NOE between H_2 and H_8. Also consistent with this assignment is the fact that the chemical shift values for H_8 in the two isomers were no longer similar (4.00 ppm for **12d** and 3.20 ppm for **14d**). The formation of **14d** could be possibly due to intermediate π-allyl-Co complexes.[28]

In summary, we have shown that N-propargyl-γ-amino vinyl sulfones, readily available in highly enantiopure fashion, are good substrates for the intramolecular Pauson-Khand reaction. The stereochemical outcome of this metal-promoted cyclization appears to be controlled not only by the substrate structure, but also by the metal carbonyl used in the reaction. While at present the mechanism and the stereochemical outcome of the standard, cobalt-mediated Pauson-Khand reactions are reasonably well understood,[29] our results suggest that further work in the area of molybdenum-promoted cyclocarbonylation of enynes is needed.

Experimental Section

General Procedures. Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured at room temperature (23 °C); concentrations are

given in g 100 ml^{-1}. Infrared spectra were recorded in a Fourier transform mode, using the NaCl film technique. Unless otherwise stated, NMR spectra were recorded in CDCl$_3$ solution. Chemical shifts are given in ppm and referenced to TMS or CHCl$_3$. Carbon multiplicities were established by DEPT experiments. Elemental analyses were performed by the "Servicios Xerais de Apoio á Investigación, Universidade da Coruña". MS spectra were performed at the "Servei de Espectrometria de Masses de la Universitat de Barcelona", using chemical ionization (CI) with ammonia or methane, electrospray ionization (ESI) or fast atom bombardment (FAB) techniques. Exact mass measurements (HRMS) were performed by the "Unidad de Espectrometría de Masas de la Universidad de Santiago de Compostela". Reactions were generally run in flame- or oven-dried glassware under a N$_2$ atmosphere, with solvents dried by routine procedures. Commercially available reagents were used as received.

3-(*tert*-Butoxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)hexa-1,3-diene (3a). To a cold (0ºC), stirred suspension of sodium hydride (6 mg, 0.2 mmol) in anhydrous tetrahydrofuran (1 ml), a solution of the γ-amino vinyl sulfone **1a**[7] (50 mg, 0.08 mmol) in tetrahydrofuran (1 ml) was added with the aid of a syringe, and stirring was maintained for 1 h. At this point, propargyl bromide (27 μl, 0.25 mmol) was added in one portion. The reaction was monitored by TLC. When no starting product remained (20 h stirring at room temperature), a saturated brine solution (2 ml) was added and stirring maintained for 5 min. The reaction mixture was extracted with diethyl ether (3x2 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 25 mg (66% yield) of the diene **3a**. ^{1}H NMR (400 MHz, CDCl$_3$),: δ = 0.98 (s, 9H), 1.45 (s, 9H), 2.32 (m, 2H), 3.62 (t, *J* = 6.0 Hz, 2H), 5.06 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 17.2 Hz, 1H), 5.49 (t , *J* = 7.6 Hz, 1H), 6.33, dd, J_1 = 17.2 Hz, J_2 = 10.4 Hz, 1H), 7.37-7.43 (m, 6H), 7.64-7.67 (m, 4H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.4 (C), 26.9 (CH$_3$), 28.3 (CH$_3$), 30.7 (CH$_2$), 63.6 (CH$_2$), 79.8 (C), 110.0 (CH), 112.5 (CH$_2$), 127.6 (CH), 129.6 (CH), 133.4 (C), 131.5 (CH), 135.5 (CH), 155.9 (C) ppm. MS: (FAB$^+$), *m/e* = 474 ([M+23]$^+$, 10%), 452 ([M+1]$^+$, 10%), 352 ([M-99]$^+$, 65%).

(3*S*,*E*)-3-[(2-Propynyl)amino)]-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-1-hexene (2'a). To a stirred solution of **1a**[7] (100 mg, 0.17 mmol) in dry dichloromethane (2 ml) trifluoroacetic acid (0.50 ml, 6.5 mmol) was added dropwise. After stirring for 1 h at rt (TLC monitoring), the solvent was removed under vacuum. The residue was mixed with K$_2$CO$_3$ (50 mg, 0.36 mmol) and dissolved with anhydrous DMF (2 ml). To the resulting solution propargyl bromide (25 μl, 0.23 mmol) was added in one portion. The reaction flask was stirred at rt, protected from sunlight, during 24 h. The resulting mixture was dilluted with CH$_2$Cl$_2$ (5 ml) and washed with H$_2$O (5 ml). The aqueous phase was separated and washed with CH$_2$Cl$_2$ (3x5 ml). The combined organic phases were dried over anhydrous MgSO$_4$ and the solvents were removed under vacuum. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 54 mg (60% yield) of the enyne **2'a**, as a colorless oil, and 15 mg of dipropargylated product. [α]$_D^{23}$ = +11.6 (*c* = 0.75, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 2931, 1447, 1428, 1308, 1148, 1111, 1086, 704, 687 cm^{-1}. ^{1}H-NMR (200 MHz, CDCl$_3$): δ = 1.03 (s, 9H),

1.51-1.64 (m, 4H), 2.14 (t, J = 2.4 Hz, 1H), 3.19 (dd, J_1 = 17.2 Hz, J_2 = 2.4 Hz, 1H), 3.19 (dd, J_1 = 17.2 Hz, J_2 = 2.4 Hz, 1H), 3.49 (m, 1H), 3.63 (t, J = 6.0 Hz, 2H,), 6.50 (dd, J_1 = 15.2 Hz, J_2 = 0.8 Hz, 1H), 6.78 (dd, J_1 = 15.2 Hz, J_2 = 7.2 Hz, 1H), 7.35-7.64 (m, NH + 13H), 7.87-7.89 (m, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.2 (C), 26.9 (CH$_3$), 28.4 (CH$_2$), 31.0 (CH$_2$), 36.0 (CH$_2$), 57.0 (CH), 63.3 (CH$_2$,), 72.0 (CH), 81.5 (C), 127.6 (CH), 127.7 (CH), 129.3 (CH), 129.4 (CH), 129.7 (CH), 131.6 (CH), 133.4 (CH), 133.7 (C), 135.6 (CH), 140.5 (C), 147.6 (CH) ppm. MS (FAB[+], NBA) m/e: 532 ([M+1][+], 30%).

(2*S*,3*S*)-3-(Benzyloxycarbonylamino-6-(*tert*-butyldiphenylsilyloxy)-1,2-hexanediol (6). A solution of azidodiol **5**[7] (1.65 g, 4.0 mmol) in anhydrous MeOH (40 ml) was stirred at room temperature under hydrogen (balloon) in the presence of 10% Pd/C (165 mg) during 16 h (TLC monitoring). After filtration through Celite[®] and removal of the solvent (2*S*,3*S*)-3-amino-6-(*tert*-butyldiphenylsilyloxy)-1,2-hexanediol (1.65 g, quant. yield) was obtained. ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.05 (s, 9H), 1.52-1.76 (m, 4H), 2.46 (br s, 2H, OH), 3.01 (m, 1H), 3.48 (m, 1H), 3.69 (m, 4H), 7.38-7.41 (m, 6H), 7.63-7.68 (m, 4H) ppm.

A solution of this crude aminodiol (2.5 g, 6.2 mmol) in anhydrous tetrahydrofuran (20 ml) was treated with triethylamine (1 ml, 7.5 mmol), 4-DMAP (75 mg, 0.6 mmol) and benzyl chloroformate (1.1 ml, 7.5 mmol) for 4 h at room temperature (TLC monitoring). The resulting solution was washed with brine (20 ml), and the aqueous phase was extracted with diethyl ether (3x10 ml). The combined organic phases were dried over anhydrous MgSO$_4$ and the solvents were removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 2.1 g (65% yield) of the title compound, as a colorless oil. $[\alpha]_D^{25}$ = -3.8 (c = 1.0, CHCl$_3$). IR (film NaCl): ν_{max} = 3400, 2933, 2860, 1700, 1522, 1457, 1428, 1245, 1111, 741, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.04 (s, 9H), 1.52-1.76 (m, 4H), 2.64 (br s, 1H, OH), 3.07 (br s, 1H, OH), 3.38 (m, 1H), 3.66 (m, 5H), 5.02 (br d, 1H, NH), 5.12 (m, 2H), 7.34-7.39 (m, 9H), 7.62-7.65 (m, 6H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ 19.2 (C), 26.9 (CH$_3$), 27.4 (CH$_2$), 28.8 (CH), 53.0 (CH), 62.9 (CH$_2$), 63.4 (CH$_2$), 67.2 (CH$_2$), 74.2 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.6 (CH), 133.7 (C), 135.5 (CH), 136.1 (C), 157.7 (C) ppm. MS (ESI) m/e: 523 ([M+1][+], 25%), 401 ([M-121][+], 100%). HRMS (ESI) C$_{30}$H$_{39}$NNaO$_5$Si (M+Na): 544.2490 calcd., 544.2471 found.

(*S*)-2-[(*S*)-1-(Benzyloxycarbonylamino)-4-(*tert*-butyldiphenylsilyloxy)butyl]oxirane (4b). To a solution of diol **5** (5.0 g, 9.6 mmol) and of triphenylphosphine (2.7 g, 10.3 mmol) in anhydrous chloroform (40 ml) a solution of diisopropylazodicarboxylate (2.0 ml, 10.3 mmol) in anhydrous chloroform (10 ml) was added dropwise. The resulting mixture was heated to reflux until total disappearance of the starting diol (14 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (silica gel, hexane-ethyl acetate mixtures as eluents) to afford 4.3 g (89% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonylamino)-4-(*tert*-butyldiphenylsilyloxy)butyl]oxirane **4b** as a colorless oil. $[\alpha]_D^{23}$ = -6.9 (c = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3330, 3070, 2931, 2858, 1710, 1428, 1239, 1111, 739, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ 1.04 (s, 9H), 1.52-1.74 (m, 4H), 2.75 (m,

2H), 2.88 (m, 1H), 3.48 (m, 1H), 3.67 (t, J = 5.4 Hz, 2H), 4.79 (br d, 1H, NH), 5.09 (s, 2H), 7.34-7.40 (m, 9H), 7.63-7.67 (m, 6H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ 19.2 (C), 26.9 (CH$_3$), 28.1 (CH$_2$), 28.5 (CH$_2$), 46.1 (CH$_2$), 52.4 (CH), 53.9 (CH), 63.3 (CH$_2$), 66.8 (CH$_2$), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.5 (CH), 133.80 (C), 133.85 (C), 135.4 (CH), 156.0 (C) ppm. MS (ESI) m/e: 505 ([M+1]$^+$, 100%). HRMS (ESI) C$_{30}$H$_{37}$NNaO$_4$Si (M+Na): 526.2384 calcd., 526.2371 found.

(2S,3S)-3-(Benzyloxycarbonylamino)-6-($tert$-butyldiphenylsilyloxy)-1-phenylthio-2-hexanol (7). To a solution of oxirane **4b** (0.90 g, 1.8 mmol) in anhydrous methanol (18 ml) triethylamine (254 μl, 1.8 mmol) and thiophenol (184 μl, 1.8 mmol) were added sequentially. The reaction mixture was heated to reflux until total disappearance of the starting oxirane (2 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) to afford 1.0 g (91% yield) of (2S,3S)-3-(benzyloxycarbonylamino)-6-($tert$-butyldiphenylsilyloxy)-1-phenylthio-2-hexanol **7** as a colorless solid. Mp 83-84ºC. [α]$_D^{23}$ = -9.4 (c = 1.0, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 3406, 3072, 2931, 2858, 1700, 1515, 1428, 1239, 1111, 1027, 739, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.04 (s, 9H), 1.46-1.76 (m, 4H), 2.87 (m, OH + 1H), 3.17 (d, J = 12.8 Hz, 1H), 3.66 (m, 4H), 4.96 (br d, 1H, NH), 5.08 (s, 2H), 7.21-7.39 (m, 16H), 7.63-7.67 (m, 4H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.4 (C), 26.1 (CH$_2$), 27.1 (CH$_3$), 29.1 (CH$_2$), 39.0 (CH$_2$), 55.2 (CH), 63.7 (CH$_2$), 67.1 (CH$_2$), 72.3 (CH), 127.0 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 130.4 (CH), 134.0 (C), 134.1 (C), 135.8 (CH), 136.6 (C), 156.8 (C) ppm. MS (ESI) m/e: 615 ([M+1]$^+$, 100%). HRMS (ESI) C$_{36}$H$_{43}$NNaO$_4$SSi (M+Na): 636.2574 calcd., 636.2551 found. Anal. (C$_{36}$H$_{43}$NO$_4$SSi), (calcd., found): %C (70.43, 70.40), %H (7.06, 7.13), %N (2.28, 2.35), %S (5.22, 4.61).

(2S,3S)-3-(Benzyloxycarbonylamino)-6-($tert$-butyldiphenylsilyloxy)-1-phenylsulfonyl-2-hexanol (8). To a solution of the hydroxysulfide **7** (1.0 g, 1.6 mmol) in anhydrous dichloromethane (30 ml) a solution of m-CPBA (0.70 g, 4.1 mmol) in dry dichloromethane (30 ml) was added dropwise. The reaction mixture was stirred at room temperature until total disappearance of the starting sulfide (2 h, TLC monitoring), and cooled to 0ºC. After addition of a 10% aqueous solution of sodium sulfite (25 ml), stirring was maintained at the same temperature for 15 min. The organic phase was separated and washed with a saturated solution of sodium bicarbonate (3x10 ml) and with brine (30 ml). The organic phase was dried over anhydrous MgSO$_4$ and the solvent was removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 1.0 g (95% yield) of (2S,3S)-3-(benzyloxycarbonylamino)-6-($tert$-butyldiphenylsilyloxy)-1-phenylsulfonyl-2-hexanol **8** as a dense, colorless oil. [α]$_D^{23}$ = -2.9 (c = 1.0, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 3355, 3070, 2933, 1702, 1522, 1447, 1428, 1306, 1241, 1146, 1111, 743 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.02 (s, 9H), 1.46-1.74 (m, 4H), 3.22 (br d, 2H), 3.62 (m, 3H), 4.15 (m, 1H), 4.96 (br d, 1H, NH), 5.05 (s, 2H), 7.32-7.38 (m, 10H), 7.60-7.63 (m, 8H), 7.89-7.93 (m, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.4 (C), 26.2 (CH$_2$), 27.1 (CH$_3$), 28.8 (CH$_2$), 55.1 (CH), 60.0 (CH$_2$), 63.5 (CH$_2$), 67.2 (CH$_2$), 68.9 (CH), 127.9 (CH),

128.2 (CH), 128.3 (CH), 128.5 (CH), 128.8 (CH), 129.7 (CH), 129.9 (CH), 133.9 (C), 134.4 (CH), 135.5 (CH), 135.8 (C), 139.4 (C), 156.4 (C) ppm. MS (ESI) *m/e*: 647 ([M+1]$^+$, 100%). HRMS (ESI) $C_{36}H_{43}NNaO_6SSi$ (M+Na): 668.2473 calcd., 668.2469 found.

(3S,E)-3-(Benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-1-hexene (1b). To a cold (0°C), stirred solution of the hydroxysulfone **8** (130 mg, 0.20 mmol) and of 4-DMAP (100 mg, 0.80 mmol) in anhydrous dichloromethane (2 ml) a solution of methanesulfonyl chloride (31 μl, 0.40 mmol) in dry dichloromethane (1 ml) was added dropwise. The reaction mixture was stirred at room temperature until total disappearance of the starting hydroxysulfone (7 h, TLC monitoring), diluted with dichloromethane (2 ml), and washed with a cold (0°C) 10% aqueous solution of HCl (5 ml) and with a saturated aqueous solution of sodium bicarbonate (5 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 94 mg (75% yield) of (3S,E)-3-(benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-1-hexene **1b** as a dense, colorless oil. $[\alpha]_D^{23}$ = +5.0 (c = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3344, 3070, 2931, 2858, 1719, 1522, 1447, 1429, 1308, 1245, 1148, 1111 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.03 (s, 9H), 1.50-1.78 (m, 4H), 3.63 (t, J = 5.4 Hz, 2H), 4.42 (br m, 1H), 4.90 (br d, 1H, NH), 6.38 (dd, J_1 = 15.0 Hz, J_2 = 1.4 Hz, 1H), 6.88 (dd, J_1 = 15.0 Hz, J_2 = 5.5 Hz, 1H), 7.31-7.40 (m, 10H), 7.52-7.64 (m, 8H), 7.82-7.89 (m, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.2 (C), 26.9 (CH$_3$), 28.4 (CH$_2$), 30.7 (CH$_2$), 51.2 (CH), 62.9 (CH$_2$), 67.1 (CH$_2$), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 129.2 (CH), 129.6 (CH), 130.4 (CH), 133.3 (C), 133.4 (CH), 135.4 (CH), 140.3 (C), 146.0 (CH), 155.5 (C) ppm. MS (ESI) *m/e*: 629 ([M+1]$^+$, 100%). HRMS (ESI) $C_{36}H_{41}NNaO_5SSi$ (M+Na): 650.2367 calcd., 650.2339 found.

3-(Benzyloxycarbonylamino)-6-(*tert*-butyldiphenylsilyloxy)hexa-1,3-diene (3b). To a cold (0°C), stirred suspension of sodium hydride (3.5 mg, 0.13 mmol) in anhydrous tetrahydrofuran (1 ml), a solution of the γ-amino vinyl sulfone **1b** (70 mg, 0.11 mmol) in dry tetrahydrofuran (1 ml) was added with the aid of a syringe, and stirring was maintained for 1 h. At this point, propargyl bromide (15 μl, 0.14 mmol) was added in one portion. The reaction was monitored by TLC. When no starting product remained (1 h stirring at room temperature), a saturated sodium bicarbonate solution (2 ml) was added and stirring maintained for 5 min. The reaction mixture was extracted with dichloromethane (3x2 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 20 mg (37% yield) of the diene **3b**. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.03 (s, 9H), 2.38 (m, 2H), 3.64 (t, J = 6.0 Hz, 2H), 5.06 (d, J = 10.4 Hz, 1H), 5.13 (s, 2H), 5.23 (d, J = 17.2 Hz, 1H), 5.54 (t , J = 7.6 Hz, 1H), 6.36 (dd, J_1 = 17.2 Hz, J_2 = 10.4 Hz, 1H), 7.35-7.39 (m, 11H), 7.62-7.66 (m, 4H) ppm.

(S)-2-[(S)-1-(Benzyloxycarbonyl-(2-propynyl)amino)-4-(*tert*-butyldiphenylsilyloxy) butyl]oxirane (9b). To a stirred suspension of sodium hydride (0.20 g, 60% in paraffines, 5.0 mmol) in anhydrous tetrahydrofuran (15 ml) a solution of oxirane **4b** (0.80 g, 1.6 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise, and stirring was maintained at room

temperature for 15 min. At this point, propargyl bromide (1.8 ml, 16 mmol) and HMPA (14 ml, 80 mmol) were added sequentially with the aid of a syringe. The resulting mixture was heated to reflux for 2 h. After cooling to room temperature, a saturated brine solution (15 ml) was added and stirring maintained for 5 min. The reaction mixture was extracted with diethyl ether (3x10 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 711 mg (82% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonyl-(2-propynyl)amino)-4-(*tert*-butyldiphenylsilyloxy)butyl]oxirane **9b** as a colorless oil. $[\alpha]_D^{23}$ = -9.0 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3745, 2931, 1702, 1654, 1559, 1540, 1507, 1457, 1256, 1111, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.04 (s, 9H), 1.46-1.82 (m, 4H), 2.18 (s, 1H), 2.67 (br m, 2H), 3.18 (br m, 1H), 3.64 (br m, 2H), 3.92 (br m, 1H), 4.04 (m, 2H), 5.16 (s, 2H,), 7.32-7.42 (m, 12H), 7.62-7.66 (m, 3H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.4 (C), 27.1 (CH$_3$), 29.1 (CH$_2$), 29.9 (CH$_2$), 34.3 (CH$_2$), 45.6 (CH$_2$), 53.6 (CH), 58.6 (CH), 63.5 (CH$_2$), 67.7 (CH$_2$), 71.6 (CH), 80.4 (C), 127.6 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.5 (CH), 133.8 (C), 135.5 (CH), 155.6 (C) ppm. MS (FAB$^+$, NBA) *m/e*: 564 ([M+23]$^+$, 100%), 542 ([M+1]$^+$, 50%). HRMS (FAB$^+$) C$_{33}$H$_{40}$NO$_4$Si (M+1): 542.2727 calcd., 542.2708 found.

(2*S*,3*S*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylthio-2-hexanol (10b). To a solution of oxirane **9b** (1.25 g, 2.3 mmol) in anhydrous methanol (25 ml), triethylamine (350 μl, 2.5 mmol) and thiophenol (250 μl, 2.5 mmol) were added sequentially. The reaction mixture was heated to reflux until total disappearance of the starting oxirane (1.5 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) to afford 1.40 g (93% yield) of (2*S*,3*S*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylthio-2-hexanol as a colorless oil. $[\alpha]_D^{23}$ = -5.2 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3295, 3071, 2930, 2858, 1700, 1427, 1256, 1111, 739, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.03 (s, 9H), 1.46 (m, 2H), 1.83 (m, 2H), 2.00 (s, 1H), 2.87 (m, OH + 1H), 3.17 (m, 1H), 3.66 (m, 3H), 3.96 (m, 3H), 5.06 (br d, 1H, NH), 5.17 (s, 2H), 7.21-7.39 (m, 16H), 7.63-7.67 (m, 4H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.4 (C), 23.1 (CH$_2$), 27.1 (CH$_3$), 29.1 (CH$_2$), 39.0 (CH$_2$), 40.8 (CH$_2$), 60.2 (CH), 63.7 (CH$_2$), 67.1 (CH$_2$), 72.0 (CH), 72.3 (CH), 80.2 (C), 127.0 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 130.4 (CH), 134.0 (C), 134.1 (C), 135.8 (CH), 136.6 (C), 156.8 (C) ppm. MS (FAB$^+$, NBA) *m/e*: 674 ([M+23]$^+$, 100%), 652 ([M+1]$^+$, 47%). HRMS (FAB$^+$) C$_{39}$H$_{46}$NO$_4$SSi (M+1): 652.2917 calcd., 652.2920 found.

(2*S*,3*S*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-2-hexanol (11b). To a solution of the hydroxysulfide **10b** (1.3 g, 2.0 mmol) in anhydrous dichloromethane (40 ml), a solution of *m*-CPBA (0.90 g, 5.0 mmol) in dry dichloromethane (40 ml) was added dropwise. The reaction mixture was stirred at room temperature until total disappearance of the starting sulfide (2 h, TLC monitoring), and cooled to 0ºC. After addition of a 10% aqueous solution of sodium sulfite (30 ml), stirring was maintained at the same temperature for 15 min. The organic phase was separated and washed with a

saturated solution of sodium bicarbonate (3x15 ml) and with brine (30 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 1.30 g (95% yield) of (2*S*,3*S*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-2-hexanol **11b** as a dense, colorless oil. $[\alpha]_D^{23}$ = -2.5 (*c* = 1.0, CHCl₃). IR (NaCl film): ν_{max} = 2933, 2858, 1700, 1447, 1428, 1306, 1250, 1144, 1111, 743, 702, 687 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 1.02 (s, 9H), 1.46-1.74 (m, 4H), 2.00 (s, 1H), 3.22-3.37 (m, 2H), 3.62 (m, 2H), 3.79-4.12 (m, 3H), 4.30 (m, 1H), 5.13 (s, 2H), 7.34-7.38 (m, 10H), 7.55-7.68 (m, 8H), 7.89-7.93 (m, 2H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 19.4 (C), 26.2 (CH₂), 27.1 (CH₃,), 28.8 (CH₂), 34.2 (CH₂), 60.0 (CH₂), 61.1 (CH), 63.7 (CH₂), 68.0 (CH₂), 68.5 (CH), 72.1 (CH), 80.0 (C), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 128.9 (CH), 129.7(CH), 129.9 (CH), 134.2 (C), 135.7 (CH), 135.8 (CH), 136.3 (C), 139.4 (C), 156.4 (C) ppm. MS (FAB⁺, NBA) *m/e*: 706 ([M+23]⁺, 100%), 684 ([M+1]⁺, 30%), 640 ([M-43]⁺, 65%). HRMS (FAB⁺) $C_{39}H_{46}NO_6SSi$ (M+1): 684.2815 calcd., 684.2837 found.

(3*S*,*E*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-1-hexene (2b). A solution of the hydroxysulfone **11b** (1.30 g, 1.90 mmol), the water-soluble carbodiimide morpho-CDI (1.60 g, 3.80 mmol) and anhydrous copper(II) chloride (28 mg, 0.19 mmol) in dry acetonitrile (50 ml) was heated to 70ºC and stirred during 16 h. After cooling to room temperature, the reaction mixture was filtered through a short pad or Celite® and silica gel, that was thoroughly washed with CH₂Cl₂. Removal of solvents under vacuum gave 1.30 g (quantitative yield) of pure (3*S*,*E*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-6-(*tert*-butyldiphenylsilyloxy)-1-phenylsulfonyl-1-hexene **2b** as a dense, colorless oil. $[\alpha]_D^{23}$ = -8.0 (*c* = 1.0, CHCl₃). IR (NaCl film): ν_{max} = 3288, 2931, 2858, 1702, 1447, 1428, 1322, 1148, 1111, 1086, 702, 689 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 1.03 (s, 9H), 1.57 (m, 2H), 1.82 (m, 2H), 2.12 (s, 1H), 3.63 (br m, 2H), 3.94 (br m, 2H), 4.60 (br m, 1H), 5.13 (br m, 2H), 6.38 (m, 1H), 6.98 (dd, J_1 =15.0 Hz, J_2 = 5.5 Hz, 1H), 7.34-7.38 (m, 10H), 7.53-7.62 (m, 8H), 7.89-7.93 (m, 2H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 19.2 (C), 27.0 (CH₃), 29.0 (CH₂), 29.7 (CH₂), 33.5 (CH₂), 56.2 (CH), 62.8 (CH₂), 67.7 (CH₂), 72.2 (CH), 80.0 (C), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.2 (CH), 129.6 (CH), 131.8 (CH), 133.4 (CH), 133.7 (C), 135.1 (C), 135.4 (CH), 139.9 (C), 144.2 (CH), 156.6 (C) ppm. MS (FAB⁺, glycerol) *m/e*: 666 ([M+1]⁺, 20%), 622 ([M-43]⁺, 30%), 608 ([M-57]⁺, 50%), 588 ([M-77]⁺, 100%). HRMS (ESI) $C_{39}H_{43}NNaO_5SSi$ (M+Na): 688.2523 calcd., 688.2525 found.

(2*R*,3*R*)-2,3-Epoxy-3-methyl-1-propanol (12c). Prepared from freshly distilled *trans*-crotyl alcohol (6.3 ml, 75.0 mmol) by catalytic asymmetric epoxidation (D-(-)-DIPT), as described in ref. 30. Yield: 53% (3.5 g). ee: 93% (¹H-NMR, Mosher's ester).³¹ ¹H-NMR (400 MHz, CDCl₃): δ = 1.34 (d, *J* = 5.2 Hz, 3H), 2.35 (br s, 1H, OH), 2.90 (m, 1H), 3.03 (m, 1H), 3.60 (dd, J_1 = 12.4 Hz, J_2 = 3.6 Hz, 1H), 3.90 (dd, J_1 = 12.4 Hz, J_2 = 1.2 Hz, 1H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ= 17.1 (CH₃), 52.0 (CH), 59.5 (CH), 61.6 (CH₂) ppm.

(2R,3R)-2,3-Epoxy-3-phenyl-1-propanol (12d). Prepared from freshly distilled *trans*-cinnamyl alcohol (2.7 g, 20.0 mmol) by catalytic asymmetric epoxidation (D-(-)-DIPT), as described in ref. 10b. Yield: 84% (2.5g). ee: > 98% (polarimetry). Mp 54-55ºC (lit:[10b] 51.5-53ºC). $[\alpha]_D^{23}$ = +50.4 (*c* = 2.4, CHCl₃) [lit (98% ee):[10b] $[\alpha]_D^{25}$ = +49.6 (*c* = 2.4, CHCl₃)].

(2S,3S)-3-Azido-1,2-butanediol (5c).[32] A solution of titanium tetra(isopropoxide) (11.2 ml, 37.5 mmol) and of azidotrimethylsilane (10.0 ml, 75.0 mmol) in anhydrous toluene (125 ml) was stirred at 90ºC during 5h under argon. After cooling to 75ºC, a solution of epoxyalcohol **12c** (2.2 g, 25.0 mmol) in dry toluene (50 ml) was added dropwise. Stirring was maintained at the same temperature for 1 h (TLC monitoring). After cooling to room temperature, a 10% aqueous solution of NaOH in brine (75 ml) was added, and the resulting mixture was stirred overnight. After filtration through Celite®, the organic phase was dried over anhydrous magnesium sulfate. Evaporation of the solvent under vacuum afforded 2.4 g (75% yield) of (2S,3S)-3-azido-1,2-butanediol **5c** as a colorless oil, that was used for the next step without further purification. $[\alpha]_D^{23}$ = +61.8 (*c* =1.05, CHCl₃). IR (NaCl film): ν_{max}= 3363, 2977, 2937, 2117, 1457, 1382, 1258, 1115, 1042 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 1.30 (d, *J*=6.4 Hz, 3H), 3.40 (br s, 2H, 2OH), 3.55-3.71 (m, 4H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ= 14.8 (CH₃), 58.8 (CH), 63.1 (CH₂), 74.4 (CH) ppm. MS (CI, NH₃) *m/e*: 149 ([M+18]⁺, 100%), 132 ([M+1]⁺, 15%), 106 (M-25, 48%).

(2S,3S)-3-Azido-3-phenyl-1,2-propanediol (5d).[33] A mixture of epoxyalcohol **12d** (0.75 g, 5.0 mmol), lithium perchlorate (13.0 g, 125 mmol) and sodium azide (1.6 g, 25 mmol) in dry acetonitrile (25 ml) was stirred at 65 ºC for 5 h (TLC monitoring). After cooling to room temperature, the reaction mixture was poured over water (310 ml). The aqueous phase was extracted with diethyl ether (3x50 ml), and the organic extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under vacuum afforded 0.91 g (94% yield) of highly pure (2S,3S)-3-azido-3-phenyl-1,2-propanediol **5d**. ¹H-NMR (200 MHz, CDCl₃): δ = 2.23 (br s, 2H, 2OH), 3.73 (m, 2H), 3.81 (m, 1H), 4.64 (d, *J* = 7.0 Hz, 1H), 7.37-7.41 (m, 5H) ppm.

(2S,3S)-3-(Benzyloxycarbonylamino)-1,2-butanediol (6c).[32] A solution of azidodiol **5c** (3.40 g, 26.0 mmol) in anhydrous MeOH (100 ml) was stirred at room temperature under hydrogen (balloon) in the presence of 10% Pd/C (0.34 g) during 2.5 h (TLC monitoring). After filtration through Celite® and removal of the solvent (2S,3S)-3-amino-1,2-butanediol (2.80 g, quantitative yield) was obtained. ¹H-NMR (200 MHz, CD₃OD): δ = 1.13 (dd, J_1 = 6.6 Hz, J_2 = 3.0 Hz, 3H), 2.96 (m, 1H), 3.50 (m, 1H), 3.61 (m, 2H) ppm.

A solution of this crude aminodiol (2.8 g, 26.0 mmol) in anhydrous tetrahydrofuran (50 ml) was treated with triethylamine (4.3 ml, 31.2 mmol), 4-DMAP (312 mg, 2.6 mmol) and benzyl chloroformate (4.4 ml, 31.2 mmol) for 2 h at room temperature (TLC monitoring). The resulting solution was washed with brine (80 ml), and the aqueous phase was extracted with diethyl ether (3x40 ml). The combined organic phases were dried over anhydrous MgSO₄ and the solvents were removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 3.4 g (55% yield from **12c**) of the title compound, as a colorless oil. ¹H-NMR (200 MHz, CDCl₃): δ = 1.21

(d, J = 6.6 Hz, 3H), 3.42 (br m, 1H), 3.62 (m, 2H), 3.74 (m, 1H), 5.09 (br s, 2H + NH), 7.34-7.37 (m, 5H) ppm.

(2*S*,3*S*)-3-(Benzyloxycarbonylamino)-3-phenyl-1,2-propanediol (6d). A solution of azidodiol **5d** (4.60 g, 23.5 mmol) in dry ethyl acetate (190 ml) was stirred at room temperature under hydrogen (balloon) in the presence of 10% Pd/C (0.46 g) during 2 h (TLC monitoring). After filtration through Celite® and removal of the solvent (2*S*,3*S*)-3-amino-3-phenyl-1,2-propanediol (4.0 g, quantitative yield) was obtained. ^{1}H-NMR (200 MHz, CD$_3$OD): δ = 3.04 (br, 3H, 2OH + NH), 3.55 (m, 2H), 3.78 (m, 1H), 4.10 (m, 1H), 7.31-7.33 (m, 5H) ppm.

A solution of this crude aminodiol (4.00 g, 23.5 mmol) in anhydrous tetrahydrofuran (50 ml) was treated with triethylamine (4.0 ml, 28.2 mmol), 4-DMAP (280 mg, 2.4 mmol) and benzyl chloroformate (4.1 ml, 28.2 mmol) for 2 h at room temperature (TLC monitoring). The resulting solution was washed with brine (80 ml), and the aqueous phase was extracted with diethyl ether (3x40 ml). The combined organic phases were dried over anhydrous MgSO$_4$ and the solvents were removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 3.70 g (53% yield from **12d**) of (2*S*,3*S*)-3-(benzyloxycarbonylamino)-3-phenyl-1,2-propanediol **6d** as a colorless solid. Mp 103-104ºC. $[\alpha]_D^{23}$ = +33.1 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 3327, 3034, 2945, 1688, 1539, 1454, 1285, 1259, 1106, 1052, 1014, 753, 697 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 2.83 (br, 2H, 2O**H**), 3.52 (br d, 1H), 3.61 (br d, 1H), 3.85 (m, 1H), 4.79 (m, 1H), 5.05 (m, 2H), 5.78 (br d, 1H, N**H**), 7.27-7.34 (m, 10H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 57.4 (CH), 63.2 (CH$_2$), 67.2 (CH$_2$), 73.7 (CH), 127.3 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 136.1 (C), 138.5 (C), 156.6 (C) ppm. MS (CI, NH$_3$) *m/e*: 319 ([M+18]$^+$, 45%), 302 ([M+1]$^+$, 100%), 258 ([M-43]$^+$, 20%). Anal. (C$_{17}$H$_{19}$NO$_4$), (calcd., found): %C (67.76, 67.22), %H (6.36, 6.46), %N (4.65, 4.66).

(*S*)-2-[(*S*)-1-(Benzyloxycarbonylamino)ethyl]oxirane (4c).[34] To a solution of diol **6c** (3.30 g, 13.8 mmol) and of triphenylphosphine (3.9 g, 15 mmol) in anhydrous chloroform (55 ml), a solution of diisopropylazodicarboxylate (2.9 ml, 15 mmol) in anhydrous chloroform (15 ml) was added dropwise. The resulting mixture was heated to reflux until total disappearance of the starting diol (18 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (silica gel, hexane-ethyl acetate mixtures as eluents) to afford 2.20 g (72% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonylamino)ethyl]oxirane **4c**. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.17 (d, J = 6.8 Hz, 3H), 2.74 (br d, 2H), 2.93 (m, 1H), 3.72 (br m, 1H), 4.92 (br s, 1H, NH), 5.09 (s, 2H), 7.30-7.38 (m, 5H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 16.3 (CH$_3$), 46.0 (CH$_2$), 47.8 (CH), 54.3 (CH), 66.7 (CH$_2$), 128.0 (CH), 128.1 (CH), 128.5 (CH), 136.3 (C), 155.7 (C) ppm.

(*S*)-2-[(*S*)-1-(Benzyloxycarbonylamino)-1-phenylmethyl]oxirane (4d). To a solution of diol **6d** (3.70 g, 12.3 mmol) and of triphenylphosphine (3.50 g, 13.2 mmol) in anhydrous chloroform (50 ml), a solution of diisopropylazodicarboxylate (2.6 ml, 13.2 mmol) in anhydrous chloroform (12 ml) was added dropwise. The resulting mixture was heated to reflux until total disappearance of the starting diol (2 h, TLC monitoring). The solvent was removed at reduced pressure and the

residue was purified by column chromatography (silica gel, hexane-ethyl acetate mixtures as eluents) to afford 3.25 g (93% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonylamino)-1-phenylmethyl]oxirane **4d** as a colorless solid. Mp 72-74ºC. $[\alpha]_D^{23}$ = +13.4 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3324, 3033, 1702, 1528, 1454, 1400, 1234, 1144, 1028, 751, 699 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 2.51 (br m, 1H), 2.75 (br m, 1H), 3.27 (br m, 1H), 4.81 (br m, 1H), 5.09 (m, 2H), 5.33 (br s, 1H, NH), 7.27-7.36 (m, 10H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 45.7 (CH$_2$), 53.6 (CH), 55.8 (CH), 67.0 (CH$_2$), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 136.1 (C), 137.8 (C), 155.7 (C) ppm. MS (CI, NH$_3$) *m/e*: 301 ([M+18]$^+$, 37%), 284 ([M+1]$^+$, 100%), 240 ([M-43]$^+$, 43%). Anal. (C$_{17}$H$_{17}$NO$_3$), (calcd., found): %C (72.07, 71.67), %H (6.05, 6.19), %N (4.94, 5.32).

(*S*)-2-[(*S*)-1-(Benzyloxycarbonyl-(2-propynyl)amino)ethyl]oxirane (9c). To a stirred suspension of sodium hydride (0.72 g, 60% in paraffines, 18.0 mmol) in anhydrous tetrahydrofuran (25 ml), a solution of oxirane **4c** (0.80 g, 3.6 mmol) in anhydrous tetrahydrofuran (25 ml) was added dropwise, and stirring was maintained at room temperature for 15 min. At this point, propargyl bromide (3.9 ml, 36 mmol) and HMPA (6.3 ml, 26 mmol) were added sequentially with the aid of a syringe. The resulting mixture was heated to reflux for 3 h. After cooling to room temperature, a saturated brine solution (15 ml) was added and stirring maintained for 5 min. The reaction mixture was extracted with diethyl ether (3x10 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 0.50 g (54% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonyl-(2-propynyl)amino)ethyl]oxirane **9c** as a colorless oil. $[\alpha]_D^{23}$ = -12.6 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3287, 2984, 1701, 1451, 1409, 1368, 1321, 1257, 1200, 1114, 738, 698 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3H), 2.21 (t, *J* = 2.0 Hz, 1H), 2.60 (br m, 1H), 2.72 (br m, 1H), 3.18 (br m, 1H), 4.11 (br m, 3H), 5.19 (s, 2H), 7.34-7.38 (m, 5H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 13.0 (CH$_3$), 33.3 (CH$_2$), 45.1 (CH$_2$), 52.1 (CH), 53.5 (CH), 67.6 (CH$_2$), 71.1 (CH), 80.6 (C), 127.6 (CH), 128.1 (CH), 128.5 (CH), 136.3 (C), 155.4 (C) ppm. MS (CI, NH$_3$) *m/e*: 277 ([M+18]$^+$, 29%), 260 ([M+1]$^+$, 100%), 216 ([M-43]$^+$, 18%). HRMS (CI, NH$_3$) C$_{15}$H$_{18}$NO$_3$ (M+1): 260.1286 calcd., 260.1279 found.

(*S*)-2-[(*S*)-1-(Benzyloxycarbonyl-(2-propynyl)amino)-1-phenylmethyl]oxirane (9d). To a stirred suspension of sodium hydride (0.70 g, 60% in paraffines, 17.7 mmol) in anhydrous tetrahydrofuran (20 ml), a solution of oxirane **4d** (1.00 g, 3.5 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise, and stirring was maintained at room temperature for 15 min. At this point, propargyl bromide (3.8 ml, 35 mmol) and HMPA (12.2 ml, 70 mmol) were added sequentially with the aid of a syringe. The resulting mixture was heated to reflux for 1 h. After cooling to room temperature, a saturated brine solution (20 ml) was added and stirring maintained for 5 min. The reaction mixture was extracted with diethyl ether (3x15 ml); the organic extracts were dried over magnesium sulfate and the solvents removed at reduced pressure. Column chromatography of the crude product (silica gel, hexane-ethyl acetate mixtures as eluents) afforded 810 mg (72% yield) of (*S*)-2-[(*S*)-1-(benzyloxycarbonyl-(2-

propynyl)amino)-1-phenylmethyl]oxirane **9d** as a colorless oil. $[\alpha]_D^{23} = +1.1$ ($c = 1.0$, CHCl$_3$). IR (NaCl film): $\nu_{max} = 3290$, 3033, 1702, 1497, 1452, 1406, 1366, 1249, 1124, 739, 698 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 2.22$ (t, $J = 2.4$ Hz, 1H), 2.76 (br m, 1H), 2.87 (br m, 1H), 3.68 (br m, 1H), 3.84 (br d, 1H), 4.21 (br d, 1H), 4.82 (br m, 1H), 5.19 (s, 2H), 7.27-7.40 (m, 10H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 35.0$ (CH$_2$), 46.8 (CH$_2$), 52.1 (CH), 62.6 (CH), 68.1 (CH$_2$), 71.9 (CH), 80.5 (C), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 136.1 (C), 137.8 (C), 155.9 (C) ppm. MS (CI, NH$_3$) m/e: 339 ([M+18]$^+$, 4%), 322 ([M+1]$^+$, 100%), 278 ([M-43]$^+$, 66%). HRMS (CI, NH$_3$) C$_{20}$H$_{20}$NO$_3$ (M+1): 322.1443 calcd., 322.1439 found.

(2S,3S)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-1-phenylthio-2-butanol (10c). To a solution of oxirane **9c** (0.44 g, 1.7 mmol) in anhydrous methanol (15 ml), triethylamine (240 µl, 1.7 mmol) and thiophenol (175 µl, 1.7 mmol) were added sequentially. The reaction mixture was heated to reflux until total disappearance of the starting oxirane (1.5 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) to give 590 mg (94% yield) of (2S,3S)-3-(benzyloxycarbonyl-(2-propynyl)amino)-1-phenylthio-2-butanol **10c** as a colorless oil. $[\alpha]_D^{23} = -3.3$ ($c = 1.0$, CHCl$_3$). IR (NaCl film): $\nu_{max} = 3433$, 3293, 2939, 1696, 1583, 1440, 1412, 1323, 1256, 1119, 1023, 739, 693 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 1.33$ (d, $J = 6.8$ Hz, 3H), 2.11 (s, 1H), 2.80-3.18 (m, 2H), 3.93-4.12 (m, 4H), 5.16 (s, 2H), 7.20-7.36 (m, 10H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 12.2$ (CH$_3$), 35.5 (CH$_2$), 38.9 (CH$_2$), 57.1 (CH), 67.6 (CH$_2$), 71.5 (CH), 72.3 (CH), 80.2 (C), 127.7 (CH), 128.1 (CH), 128.5 (CH), 129.1 (CH), 129.8 (CH), 130.5 (CH), 135.1 (C), 136.3 (C), 155.9 (C) ppm. MS (CI, NH$_3$) m/e: 370 ([M+1]$^+$, 54%), 279 ([M-90]$^+$, 100%), 262 ([M-107]$^+$, 50%). HRMS (CI, NH$_3$) C$_{21}$H$_{24}$NO$_3$S (M+1): 370.1477 calcd., 370.1474 found.

(2S,3S)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylthio-2-propanol (10d). To a solution of oxirane **9d** (0.74 g, 2.3 mmol) in anhydrous methanol (23 ml), triethylamine (350 µl, 2.5 mmol) and thiophenol (255 µl, 2.5 mmol) were added sequentially. The reaction mixture was heated to reflux until total disappearance of the starting oxirane (1.5 h, TLC monitoring). The solvent was removed at reduced pressure and the residue was purified by column chromatography (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) to afford 890 mg (91% yield) of (2S,3S)-3-(benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylthio-2-propanol **10d** as a colorless oil. $[\alpha]_D^{23} = +52.5$ ($c =1.0$, CHCl$_3$). IR (NaCl film): $\nu_{max}= 3291$, 3032, 1699, 1583, 1454, 1408, 1250, 1113, 740, 697 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): $\delta = 1.97$ (s, 1H), 3.02 (br m, 1H), 3.38 (br d, 1H), 3.74 (br m, 1H), 3.97 (br m, 1H), 4.54 (m, 1H), 5.22 (m, 3H), 7.21-7.43 (m, 15H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): $\delta = 34.2$ (CH$_2$), 39.7 (CH$_2$), 63.6 (CH), 67.9 (CH$_2$), 68.8 (CH), 71.8 (CH), 79.9 (C), 126.8 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 131.0 (C), 136.3 (CH), 140.0 (C), 155.9 (C) ppm. MS (CI, NH$_3$) m/e: 432 ([M+1]$^+$, 100%), 431 ([M]$^+$, 13%), 341 ([M-90]$^+$, 12%). HRMS (CI, NH$_3$) C$_{26}$H$_{26}$NO$_3$S (M+1): 432.1633 calcd., 432.1624 found.

(2*S*,3*S*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-1-phenylsulfonyl-2-butanol (11c). To a solution of the hydroxysulfide **10c** (0.52 g, 1.4 mmol) in anhydrous dichloromethane (30 ml), a solution of *m*-CPBA (0.60 g, 3.5 mmol) in dry dichloromethane (30 ml) was added dropwise. The reaction mixture was stirred at room temperature until total disappearance of the starting sulfide (2 h, TLC monitoring), and cooled to 0ºC. After addition of a 10% aqueous solution of sodium sulfite (20 ml), stirring was maintained at the same temperature for 15 min. The organic phase was separated and washed with a saturated solution of sodium bicarbonate (3x10 ml) and with brine (25 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) afforded 555 mg (quantitative yield) of (2*S*,3*S*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-1-phenylsulfonyl-2-butanol **11c** as a dense, colorless oil. $[\alpha]_D^{23}$ = -2.3 (*c* =1.0, CHCl₃). IR (NaCl film): ν_{max} = 3469, 3289, 2935, 1697, 1448, 1412, 1304, 1245, 1145, 1083, 1023, 748 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 1.32 (d, *J* = 6.8 Hz, 3H), 2.12 (br s, 1H), 3.29 (m, 2H), 3.92-4.08 (m, 3H), 4.34 (br m, 1H), 5.12 (s, 2H), 7.33-7.90 (m, 10H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 12.9 (CH₃), 34.3 (CH₂), 56.5 (CH), 59.8 (CH₂), 67.6 (CH₂), 68.5 (CH), 71.7 (CH), 80.0 (C), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.4 (CH), 134.0 (CH), 136.2 (C), 139.2 (C), 155.6 (C) ppm. MS (CI, NH₃) *m/e*: 419 ([M+18]⁺, 96%), 402 ([M+1]⁺, 100%), 358 ([M-43]+, 59%), 311 ([M-90]⁺, 69%), 250 ([M-151]⁺, 32%). HRMS (CI, NH₃) C₂₁H₂₄NO₅S (M+1): 402.1375 calcd., 402.1373 found.

(2*S*,3*S*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylsulfonyl-2-propanol (11d). To a solution of the hydroxysulfide **10d** (0.78 g, 1.8 mmol) in anhydrous dichloromethane (35 ml), a solution of *m*-CPBA (0.77 g, 4.5 mmol) in dry dichloromethane (35 ml) was added dropwise. The reaction mixture was stirred at room temperature until total disappearance of the starting sulfide (2 h, TLC monitoring), and cooled to 0ºC. After addition of a 10% aqueous solution of sodium sulfite (25 ml), stirring was maintained at the same temperature for 15 min. The organic phase was separated and washed with a saturated solution of sodium bicarbonate (3x15 ml) and with brine (30 ml). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. Column chromatography of the crude product (2.5% v/v triethylamine-pretreated silica gel, hexane-ethyl acetate mixtures as eluents) gave 760 mg (91% yield) of (2*S*,3*S*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylsulfonyl-2-propanol **11d** as a colorless semi-solid. $[\alpha]_D^{23}$ = +53.5 (*c* = 1.0, CHCl₃). IR (NaCl film): ν_{max} = 3491, 3292, 3032, 1698, 1497, 1448, 1408, 1306, 1253, 1142, 1085, 748 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 1.97 (br s, 1H), 3.36-3.65 (m, 4H), 3.98 (br m, 1H), 5.20 (m, 3H), 7.36-7.93 (m, 15H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 34.1 (CH₂), 60.1 (CH₂), 63.4 (CH), 66.2 (CH), 68.1 (CH₂), 72.4 (CH), 79.8 (C), 127.7 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 134.4 (CH), 135.5 (C), 136.2 (C), 140.1 (C), 155.6 (C) ppm. MS (CI, NH₃) *m/e*: 481 ([M+18]⁺, 71%), 464 ([M+1]⁺, 100%), 420 ([M-43]⁺, 28%), 373 ([M-90]⁺, 46%). HRMS (CI, NH₃) C₂₆H₂₆NO₅S (M+1): 464.1532 calcd., 464.1532 found.

(3*S*,*E*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-1-phenylsulfonyl-1-butene (2c). A solution of the hydroxysulfone **11c** (0.48 g, 1.2 mmol), the water-soluble carbodiimide morpho-

CDI (1.0 g, 2.4 mmol) and anhydrous copper(II) chloride (16 mg, 0.12 mmol) in dry acetonitrile (50 ml) was heated to 70ºC and stirred during 20 h. After cooling to room temperature, the reaction mixture was filtered through a short pad or Celite® and silica gel, that was thoroughly washed with CH_2Cl_2. Removal of solvents under vacuum gave 450 mg (98% yield) of (3*S*,*E*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-1-phenylsulfonyl-1-butene **2c** as a colorless semi-solid. $[\alpha]_D^{23}$ = -28.4 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3276, 2935, 1701, 1447, 1409, 1318, 1258, 1148, 1086, 753, 689 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.41 (d, *J* = 6.8 Hz, 3H), 2.16 (s, 1H), 3.98 (br d, 2H), 5.03 (br m, 1H), 5.15 (s, 2H), 6.39 (d, *J* = 15.0 Hz, 1H), 7.01 (dd, *J$_1$* = 15.0 Hz, *J$_2$* = 4.4 Hz, 1H), 7.31-7.88 (m, 10H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 16.7 (CH$_3$), 33.9 (CH$_2$), 51.9 (CH), 67.8 (CH$_2$), 72.1 (CH), 79.8 (C), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 129.3 (CH), 131.3 (CH), 133.5 (CH), 135.9 (C), 140.0 (C), 145.6 (CH), 155.1 (C) ppm. MS (CI, NH$_3$) *m/e*: 401 ([M+18]$^+$, 100%), 384 ([M+1]$^+$, 18%), 340 ([M-43]$^+$, 21%). HRMS (CI, NH$_3$) C$_{21}$H$_{22}$NO$_4$S (M+1): 384.1270 calcd., 384.1266 found.

(3*S*,*E*)-3-(Benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylsulfonyl-1-propene (2d). A solution of the hydroxysulfone **11d** (0.70 g, 1.5 mmol), the water-soluble carbodiimide morpho-CDI (1.30 g, 3.0 mmol) and anhydrous copper(II) chloride (21 mg, 0.12 mmol) in dry acetonitrile (50 ml) was heated to 70ºC and stirred during 1 h. After cooling to room temperature, the reaction mixture was filtered through a short pad or Celite® and silica gel, that was thoroughly washed with CH_2Cl_2. Removal of solvents under vacuum afforded 680 mg (quantitative yield) of pure (3*S*,*E*)-3-(benzyloxycarbonyl-(2-propynyl)amino)-3-phenyl-1-phenylsulfonyl-1-propene **2d** as a colorless dense oil. $[\alpha]_D^{23}$ = +43.7 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 3290, 3062, 1703, 1497, 1448, 1406, 1319, 1253, 1148, 1086, 750, 699 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 2.11 (s, 1H), 3.65 (dd, *J$_1$* = 18.4 Hz, *J$_2$* = 2.4 Hz, 1H), 4.03 (br m, 1H), 5.15 (s, 2H), 6.06 (br m, 1H), 6.59 (dd, *J$_1$* = 15.2 Hz, *J$_2$* = 1.6 Hz, 1H), 7.24-7.91 (m, 16H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ 34.1 (CH$_2$), 60.1 (CH), 68.1 (CH$_2$), 72.4 (CH), 79.8 (C), 127.7 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 133.2 (CH), 133.5 (CH), 135.7 (C), 140.1 (C), 142.4 (CH), 155.8 (C) ppm. MS (CI, NH$_3$) *m/e*: 463 ([M+18]$^+$, 100%), 446 ([M+1]$^+$, 7%). HRMS (CI, NH$_3$) C$_{26}$H$_{24}$NO$_4$S (M+1): 446.1426 calcd., 446.1416 found.

General procedures for the intramolecular Pauson-Khand reaction

Method A: with Co$_2$(CO)$_8$ and thermal activation. To a solution of Co$_2$(CO)$_8$ (45 mg, 0.13 mmol, 1.3 equiv) in dry toluene (2 ml), at room temperature and under argon atmosphere, a solution of enyne **2b-d** (0.10 mmol) in dry toluene (2 ml) was added dropwise. The resulting red-colored solution was stirred at room temperature for 30 min, and heated to reflux until complete disappearance of the dicobalt-enyne complex (TLC monitoring). After cooling to room temperature, the reaction mixture was filtered through Celite®, and washed with toluene. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate mixtures as eluent).

Enyne	Products (% yield)
2b	11 mg **12b** (27), 6 mg **13 b** (14)
2c	5 mg **12c** (6), 5 mg **13c** (6)
2d	22 mg **12d** (27)**,** 16 mg **14 d** (19)

Method B: with Co$_2$(CO)$_8$ and activation with amine *N*-oxides. To a solution of Co$_2$(CO)$_8$ (43 mg, 0.12 mmol) in anhydrous toluene (2 ml), at room temperature and under argon atmosphere, a solution of enyne **2b-d** (0.10 mmol) in dry toluene (2 ml) was added dropwise. The resulting red-colored solution was stirred at room temperature for 30 min, and the amine *N*-oxide (0.78 mmol) was added in one portion. Stirring was maintained until complete disappearance of the dicobalt-enyne complex (TLC monitoring), and the reaction mixture was filtered through Celite®, and washed with toluene. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate mixtures as eluent).

Enyne	*N*-oxide	Products (% yield)
2b	NMO	9 mg **12b** (22)
2b	TMANO	17 mg **12b** (24)
2d	TMANO	8 mg **12d** (8)**,** 8 mg **14d** (8)

Method C: with Mo(CO)$_6$. To a solution of Mo(CO)$_6$ (32 mg, 0.12 mmol) and of enyne **2b-d** (0.10 mmol) in anhydrous toluene (5 ml), at room temperature and under argon atmosphere, DMSO (36 μλ, 0.50 mmol) was added in one portion. The resulting solution was heated to reflux until complete disappearance of the starting enyne (TLC monitoring). After cooling to room temperature, the reaction mixture was filtered through Celite®, and washed with toluene. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, hexanes-ethyl acetate mixtures as eluents).

Enyne	Products (% yield)
2b	10 mg **12b** (14), 40 mg **13b** (56)
2c	22 mg **12c** (26), 44 mg **13c** (51)
2d	62 mg **12d** (65)

***(1R,2S,8R)-N*-(Benzyloxycarbonyl)-2-(*tert*-butyldiphenylsilyloxy)propyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one 12b.** $[\alpha]_D^{23}$ = +38.4 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν_{max} = 2931, 1702, 1654, 1447, 1409, 1310, 1152, 1111, 1084, 702 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.07 (s, 9H), 1.60 (m, 2H), 1.74 (m, 2H), 3.71 (br, 4H), 3.85 (d, *J* = 3.2 Hz, 1H), 4.17 (d, *J* = 16.4 Hz, 1H), 4.52 (br d, 1H), 5.11 (s, 2H), 5.99 (s, 1H), 7.31-7.40 (m, 12H), 7.54 (t, *J* = 8.0 Hz, 2H), 7.66-7.70 (m, 4H), 7.93 (d, *J* = 7.2 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.2 (C), 26.2 (CH$_2$), 26.9 (CH$_3$), 29.7 (CH$_2$), 48.1 (CH$_2$), 48.7 (CH), 62.2 (CH), 64.0 (CH$_2$), 67.5 (CH$_2$), 72.5 (CH), 124.7 (CH), 127.6 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH),

129.2 (CH), 129.5 (CH), 134.2 (C), 134.4 (CH), 135.6 (CH), 136.0 (C), 137.8 (C), 154.8 (C), 176.5 (C), 195.3 (C) ppm. MS (CI, NH$_3$) *m/e*: 711 ([M+18]$^+$, 35%).

(1*S*,2*S*,8*S*)-*N*-(Benzyloxycarbonyl)-2-(*tert*-butyldiphenylsilyloxy)propyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (13b). ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.98 (s, 9H), 1.42-1.64 (br m, 4H), 3.50-3.66 (m, 2H), 3.84 (d, *J* = 4.0 Hz, 1H), 3.92 (m, 1H), 4.15 (m, 1H), 4.39 (br, 1H), 4.52 (m, 1H), 5.14 (s, 2H), 6.03/6.05 (s, 1H), 7.32-7.40 (m, 11H), 7.53-7.57 (m, 6H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H) ppm. ^{1}H-NMR (300 MHz, *d$_6$*-DMSO, 60ºC): δ = 0.99 (s, 9H), 1.29 (br, 2H), 1.42 (br, 2H), 3.56 (br s, 2H), 3.94 (br m, 2H), 4.18 (br, 1H), 4.45 (d, *J* = 4.2 Hz, 1H), 4.52 (br d, 1H), 5.10 (s, 2H), 6.19 (s, 1H), 7.34-7.46 (m, 11H), 7.57-67 (m, 7H), 7.95 (d, *J* = 7.2 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 19.2 (C), 26.2 (CH$_2$), 26.9 (CH$_3$), 29.7 (CH$_2$), 46.1 (CH$_2$), 49.2/49.9 (CH), 67.0 (CH), 63.3 (CH$_2$), 67.7/68.0 (CH$_2$), 69.8/69.9 (CH, CHS), 124.8 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 129.2 (CH), 129.4 (CH), 129.8 (CH), 134.2 (C), 134.4 (CH), 135.6 (CH), 136.0/136.2 (C), 138.1/138.2 (C), 154.8/155.3 (C), 179.1/179.5 (C), 195.3 (C) ppm. MS (CI, NH$_3$) *m/e*: 694 ([M+1]$^+$, 21%).

(1*R*,2*S*,8*R*)-*N*-(Benzyloxycarbonyl)-2-methyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (12c). [α]$_D^{23}$ = +78.4 (*c* = 0.25, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 2927, 1700, 1447, 1409, 1353, 1310, 1150, 1084, 1027 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 1.65 (d, *J* = 5.6 Hz, 3H), 3.56 (br, 1H), 3.63 (m, 1H), 3.87 (d, *J* = 3.6 Hz, 1H), 4.32 (d, *J* = 16.4 Hz, 1H), 4.32 (br d, 1H), 5.15 (m, 2H), 5.99 (s, 1H), 7.33-7.40 (m, 5H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 25.2 (CH$_3$), 47.7 (CH$_2$), 52.8 (CH), 58.8 (CH), 67.4 (CH$_2$), 72.3 (CH), 124.5 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.2 (CH), 129.4 (CH), 134.5 (CH), 136.2 (C), 137.6 (C), 155.2 (C), 176.3 (C), 195.8 (C) ppm. MS (CI, CH$_4$) *m/e*: 412 ([M+1]$^+$, 68%), 368 ([M-43]$^+$, 46%). HRMS (ESI-TOF) C$_{22}$H$_{22}$NO$_5$S (M+1): 412.1219 calcd., 412.1230 found.

(1*S*,2*S*,8*S*)-*N*-(Benzyloxycarbonyl)-2-methyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (13c). [α]$_D^{23}$ = -66.0 (*c* = 1.0, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 2927, 1702, 1654, 1447, 1414, 1355, 1310, 1268, 1154, 1084, 756 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 0.97/0.99 (d, *J*=6.0 Hz, 3H), 3.84/3.87 (d, *J* = 4.8 Hz, 1H), 3.89/3.96 (br, 1H), 4.22/4.26 (d, *J* = 4.4 Hz, 1H), 4.37-4.49 (m, 2H), 5.17 (m, 2H), 6.08/6.09 (s, 1H), 7.36-7.39 (m, 5H), 7.59 (t, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 14.2/15.0 (CH$_3$), 45.4/45.6 (CH$_2$), 49.0/49.4 (CH), 52.9 (CH), 67.3/67.5 (CH$_2$), 69.4/69.6 (CH), 125.2/125.3 (CH), 128.0/128.1 (CH), 128.3 (CH), 128.5/128.6 (CH), 129.0/129.1 (CH), 129.3 (CH), 134.4 (CH), 136.2 (C), 137.6/137.9 (C), 153.9/154.2 (C), 177.5/177.9 (C), 196.2 (C) ppm. MS (CI, CH$_4$) *m/e*: 412 ([M+1]$^+$, 71%), 368 ([M-43]$^+$, 35%). HRMS (ESI-TOF) C$_{22}$H$_{22}$NNaO$_5$S (M+23): 434.1028 calcd., 434.1033 found.

(1*R*,2*R*,8*R*)-*N*-(Benzyloxycarbonyl)-2-phenyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (12d). [α]$_D^{23}$ = +81.7 (*c* = 0.25, CHCl$_3$). IR (NaCl film): ν$_{max}$ = 2926, 1702, 1658, 1409, 1352, 1320, 1150, 1084, 730, 699 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 3.81 (m, 1H), 4.04 (d, *J* = 3.6 Hz, 1H), 4.42 (d, *J* = 8.8 Hz, 1H), 4.55 (d, *J* = 16.2 Hz, 1H), 4.67 (d, *J* = 16.2 Hz, 1H), 4.85 (br, 1H), 4.98 (br, 1H), 6.09 (s, 1H), 7.21-7.31 (m, 10H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.2

Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 48.3 (CH$_2$), 55.6 (CH), 66.2 (CH), 67.5 (CH$_2$), 71.7 (CH), 125.2 (CH), 126.1 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 134.3 (CH), 136.0 (C), 137.6 (C), 154.8 (C), 175.7 (C), 195.3 (C) ppm. MS (CI, NH$_3$) *m/e*: 491 ([M+18]$^+$, 100%), 474 ([M+1]$^+$, 36%), 430 ([M-43]$^+$, 11%). HRMS (ESI-TOF) C$_{27}$H$_{24}$NO$_5$S (M+1): 474.1375 calcd., 474.1370 found.

(1R,2R,8S)-N-(Benzyloxycarbonyl)-2-phenyl-8-phenylsulfonyl-3-azabicyclo[3.3.0]oct-5-en-7-one (14d). IR (NaCl film): ν$_{max}$ = 2926, 1716, 1657, 1448, 1410, 1354, 1288, 1153, 1114, 1083, 699 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 3.21 (d, J = 4.0 Hz, 1H), 4.21/4.29 (m, 1H), 4.62/4.64 (s, 2H), 5.09/5.20 (d, J = 12.0 Hz, 1H), 5.05-5.21 (m, 2H), 5.36/5.43 (d, J = 8.8 Hz, 1H), 6.09/6.10 (s, 1H), 6.88-6.96 (m, 3H), 7.20-7.36 (m, 7H), 7.56 (m, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H) ppm. ^{13}C-NMR (100 MHz, CDCl$_3$): δ = 47.7/47.9 (CH$_2$), 50.4/50.9 (CH), 61.6 (CH), 67.5/67.9 (CH$_2$), 70.1/70.4 (CH), 126.1/126.2 (CH), 126.4 (CH), 127.5 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 129.5 (CH), 134.6 (CH), 136.2/136.9 (C), 137.5 (C), 138.1/138.5 (C), 154.1/154.6 (C), 175.8/176.5 (C), 196.0 (C) ppm. MS (CI, NH$_3$) *m/e*: 491 ([M+18]$^+$, 100%), 474 ([M+1]$^+$, 32%), 430 ([M-43]$^+$, 14%).

Acknowledgments

References and Footnotes

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