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Sulfoxide-Directed Intramolecular [4 + 2] Cycloadditions between 2-Sulfinyl Butadienes and Unactivated Alkynes

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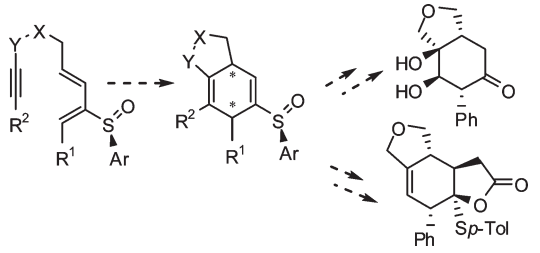

Sulfinyl dienynes undergo thermal and catalyzed IMDA cycloadditions, often at room temperature, to produce cyclohexa-1,4-dienes with good yields and high selectivities. Additionally, the products preserve a synthetically useful vinyl sulfoxide functionality. The selective manipulation of the double bonds in the cycloadducts has also been examined in this work.

Introduction

The Diels−Alder reaction is one of the most powerful methods for stereospecific carbon−carbon bond formation.[1] The asymmetric version is a fundamental process in modern synthetic chemistry, since compounds with up to four enantio- and diastereomerically pure stereogenic centers are created in a single step.[2] In this context, the use of chiral dienophiles has been extensively studied, and more recently the use of chiral Lewis acids and catalysts has resulted in good levels of asymmetric induction. However, the use of enantiopure dienes has received less attention. In most cases,[3] the nature of the chiral auxiliary (chiral tetrahydropyrans,[3d] chiral amines and oxazolidinones,[3e] or homochiral anthracenes[3m] among others) does not allow for subsequent chirality transfer operations. Simple 2-sulfinyl dienes are therefore attractive because a vinyl sulfoxide is generated upon a highly selective Diels−Alder cycloaddition.[4]

In recent years, we have been involved in the development of different strategies for the synthesis of enantiopure hydroxy sulfinyl dienes,[5] and we have carried out a general study of their intermolecular Diels−Alder reactivity.[6] To extend this study, we decided to test the intramolecular Diels−Alder[7] (IMDA) variant using 2-sulfinyl dienes **A**, and we focused our attention on the cycloadditions of dienynes **B** (Figure 1) to produce cyclohexa-1,4-dienes **C**,[8] which preserve a synthetically useful vinyl sulfoxide.[9,10] In the absence of a sulfinyl moiety, IMDA cycloadditions of this class of dienynes generally requires harsh thermal conditions that limit their

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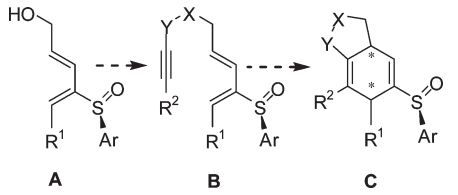

FIGURE 1. Intramolecular Diels−Alder cycloaddition with sulfinyl dienynes.

application in synthesis. The use of transition metal catalysts provides a useful alternative affording cyclohexa-1,4-dienes by a different mechanism.[11] Metals such as Ni, Rh, Pd, Au, and Cu have been successfully used with this aim, but a general enantioselective variant of the process remains elusive.[12] In this report, we describe in full our results on the diastereoselective IMDA cycloadditions of dienynes **B** to afford cyclohexa-1,4-dienes **C** that take place under remarkably mild conditions, with good selectivities and with preservation of the synthetically useful vinyl sulfoxide.

Results and Discussion

Synthesis of Starting Substrates. To carry out our study, we synthesized several sulfinyl dienes (Scheme 1) by using a Stille coupling from the corresponding iodo vinyl sulfoxides and vinyl stannanes.[5a,b,13] Dienols **1a**−**g** were selected to evaluate the effect of different substituents on the diene and different Ar groups on sulfur. Additionally, dienes **1h,i** were prepared in order to study the influence of the sulfoxide on different positions of the diene.

Diels−Alder Cycloaddition with Sulfinyl Dienynes. For our initial study, we selected dienyne **2a** and triene **2a′** (Scheme 2), which were readily available by standard propargylation and allylation of dienol **1a**. Dienyne **2a** gave a 67:33 mixture of cycloadducts **3a** and **4a** under exceptionally mild conditions (rt, $CDCl_3$, 10 days, Table 1, entry 1) in contrast with the high temperature needed for the IMDA cycloaddition of related dienynes lacking the sulfinyl group.[11a,14] Next, we studied the effect of Lewis acid catalysis (Table 1, entries 2−4), observing an enhancement of rate and selectivity with $ZnBr_2$. Unfortunately, the IMDA reaction of **2a′** was not successful under any of the conditions described above. Finally, we were also interested in testing the influence of copper salts in the reaction. Recently, Fürstner et al. have suggested the intervention of copper acetylide species for the

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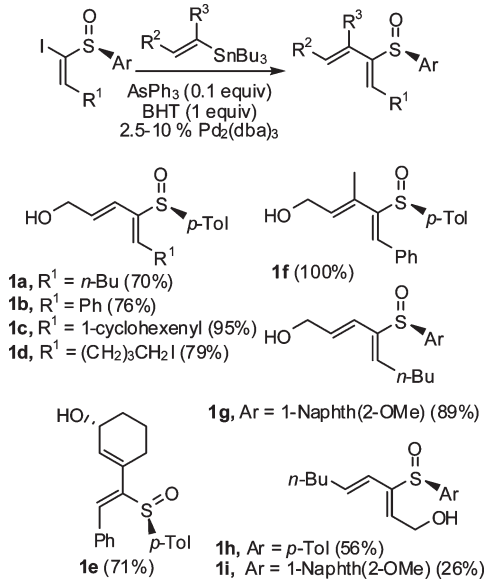
SCHEME 1. Hydroxy Sulfinyl Dienes



SCHEME 2. IMDA of Dienyne 2a

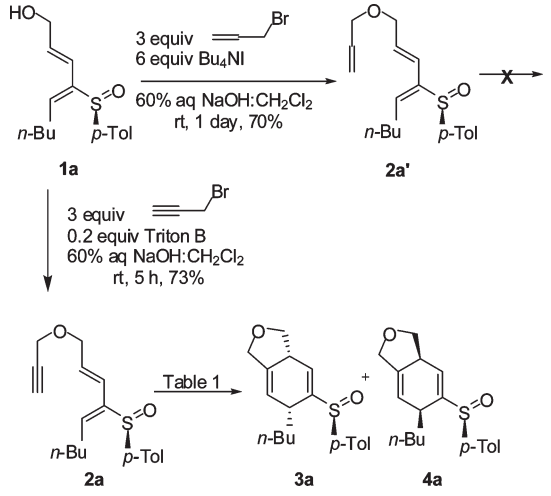


TABLE 1. Optimization of IMDA Cycloaddition for Dienyne 2a

entry	conditions	yield [%]	3a[a]	4a[a]
1	$CDCl_3$, rt, 10 days	**95**	**67**	**33**
2	4 equiv Et_2AlCl, CH_2Cl_2, rt, 6 days	[b,c]	**67**	**33**
3	4 equiv ZnI_2, CH_2Cl_2, rt, 2 days	**79**	**67**	**33**
4	4 equiv $ZnBr_2$, CH_2Cl_2, rt, 3 days	**79**	**73**	**27**
5	0.1 equiv CuI, Et_3N, CH_2Cl_2, rt, 18 h	**81**	**80**	**20**

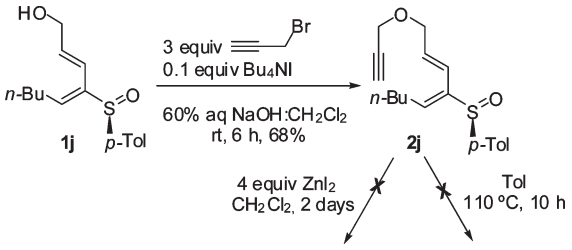
[a]Ratios determined by ^1H NMR spectra of the crude product. [b]Yield was not determined. [c]Isolated 15% of aromatized cycloadduct.

copper-catalyzed intramolecular Diels–Alder reactions of unactivated alkynes.[11k] To our delight, we found not only a reduction of the reaction time but also an enhancement in the selectivity of the process (Table 1, entry 5).

The influence of the geometry of the vinyl sulfoxide on the diene was next addressed with dienyne **2j** (Scheme 3). Unfortunately, we found a total absence of reactivity, even at higher temperatures or in the presence of a Lewis acid.

Encouraged by the results obtained with **2a**, we examined the reaction scope on several substrates bearing different

SCHEME 3. Change of the Diene Geometry



substituents on the diene, with various 3-atom tethers and with a *p*-toluenesulfinyl auxiliary (Table 2). Dienynes **2b–f** and **2l** were prepared by standard propargylation (Method A) following the procedure described above for **2a**.[13] Compound **2k** was synthesized from **2a** by treatment with *N*-bromosuccinimide and $AgNO_3$ (Method B). Standard esterification (Method C) of **1a** afforded ester **2m**, and dienynes **2n** and **2o** were prepared from **1b** using Mitsunobu conditions (Methods D and E).[15]

Substitution of the *n*-butyl chain with a phenyl or a cyclohexenyl group (**2b** and **2c**) produced an enhancement of the rate and diastereoselectivity of the cycloaddition even in the absence of CuI (Table 2, entries 1 and 3). The use of CuI with **2b** further increased the reaction rate but had no effect on the final diastereomeric ratio (Table 2, entry 2). Dienyne **2e**, with a cyclohexenyl moiety as part of the diene, afforded tricyclic compound **3e** as a single diastereomer. In this case, the cycloaddition needed 10 days at 23 °C for completion (Table 2, entry 4), but moderate heating gave **3e** in just 38 h without affecting the diastereoselectivity of the process. In contrast, tetrasubstituted dienyne **2f** gave a 66:34 mixture of **3f** and **4f**. The reduced diastereoselectivity observed may be due to conformational changes around the carbon–sulfur bond in order to minimize $A_{1,2}$ allylic strain on the diene moiety.[16] As alkynyl bromides are known to be effective substrates in thermal cycloadditions of similar dienynes not bearing the sulfinyl moiety,[11h] we decided to study the IMDA of dienyne **2k**. Internal dienyne **2k** required heating to give the desired cycloadducts with high yield but modest selectivity (Table 2, entry 7). In the case of a methyl-substituted alkyne (**2l**), we first attempted $ZnBr_2$ conditions but observed primarily the undesired aromatized product (Table 2, entry 8). Instead, thermal conditions were applied (Table 2, entry 9), affording cycloadducts **3l** and **4l** with high yield and good diastereoselectivity.

We next introduced modifications on the 3-atom tether. Propiolate **2m** required heating at 80 °C for 8 h to give bicyclic lactones **3m** and **4m** in excellent yield and high diastereoselectivity. Gratifyingly, replacement of the oxygen for a tosylamido nitrogen (**2n**) or by a bis-phenylsulfonylmethane carbon tether (**2o**) resulted in spontaneous cycloaddition and higher selectivity. The cycloaddition has been run

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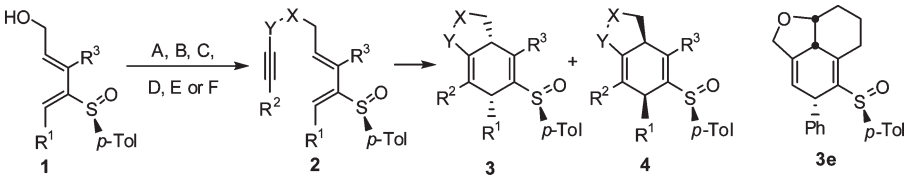
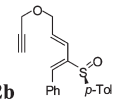
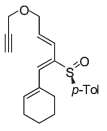
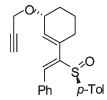
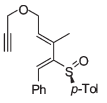
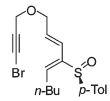
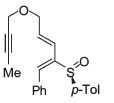
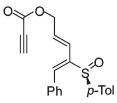
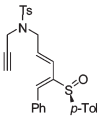
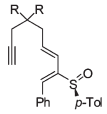
(16) This rationalization is in agreement with the results observed by Aversa et. al for the intermolecular Diels–Alder cycloaddition of related 2-sulfinyl dienes substituted at C-3: Aversa, M. C.; Barattuci, A.; Bonaccorsi, P.; Giannetto, P. *Arkivoc* **2002**, *xi*, 79–98.

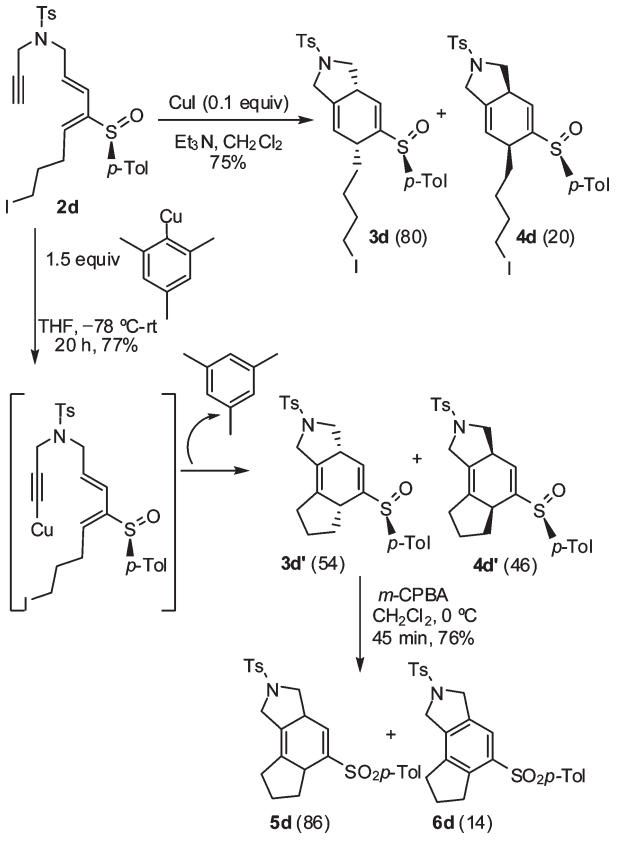
TABLE 2. IMDA of Dienynes with a 3-Atom Tether



Entry	Diene	Method[a]	Yield [%][b]	Dienyne	Conditions	3:4[c]	Yield [%][d]
1	**1b**	A	–[e]		$CDCl_3$, rt, 2 days	**3b** (92):**4b** (8)	70[g]
2	**1b**		–[e]	**2b**	CuI, Et_3N, CH_2Cl_2, rt, 18 h	**3b** (92):**4b** (8)	85[g]
3	**1c**	A	39	 **2c**	$CDCl_3$, rt, 4 days	**3c** (87):**4c** (13)	70
4	**1e**	A	44		$CDCl_3$, rt, 10 days	**3e** (100):**4e** (0)	–[f]
5	**1e**			**2e**	C_6D_6, 70 ºC, 38 h	**3e** (100):**4e** (0)	73
6	**1f**	A	53	 **2f**	Tol, 80 ºC, 3 days	**3f** (66):**4f** (34)	100
7	**1a**	1) A 2) B	46[g]	 **2k**	Tol, 60 ºC, 5 h	**3k** (70):**4k** (30)	73
8	**1b**	A	87		$ZnBr_2$, CH_2Cl_2, rt, 6 days	**3l** (80):**4l** (20)	20[h]
9				**2l**	Tol, 90 ºC, 6 h	**3l** (80):**4l** (20)	80[i]
10	**1b**	C	70	 **2m**	Tol, 80 ºC, 8 h	**3m** (84):**4m** (16)	86
11	**1b**	D	–[e]	 **2n**	THF, rt, 12 h	**3n** (94):**4n** (6)	95[g]
12	**1b**	E	–[e]	 **2o** R = SO_2Ph	C_6H_6, rt, 3 h	**3o** (98):**4o** (2)	94[g]

[a]Method A: propargyl bromide (3 equiv), triton B (0.2−0.5 equiv), NaOH/CH_2Cl_2. Method B: NBS (1.1 equiv), $AgNO_3$ (0.9 equiv), acetone. Method C: propiolic acid (1.5 equiv), DCC (1.5 equiv), DMAP (0.4 equiv), CH_2Cl_2. Method D: Ph_3P (2 equiv), *N*-(prop-2-ynyl)-*p*-tolylsulfonamide, DIAD (1.5 equiv), THF. Method E: Ph_3P (1.5 equiv), DIAD (1.5 equiv), 4,4-bis-benzenesulfonylbut-1-yne (1.1 equiv), C_6H_6. [b]Yield of isolated dienyne. [c]Diastereomeric ratios are shown in parentheses. Ratios determined by ^1H NMR spectra of the crude product. [d]Combined yields of pure products after chromatography. [e]Not determined because of spontaneous cycloaddition. [f]Yield was not determined. [g]Yield calculated over two steps. [h]Isolated 30% of aromatized compound and 50% of isomerized dienyne (7*E*,9*E*). [i]Isolated 2% of isomerized dienyne and aromatized compound after chromatography.

SCHEME 4. Copper-Promoted Tandem Cyclization

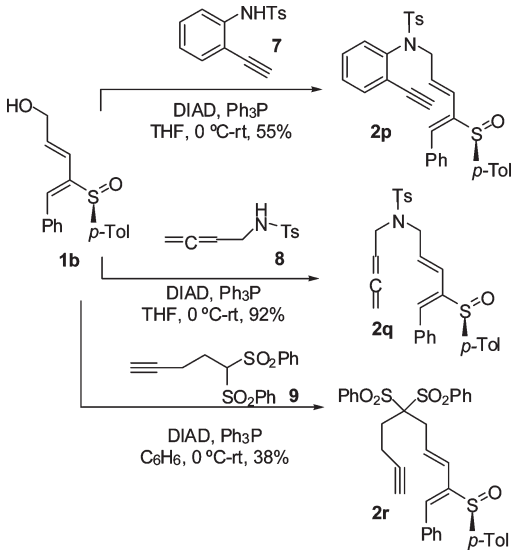


in a variety of solvents without observing any noticeable differences.

Recently, Fürstner et al. have reported a copper-mediated [4 + 2] cycloaddition−alkylation cascade to obtain tricyclic compounds.[11k] They found that stoichiometric mesitylcopper (instead of catalytic CuI, Et_3N) was necessary in order to avoid protonation of the vinyl copper intermediate formed after cycloaddition. In order to try this copper-mediated cycloaddition−alkylation cascade, we synthesized dienyne **2d** with a pendant alkyl iodide (Scheme 4). As in Fürstner's case, treatment of dienyne with catalytic copper iodide and Et_3N gave cycloadducts **3d** and **4d** with good diastereoselectivity but without subsequent cyclization to the alkyl iodide. Using a slight excess of mesityl copper instead, the cycloaddition−alkylation cascade took place but with nearly complete loss of diastereoselectivity (54:46 mixture of **3d′** and **4d′**). Oxidation of a mixture of **3d′** and **4d′** afforded nearly racemic sulfone **5d** along with some aromatized product **6d**. The ^{1}H NMR spectra of the crude product showed a single compound (**5d**), proving that **3d′** and **4d′** had the opposite absolute stereochemistry in the two new stereocenters generated during the cycloaddition.

The use of a 4-atom tether was then addressed with dienynes **2p**, **2q**, and **2r**, prepared from **1b** using Mitsunobu conditions (Scheme 5).[15] In all cases, heating at 80 °C was necessary to promote the IMDA reaction (Table 3). Heating a toluene solution of **2p** at 80 °C for 5 days provided tricyclic compounds **3p** and **4p** with moderate yield (57%) but high diastereomeric ratio (87:13, Table 3, entry 1). Next, we tested the use of an allene as a dienophile with compound **2q**. Only the external double bond of the allene participated in the IMDA reaction, as revealed by the absence of an exocyclic

SCHEME 5. Synthesis of Dienynes 2p, 2q, and 2r



double bond in the ^{1}H NMR spectra, to give an 85:15 mixture of **3q** and **4q** in good yield (75%). Finally, dienyne **2r**, with a bis-phenylsulfonylmethane moiety, afforded a 91:9 mixture of cycloadducts **3r** and **4r**.

To test the influence of the aryl substituent on sulfur, dienyne **2g**, bearing a readily available 2-methoxy-1-naphthyl moiety, was synthesized from diene **1g** employing standard propargylation conditions (Scheme 6). Dienyne **2g** underwent smooth Diels−Alder cycloaddition affording **3g** and **4g** with higher selectivity than the *p*-tolyl analogue (Scheme 2). In the presence of $ZnBr_2$, the cycloaddition was complete in just 12 h at 23 °C. Additionally, preliminary studies with a *tert*-butylsulfinyl moiety showed results similar to those using the *p*-tolyl analogue and therefore it was not pursued any further.

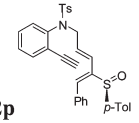
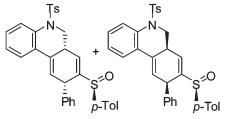
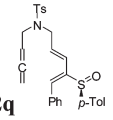
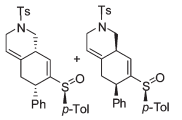
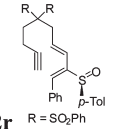
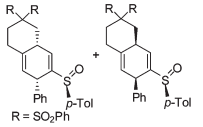
The IMDA reaction with the regioisomeric dienyne **2h** occurred more rapidly (1 day) to produce **3h** and **4h** with excellent yield and selectivity (Scheme 7). Again, the use of the 2-methoxy-1-naphthyl derivative **2i** improved the diastereoselectivity of the cycloaddition (**3i**:**4i**, 89:11). In these examples, the spontaneous cycloaddition prevented us from isolating pure samples of dienynes **2h** and **2i**.

We believe the IMDA reaction of sulfinyl dienynes, at least for nonactivated alkynes, is consistent with an inverse electron demand Diels−Alder primarily controlled by stereoelectronic effects.[17,18] To probe this, we thought it would be

(17) For recent selected examples of inverse electron demand Diels−Alder reactions, see: (a) Li, P.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628–16629. (b) Jung, M. E.; Chu, H. V. *Org. Lett.* **2008**, *10*, 3647–3649. (c) Kienzler, M. A.; Suseno, S.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 8604–8605. (d) Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233–236. (e) Juhl, M.; Nielsen, T. E.; Le Quement, S.; Tanner, D. *J. Org. Chem.* **2006**, *71*, 265–280. A significant number of the reported inverse electron demand Diels−Alder reactions can be classified as hetero-Diels−Alder reactions. For a review, see: Boger, D. L. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 451−512.

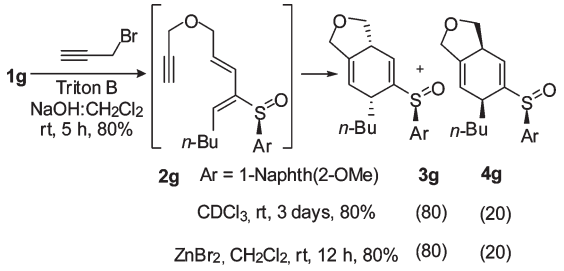
(18) For examples of inverse electron demand Diels−Alder reactions with sulfoxide-substituted dienes and heterodienes, see the following. Sulfinyl pyrones: (a) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72–78. *β*-Sulfinyl *α*,*β*-unsaturated compounds: (b) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Policicchio, M. *J. Org. Chem.* **2001**, *66*, 4845–4851. Sulfinyl tetrazines: (c) Hamasaki, A.; Ducray, R.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185–193. (d) Seitz, G.; Dietrich, S.; Görge, L.; Richter, J. *Tetrahedron Lett.* **1986**, *27*, 2747–2750.

TABLE 3. IMDA Reaction of Dienynes and Allenyl Dienes with a 4-Atom Tether

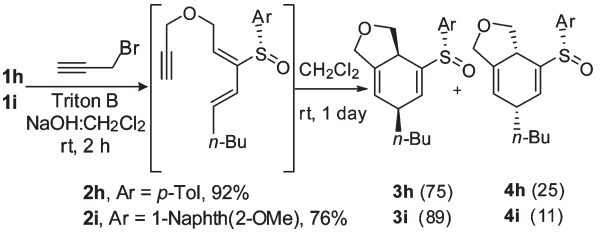
Entry	Substrate	Conditions	Product[a]	Yield [%][b]
1	 **2p**	Tol, 80 °C, 5 days	 **3p** (87) **4p** (13)	57%
2	 **2q**	Tol, 80 °C, 30 h	 **3q** (85) **4q** (15)	75%
3	 **2r** R = SO_2Ph	Tol, 80 °C, 14 h	 **3r** (91) **4r** (9)	90%

[a]Diastereomeric ratios are shown in parentheses. Ratios determined by ^{1}H NMR spectra of the crude product. [b]Combined yields of pure products after chromatography.

SCHEME 6. Sulfur Substitution in the Sulfoxide Group



SCHEME 7. Diels−Alder Cycloaddition with Regioisomeric Dienynes



interesting to compare the reactivity of sulfinyl dienynes with their analogous sulfones and sulfoximines (Scheme 8). Oxidation of **2a** with *m*-CPBA at low temperature afforded racemic sulfone **5a** along with a small amount of aromatized product **6a** (83:17 mixture, 70%). The cycloaddition proceeded smoothly, and no sulfonyl dienyne **2s** was isolated. Additionally, sulfoximine **2t** was synthesized from sulfoxide **2a** using a copper-catalyzed imination reaction with moderate yield.[19] The rate of cycloaddition was similarly increased but unfortunately with lower diastereoselectivity (**10**:**11**, 60:40). Cycloadduct **3a** was treated under the same imination conditions to give a 25:75 mixture of **10** and aromatized sulfoximine **10′**. Despite the low yield, this experiment showed that **10** and **3a** had the same absolute stereochemistry in the two new stereogenic centers generated during the cycloaddition.

Reactivity of Sulfinyl Cyclohexane-1,4-dienes. The methodology described above allows for the preparation of cyclohexane-1,4-dienes with two stereoelectronically differentiated double bonds ready for selective functionalization. Taking advantage of the electron-withdrawing character of the sulfinyl group, we carried out several chemoselective transformations on the more electron-rich double bond (Scheme 9). Hydrogenation and electrophilic epoxidation of **3a** and **3b** proceeded smoothly to give **12a,b** and **13a,b** with good yields. Additionally, we were able to find conditions that allowed us to obtain diols **14a,b** and **15** without oxidizing the sulfoxide to sulfone. In all cases a single diastereomer was observed.

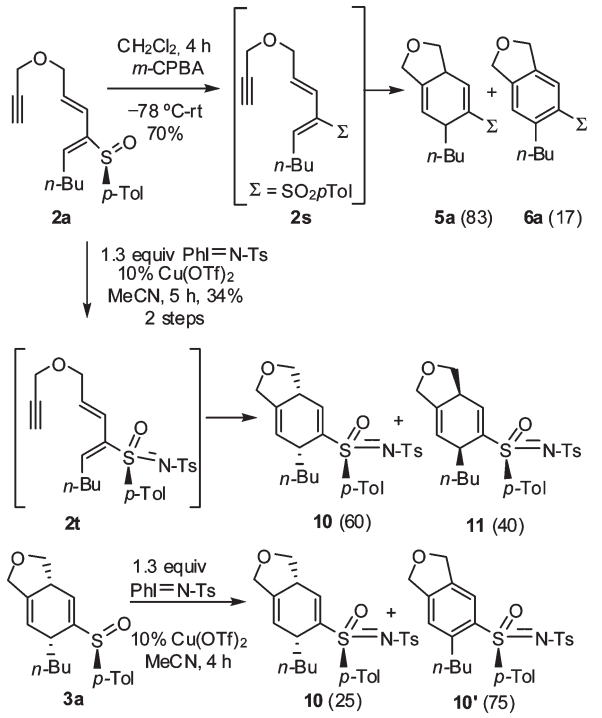
Finally, functionalization of the vinyl sulfoxide handle was addressed (Scheme 10). Oxidation followed by nucleophilic epoxidation of diol **14b** gave epoxy sulfone **17** as a single diastereomer. Next, epoxide opening with $MgBr_2$ afforded a mixture of bromides **19** and dehalogenated compound **18**.[20] Further treatment of **19** with aluminum amalgam produced the highly functionalized bicyclic ketone **18**. Additionally, we tested the lactonization conditions described by Marino.[21] For the sulfoxide configuration of

(19) Leca, D.; Song, L.; Amatore, M.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem.—Eur. J.* **2004**, *10*, 906–916.

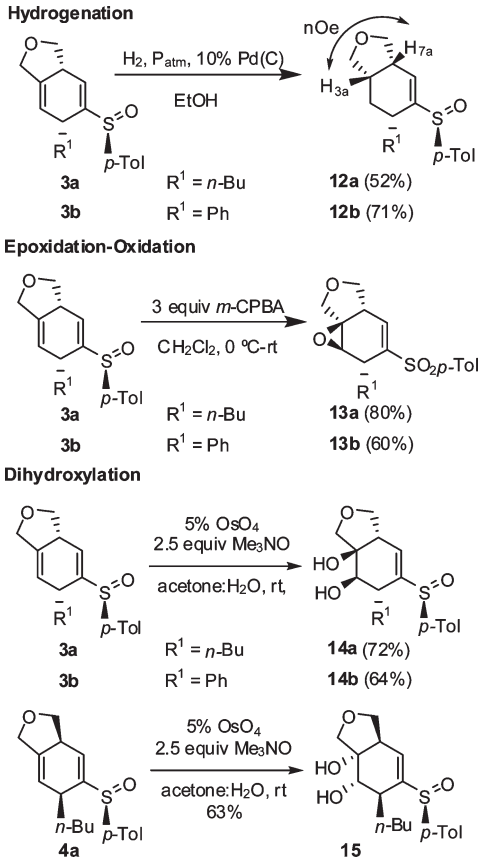
(20) Reinach-Hirtzbach, F.; Durst, T. *Tetrahedron Lett.* **1976**, *17*, 3677–3680.

(21) (a) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687–7689. (b) Marino, J. P.; Pérez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643–7644. For a recent application, see: (c) Marino, J. P.; Gao, G. *Tetrahedron Lett.* **2006**, *47*, 7711–7713. For a recent review, see: Fernández de la Pradilla, R.; Tortosa, M.; Viso, A. *Top. Curr. Chem.* **2007**, *275*, 103–129.

SCHEME 8. Diels–Alder Cycloaddition of Dienyl Sulfones and Sulfoximines

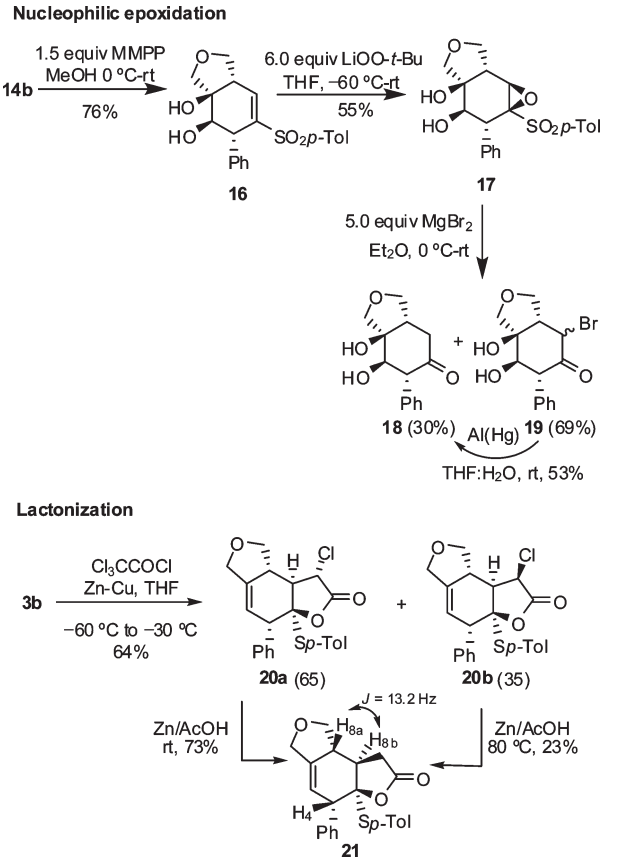


SCHEME 9. Double Bond Functionalization



cycloadduct **3b**, lactonization was expected to occur on the convex face of the bicycle, which is also the less hindered face.

SCHEME 10. Vinyl Sulfoxide Reactivity



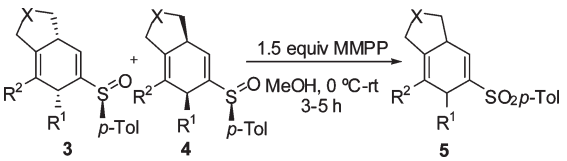
Treatment of cycloadduct **3b** with trichloroacetyl chloride and Zn–Cu gave a 65:35 mixture of chlorides **20a** and **20b**. To our delight, both α-chlorolactones **20a,b** afforded the same dehalogenated product **21** upon treatment with Zn in AcOH. This result proves that the lactonization occurs with complete diastereoselectivity on the convex face of the bicycle.[13] Additionally, the coupling constant (J = 13.2 Hz) between H-8a and H-8b in **21** and the absence of NOE effect between H-8b and H-8a or H-4 is consistent with the proposed structure.

Relative Stereochemistry. To ensure the relative stereochemistry of **3** and **4**, mixtures of these sulfoxides were oxidized with magnesium monoperoxyphthalate (MMPP, Table 4). The ^{1}H NMR of the crude product showed a single cyclohexadienyl sulfone **5** in each case, demonstrating that **3** and **4** had opposite absolute stereochemistry in the two new stereogenic centers generated during the cycloaddition.

The relative *cis–trans* stereochemistry between the substituents at C_{3a} and C_6 was derived from the characteristic homoallylic coupling of 1,4-cyclohexadienes. The coupling constants J_{H3a-H6} of cycloadducts **3m** and **4m** (Figure 2) are in good agreement with previous data that reported values of 9.1 and 5.3 Hz, respectively, for related *cis* and *trans* compounds.[11d] For all **3** and **4** cycloadducts the assignment was made by assuming a similar stereochemical course for the IMDA and by comparison of their spectral features with those of compounds **3m** and **4m**.

The relative stereochemistry of diols **14a** and **15** was based on the coupling constants of the diols and nuclear

TABLE 4. Sulfoxide Oxidation to the Corresponding Sulfones



entry	X	R^1	R^2	3	4	yield [%][a]
1	O	*n*-Bu	H	**3a** (67)	**4a** (33)	95
2	O	Ph	H	**3b** (75)	**4b** (25)	80
3	O	Ph	Me	**3l** (65)	**4l** (35)	73
4	NTs	Ph	H	**3n** (58)	**4n** (42)	79
5	$CH_2C(SO_2Ph)_2$	Ph	H	**3r** (74)	**4r** (26)	75

[a]Yield of pure product (**5**) after chromatography.

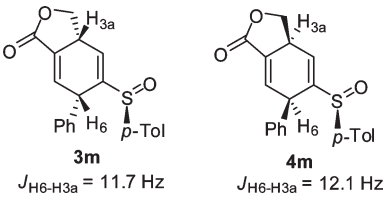


FIGURE 2. Structural assignment for cycloadducts **3** and **4**.

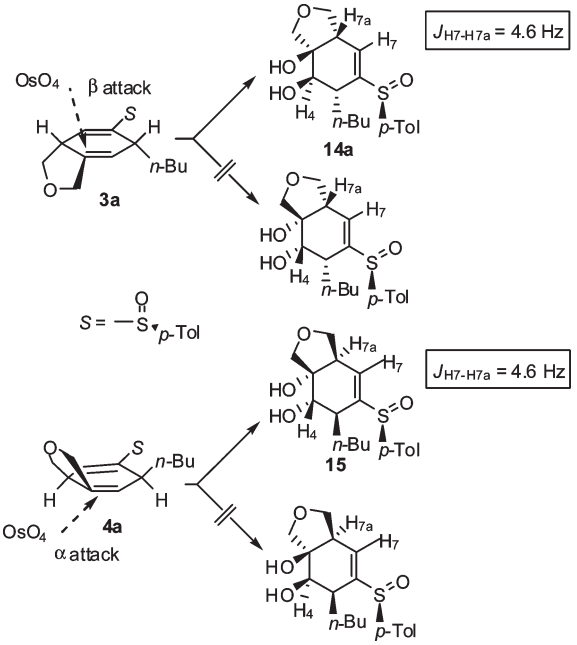
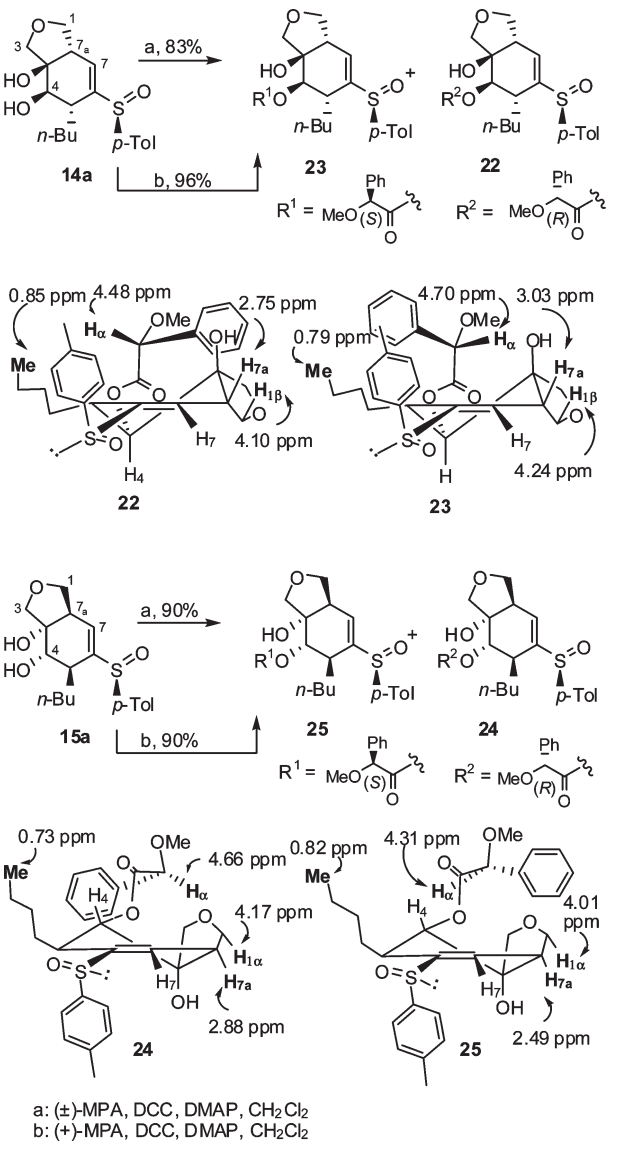


FIGURE 3. Relative stereochemistry assignment.

Overhauser (NOE) experiments. The absence of NOE effect between H_4 and H_{7a} in compound **14a** (Figure 3) is in agreement with a *cis* fusion on the bicycle and the coupling constant J_{H7-H7a} (4.6 Hz) is in agreement with previously reported data for *cis* ($J = 3-4$ Hz) and *trans* ($J = 1-1.5$ Hz) related compounds.[22] These arguments support approach by osmium to the less hindered face of the 1,4-cyclohexadiene

SCHEME 11. Absolute Stereochemistry Assignment



moiety. The stereochemical assignment of diol **15** was made similarly.

Absolute Stereochemistry. The absolute stereochemistry of cycloadducts **3** and **4** was also derived from their dihydroxylated derivatives. To determine the absolute stereochemistry of diol **14a**, we synthesized the (*R*)- and (*S*)-methoxy phenylacetates **22** and **23** by selective esterification of the secondary alcohol (Scheme 11). Previous studies have shown that in the L_2L_1CH-CO-CHPh-OMe fragment the preferred conformer is that where the $C_\alpha-OMe$ bond, the C=O, and the C_4-H_4 bond are nearly eclipsed.[23] For the C−S bond we suggest that the main conformer in each case is the one that places the bulky *p*-tolyl group away from the bicyclo concave face. As shown in Scheme 11, H_{7a} (2.75 ppm), $H_{1\beta}$ (4.10 ppm), and H_α (4.48 ppm) are further upfield in the (*R*)-isomer **22** compared to **23** (H_{7a} 3.03 ppm, $H_{1\beta}$ 4.24 ppm, and H_α 4.70

(22) (a) Areces, P.; Jiménez, J. L.; Pozo, M. C.; Roman, E.; Serrano, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 754–762. (b) Becher, J.; Nielsen, H. C.; Jacobsen, J. P.; Simonsen, O.; Clausen, H. *J. Org. Chem.* **1988**, *53*, 1862–1871.

(23) (a) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577. For a review, see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.

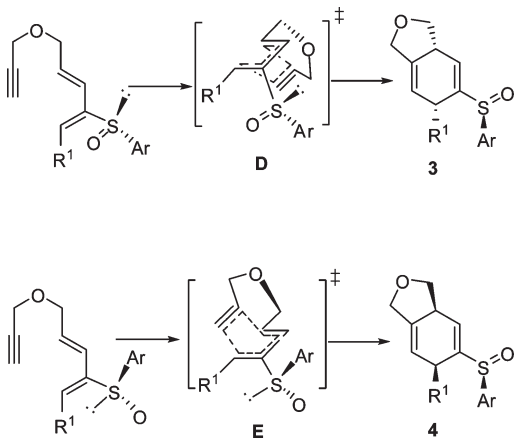


FIGURE 4. Favored transition states for sulfoxide-directed IMDA.

ppm) due to the shielding effect of the phenyl group (on H_{7a} and $H_{1\beta}$) and the *p*-tolyl group (on H_α) in (*R*)-isomer **22**. In contrast, in the (*S*)-isomer **23**, the phenyl group is shielding the methyl group of the *n*-butyl chain (0.79 ppm for **23** and 0.85 ppm for **22**). The absolute stereochemical assignment of diol **15a** was made similarly. We synthesized the (*R*) and (*S*)-methoxy phenylacetates **24** and **25** from diol **15a**. As shown in Scheme 11, H_{7a} (2.49 ppm), $H_{1\alpha}$ (4.01 ppm) and H_α (4.31 ppm) are further upfield in **25** compared to **24** (H_{7a} 2.88 ppm, $H_{1\alpha}$ 4.17 ppm and H_α 4.66 ppm) due to the shielding effect of the phenyl group (on H_{7a} and $H_{1\alpha}$) and the *p*-tolyl group (on H_α) in (*S*)-isomer **25**. In contrast, in the (*R*)-isomer **24**, the phenyl group is shielding the methyl group of the *n*-butyl chain (0.73 ppm for **24** and 0.82 ppm for **25**).

Stereochemical Pathway. These results may be tentatively rationalized in terms of diastereomeric transition states **D** and **E** for which *S-cis* C=C/S=O and *S-cis* C=C/S−: conformations around the C−S bond are proposed, respectively (Figure 4).[24] We believe the IMDA reaction of sulfinyl dienynes, at least for nonactivated alkynes, is consistent with an inverse electron demand Diels−Alder cycloaddition primarily controlled by stereoelectronic effects. The electron-rich alkyne moiety would approach the moderately electron-deficient diene *anti* to the highest electron density to avoid electron−electron interactions (β face for **E**, and α face for **D**). Delocalization of the sulfur lone pair in transition state **D** (this delocalization is not possible in transition state **E**) could explain the preferred formation of diastereomer **3** in most cases. This model is also consistent with data observed upon addition of resonance stabilization to the diene (e.g., R^1 = Ph or cyclohexenyl, Table 2, entries 1 and 3) which significantly improves the diastereoselectivity by increasing the delocalization of the sulfur lone pair in transition state **D**. The low diastereoselectivity observed for dienyne **2f** (Table 2, entry 6) could be explained by destabilization of transition state **D** due to increased $A_{1,2}$ allylic strain on the diene moiety. Aditionally, the unexpected loss of diastereoselectivity observed for dienyne **2d** in the presence of mesityl copper (Scheme 4) could be explained by coordination of the metal to the sulfoxide. We believe that this coordination could be changing the conformational preferences around the C−S bond and consequently modifying the diastereoselectivity of the process.

(24) The energy difference between the more stable conformers for a simple *Z*-propenyl sulfoxide (*s-cis*, C=C/S=O and *s-cis*, C=C/S−:) has been evaluated as just −0.4 kcal mol^{-1}. See: Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952–7958.

Conclusions

Sulfinyl dienynes undergo thermal and catalyzed IMDA cycloadditions under remarkable mild conditions. The strategy described herein allows for the construction of a broad number of carbo- and heterocycles, with a bicyclic or tricyclic structure, in generally good yields and high diastereoselectivities. Importantly, the methodology provides cycloadducts with two electronically differentiated double bonds, one of them bearing a synthetically useful vinyl sulfoxide. The selective manipulation of the alkenes allows for the preparation of highly functionalized compounds with broad structural diversity. We are currently exploring the application of this methodology to the synthesis of natural products.

Experimental Section

General Procedure for the Synthesis of Dienyne Ethers. To a solution of the corresponding dienyl sulfoxide in CH_2Cl_2 (10 mL/mmol of sulfoxide) were added 3 equiv of propargyl bromide (80 wt %), 0.2−0.5 equiv of Triton B (40 wt %) and 60% aqueous sodium hydroxide (10 mL/mmol of sulfoxide). The mixture was vigorously stirred at room temperature and monitored by TLC until starting material disappearance. Then the reaction mixture was filtered through Celite, a saturated solution of NaCl (5 mL/mmol of sulfoxide) was added and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered to give, after evaporation of the solvents, a crude product that was purified by chromatography on silica gel using the appropriate mixture of solvents.

General Procedure for Mitsunobu-Type Reaction of Hydroxy 4-sulfinyl Butadienes. To a solution of dienyl sulfoxide in THF or benzene (5 mL/mmol sulfoxide), under an argon atmosphere, were added 1.5 equiv of Ph_3P (recrystallized), 1.1 equiv of a propargylic derivative in anhydrous THF or benzene (10 mL/mmol of sulfoxide) and 1.5 equiv of diisopropyl azodicarboxylate. The reaction was monitored by TLC until starting material disappearance. Then the solvent was removed and the crude product was purified by chromatography on silica gel using the appropriate mixture of solvents.

General Procedure for the Thermal Diels−Alder Reaction of Sulfinyl Dienynes. A kimble vial equipped with a stirring bar was charged with a solution of the corresponding dienyne and 0.2 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in anhydrous toluene (10 mL/mmol of dienyne). Argon was bubbled through the solution for 15 min using a needle, and the vial was quickly stoppered. The vial was then immersed in a preheated oil bath (80−90 °C) if appropriate and the reaction was monitored by TLC until starting material disappearance. The solvent was removed and the crude product was purified by chromatography using the appropriate mixture of solvents.

General Procedure for the Diels−Alder Reaction of Sulfinyl Dienynes in the Presence of $ZnBr_2$. To a solution of sulfinyl dienyne in anhydrous CH_2Cl_2 (10 mL/mmol), under an argon atmosphere, was added $ZnBr_2$ (4.0 equiv). The reaction mixture was stirred until starting material disappearance (TLC). The reaction was quenched with a 5% solution of $NaHCO_3$, phases were separated and the aqueous layer was extracted with

CH_2Cl_2 (twice). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude was purified by chromatography using the appropriate mixture of solvents.

General Procedure for the CuI-Catalyzed Diels−Alder Reaction of Sulfinyl Dienynes. To a solution of sulfinyl dienyne in CH_2Cl_2 (4 mL/mmol) were added 0.1 equiv of CuI and 1.0 equiv of Et_3N at room temperature. The mixture was stirred until starting material disappearance (TLC). Then the solvent was removed under reduced pressure and the resulting crude product was purified by chromatography using the appropriate mixture of solvents.

Synthesis of (−)-(*S*)-4-Oxa-8-(*p*-tolylsulfinyl)-6-(*E*)-8-(*Z*)-tridecadien-1-yne, 2a, (+)-(3a*R*,6*R*,*S*$_S$)-6-*n*-Butyl-5-(*p*-tolylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 3a, and (−)-(3a*S*,6*S*,*S*$_S$)-6-*n*-Butyl-5-(*p*-tolylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 4a. From sulfinyl diene **1a** (835 mg, 3.00 mmol), propargyl bromide (1.29 mL, 1.78 g, 12.00 mmol), Triton B (0.30 mL, 275 mg, 0.60 mmol) and 60% aqueous sodium hydroxide (15 mL) following the general procedure (5 h), compound **2a** was obtained. Purification by chromatography (20−50% EtOAc/hexane) afforded **2a** (518 mg, 1.86 mmol, 62%) as a yellow oil, 92 mg (0.33 mmol, 11%) of a 67:33 mixture of **3a** and **4a** and 84 mg (0.30 mmol, 10%) of starting material.

Data for **2a**: R_f = 0.22 (30% EtOAc/hexane); $[\alpha]^{20}_D$ = −161.1 (*c* 1.11); ^{1}H NMR (300 MHz) δ 0.93 (t, *J* = 7.0 Hz, 3 H, Me-*n*-Bu), 1.33−1.54 (m, 4 H, 2 CH_2-*n*-Bu), 2.35−2.37 (m, 4 H, Me-*p*-Tol, H-1), 2.49 (m, 1 H, H-10), 2.71 (m, 1 H, H-10), 3.90 (dd, *J* = 2.4, 1.4 Hz, 2 H, 2 H-3), 3.98 (m, 2 H, 2 H-5), 5.98 (dt, *J* = 15.9, 5.9 Hz, 1 H, H-6), 6.12 (d, *J* = 15.7 Hz, 1 H, H-7), 6.24 (dd, *J* = 8.3, 7.4 Hz, 1 H, H-9), 7.25 (d, *J* = 8.1 Hz, 2 H, *p*-Tol), 7.39 (d, *J* = 8.3 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz) δ 13.8 (Me-*n*-Bu), 21.3 (Me-*p*-Tol), 22.3, 28.6, 31.5, 56.7, 69.6, 74.4, 79.5, 124.2 (2 C), 124.4, 128.3, 129.5, 129.8 (2 C), 139.0, 140.6, 142.1; IR (film) 3036, 2955, 2929, 2859, 1595, 1492, 1465, 1399, 1379, 1303, 1178, 1147, 1083, 1049, 1014, 899, 844, 810, 705 cm^{-1}; MS (ES) *m*/*z* (%) 633 $[2M + H]^+$, 317 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{24}O_2S$: C 72.11, H 7.64, S 10.13. Found: C 71.97, H 7.35, S 10.36.

From **2a** (492 mg, 1.55 mmol) and $ZnBr_2$ (1400 mg, 6.20 mmol) following the general procedure (3 days), a 73:27 mixture of **3a** and **4a** with traces of **2j** was obtained. Purification by chromatography (10−50% EtOAc/hexane) afforded 5 mg of **2j** as a colorless oil, 47 mg (0.15 mmol, 10%) of **4a** as a colorless oil, 168 mg (0.53 mmol, 34%) of a mixture of **4a** and **3a** and 172 mg (0.54 mmol, 35%) of **3a** as a white solid that was recrystallized from Et_2O-hexane.

In a related experiment a solution of **2a** in $CDCl_3$ was kept at room temperature and monitored by ^{1}H NMR until cycloaddition was complete (10 days), affording a 67:33 mixture of **3a** and **4a**.

From **2a** (96 mg, 0.30 mmol), CuI (6 mg, 0.03 mmol) and Et_3N (40 μL, 0.30 mmol) following the general procedure (18 h), an 80:20 mixture of **3a** and **4a** was obtained. Purification by chromatography (10−50% EtOAc/hexane) afforded 48 mg (0.015 mmol, 50%) of an 83:17 mixture of **3a** and **4a** and 28 mg (0.093 mmol, 31%) of pure **3a**.

Data for **2j**: R_f = 0.27 (30% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 0.89 (t, *J* = 7.1 Hz, 3 H, Me-*n*-Bu), 1.22−1.55 (m, 4 H, 2 CH_2-*n*-Bu), 2.25−2.39 (m, 3 H), 2.35 (s, 3 H, Me-*p*-Tol), 3.94 (d, *J* = 2.4 Hz, 2 H, 2 H-3), 4.00 (d, *J* = 5.6 Hz, 2 H, 2 H-5), 5.89 (dt, *J* = 16.3, 5.6 Hz, 1 H, H-6), 6.20 (d, *J* = 16.3 Hz, 1 H, H-7), 6.50 (t, *J* = 7.6 Hz, 1 H, H-9), 7.22 (d, *J* = 8.1 Hz, 2 H, *p*-Tol), 7.46 (d, *J* = 8.2 Hz, 2 H, *p*-Tol). Anal. Calcd for $C_{19}H_{24}O_2S$: C 72.11 H 7.64, S 10.13. Found: C 72.34 H 7.35, S 10.41.

Data for **3a**: R_f = 0.22 (50% EtOAc/hexane); mp 83−85 °C; $[\alpha]^{20}_D$ = +179.2 (*c* 1.00); ^{1}H NMR (300 MHz) δ 0.87 (t, *J* = 7.0 Hz, 3 H, Me-*n*-Bu), 1.08−1.38 (m, 4 H, 2 CH_2-*n*-Bu), 1.57−1.67 (m, 2 H, CH_2-*n*-Bu), 2.39 (s, 3 H, Me-*p*-Tol), 2.58 (m, 1 H, H-6), 3.32−3.34 (m, 2 H, H-3a, 1 H-3), 4.25−4.41 (m, 3 H, 1 H-3, 2 H-1), 5.36 (br s, 1 H, H-7), 6.86 (t, *J* = 2.2 Hz, 1 H, H-4), 7.23 (d, *J* = 8.1 Hz, 2 H, *p*-Tol), 7.53 (d, *J* = 8.1 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz) δ 13.9 (Me-*n*-Bu), 21.5 (Me-*p*-Tol), 22.8, 26.4, 31.7, 36.0, 41.0, 69.0, 71.4, 119.1, 123.0, 126.4 (2 C), 130.2 (2 C), 137.9, 139.4, 142.6, 146.6; IR (KBr) 2952, 2930, 2859, 1631, 1593, 1493, 1455, 1378, 1306, 1182, 1082, 1044, 1012, 896, 872, 819 cm^{-1}; MS (ES) *m*/*z* (%) 633 $[2M + H]^+$, 317 (100) $[M + H]^+$. Anal. Calcd for $C_{19}H_{24}O_2S$: C 72.11, H 7.64, S 10.13. Found: C 72.30, H 7.93, S 10.41.

Data for **4a**: R_f = 0.27 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = −11.4 (*c* 1.19); ^{1}H NMR (300 MHz) δ 0.80 (t, *J* = 7.0 Hz, 3 H, Me-*n*-Bu), 1.11−1.25 (m, 4 H, 2 CH_2-*n*-Bu), 1.62−1.75 (m, 2 H, CH_2-*n*-Bu), 2.39 (s, 3 H, Me-*p*-Tol), 3.05 (m, 1 H, H-6), 3.28 (m, 1 H, H-3a), 3.33 (dd, *J* = 10.9, 6.6 Hz, 1 H, H-3), 4.21−4.27 (m, 2 H, H-3, H-1), 4.35 (dm, *J* = 12.0 Hz, 1 H, H-1), 5.37 (m, 1 H, H-7), 6.63 (t, *J* = 2.4 Hz, 1 H, H-4), 7.29 (d, *J* = 7.9 Hz, 2 H, *p*-Tol), 7.48 (d, *J* = 8.3 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz) δ 13.9 (Me-*n*-Bu), 21.3 (Me-*p*-Tol), 22.6, 27.6, 31.9, 36.6, 41.2, 69.0, 70.8, 120.2, 125.3 (2 C), 129.8 (2 C), 131.5, 136.1, 138.7, 141.2, 148.3; IR (film) 2956, 2926, 2857, 1651, 1456, 1260, 1084, 1048, 898, 809 cm^{-1}; MS (ES) *m*/*z* (%) 633 (100) $[2M + H]^+$, 317 $[M + H]^+$. Anal. Calcd for $C_{19}H_{24}O_2S$: C 72.11, H 7.64, S 10.13. Found: C 72.20, H 7.78, S 10.27.

Synthesis of (*S*)-4-Oxa-9-phenyl-8-(*p*-tolylsulfinyl)-6-(*E*)-8-(*Z*)-nonadien-1-yne, 2b, (+)-(3a*R*,6*S*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 3b, and (+)-(3a*S*,6*R*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 4b. From sulfinyl diene **1b** (298 mg, 1 mmol), propargyl bromide (0.32 mL, 446 mg, 3 mmol), Triton B (0.10 mL, 91 mg, 0.2 mmol) and 60% aqueous sodium hydroxide (10 mL) following the general procedure (2 h) compound **2b** was obtained. The ^{1}H NMR spectra of the crude product run after the workup procedure showed a 30:65:5 mixture of **2b**, **3b** and **4b**. After 2 days at room temperature the cycloaddition was complete and a 92:8 mixture of **3b** and **4b** was obtained. Purification by chromatography (20−80% EtOAc/hexane) afforded 14 mg of a 1:1 mixture of isomerized 8-(*E*)-dienyne **SI-34** (2%) and the aromatized cycloaduct **SI-35** (2%), 218 mg (0.65 mmol, 65%) of **3b** as a white solid that was recrystallized from EtOAc/hexane, 19 mg (0.05 mmol, 5%) of **4b** and 7 mg (0.02 mmol, 2%) of starting material **1b**.

From sulfinyl dienyne **2b** (165 mg, 0.49 mmol), CuI (9 mg, 0.04 mmol) and Et_3N (68 μL, 0.49 mmol) following the general procedure (18 h), a 92:8 mixture of **3b** and **4b** was obtained. Purification by chromatography afforded **3b** (124 mg, 0.34 mmol, 75%) as a white solid that was recrystallized from EtOAc/hexane, and 17 mg (0.05 mmol, 10%) of a mixture of **3b** and **4b**.

Data for **2b**: R_f = 0.37 (50% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 2.36 (s, 3 H, Me-*p*-Tol), 2.37 (m, 1 H, H-1 overlapped), 3.94 (m, 2 H, 2 H-3), 4.04 (m, 2 H, 2 H-5), 6.17 (dt, *J* = 15.7, 5.6 Hz, 1 H, H-6), 6.31 (dd, *J* = 15.7, 1.0 Hz, 1 H, H-7), 7.23−7.29 (m, 4 H), 7.35−7.42 (m, 4 H), 7.48−7.51 (m, 2 H).

Data for **SI-34**: R_f = 0.37 (50% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 2.36 (s, 3 H, Me-*p*-Tol), 2.89 (t, *J* = 2.4 Hz, 1 H, H-1), 3.87 (d, *J* = 2.4 Hz, 2 H, 2 H-3), 3.96 (d, *J* = 6.0 Hz, 2 H, 2 H-5), 6.07 (dt, *J* = 16.3, 5.8 Hz, 1 H, H-6), 6.43 (d, *J* = 16.5 Hz, 1 H, H-7), 7.31−7.47 (m, 8 H), 7.55 (d, *J* = 8.2 Hz, 2 H).

Data for **3b**: R_f = 0.11 (50% EtOAc/hexane); mp 164 °C; $[\alpha]^{20}_D$ = +243.3 (*c* 0.55); ^{1}H NMR (300 MHz) δ 2.39 (s, 3 H, Me-*p*-Tol), 3.41 (m, 1 H, H-3a), 3.47 (ddd, *J* = 11.0, 7.0, 0.7 Hz, 1 H, H-3), 3.56 (m, 1 H, H-6), 4.26 (dm, *J* = 11.7 Hz, 1 H, H-1), 4.37−4.43 (m, 2 H, H-3, H-1), 5.34 (t, *J* = 2.0 Hz, 1 H, H-7), 6.92−6.96 (m, 2 H), 6.99 (t, *J* = 2.2 Hz, 1 H, H-4), 7.22−7.33 (m, 7 H); ^{13}C NMR (75 MHz) δ 21.5 (Me-*p*-Tol), 40.8, 43.4, 68.9, 71.5, 119.6, 122.9, 126.9 (2 C), 127.6, 128.8 (2 C), 129.1 (2 C), 130.0 (2 C), 136.6, 138.9, 140.5, 142.6, 147.4; IR (KBr) 3026,

2922, 2859, 1629, 1595, 1493, 1452, 1328, 1306, 1182, 1082, 1047, 1014, 959, 896, 851, 813, 763, 700 cm^{-1}; MS (ES) *m*/*z* (%) 695 (100) $[2M + Na]^+$, 673 $[2M + H]^+$, 659 $[M + Na]^+$, 337 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_2S$: C 74.97, H 5.99, S 9.53. Found: C 74.68, H 6.10, S 9.42.

Data for **4b**: R_f = 0.20 (50% EtOAc/hexane); mp 175−177 °C; $[\alpha]^{20}_D$ = +3.5 (*c* 0.35); ^{1}H NMR (300 MHz) δ 2.31 (s, 3 H, Me-*p*-Tol), 3.40−3.48 (m, 2 H, H-3a, 1 H-3), 4.26−4.35 (m, 2 H, 1 H-1, 1 H-6), 4.39−4.47 (m, 2 H, 1 H-1, 1 H-3), 5.46 (br s, 1 H, H-7), 6.70 (t, *J* = 2.3 Hz, 1 H, H-4), 6.90−6.94 (m, 2 H), 6.97−7.15 (m, 7 H); ^{13}C NMR (75 MHz) δ 21.3 (Me-*p*-Tol), 40.8, 43.9, 69.0, 71.3, 119.5, 125.6 (2 C), 125.9, 127.3, 128.4 (2 C), 129.4 (2 C), 129.5 (2 C), 136.9, 139.6, 139.9, 141.2, 148.6; IR (KBr) 3026, 2922, 2859, 1595, 1493, 1452, 1306, 1082, 1047, 1014, 959, 896, 813, 763, 700 cm^{-1}; MS (ES) *m*/*z* (%) 659 $[M + Na]^+$, 337 (100) $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_2S$: C 74.97, H 5.99, S 9.53. Found: C 74.80, H 6.04, S 9.42.

Synthesis of (1*R*,*S*$_S$)-(*Z*)-(2-[(3-Prop-2-ynyloxy)cyclohex-1-enyl]-2-(*p*-tolylsulfinyl)vinyl)benzene, 2e, and (−)-(2a*S*,4*S*,8a*R*,*S*$_S$)-4-Phenyl-5-(*p*-tolylsulfinyl)-2a,4,6,7,8,8a-hexahydro-2*H*-naphtho[1,8-*bc*]furan, 3e. From diene **1e** (40 mg, 0.12 mmol, 1.0 equiv), propargyl bromide (0.20 mL, 1.77 mmol, 15.0 equiv) and Triton B (27 μL, 0.059 mmol, 0.5 equiv) following the general procedure (6 h), dienyne **2e** was obtained. Purification by flash chromatography afforded dienyne **2e** (7 mg, 0.019 mmol, 16%, 44% based on recovered starting material) as a yellow oil, and 24 mg (0.017 mmol, 60%) of **1e**.

A solution of **2e** in $CDCl_3$ was kept at room temperature and monitored by ^{1}H NMR until cycloaddition was complete (10 days) affording **3e** as a single diastereomer.

In a related experiment, a solution of **2e** in C_6D_6 was heated at 70 °C for 38 h affording **3e** as a single diastereomer. Purification by chromatography (10−50% EtOAc/hexane) gave **3e** (11 mg, 0.029 mmol, 73%) as a colorless oil.

Data for **2e**: R_f = 0.33 (30% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 1.36−1.72 (m, 4 H), 1.83−1.92 (m, 1 H), 2.16−2.27 (m, 1 H), 2.37 (s, 3 H, Me-*p*-Tol), 2.38 (brs, 1 H, H-alkyne), 3.94−3.98 (m, 1 H), 4.05 (d, *J* = 2.4 Hz, 2 H), 5.79−5.80 (m, 1 H), 7.15 (s, 1 H), 7.23 (d, *J* = 7.9 Hz, 2 H), 7.35−7.40 (m, 5 H), 7.52−7.55 (m, 2 H); MS (ES) *m*/*z* (%) 399 (100) $[M + Na]^+$. Anal. Calcd for $C_{24}H_{24}O_2S$: C 76.56, H 6.42, S 8.52. Found: C 76.41, H 6.37, S 8.75.

Data for **3e**: R_f = 0.20 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = −62.3 (*c* 0.19); ^{1}H NMR (300 MHz) δ 1.29−1.40 (m, 1 H), 1.75−1.89 (m, 2 H), 1.95−2.04 (m, 1 H), 2.20−2.33 (m, 1 H), 2.27 (s, 3 H, Me-*p*-Tol), 3.29 (m, 1 H), 3.26−3.40 (m, 1 H), 4.27 (m, 2 H), 4.31−4.41 (m, 2 H), 5.50 (dd, *J* = 3.0, 1.5 Hz, 1 H), 6.78−6.81 (m, 3 H), 6.90−6.93 (m, 6 H); ^{13}C NMR (75 MHz) δ 19.3, 21.1, 26.0, 28.2, 43.9, 45.2, 68.8, 77.5, 123.1 (3 C), 123.2, 126.4, 127.4, 129.2 (2 C), 130.1, 132.1, 134.7, 138.3, 138.7, 140.2 (2 C), 146.4; IR (film) 3027, 2925, 2856, 1598, 1492, 1454, 1376, 1081, 1042, 863, 806, 768, 734, 699, 619, cm^{-1}; HRMS calcd for $C_{24}H_{25}O_2S$ $[M + H]^+$ 377.1575, found 377.1569.

Synthesis of (±)-2-(*E*)-4-(*Z*)-5-Phenyl-4-(*p*-tolylsulfinyl)penta-2,4-dienyl propiolate, 2m, (±)-(3a*R*,6*S*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-3a,6-dihydro-3*H*-isobenzofuran-1-one, 3m, (±)-(3a*S*,6*R*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-3a,6-dihydro-3*H*-isobenzofuran-1-one, 4m. To solution of (±)-**1b** (120 mg, 0.40 mmol), and propiolic acid (37 μL, 42 mg, 0.60 mmol) in 4 mL of CH_2Cl_2, at 0 °C, dicyclohexylcarbodiimide (124 mg, 0.6 mmol) and dimethylaminopyridine (20 mg, 0.16 mmol) were added. The mixture was allowed to warm to room temperature and monitored by TLC until starting material disappearance (1 h). The reaction mixture was filtered to remove dicyclohexylurea and the ester was purified by column chromatography (20% EtOAc/hexane) affording **2m** (83 mg, 0.28 mmol, 70%) as a colorless oil that cyclized slowly upon standing in solution.

Data for **2m**: R_f = 0.41 (50% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 2.38 (s, 3 H, Me-*p*-Tol), 2.87 (s, 1 H, H-3′), 4.66 (d, *J* = 5.9 Hz, 2 H, H-1), 6.25 (dt, *J* = 15.9, 6.0 Hz, 1 H, H-2), 6.38 (dm, *J* = 15.6 Hz, 1 H, H-3), 7.25−7.28 (m, 3 H), 7.38−7.44 (m, 5 H), 7.51−7.54 (m, 2 H); ^{13}C NMR (50 MHz) δ 21.3 (Me-*p*-Tol), 65.9 (C-1), 74.3, 75.1, 124.4 (2 C), 126.6, 127.2, 128.6 (2 C), 129.3, 129.9 (2 C), 130.0 (2 C), 133.7, 136.6, 139.3, 141.0, 142.2, 152.2 (CO). Anal. Calcd for $C_{21}H_{18}O_3S$: C 71.98, H 5.18, S 9.15. Found: C 72.19, H 5.30, S 8.96.

From dienyne **2m** (62 mg, 0.17 mmol) following the general procedure for the thermal cycloaddition (80 °C, 8 h) an 84:16 mixture of **3m** and **4m** was obtained. Purification by chromatography (5−20% EtOAc-CH_2Cl_2) afforded **3m** (45 mg, 0.12 mmol, 72%) as a white solid that was recrystallized from EtOAc/hexane and **4m** (9 mg, 0.025, 14%) as a white solid that was recrystallized from Et_2O.

Data for **3m**: R_f = 0.26 (80% EtOAc/hexane); mp 208−210 °C; ^{1}H NMR (300 MHz) δ 2.41 (s, 3 H, Me-*p*-Tol), 3.71 (dt, *J* = 11.7, 2.2 Hz, 1 H, H-6), 3.84 (m, 1 H, H-3a), 4.06 (dd, *J* = 10.1, 8.2 Hz, 1 H, 1 H-3), 4.84 (t, *J* = 8.4 Hz, 1 H, 1 H-3), 6.55 (t, *J* = 2.4 Hz, 1 H, H-7), 6.91−6.94 (m, 2 H), 7.03 (t, *J* = 2.3 Hz, 1 H, H-4), 7.27 (m, 4 H), 7.32−7.35 (m, 3 H); ^{13}C NMR (50 MHz) δ 21.6 (Me-*p*-Tol), 38.4, 43.9, 70.1 (C-3), 122.2, 126.2, 126.8 (2 C), 128.4, 129.1 (2 C), 129.2 (2 C), 130.2 (2 C), 135.7, 137.9, 138.0, 143.1, 148.3, 168.3 (CO); IR (KBr) 3027, 2912, 1760, 1693, 1627, 1492, 1454, 1333, 1205, 1182, 1085, 1048, 1021, 974, 897, 809, 757, 739, 701 cm^{-1}; MS (ES) *m*/*z* (%) 373 $[M + Na]^+$, 351 (100) $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}O_3S$: C 71.98, H 5.18, S 9.15. Found: C 72.12, H 5.35, S 9.32.

Data for **4m**: R_f = 0.21 (80% EtOAc/hexane); mp 202−204 °C; ^{1}H NMR (300 MHz) δ 2.31 (s, 3 H, Me-*p*-Tol), 3.86 (m, 1 H, H-3a), 3.99 (dd, *J* = 10.3, 8.7 Hz, 1 H, 1 H-3), 4.59 (dt, *J* = 12.1, 2.3 Hz, 1 H, H-6), 4.79 (t, *J* = 8.7 Hz, 1 H, 1 H-3), 6.70 (m, 1 H, H-7), 6.77 (t, *J* = 2.6 Hz, 1 H, H-4), 6.85−6.87 (m, 2 H), 6.93−7.19 (m, 7 H); ^{13}C NMR (50 MHz) δ 21.4 (Me-*p*-Tol), 38.3, 44.5, 69.9 (C-3), 124.9, 125.6 (2 C), 127.0, 128.0, 128.7 (2 C), 129.4 (2 C), 129.7 (2 C), 135.8, 137.3, 139.2, 141.8, 149.3, 168.1 (CO); IR (KBr) 3038, 2917, 1753, 1626, 1454, 1178, 1080, 1045, 981, 807, 759, 702 cm^{-1}; MS (ES) *m*/*z* (%) 373 $[M + Na]^+$, 351 (100) $[M + H]^+$. Anal. Calcd for $C_{21}H_{18}O_3S$: C 71.98, H 5.18, S 9.15. Found: C 72.18, H 5.26, S 9.32.

Synthesis of (±)-*N*-[5-Phenyl-4-(*p*-tolylsulfinyl)penta-2-(*E*)-4-(*Z*)-dienyl]-*N*-prop-2-ynyl-*p*-tolylsulfonamide, 2n, (±)-(3a*R*,6*S*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-2-(*p*-tolylsulfonyl)-2,3,3a,6-tetrahydroisoindole, 3n, and (±)-(3a*S*,6*R*,*S*$_S$)-6-Phenyl-5-(*p*-tolylsulfinyl)-2-(*p*-tolylsulfonyl)-2,3,3a,6-tetrahydroisoindole, 4n. From dienol **1b** (60 mg, 0.2 mmol), Ph_3P (79 mg, 0.3 mmol), *N*-(prop-2-ynyl)-*p*-tolylsulfonamide (63 mg, 0.3 mmol) and diisopropyl azodicarboxylate (60 μL, 61 mg, 0.3 mmol), following the general procedure for Mitsunobu transformations, (THF, 0 °C, 1 h 30 min) compound **2n** was obtained. Purification by chromatography (20−50% EtOAc/hexane) afforded a 72:28 mixture of **2n** and **3n** with traces of **4n** (95 mg, 0.19 mmol, 95%).

A solution of this mixture in $CDCl_3$ was cooled at 5 °C and monitored by ^{1}H NMR until cycloaddition was complete (3 days), affording a 94:6 mixture of **3n** and **4n**. Purification by chromatography (20−50% EtOAc/hexane) afforded **3n** (89 mg, 0.18 mmol, 90%) as white solid that was recrystallized from EtOAc/hexane and **4n** (5 mg, 0.01 mmol, 5%) as a white solid that was recrystallized from EtOAc/hexane.

When the amino-Mitsunobu reaction was carried out at room temperature **2n** was not detected and a mixture of **3n** and **4n** was obtained after chromatography in an identical diastereomeric ratio to that described above.

Partial data for **2n**: R_f = 0.12 (30% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 2.35 (s, 3 H, Me-*p*-Tol), 2.37 (m, 1 H, H-1 overlapped), 2.38 (s, 3 H, Me-*p*-Tol), 3.50−3.90 (m, 4 H, 2 H-3, 2 H-5), 5.97 (dt, *J* = 15.6, 6.8 Hz, 1 H, H-6), 6.30 (dd, *J* = 15.7, 0.9 Hz, 1 H, H-7).

Data for **3n**: R_f = 0.19 (50% EtOAc/hexane); mp 97−98 °C; ^{1}H NMR (300 MHz-COSY) δ 2.37 (s, 3 H, Me-*p*-Tol), 2.43 (s, 3 H, Me-*p*-Tol), 2.89 (dd, J = 11.2, 9.3 Hz, 1 H, H-3), 3.23 (m, 1 H, H-3a), 3.44 (m, 1 H, H-6), 3.76 (dd, J = 13.4, 1.2 Hz, 1 H, H-1), 4.00 (m, 1 H, H-1), 4.04 (dd, J = 9.0, 8.3 Hz, 1 H, H-3), 5.29 (t, J = 1.8 Hz, 1 H, H-7), 6.76−6.82 (m, 2 H), 6.87 (t, J = 2.4 Hz, 1 H, H-4), 7.20−7.27 (m, 7 H), 7.32 (m, 2 H), 7.71 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (50 MHz) δ 21.5 (2 C, 2 Me-*p*-Tol), 39.2 (C-3a), 42.8 (C-6), 50.3 (C-1), 52.2 (C-3), 121.7, 122.5, 126.7 (2 C), 127.5 (2 C), 127.7, 128.7 (2 C), 128.9 (2 C), 129.8 (2 C), 130.0 (2 C), 132.9, 133.7, 138.5, 139.8, 142.7, 143.7, 147.2; IR (KBr) 2923, 2862, 1630, 1492, 1453, 1346, 1163, 1095, 1051, 811, 703 cm^{-1}; MS (ES) m/z (%) 979 [2M + H]$^+$, 490 (100) [M + H]$^+$. Anal. Calcd for $C_{28}H_{27}NO_3S_2$: C 68.68, H 5.56, N 2.86, S 13.10. Found: C 68.57, H 5.35, N 2.82, S 13.42.

Data for **4n**: R_f = 0.14 (50% EtOAc/hexane); mp 140−142 °C; ^{1}H NMR (300 MHz) δ 2.29 (s, 3 H, Me-*p*-Tol), 2.42 (s, 3 H, Me-*p*-Tol), 2.86 (dd, J = 11.2, 9.3 Hz, 1 H, H-3), 3.15 (m, 1 H, H-3a), 3.83 (dd, J = 14.2, 1.0 Hz, 1 H, H-1), 3.95 (ap t, J = 8.5 Hz, 1 H, H-3), 3.97 (m, 1 H, H-1), 4.29 (m, 1 H, H-6), 5.40 (br s, 1 H, H-7), 6.53 (t, J = 2.6 Hz, 1 H, H-4), 6.73−6.80 (m, 2 H), 6.93−7.12 (m, 7 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.70 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz) δ 21.4 (Me-*p*-Tol), 21.6 (Me-*p*-Tol), 39.1 (C-3a), 43.4 (C-6), 50.4 (C-1), 52.1 (C-3), 121.7, 125.5 (2 C), 125.6, 127.4, 127.5 (2 C), 128.4 (2 C), 129.2 (2 C), 129.5 (2 C), 129.9 (2 C), 133.1, 134.0, 139.3, 141.4, 143.8 (2 C), 148.6; IR (KBr) 2922, 2851, 1631, 1493, 1453, 1344, 1155, 1091, 1038, 805, 756, 701, 667 cm^{-1}; MS (ES) m/z (%) 490 [M + H]$^+$. Anal. Calcd for $C_{28}H_{27}NO_3S_2$: C 68.68, H 5.56, N 2.86, S 13.10. Found: C 68.71, H 5.43, N 2.91, S 13.12.

Synthesis of (±)-(3a*R*,6*S*,*S*$_S$)-2,2-Bis-benzenesulfonyl-6-phenyl-5-(*p*-tolylsulfinyl)-2,3,3a,6-tetrahydro-1*H*-indene, 3o, and (±)-(3a*S*,6*R*,*S*$_S$)-2,2-Bis-benzenesulfonyl-6-phenyl-5-(*p*-tolylsulfinyl)-2,3,3a,6-tetrahydro-1*H*-indene, 4o. From dienol **1b** (49 mg, 0.16 mmol), Ph_3P (63 mg, 0.24 mmol), 4,4-bis-benzenesulfonylbut-1-yne (60 mg, 0.18 mmol) and diisopropyl azodicarboxylate (50 μL, 49 mg, 0.24 mmol), following the general procedure for Mitsunobu transformations (C_6H_6, rt, 1 h 30 min), a 98:2 mixture of **3o** and **4o** was obtained. Dienyne **2o** was not detected in the ^{1}H NMR spectra of the crude product. Purification by chromatography (20−50% EtOAc/hexane) afforded **3o** (90 mg, 0.146 mmol, 90%) as a white solid that was recrystallized from EtOAc/hexane and **4o** (2 mg, 0.003 mmol, 2%) as a white solid.

Data for **3o**: R_f = 0.45 (80% EtOAc/hexane); mp 229−230 °C; ^{1}H NMR (300 MHz) δ 2.37−2.42 (m, 1 H), 2.40 (s, 3 H, Me-*p*-Tol), 3.08 (t, J = 7.3 Hz, 1 H), 3.16 (d, J = 18.6 Hz, 1 H), 3.37 (m, 1 H), 3.41−3.54 (m, 2 H), 5.23 (br s, 1 H, H-7), 6.78−6.82 (m, 2 H), 6.93 (br s, 1 H, H-4), 7.24−7.35 (m, 6 H), 7.54−7.78 (m, 7 H), 7.99 (m, 2 H), 8.13 (m, 2 H); ^{13}C NMR (50 MHz) δ 21.5 (Me-*p*-Tol), 35.7, 37.3, 39.7, 42.9, 89.9, 121.7, 124.2, 126.9 (2 C), 127.6, 128.7 (2 C), 128.8 (2 C), 128.9 (2 C), 129.0 (2 C), 130.0 (2 C), 131.3 (2 C), 131.5 (2 C), 134.1, 134.7, 134.9, 135.8, 135.9, 138.6, 140.0, 142.7, 145.6; IR (KBr) 3060, 3021, 2917, 2840, 1631, 1491, 1448, 1323, 1312, 1143, 1077, 1051, 757, 733, 703 cm^{-1}; MS (ES) m/z (%) 615 (100) [M + H]$^+$. Anal. Calcd for $C_{34}H_{30}O_5S_3$: C 66.42, H 4.92, S 15.65. Found: C 66.33, H 5.08, S 15.43.

Data for **4o**: R_f = 0.41 (80% EtOAc/hexane); mp 114−115 °C; ^{1}H NMR (300 MHz) δ 2.32 (s, 3 H, Me-*p*-Tol), 2.36 (m, 1 H), 2.98 (dd, J = 14.4, 8.1 Hz, 1 H), 3.14 (d, J = 9.4 Hz, 1 H), 3.23−3.47 (m, 2 H), 4.28 (m, 1 H), 5.35 (br s, 1 H, H-7), 6.59 (t, J = 2.6 Hz, 1 H, H-4), 6.83 (dd, J = 8.1, 1.7 Hz, 1 H), 6.98−7.11 (m, 7 H), 7.50−7.77 (m, 6 H), 8.00 (dd, J = 8.5, 1.2 Hz, 2 H), 8.09 (dd, J = 8.5, 1.2 Hz, 2 H); ^{13}C NMR (50 MHz) δ 21.4 (Me-*p*-Tol), 36.2, 36.8, 39.4, 43.6, 90.0 (C-2), 122.0, 125.5 (2 C), 127.3, 127.8, 128.4 (2 C), 128.9 (2 C), 129.0 (2 C), 129.4 (2 C), 129.5 (2 C), 131.3 (2 C), 131.4 (2 C), 134.2, 134.7, 135.0, 136.1, 139.5, 139.6, 141.3, 147.2, 153.1; IR (KBr) 3060, 2924, 2851, 1631, 1492, 1447, 1331, 1312, 1146, 1078, 1042, 809, 757, 730 cm^{-1}; MS (ES) m/z (%) 615 (100) [M + H]$^+$. Anal. Calcd for $C_{34}H_{30}O_5S_3$: C 66.42, H 4.92, S 15.65. Found: C 66.29, H 5.15, S 15.57.

Synthesis of (±)-5,5-Bis-benzenesulfonyl-10-phenyl-9-(*p*-tolylsulfinyl)-7-(*E*)-9-(*Z*)-decadien-1-yne, 2r, (±)-(4a*R*,7*S*,*S*$_S$)-3,3-Bis-benzenesulfonyl-7-phenyl-6-(*p*-tolylsulfinyl)-1,2,3,4,4a,7-hexahydronaphthalene, 3r, and (±)-(4a*S*,7*R*,*S*$_S$)-3,3-Bis-benzenesulfonyl-7-phenyl-6-(*p*-tolylsulfinyl)-1,2,3,4,4a,7-hexahydronaphthalene, 4r. From 3-butyn-1-ol (76 μL, 1.0 mmol), PPh_3 (525 mg, 2.0 mmol), 4,4-bis-benzenesulfonylmethane (385 mg, 1.3 mmol) and diisopropyl azodicarboxylate (0.39 mL, 2.0 mmol), following the general procedure for Mitsunobu transformations (C_6H_6, 2 h), compound **9** was obtained. Purification by chromatography (60−100% CH_2Cl_2-hexane) afforded **9** (174 mg, 0.5 mmol, 50%) as a white solid.

From dienol **1b** (39 mg, 0.13 mmol), PPh_3 (52 mg, 0.20 mmol, 1.5 equiv), 5,5-bis-benzenesulfonyl-pent-1-yne **9** (50 mg, 0.14 mmol) and diisopropyl azodicarboxylate (40 μL, 40 mg, 0.20 mmol, 1.5 equiv) following the general procedure (C_6H_6, rt, 1 h) compound **2r** was obtained. Purification by chromatography (10−50% EtOAc/hexane) afforded 70 mg of impure **2r**. A second chromatography (5−50% EtOAc-CH_2Cl_2) afforded pure **2r** (30 mg, 0.05 mmol, 38%).

Data for **2r**: R_f = 0.18 (60% Et_2O-hexane); mp 84−85 °C; ^{1}H NMR (300 MHz) δ 1.97 (t, J = 2.3 Hz, 1 H, H-1), 2.24−2.48 (m, 4 H, 2 H-3, 2 H-4), 2.38 (s, 3 H, Me-*p*-Tol), 2.93 (d, J = 6.6 Hz, 2 H, 2 H-6), 6.17 (d, J = 16.1 Hz, 1 H, H-8), 6.39 (dt, J = 15.7, 6.6 Hz, 1 H, H-7), 7.21−7.75 (m, 15 H), 7.95−7.99 (m, 4 H); ^{13}C NMR (75 MHz) δ 13.5, 21.4 (Me-*p*-Tol), 28.8, 33.0, 69.5, 82.3, 89.5, 124.5 (2 C), 126.7, 127.1, 128.6 (2 C), 128.8 (4 C), 130.0 (2 C), 130.1 (2 C), 131.1 (5 C), 133.8, 134.7, 136.1, 136.3, 139.6, 140.9, 142.5; IR (KBr) 3060, 2917, 1631, 1447, 1310, 1144, 1079, 724 cm^{-1}; MS (ES) m/z (%) 629 (100) [M + H]$^+$. Anal. Calcd for $C_{35}H_{32}O_5S_3$: C 66.85, H 5.13, S 15.30. Found: C 66.73, H 5.34, S 15.47.

From dienyne **2r** (30 mg, 0.05 mmol) following the general procedure for thermal cycloadditions (80 °C, 14 h) a 91:9 mixture of **3r** and **4r** was obtained. Purification by chromatography (2−5% EtOAc-CH_2Cl_2) afforded pure **3r** (18 mg, 0.029 mmol, 58%) as a white solid that was recrystallized from EtOAc/hexane and a mixture of **3r** and **4r** (10 mg, 0.016 mmol, 32%).

Data for **3r**: R_f = 0.23 (10% EtOAc-CH_2Cl_2); mp 223−225 °C; ^{1}H NMR (300 MHz) δ 2.00−2.27 (m, 3 H), 2.40 (s, 3 H, Me-*p*-Tol), 2.58 (m, 1 H), 2.88−3.00 (m, 2 H), 3.45 (m, 1 H, H-7), 3.88 (m, 1 H, H-4a), 5.30 (t, J = 1.7 Hz, 1 H, H-8), 6.71 (dd, J = 3.4, 1.2 Hz, 1 H, H-5), 6.82−6.88 (m, 2 H), 7.20−7.29 (m, 5 H), 7.41 (d, J = 8.3 Hz, 2 H), 7.58−7.68 (m, 4 H), 7.71−7.79 (m, 2 H), 7.96 (d, J = 8.3 Hz, 2 H), 8.14 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (50 MHz) δ 21.5 (Me-*p*-Tol), 27.9, 29.7, 33.9, 34.6, 42.3, 87.5 (C-3), 122.7, 126.5, 126.6 (2 C), 127.4, 128.4 (2 C), 128.8 (4 C), 128.9 (2 C), 130.1 (2 C), 131.1 (2 C), 131.5 (2 C), 132.1, 134.6, 134.8, 135.7, 136.6, 138.8, 140.5, 142.7, 144.6; IR (KBr) 3060, 2921, 2851, 1633, 1491, 1447, 1376, 1325, 1310, 1146, 1080, 1049, 810, 756, 724, 704, 687 cm^{-1}; MS (ES) m/z (%) 629 (100) [M + H]$^+$. Anal. Calcd for $C_{35}H_{32}O_5S_3$: C 66.85, H 5.13, S 15.30. Found: C 67.02, H 5.40, S 15.14.

Partial data for **4r** (from the mixture): R_f = 0.21 (10% EtOAc-CH_2Cl_2); ^{1}H NMR (300 MHz) δ 2.33 (s, 3 H, Me-*p*-Tol), 3.85 (m, 1 H, H-4a), 4.19 (m, 1 H, H-7), 5.37 (m, 1 H, H-8), 6.46 (d, J = 3.8 Hz, 1 H, H-5).

Synthesis of (±)-(3a*S*,6*R*,*R*$_S$)-6-*n*-Butyl-4-(2-methoxynaphthalene-1-ylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 3i, and (±)-(3a*R*,6*S*,*R*$_S$)-6-*n*-Butyl-4-(2-methoxynaphthalene-1-ylsulfinyl)-1,3,3a,6-tetrahydroisobenzofuran, 4i. From diene **1i** (25 mg, 0.072 mmol), propargyl bromide (39 μL, 54 mg, 0.36 mmol), Triton B (8 μL, 7 mg, 0.04 mmol) and 60% aqueous sodium hydroxide (0.7 mL) following the general procedure (3 h) compound **2i** was obtained. The ^{1}H NMR of the crude product,

recorded immediately after workup showed a 64:32:4 mixture of **2i**, **3i** and **4i**. After 1 day at room temperature the cycloaddition was complete and an 89:11 mixture of **3i** and **4i** was obtained. Purification by chromatography (20−40% EtOAc/hexane) afforded **3i** (18 mg, 0.047 mmol, 65%) as a white solid that was recrystallized in EtOAc/hexane and **4i** (3 mg, 0.008 mmol, 11%) as a white solid.

Data for **3i**: R_f = 0.46 (80% EtOAc/hexane); mp 155−156 °C; ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7.0 Hz, 3 H, Me-*n*-Bu), 1.29−1.44 (m, 4 H, CH_2-*n*-Bu), 1.61−1.68 (m, 2 H, CH_2-*n*-Bu), 2.51 (m, 1 H, H-3a), 3.05 (m, 1 H, H-6), 3.39 (dd, J = 10.9, 7.7 Hz, 1 H, H-3), 3.97 (t, J = 7.8 Hz, 1 H, H-3), 4.00 (s, 3 H, OMe), 4.17 (br s, 2 H, H-1), 5.47 (br s, 1 H, H-7), 6.78 (m, 1 H, H-5), 7.25 (d, J = 9.1 Hz, 1 H, H-3′), 7.37 (ddd, J = 8.1, 7.0, 1.1 Hz, 1 H, H-6′), 7.49 (ddd, J = 8.4, 7.0, 1.5 Hz, 1 H, H-7′), 7.78 (d, J = 8.1 Hz, 1 H, H-5′), 7.96 (d, J = 9.2 Hz, 1 H, H-4′), 8.66 (d, J = 8.5 Hz, 1 H, H-8′); ^{13}C NMR (50 MHz) δ 14.0 (Me-*n*-Bu), 22.9, 28.6, 34.9, 38.1, 39.3, 56.9, 68.5, 70.7, 112.8, 118.8, 120.0, 122.6, 124.6, 128.2, 128.8, 129.5, 132.2, 132.5, 135.3, 137.7, 138.1, 158.0; IR (KBr) 2958, 2932, 2856, 1620, 1592, 1505, 1458, 1432, 1336, 1273, 1250, 1150, 1047, 1027, 904, 879, 829, 777, 753 cm^{-1}; MS (ES) m/z (%) 383 (100) $[M + H]^+$. Anal. Calcd for $C_{23}H_{26}O_3S$: C 72.22, H 6.85, S 8.38. Found: C 72.68, H 6.72, S 8.45.

Data for **4i**: R_f = 0.43 (80% EtOAc/hexane); mp 114−116 °C; ^{1}H NMR (300 MHz) δ 0.91 (t, J = 6.8 Hz, 3 H, Me-*n*-Bu), 1.27−1.39 (m, 4 H, CH_2-*n*-Bu), 1.57−1.66 (m, 2 H, CH_2-*n*-Bu), 2.33 (dd, J = 10.7, 7.6 Hz, 1 H, H-3), 3.15 (m, 1 H, H-6), 3.36 (m, 1 H, H-3a), 3.49 (t, J = 7.5 Hz, 1 H, H-3), 4.00 (s, 3 H, OMe), 4.03 (m, 1 H, H-1), 4.22 (dm, J = 12.0 Hz, 1 H, H-1), 5.43 (br s, 1 H, H-7), 6.75 (m, 1 H, H-5), 7.23 (d, J = 9.3 Hz, 1 H, H-3′), 7.36 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H, H-6′), 7.47 (ddd, J = 8.3, 6.8, 1.5 Hz, 1 H, H-7′), 7.76 (dd, J = 6.6, 0.7 Hz, 1 H, H-5′), 7.95 (d, J = 9.0 Hz, 1 H, H-4′), 8.69 (dd, J = 8.5, 1.0 Hz, 1 H, H-8′); ^{13}C NMR (50 MHz) δ 14.1 (Me-*n*-Bu), 22.9, 28.5, 35.0, 38.0, 38.9, 56.8, 68.3, 70.0, 112.8, 119.8, 123.1, 124.6, 128.0, 128.3, 128.8, 129.4, 132.5, 133.7, 135.2, 137.4, 138.6, 157.9; IR (KBr) 2927, 2856, 1621, 1593, 1506, 1465, 1431, 1335, 1272, 1250, 1151, 1034, 908, 813, 747 cm^{-1}; MS (ES) m/z (%) 421, 419 (100), 383 $[M + H]^+$. Anal. Calcd for $C_{23}H_{26}O_3S$: C 72.22, H 6.85, S 8.38. Found: C 72.37, H 6.59, S 8.52.

General Procedure for the Catalytic Hydrogenation of Cycloadducts. To a solution of the corresponding cycloadduct in EtOH (10 mL/mmol) under an argon atmosphere, a 10% mol of Pd on charcoal was added. A hydrogen atmosphere was achieved using a balloon charged with H_2, and the reaction was stirred until the complete disappearance of the starting material (TLC). The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by chromatography using the appropriate mixture of solvents.

Synthesis of (+)-(3a*S*,5*R*,7a*S*,*S*$_S$)-5-*n*-Butyl-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran, 12a. From **3a** (10 mg, 0.03 mmol) and Pd (C) (3 mg, 0.003 mmol) following the general procedure (2 days), compound **12a** was obtained. Purification by chromatography (10−70% EtOAc/hexane) afforded **12a** (5 mg, 0.015 mmol, 52%) as a colorless oil.

Data for **12a**: R_f = 0.13 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = +26.7 (c 0.46); ^{1}H NMR (400 MHz) δ 0.83 (t, J = 7.1 Hz, 3 H, Me-*n*-Bu), 1.05−1.44 (m, 6 H), 1.55−1.63 (m, 1 H), 1.74 (dt, J = 13.1, 4.8 Hz, 1 H, H-4), 1.84−1.90 (m, 1 H, H-3a), 2.18−2.30 (m, 1 H, H-5), 2.39 (s, 3 H, Me-*p*-Tol), 2.92−3.00 (m, 1 H, H-7a), 3.48 (dd, J = 9.2, 8.2 Hz, 1 H, H-3), 3.64 (dd, J = 8.7, 1.9 Hz, 1 H, H-1), 3.95 (dd, J = 8.7, 5.9 Hz, 1 H, H-1), 4.10 (t, J = 8.4 Hz, 1 H, H-3), 6.76 (dd, J = 4.8, 2.1 Hz, 1 H, H-7), 7.27 (d, J = 7.9 Hz, 2 H), 7.52 (d, J = 8.1 Hz, 2 H); ^{13}C NMR (100 MHz) δ 13.9, 21.5, 22.6, 27.7, 31.2, 31.9, 34.6, 36.5, 39.9, 71.7, 74.1, 126.1, 126.6 (2 C), 130.1 (2 C), 139.8, 142.3, 147.0; IR (film) 2927, 2857, 1732, 1596, 1492, 1456, 1378, 1261, 1082, 1050, 1015, 809 cm^{-1}; MS (EI) m/z (%) 318 $[M]^+$, 301 (100). Anal. Calcd for $C_{19}H_{26}O_2S$: C 71.66, H 8.23, S 10.07. Found: C 71.42, H 8.15, S 10.13.

Synthesis of (+)-(3a*S*,5*S*,7a*S*,*S*$_S$)-5-Phenyl-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran, 12b. From **3b** (60 mg, 0.18 mmol) and Pd (C) (20 mg, 0.018 mmol), following the general procedure (20 h), compound **12b** was obtained. Purification by chromatography (20−70% EtOAc/hexane) afforded **12b** (43 mg, 0.13 mmol, 71%) as a white solid.

Data for **12b**: R_f = 0.28 (70% EtOAc/hexane); mp 145−147 °C; $[\alpha]^{20}_D$ = +14.8 (c 1.22); ^{1}H NMR (400 MHz-COSY) δ 1.65 (ap q, J = 13.0 Hz, 1 H, H-4), 1.82 (dt, J = 13.3, 4.8 Hz, 1 H, H-4), 2.30 (s, 3 H, Me-*p*-Tol), 2.25−2.35 (m, 1 H, H-3a), 2.85 (dquint, J = 11.1, 2.5 Hz, 1 H, H-5), 2.95−3.03 (m, 1 H, H-7a), 3.51 (dd, J = 8.8, 1.8 Hz, 1 H, H-3), 3.56 (t, J = 8.4 Hz, 1 H, H-1), 3.88 (dd, J = 8.8, 5.9 Hz, 1 H, H-3), 4.12 (t, J = 8.4 Hz, 1 H, H-1), 6.86−6.88 (m, 3 H), 7.06 (d, J = 8.3 Hz, 2 H), 7.10 (d, J = 8.1 Hz, 2 H), 7.17−7.21 (m, 3 H); ^{13}C NMR (75 MHz) δ 21.5, 36.9, 37.2, 39.8, 42.2, 71.8, 73.8, 126.7 (2 C), 127.0, 127.3, 128.5 (2 C), 128.9 (2 C), 129.8 (2 C), 139.2, 140.5, 142.3, 146.8. NOESY-2D (400 MHz): a correlation peak between H-3a and H-7a was observed; IR (KBr) 2924, 2849, 1631, 1595, 1493, 1455, 1084, 1043, 1014, 816, 759, 700, 516 cm^{-1}; MS (ES) m/z (%) 361 $[M + Na]^+$, 339 $[M + H]^+$. Anal. Calcd for $C_{21}H_{22}O_2S$: C 74.52, H 6.55, S 9.47. Found: C 74.67, H 6.46, S 9.51.

General Procedure for the Oxidation−Epoxidation of Cycloadducts. To a cold (0 °C) solution of the corresponding cycloadduct (1.0 equiv) in CH_2Cl_2 (10 mL/mmol), *m*-CPBA (3.0 equiv) was added. The mixture was allowed to reach room temperature and was stirred until starting material disappearance (TLC). Then the reaction mixture was quenched with a 1 M solution of $Na_2S_2O_4$ (2 mL/mmol peracid) and a saturated solution of $NaHCO_3$ (2 mL/mmol peracid) and diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (twice), the organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the appropriate mixture of solvents.

Synthesis of (+)-(3a*R*,4*R*,5*R*,7a*S*)-5-*n*-Butyl-3a,4-epoxy-6-tosyl-1,3,3a,4,5,7a-hexahydroisobenzofuran, 13a. From **3a** (28 mg, 0.09 mmol) and *m*-CPBA (67 mg, 0.27 mmol) following the general procedure (3 days), compound **13a** was obtained. Purification by chromatography (50% CH_2Cl_2/hexane/10% EtOAc/CH_2Cl_2) afforded **13a** (27 mg, 0.072 mmol, 80%) as a white solid that was recrystallized from Et_2O/hexanes.

Data for **13a**: R_f = 0.40 (50% EtOAc/hexane); mp 138−140 °C; $[\alpha]^{20}_D$ = +61.8 (c = 1.07); ^{1}H NMR (400 MHz-COSY) δ 0.81 (t, J = 7.1 Hz, 3 H, Me-*n*-Bu), 1.09−1.26 (m, 4 H), 1.72−1.90 (m, 2 H), 2.41 (s, 3 H, Me-*p*-Tol), 2.92 (ap quint, J = 3.1 Hz, 1 H, H-5) 3.09 (s, 1 H, H-4), 3.22−3.29 (m, 1 H, H-7a), 3.55 (dd, J = 11.2, 8.4 Hz, 1 H, H-1), 3.80 (d, J = 9.9 Hz, 1 H, H-3), 3.94 (d, J = 9.9 Hz, 1 H, H-3), 4.34 (t, J = 8.3 Hz, 1 H, H-1), 6.84 (dd, J = 5.1, 0.9 Hz, 1 H, H-7), 7.31 (d, J = 7.9 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz) δ 12.3, 21.6, 22.6, 27.9, 30.6, 35.1, 39.8, 62.1, 64.1, 67.3, 70.6, 128.1 (2 C), 129.8 (2 C), 132.1, 136.1, 142.1, 144.6; IR (KBr) 2955, 2927, 2872, 1642, 1596, 1465, 1303, 1143, 1092, 1083, 1044, 1008, 902, 686, 544 cm^{-1}; MS (ES) m/z (%) 371 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{24}O_3S$: C 68.64, H 7.28, S 9.64. Found: C 68.36, H 7.09, S 9.55.

Synthesis of (+)-(3a*R*,4*R*,5*R*,7a*S*)-3a,4-Epoxy-5-phenyl-6-tosyl-1,3,3a,4,5,7a-hexahydroisobenzofuran, 13b. From **3b** (82 mg, 0.24 mmol) and *m*-CPBA (124 mg, 0.72 mmol), following the general procedure (3 days), compound **13b** was obtained along with aromatized sulfone **6b**. Purification by chromatography (10−50% EtOAc/hexane) afforded **13b** (53 mg, 0.14 mmol, 60%) and **6b** (4 mg, 0.012 mmol, 5%) both as white solids that were recrystallized from Et_2O/hexane.

Data for **13b**: R_f = 0.48 (50% EtOAc/hexane); mp 179−182 °C; $[\alpha]^{20}_D$ = +59.8 (c 0.93); ^{1}H NMR (400 MHz-COSY) δ 2.23

(s, 3 H, Me-*p*-Tol), 3.09 (s, 1 H, H-4), 3.38 (m, 1 H, H-7a), 3.64 (d, J = 8.7 Hz, 1 H), 3.67 (d, J = 8.4 Hz, 1 H), 3.88 (d, J = 10.0 Hz, 1 H, H-3), 4.23 (d, J = 3.4 Hz, 1 H, H-5), 4.43 (ap t, J = 8.3 Hz, 1 H, H-1), 6.86 (m, 2 H), 6.91 (d, J = 8.3 Hz, 2 H), 7.00−7.09 (m, 4 H), 7.18 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (100 MHz) δ 21.4, 40.0, 42.5, 61.9, 64.0, 67.5, 71.1, 127.6, 127.8 (2 C), 128.6 (2 C), 128.9 (2 C), 129.3 (2 C), 132.3, 136.6, 136.7, 142.3, 143.7; IR (KBr) 3027, 2923, 1644, 1598, 1492, 1457, 1305, 1147, 1089, 1040, 702, 684, 538 cm^{-1}; MS (ES) m/z (%) 391 [M + Na]$^+$, 369 [M + H]$^+$. Anal. Calcd for $C_{21}H_{20}O_3S$: C 71.56, H 5.72, S 9.10. Found: C 71.67, H 5.68, S 9.23.

Data for **6b**: R_f = 0.60 (70% EtOAc/hexane); mp 161−165 °C; ^{1}H NMR (400 MHz) δ 2.31 (s, 3 H, Me-*p*-Tol), 5.12 (s, 2 H), 5.22 (s, 2 H), 6.92−6.97 (m, 4 H), 7.04−7.07 (m, 3 H), 7.15−7.19 (m, 2 H), 7.26−7.30 (m, 1 H), 8.29 (s, 1 H); ^{13}C NMR (100 MHz) δ 21.5, 73.2, 73.3, 121.4, 125.2, 127.2 (2 C), 127.6, 127.7 (2 C), 128.9 (2 C), 130.1 (2 C), 137.8, 138.0, 138.9, 139.5, 141.8, 143.4, 144.4; IR (KBr) 2921, 1631, 1460, 1306, 1162, 1138, 1088, 710, 555 cm^{-1}; MS (ES) m/z (%) 373 [M + Na]$^+$, 351 [M + H]$^+$. Anal. Calcd for $C_{21}H_{18}O_3S$: C 71.98, H 5.18, S 9.15. Found: C 72.14, H 5.34, S 9.28.

General Procedure for Osmium-Catalyzed Dihydroxylation. To a solution of the sulfoxide in a 9:1 mixture of acetone and H_2O (0.1 M), at rt, were added 2.5 equiv of Me_3NO and 0.05 equiv of OsO_4. The solution was stirred until starting material disappearance and then quenched with a solution of aqueous $Na_2S_2O_4$ (1 M, 5 mL/mmol). The solvent was evaporated and the crude product was filtered through a short pad of silica gel.

Synthesis of (+)-(3a*S*,4*R*,5*R*,7a*S*,*S*$_S$)-5-*n*-Butyl-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-3a,4-diol, 14a. From sulfoxide **3a** (32 mg, 0.100 mmol), Me_3NO (28 mg, 0.250 mmol) and OsO_4 (65 μL, 52 mg (2.5 wt %), 0.005 mmol) following the general procedure (15 min), a 96:4 mixture of sulfoxide **14a** and sulfone **SI-39** was obtained. Purification by chromatography (20−50% EtOAc/hexane) afforded 1 mg (0.003 mmol, 3%) of sulfone **SI-39** as a colorless oil and sulfoxide **14a** (25 mg, 0.072 mmol, 72%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **14a**: R_f = 0.27 (100% EtOAc); mp 148−150 °C; $[\alpha]^{20}_D$ = +108.2 (c 0.65); ^{1}H NMR (300 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H, Me-*n*-Bu), 1.31−1.38 (m, 4 H, 2 CH_2-*n*-Bu), 1.42 (m, 1 H, *n*-Bu), 1.62 (m, 1 H, *n*-Bu), 2.13 (m, 1 H, H-5), 2.38 (s, 3 H, Me-*p*-Tol), 2.39 (m, 1 H, OH), 2.79 (s, 1 H, OH), 3.03 (m, 1 H, H-7a), 3.60 (d, J = 9.3 Hz, 1 H, H-3), 3.61 (dd, J = 8.8, 7.0 Hz, 1 H, H-1), 3.78 (ap t, J = 6.9 Hz, 1 H, H-4), 3.99 (d, J = 9.3 Hz, 1 H, H-3), 4.25 (t, J = 8.7 Hz, 1 H, H-1), 6.65 (dd, J = 4.6, 1.7 Hz, 1 H, H-7), 7.28 (d, J = 7.8 Hz, 2 H, *p*-Tol), 7.53 (d, J = 8.3 Hz, 2 H, *p*-Tol); DNOE between H-5/OH-4: 1.9%; between H-5/OH-3: 1.6%; between H-5/H-4: 2.1%; between H-5/H-*p*-Tol: 1.8%; between H-7a/H-1 (3.61 ppm): 4.6%; between H-7a/H-1 (4.25 ppm): 1.8%; between H-7a/H-7: 4.4%; between H-4/Me-*n*-Bu: 3.1%; between H-4/CH_2-*n*-Bu: 6.8%; between H-4/H-5: 3.9%; between H-4/CH_3-*p*-Tol: 4.5%; between H-3 (3.99 ppm)/H-3 (3.60 ppm): 19.0%; between H-1 (4.25 ppm)/H-7a: 5.7%; between H-1 (4.25 ppm)/H-7a: 5.7%; between H-1 (4.25 ppm)/H-1 (3.61 ppm): 20.7%; ^{13}C NMR (50 MHz) δ 13.9 (Me-*n*-Bu), 21.5 (Me-*p*-Tol), 22.9, 27.1, 27.9, 38.9 (C-5), 47.0 (C-7a), 70.4 (C-4), 72.2 (C-1), 75.4 (C-3), 79.1 (C-3a), 126.4 (C-7), 126.8 (2 C), 130.3 (2 C), 139.0, 142.9, 143.3; IR (KBr) 3436, 2959, 2873, 1637, 1454, 1350, 1277, 1082, 1033, 917, 808 cm^{-1}; MS (ES) m/z (%) 351 (100) [M + H]$^+$. Anal. Calcd for $C_{19}H_{26}O_4S$: C 65.11, H 7.48, S 9.15. Found: C 64.78, H 7.36, S 9.40.

Data for **SI-39**: R_f = 0.18 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = +43.4 (c 0.58); ^{1}H NMR (300 MHz) δ 0.83 (t, J = 7.1 Hz, 3 H, Me-*n*-Bu), 1.17−1.45 (m, 5 H, *n*-Bu), 1.78 (m, 1 H, *n*-Bu), 1.90 (d, J = 5.1 Hz, 1 H, OH), 2.42 (s, 3 H, Me-*p*-Tol), 2.62 (dt, J = 10.3, 3.4 Hz, 1 H, H-5), 2.88 (m, 1 H, H-7a), 3.01 (s, 1 H, OH), 3.63 (d, J = 10.2 Hz, 1 H, H-3), 3.76 (dd, J = 9.0, 2.9 Hz, 1 H, H-1), 3.91 (d, J = 10 Hz, 1 H, H-3), 3.98 (dd, J = 4.9, 3.4 Hz, 1 H, H-4), 4.15 (dd, J = 8.8, 7.3 Hz, 1 H, H-1), 6.93 (d, J = 4.6 Hz, 1 H, H-7), 7.31 (d, J = 8.5 Hz, 2 H, *p*-Tol), 7.72 (d, J = 8.5 Hz, 2 H, *p*-Tol); DNOE between H-5/H-4: 2.0%; between H-7a/H-1 (4.15 ppm): 4.2%; between H-7a/H-7: 3.4%; between H-3 (3.63 ppm)/H-3 (3.91 ppm): 13.9%; between H-1 (3.76 ppm)/H-1 (4.15 ppm): 17.4; between H-1 (3.76 ppm)/H-7: 2.2%; between H-3 (3.91 ppm)/H-3 (3.63 ppm): 73.2%; between H-4/H-3 (3.91 ppm): 5.5%; between H-1 (4.15 ppm)/H-7a: 3.2%; H-1 (4.15 ppm)/H-1 (3.76 ppm): 12.4%; ^{13}C NMR (50 MHz) δ 13.8 (Me-*n*-Bu), 21.6 (Me-*p*-Tol), 22.4, 29.2, 30.3, 42.5 (C-5), 47.5 (C-7a), 69.7 (C-4), 71.6 (C-1), 76.1 (C-3), 80.0 (C-3a), 128.0 (2 C), 129.9 (2 C), 136.4, 138.3, 141.3, 144.5; IR (film) 3435, 2962, 2925, 2862, 1642, 1597, 1261, 1147, 1088, 1020, 803, 671 cm^{-1}; MS (ES) m/z (%) 349 (100) [(M − 18) +1]$^+$. Anal. Calcd for $C_{19}H_{26}O_5S$: C 62.27, H 7.15, S 8.75. Found: C 62.53, H 7.29, S 8.54.

Synthesis of (−)-(3a*R*,4*S*,5*S*,7a*R*,*S*$_S$)-5-*n*-Butyl-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-3a,4-diol, 15. From sulfoxide **4a** (23 mg, 0.073 mmol), Me_3NO (20 mg, 0.180 mmol) and OsO_4 (51 μL, 41 mg (2.5 wt %), 0.004 mmol) following the general procedure (15 min), an 83:17 mixture of sulfoxide **15** and sulfone **SI-40** was obtained. Purification by chromatography (20−50% EtOAc/hexane) afforded sulfone **SI-40** (4 mg, 0.011 mmol, 15%) and sulfoxide **15** (16 mg, 0.046 mmol, 63%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **15**: R_f = 0.21 (100% EtOAc); mp 137−138 °C; $[\alpha]^{20}_D$ = −19.1 (c 0.71); ^{1}H NMR (300 MHz-COSY) δ 0.83 (t, J = 7.0 Hz, 3 H, Me-*n*-Bu), 1.18−1.32 (m, 4 H, 2 CH_2-*n*-Bu), 1.48−1.61 (m, 1 H, *n*-Bu), 1.73−1.83 (m, 1 H, *n*-Bu), 2.15 (br s, 1 H, OH), 2.39 (s, 3 H, Me-*p*-Tol), 2.52 (ap quint, J = 4.4 Hz, 1 H, H-5), 2.86 (m, 1 H, H-7a), 3.17 (br s, 1 H, OH), 3.62 (d, J = 9.8 Hz, 1 H, H-3), 3.70 (dd, J = 8.8, 4.4 Hz, 1 H, H-1), 3.84 (t, J = 4.9 Hz, 1 H, H-4), 3.98 (d, J = 9.8 Hz, 1 H, H-3), 4.17 (dd, J = 8.8, 7.8 Hz, 1 H, H-1), 6.37 (dd, J = 4.6, 1.0 Hz, 1 H, H-7), 7.30 (d, J = 8.5 Hz, 2 H, *p*-Tol), 7.46 (d, J = 8.3 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz-HMQC) δ 13.9 (Me-*n*-Bu), 21.4 (Me-*p*-Tol), 22.6, 28.9, 30.2, 41.0 (C-5), 47.6 (C-7a), 70.0 (C-4), 71.9 (C-1), 75.8 (C-3), 79.7 (C-3a), 125.2 (2 C), 130.0 (2 C), 133.8 (C-7), 138.7, 141.6, 145.6; IR (KBr) 3466, 2955, 2870, 1630, 1413, 1309, 1082, 1022, 1004, 928, 819, 705 cm^{-1}; MS (ES) m/z (%) 701 (100) [2M + H]$^+$, 351 [M + H]$^+$. Anal. Calcd for $C_{19}H_{26}O_4S$: C 65.11, H 7.48, S 9.15. Found: C 64.88, H 7.19, S 8.98.

Data for **SI-40** is identical to that described above for **SI-39** except for optical rotation: $[\alpha]^{20}_D$ = −56.4 (c 0.54).

Synthesis of (+)-(3a*R*,4*R*,5*R*,7a*S*,*S*$_S$)-5-Phenyl-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-3a,4-diol, 14b. From **3b** (45 mg, 0.13 mmol, 1.0 equiv), Me_3NO (37 mg, 0.33 mmol, 2.5 equiv) and OsO_4 (2.5% in *t*-butanol, 88 μL, 0.007 mmol, 0.05 equiv), following the general procedure (20 h), compound **14b** was obtained. Purification by chromatography (0−80% EtOAc/hexane) afforded diol **14b** (31 mg, 0.083 mmol, 64%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **14b**: R_f = 0.15 (EtOAc); mp 191−194 °C; $[\alpha]^{20}_D$ = +5.8 (c 1.01); ^{1}H NMR (400 MHz-COSY) δ 2.07 (d, J = 3.8 Hz, 1 H, OH), 2.36 (s, 3 H, Me-*p*-Tol), 2.75 (s, 1 H, OH), 3.06 (dt, J = 9.1, 2.2 Hz, 1 H, H-5), 3.17−3.23 (m, 1 H, H-7a), 3.61 (d, J = 9.1 Hz, 1 H, H-3), 3.66 (t, J = 8.6 Hz, 1 H, H-1), 3.84 (dd, J = 9.1, 3.8 Hz, 1 H, H-4), 3.96 (d, J = 9.1 Hz, 1 H, H-3), 4.34 (t, J = 9.1 Hz, 1 H, H-1), 6.78 (dd, J = 4.2, 2.4 Hz, 1 H, H-7), 6.94−6.96 (m, 2 H), 7.06−7.09 (m, 2 H), 7.15 (d, J = 8.4 Hz, 2 H), 7.28−7.31 (m, 3 H); ^{13}C NMR (100 MHz) δ 21.5, 46.0, 46.8, 72.2, 75.7, 75.8, 78.5, 126.2, 127.1 (2 C), 128.2, 128.8 (2 C), 129.9 (2 C), 130.1 (2 C), 136.2, 138.3, 142.7, 142.9; IR (KBr) 3412, 2922, 1638, 1493, 1452, 1320, 1082, 1041, 913, 811, 749, 702, 646, 515 cm^{-1}; MS (ES) m/z (%) 393 [M + Na]$^+$, 371 [M + H]$^+$. Anal. Calcd for $C_{21}H_{22}O_4S$: C 68.08, H 5.99, S 8.66. Found: C 68.13, H 6.09, S 8.93.

Synthesis of (−)-(3a*R*,4*R*,5*R*,6*R*,7*R*,7a*R*)-6,7-Epoxy-5-phenyl-6-tosyl-1,3,3a,4,5,6,7,7a-octahydroisobenzofuran-3a,4-diol, 17. In a two-necked round-bottomed flask, using polyethylene stoppers, anhydrous THF (10 mL/mmol) was charged and cooled to 0 °C. Then *n*-BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol, 6.0 equiv) and HOO-*t*-Bu (80 wt % in *t*-BuOO-*t*-Bu, 54 μL, 0.54 mmol, 6.5 equiv) were added. The mixture was stirred for 30 min and cooled to −60 °C. Then a solution of **16** (32 mg, 0.083 mmol, 1.0 equiv) in THF (10 mL/mmol) was slowly added. The mixture was allowed to reach room temperature and stirred until starting material disappearance (TLC, 2 days). Then the reaction mixture was quenched with a 1 M solution of $Na_2S_2O_4$, extracted with EtOAc (3 times), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography (20−100% EtOAc/CH_2Cl_2) afforded **17** (18 mg, 0.045 mmol, 55%) as a white solid that was recrystallized from Et_2O/hexane.

Data for **17**: R_f = 0.22 (40% EtOAc/hexane); mp 227−229 °C; $[\alpha]^{20}_D$ = −46.4 (*c* 0.11); ^{1}H NMR (400 MHz-COSY) δ 2.40 (s, 3 H, Me-*p*-Tol), 2.62 (d, *J* = 8.6 Hz, 1 H, OH), 2.91 (qd, *J* = 4.6, 1.2 Hz, 1 H, H-7a), 3.16 (s, 1 H, OH), 3.41 (d, *J* = 9.8 Hz, 1 H, H-3), 3.50 (d, *J* = 9.8 Hz, 1 H, H-3), 3.60 (d, *J* = 6.0 Hz, 1 H, H-5), 3.85 (dd, *J* = 8.4, 5.8 Hz, 1 H, H-4), 4.06 (s, 1 H, H-7), 4.08 (dd, *J* = 9.5, 4.6 Hz, 1 H, H-1), 4.24 (dd, *J* = 9.5, 7.9 Hz, 1 H, H-1), 7.17 (d, *J* = 8.5 Hz, 2 H), 7.18−7.31 (m, 5 H), 7.32 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz) δ 21.7, 45.8, 47.1, 59.0, 69.9, 74.1, 74.6, 76.7, 78.1, 128.1 (2 C), 128.2 (2 C), 129.0 (2 C), 129.6 (2 C), 130.6, 132.9, 133.2, 145.4; IR (KBr) 3435, 2923, 2851, 1631, 1321, 1148, 1085, 934, 809, 702, 536 cm^{-1}; MS (ES) *m*/*z* (%) 425 $[M + Na]^+$. Anal. Calcd for $C_{21}H_{22}O_6S$: C 62.67, H 5.51, S 7.97. Found: C 62.89, H 5.89, S 8.05.

Synthesis of (−)-(3a*S*,6*R*,7*R*,7a*R*)-7,7a-Dihydroxy-6-phenylhexahydroisobenzofuran-5-(1*H*)-one, 18. A two-necked round-bottomed flask equipped with a reflux condenser was charged with Mg(0) (39 mg, 1.6 mmol, 1.0 equiv) and Et_2O (5 mL/mmol). Then 1,2-dibromoethane (0.16 mL, 1.9 mmol, 1.2 equiv) was added dropwise. The mixture was stirred at room temperature until consumption of Mg(0), affording a $MgBr_2$ solution that was used immediately.

To a cold solution (0 °C) of **17** (10 mg, 0.025 mmol) in a 50:50 mixture of Et_2O/CH_2Cl_2 (0.5 mL) and under an argon atmosphere was slowly added 0.63 mL of a freshly prepared $MgBr_2$ solution (0.2 M, 0.125 mmol, 5.0 equiv). The mixture was allowed to reach room temperature and stirred until starting material disappearance (TLC, 20 h). The reaction was quenched with a 5% solution of $NaHCO_3$ (1 mL) and a 1 M solution of $Na_2S_2O_4$ (1 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 times), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by chromatography (30−100% EtOAc/hexane) afforded **19** (5 mg, 0.017 mmol, 69%) as a colorless oil and **18** (2 mg, 0.008 mmol, 30%) as a white solid.

Partial data for **19** (from a mixture of epimers in C-4): R_{f1} = 0.44; R_{f2} = 0.38 (EtOAc); ^{1}H NMR (300 MHz) δ 4.96 (d, *J* = 6.4 Hz, 1 H, H-4), 5.04 (d, *J* = 5.1 Hz, 1 H, H-4), 7.17−7.44 (m); MS (ES) *m*/*z* (%) 351 $[M(Br^{81}) + Na]^+$, 349 $[M(Br^{79}) + Na]^+$.

To a solution of **19** (10 mg, 0.031 mmol, 1.0 equiv) in a 9:1 mixture of THF/H_2O (30 mL/mmol) was added amalgamated Al (5 mg, 0.186 mmol, 6.0 equiv) (Al was introduced for a few seconds in a 10% solution of $HgCl_2$, then in EtOH and finally in Et_2O). The reaction was stirred at room temperature until starting material disappearance (TLC, 20 h). Then the solution was filtered through a pad of Celite and the solvent was removed under reduced pressure. The crude product was purified by chromatography (0−100% EtOAc/CH_2Cl_2) to afford **18** (4 mg, 0.016 mmol, 53%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **18**: R_f = 0.38 (EtOAc); mp 138−142 °C; $[\alpha]^{20}_D$ = −59.3 (*c* 0.26); ^{1}H NMR (400 MHz-COSY) δ 2.40 (dd, *J* = 17.4, 10.7 Hz, 1 H, H-4), 2.75 (d, *J* = 10.7 Hz, 1 H, H-4), 2.72−2.80 (m, 1 H, H-3a), 3.56 (dd, *J* = 9.2, 6.6 Hz, 1 H, H-3), 3.77 (d, *J* = 9.1 Hz, 1 H, H-1), 3.82 (d, *J* = 11.6 Hz, 1 H, H-6), 4.06 (d, *J* = 9.1 Hz, 1 H, H-1), 4.19 (d, *J* = 11.6 Hz, 1 H, H-7), 4.21 (dd, *J* = 9.1, 7.7 Hz, 1 H, H-3), 7.14−7.18 (m, 2 H), 7.30−7.42 (m, 3 H); ^{13}C NMR (100 MHz) δ 40.0, 42.7, 58.5, 72.6, 73.6, 77.6, 78.9, 128.2, 129.2 (2 C), 129.5 (2 C), 134.7, 207.0 (C═O); IR (KBr) 3440, 2924, 2851, 1713, 1630, 1071, 1029 cm^{-1}; MS (ES) *m*/*z* (%) 271 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{16}O_4$: C 67.73, H 6.50. Found: C 67.92, H 6.76.

Sulfoxide-Directed Lactonization of Cycloadducts. To a solution of **3b** (28 mg, 0.083 mmol, 1.0 equiv) in anhydrous THF (20 mL/mmol) was added Zn−Cu (84 mg, 1.3 mmol, 20 equiv), and the mixture was cooled to −60 °C. Then, a solution of freshly distilled trichloroacetyl chloride (36 μL, 0.325 mmol, 5.0 equiv) in anhydrous THF (30 mL/mmol) was added dropwise. The reaction mixture was stirred and allowed to warm up slowly. After 2 h (−30 °C), the reaction mixture was filtered through a pad of Celite and poured into a saturated solution of $NaHCO_3$. The biphasic mixture was stirred for 30 min and then extracted with Et_2O (3 times), washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (10−30% EtOAc/hexane) to afford a 65:35 mixture of two diastereomeric monochlorolactones (22 mg, 0.053 mmol, 64%) and 10 mg (0.029 mmol, 35%) of starting material. A second chromatography (10−30% EtOAc/hexane) afforded 14 mg (0.047 mmol) of **20a** and 7 mg (0.024 mmol) of **20b**.

Data for major lactone **20a**: R_f = 0.42 (30% EtOAc/hexane); $[\alpha]^{20}_D$ = +11.1 (*c* 0.52); ^{1}H NMR (400 MHz) δ 2.30 (s, 3 H, Me-*p*Tol), 2.56 (dd, *J* = 9.6, 5.3 Hz, 1 H, H-8b), 2.83−2.90 (m, 1 H, H-8a), 3.47 (dd, *J* = 9.6, 8.3 Hz, 1 H, H-8), 3.85 (m, 1 H, H-4), 4.27 (t, *J* = 8.2 Hz, 1 H, H-8), 4.35 (d, *J* = 9.6 Hz, 1 H, H-1), 4.46−4.57 (m, 2 H, H-6), 6.03−6.05 (m, 1 H, H-5), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.35−7.42 (m, 5 H); ^{13}C NMR (100 MHz) δ 21.2, 44.7, 48.6, 50.9, 57.5, 69.4, 72.5, 99.5, 117.5, 124.4, 128.1, 128.2 (2 C), 130.2 (2 C), 130.4 (2 C), 136.2, 137.0 (2 C), 140.6, 142.1, 169.0 (C═O); IR (film) 3033, 2925, 2856, 1791, 1688, 1597, 1492, 1454, 1265, 1188, 1105, 1038, 944, 813, 758, 737, 701, 612, 500 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{22}ClO_3SNa$ $[M + Na]^+$ 435.0794, found 435.0793 $[M + H]^+$.

Data for minor lactone **20b**: R_f = 0.33 (30% EtOAc/hexane); $[\alpha]^{20}_D$ = −281.1 (*c* 0.91); ^{1}H NMR (300 MHz, C_6D_6) δ 1.98 (s, 3 H, Me-*p*Tol), 2.43 (t, *J* = 11.2 Hz, 1 H, H-8b), 2.73−2.83 (m, 1 H, H-8a), 3.33 (dd, *J* = 10.2, 8.3 Hz, 1 H, H-8), 4.06−4.10 (m, 2 H, H-4 and H-6), 4.19 (t, *J* = 7.9 Hz, 1 H, H-8), 4.28 (d, *J* = 11.8 Hz, 1 H, H-1), 4.34−4.38 (m, 1 H, H-6), 5.14−5.15 (m, 1 H, H-5), 6.85−6.89 (m, 4 H), 6.92−6.99 (m, 3 H), 7.53 (d, *J* = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.0, 41.9, 49.0, 51.1, 55.0, 68.9, 71.5, 94.8, 117.6, 124.9, 127.8, 128.1 (2 C), 130.0 (2 C), 130.4 (2 C), 135.9, 137.4 (2 C), 140.5, 143.5, 169.6 (C═O); IR (film) 3027, 2925, 2856, 1809, 1596, 1492, 1452, 1400, 1364, 1302, 1264, 1236, 1211, 1172, 1129, 1048, 938, 871, 812, 733, 700, 594 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{22}ClO_3S$ $[M + H]^+$ 413.0978, found 413.0976 $[M + H]^+$.

Dechlorination of α-Chlorolactones 20. To a solution of the major lactone **20a** (15 mg, 0.036 mmol, 1.0 equiv) in AcOH (10 mL/mmol) was added Zn powder (23 mg, 0.36 mmol, 10 equiv). The reaction mixture was stirred at ambient temperature until starting material disappearance (8 h) (TLC). Then it was filtered by Celite, treated with saturated solution of $NaHCO_3$ and extracted with EtOAC (3 times). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude was then purified by flash chromatography (20−50% EtOAc/hexane) to afford **21** (10 mg, 0.026 mmol, 73%) as a colorless oil.

When the minor lactone **20b** (14 mg, 0.034 mmol, 1 equiv) was treated with Zn/AcOH under the same reaction conditions, it

was necessary to heat the reaction at 80 °C. After 8 h lactone **21** was obtained (3 mg, 0.0079 mmol, 23%) along with recovered starting material 5 mg (0.012 mmol, 35%).

Data for **21**: R_f = 0.29 (50% EtOAc/hexane); $[\alpha]^{20}_D$ = −110.5 (*c* 0.62); ^{1}H NMR (500 MHz-COSY) δ 1.46 (dd, 1 H, *J* = 18.3, 10.6 Hz, 1 H, H-1), 1.94 (dd, *J* = 18.3, 2.9 Hz, 1 H, H-1), 2.30 (s, 3 H, Me-*p*Tol), 2.46, (ddd, *J* = 13.2, 10.2, 2.9 Hz, 1 H, H-8b), 2.55−2.61 (m, 1 H, H-8a), 3.51 (dd, 1 H, *J* = 8.9, 6.3 Hz, H-8), 3.86−3.88 (m, 1 H, H-4), 4.16 (dd, 1 H, *J* = 8.8, 7.5 Hz, H-8), 4.42−4.53 (m, 2 H, H-6), 6.06−6.08 (m, 1 H, H-5), 7.16 (d, 2 H, *J* = 7.8 Hz), 7.28 (d, 2 H, *J* = 8.0 Hz), 7.34−7.42 (m, 3 H), 7.49−7.51 (m, 2 H); ^{13}C NMR (125 MHz) δ 21.2, 29.7, 34.8, 45.8, 46.2, 52.9, 70.0, 72.5, 102.1, 117.3, 125.6, 127.8, 128.2 (2 C), 130.1 (2 C), 130.3 (2 C), 137.1 (2 C), 140.2, 144.4, 175.1 (C=O); IR (film) 2920, 2850, 1786, 1597, 1493, 1413, 1189, 1094, 1032, 933, 814, 736, 700, 606 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{23}O_3S$ $[M + H]^+$ 379.1360, found 379.1359 $[M + H]^+$.

General Procedure for Oxidation of Sulfoxides with MMPP. To a cold (0 °C) solution of the sulfoxide in MeOH (10 mL/mmol) was added 1.5 equiv of magnesium monoperoxyphthalate hexahydrate (MMPP). The mixture was allowed to warm to rt, monitored by TLC until completion and then quenched with a saturated solution of $NaHCO_3$ (4 mL/mmol). After removal of MeOH under reduced pressure, the mixture was diluted with EtOAc (5 mL/mmol), the layers were separated and the aqueous phase was extracted with EtOAc (3 times, 4 mL/mmol). The combined organic layers were washed with a saturated solution of NaCl (1 mL/mmol), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by chromatography on silica gel using the appropriate mixture of solvents.

Synthesis of (+)-(3a*R*,4*R*,5*R*,7a*S*)-5-Phenyl-6-tosyl-1,3,3a,4,5,7a-hexahydroisobenzofuran-3a,4-diol, 16. From **14b** (31 mg, 0.082 mmol) and MMPP (61 mg, 0.123 mmol) following the general procedure (20 h), compound **16** was obtained. Purification by chromatography (30−100% EtOAc/hexane) afforded sulfone **16** (24 mg, 0.062 mmol, 76%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **16**: R_f = 0.40 (EtOAc); mp 200−207 °C; $[\alpha]^{20}_D$ = +35.7 (*c* 0.30); ^{1}H NMR (300 MHz, CD_3OD-COSY) δ 2.35 (s, 3 H, Me-*p*-Tol), 3.13 (m, 1 H, H-7a), 3.39 (d, *J* = 9.3 Hz, 1 H, H-3), 3.68 (d, *J* = 9.3 Hz, 1 H, H-3), 3.79 (dd, *J* = 8.8, 6.3 Hz, 1 H, H-1), 3.86 (d, *J* = 6.6 Hz, 1 H, H-5), 3.99 (dm, *J* = 6.6 Hz, 1 H, H-4), 4.26 (t, *J* = 8.5 Hz, 1 H, H-1), 6.92−7.12 (m, 7 H), 7.22−7.29 (m, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 21.4, 48.8, 49.2, 72.4, 75.6, 76.1, 79.8, 127.8, 128.8 (2 C), 128.9 (2 C), 130.5 (2 C), 130.8 (2 C), 138.7, 139.1, 140.5, 142.4, 145.1; IR (KBr) 3448, 2920, 2868, 1632, 1452, 1298, 1146, 1059, 918, 810, 700, 678, 557 cm^{-1}; MS (ES) *m*/*z* (%) 795 $[2M + Na]^+$, 409 $[M + Na]^+$, 387 $[M + H]^+$. Anal. Calcd for $C_{21}H_{22}O_5S$: C 65.27, H 5.74, S 8.30. Found: C 65.36, H 5.99, S 8.21.

Synthesis of (3a*R,6*R**)-6-*n*-Butyl-5-(*p*-tolylsulfonyl)-1,3,3a,6-tetrahydroisobenzofuran, 5a.** From a 67:33 mixture of **3a** and **4a** (13 mg, 0.041 mmol) and MMPP (38 mg (80%), 0.061 mmol) following the general procedure (3 h), a scalemic sulfone **5a** was obtained. Purification by chromatography (10−30% EtOAc/hexane) gave **5a** (13 mg, 0.039 mmol, 95%) as a colorless oil.

Data for **5a**: R_f = 0.20 (30% EtOAc/hexane); ^{1}H NMR (300 MHz) δ 0.72 (t, *J* = 7.0 Hz, 3 H, Me-*n*-Bu), 0.80−1.18 (m, 4 H, 2 CH_2-*n*- Bu), 1.49−1.79 (m, 2 H, CH_2-*n*-Bu), 2.42 (s, 3 H, Me-*p*-Tol), 3.27 (m, 1 H, H-6), 3.32−3.40 (m, 2 H, H-3a, 1 H-3), 4.22−4.27 (m, 2 H, 1 H-3, 1 H-1), 4.35 (m, 1 H, H-1), 5.38 (br s, 1 H, H-7), 7.09 (t, *J* = 2.2 Hz, 1 H, H-4), 7.31 (d, *J* = 7.8 Hz, 2 H, *p*-Tol), 7.73 (d, *J* = 8.3 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz) δ 13.9 (Me-*n*-Bu), 21.5 (Me-*p*-Tol), 22.6, 27.0, 32.2, 36.2, 41.3, 68.8, 70.1, 120.1, 128.0 (2 C), 129.7 (2 C), 129.9, 135.1, 135.6, 137.3, 144.3; IR (film) 2956, 2928, 2870, 1766, 1597, 1494, 1464, 1402, 1380, 1302, 1151, 1086, 1047, 1017, 902, 845, 814, 709 cm^{-1}; MS (ES) *m*/*z* (%) 331 (100) $[(M - 2) + 1]^+$. Anal. Calcd for $C_{19}H_{24}O_3S$: C 68.64, H 7.28, S 9.64. Found: C 68.76, H 7.34, S 9.87.

Synthesis of (3a*R,6*S**)-6-Phenyl-5-(*p*-tolylsulfonyl)-1,3,3a,6-tetrahydroisobenzofuran, 5b.** From a 75:25 mixture of **3b** and **4b** (19 mg, 0.056 mmol) and MMPP (52 mg (80%), 0.084 mmol) following the general procedure (4 h), scalemic sulfone **5b** was obtained. Purification by chromatography (10−30% EtOAc/hexane) afforded **5b** (16 mg, 0.045 mmol, 80%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **5b**: R_f = 0.41 (50% EtOAc/hexane); mp 145−147 °C; ^{1}H NMR (300 MHz) δ 2.28 (s, 3 H, Me-*p*-Tol), 3.41−3.57 (m, 2 H, H-3a, 1 H-3), 4.24 (d, *J* = 11.5 Hz, 1 H, 1 H-1), 4.36−4.43 (m, 2 H, 1 H-3, 1 H-1), 4.50 (m, 1 H, H-6), 5.38 (t, *J* = 1.9 Hz, 1 H, H-7), 6.83−7.14 (m, 9 H), 7.34 (t, *J* = 2.4 Hz, 1 H, H-4); ^{13}C NMR (75 MHz) δ 21.4 (Me-*p*-Tol), 41.2, 43.3, 68.8, 70.8, 120.1, 126.9, 127.3 (2 C), 128.1 (2 C), 129.0 (2 C), 129.5 (2 C), 134.2, 134.6, 137.6, 139.9, 142.9, 144.6; IR (KBr) 3060, 3027, 2857, 1626, 1492, 1453, 1310, 1153, 1076, 1043, 1016, 812, 766, 700 cm^{-1}; MS (ES) *m*/*z* (%) 370 (100) $[M + NH_4]^+$, 353 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_3S$: C 71.56, H 5.72, S 9.10. Found: C 71.32, H 5.34, S 9.07.

Synthesis of (3a*R,6*S**)-6-Phenyl-2,5-bis(*p*-tolylsulfonyl)-2,3,3a,6-tetrahydroisoindole, 5n.** From a 58:42 mixture of **3n** and **4n** (10 mg, 0.020 mmol) and MMPP (18 mg (80%), 0.03 mmol) following the general procedure scalemic sulfone **5n** was obtained. Purification by chromatography (20−30% EtOAc/hexane) afforded **5n** (8 mg, 0.016 mmol, 79%) as a white solid that was recrystallized from EtOAc/hexane.

Data for **5n**: R_f = 0.43 (50% EtOAc/hexane); mp 183−185 °C; ^{1}H NMR (300 MHz) δ 2.28 (s, 3 H, Me-*p*-Tol), 2.42 (s, 3 H, Me-*p*-Tol), 2.25 (dd, *J* = 11.2, 9.3 Hz, 1 H, H-3), 3.23 (m, 1 H, H-3a), 3.80 (dd, *J* = 13.2, 1.2 Hz, 1 H, H-1), 3.95 (m, 1 H, H-1), 4.00 (dd, *J* = 9.0, 8.1 Hz, 1 H, H-3), 4.39 (dm, *J* = 13.2 Hz, 1 H, H-6), 5.35 (t, *J* = 1.7 Hz, 1 H, H-7), 6.69 (m, 2 H), 6.88−6.94 (m, 4 H), 6.98−7.06 (m, 3 H), 7.21 (dd, *J* = 3.3, 1.8 Hz, 1 H, H-4), 7.32 (m, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (50 MHz) δ 21.4 (Me-*p*-Tol), 21.6 (Me-*p*-Tol), 39.5 (C-3a), 42.8 (C-6), 50.2 (C-1), 51.8 (C-3), 122.2, 127.0, 127.3 (2 C), 127.4 (2 C), 128.2 (2 C), 129.1 (2 C), 129.3 (2 C), 129.9 (2 C), 130.7, 134.1 (2 C), 137.2, 139.2, 143.2, 143.9, 144.6; IR (KBr) 3054, 2923, 2862, 1629, 1599, 1492, 1454, 1349, 1303, 1157, 1092, 1042, 984, 809, 763, 702, 683, 667 cm^{-1}; MS (ES) *m*/*z* (%) 506 (100) $[M + H]^+$. Anal. Calcd for $C_{28}H_{27}NO_4S_2$: C 66.51, H 5.38, N 2.77, S 12.68. Found: C 66.80, H 5.35, N 2.39, S 12.57.

General Procedure for the Synthesis of 2-Methoxy-2-phenyl Acetates. To a solution of the corresponding alcohol in CH_2Cl_2 (10 mL/mmol of sulfoxide), at 0 °C, were added 1 equiv of 2-methoxy-2-phenylacetic acid, 1.2 equiv of dicyclohexylcarbodiimide and 0.4 equiv of dimethylaminopyridine. The mixture was allowed to warm to room temperature and monitored by TLC until starting material disappearance (1 h). The reaction mixture was filtered to remove dicyclohexylurea and the ester was purified by chromatography using the appropriate mixture of solvents.

Synthesis of (+)-(3a*S*,4*R*,5*R*,7a*S*,*S*$_S$)-5-*n*-Butyl-3a-hydroxy-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-yl-(*S*)-2-methoxy-2-phenyl Acetate, 23, and (3a*S*,4*R*,5*R*,7a*S*,*S*$_S$)-5-*n*-Butyl-3a-hydroxy-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-yl-(*R*)-2-methoxy-2-phenyl Acetate, 22. From diol **14a** (10 mg, 0.028 mmol), (±)-2-methoxy-2-phenylacetic acid (4 mg, 0.028 mmol), DCC (7 mg, 0.034 mmol) and DMAP (1 crystal), following the general procedure, a 50:50 mixture of **22** and **23** was obtained. Purification by chromatography afforded 12 mg (0.023 mmol, 83%) of **22** and **23**.

In an identical experiment with (+)-2-methoxy-2-phenylacetic acid, **23** (14 mg, 0.027 mmol, 96%) was obtained as a white solid that was recrystallized from EtOAc/hexane. The ^{1}H NMR of the crude product did not show any signal of compound **22** and thus the optical purity of **14a** was established.

Data for **23**: R_f = 0.33 (100% EtOAc); mp 60−61 °C; $[\alpha]^{20}_D$ = +51.0 (*c* 1.23); ^{1}H NMR (300 MHz) δ 0.79 (t, *J* = 7.3 Hz, 3 H, Me-*n*-Bu), 0.99−1.27 (m, 6 H, *n*-Bu), 2.21 (m, 2 H, H-5, OH), 2.39 (s, 3 H, Me-*p*-Tol), 3.03 (m, 1 H, H-7a), 3.32 (s, 3 H, OMe), 3.48 (d, *J* = 9.3 Hz, 1 H, H-3), 3.62 (d, *J* = 9.5 Hz, 1 H, H-3), 3.64 (t, *J* = 8.1 Hz, 1 H, H-1), 4.24 (t, *J* = 8.7 Hz, 1 H, H-1), 4.70 (s, 1 H, H_α), 5.21 (d, *J* = 7.8 Hz, 1 H, H-4), 6.66 (dd, *J* = 4.4, 1.9 Hz, 1 H, H-7), 7.26 (d, *J* = 8.1 Hz, 2 H, *p*-Tol), 7.34 (m, 5 H, Ph), 7.48 (d, *J* = 8.1 Hz, 2 H, *p*-Tol); ^{13}C NMR (50 MHz) δ 13.7 (Me-*n*-Bu), 21.5 (Me-*p*-Tol), 22.6, 26.5, 27.1, 37.0 (C-5), 47.7 (C-7a), 57.4 (OMe), 71.9 (C-4), 73.4 (C-1), 75.2 (C-3), 78.8 (C-3a), 82.8 (C_α), 125.8, 126.7 (2 C), 126.8 (2 C), 128.8 (2 C), 129.1, 130.3 (2 C), 135.8, 139.3, 142.8, 143.2, 170.0; IR (KBr) 3436, 2956, 2930, 2868, 1750, 1638, 1456, 1174, 1108, 1039, 811, 733, 698 cm^{-1}; MS (ES) *m*/*z* (%) 499 (100) $[M + H]^+$. Anal. Calcd for $C_{28}H_{34}O_6S$: C 67.44, H 6.87, S 6.43. Found: C 67.57, H 7.02, S 6.70.

Data for **22** (from a mixture of **22** and **23**): R_f = 0.27 (100% EtOAc); ^{1}H NMR (300 MHz) δ 0.85 (t, *J* = 7.3 Hz, 3 H, Me-*n*-Bu), 2.10−2.24 (m, 2 H, H-5, OH), 2.40 (s, 3 H, Me-*p*-Tol), 2.75 (m, 1 H, H-7a), 3.30 (s, 3 H, OMe), 3.52 (d, *J* = 9.8 Hz, 1 H, H-3), 3.62 (m, 2 H, 1 H-1, H-3), 4.10 (dd, *J* = 8.7, 7.7 Hz, 1 H, H-1), 4.48 (s, 1 H, H_α), 5.11 (d, *J* = 5.6 Hz, 1 H, H-4), 6.62 (dd, *J* = 4.4, 1.5 Hz, 1 H, H-7), 7.30−7.36 (m, 7 H), 7.52 (d, *J* = 8.1 Hz, 2 H).

Synthesis of (+)-(3a*R*,4*S*,5*S*,7a*R*,*S*$_S$)-5-*n*-Butyl-3a-hydroxy-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-yl-(*S*)-2-methoxy-2-phenyl Acetate, 25, and (3a*R*,4*S*,5*S*,7a*R*,*S*$_S$)-5-*n*-Butyl-3a-hydroxy-6-(*p*-tolylsulfinyl)-1,3,3a,4,5,7a-hexahydroisobenzofuran-4-yl-(*R*)-2-methoxy-2-phenyl Acetate, 24. From diol **15** (8 mg, 0.023 mmol), (±)-2-methoxy-2-phenylacetic acid (4 mg, 0.023 mmol), DCC (7 mg, 0.034 mmol) and DMAP (1 crystal), following the general procedure, a 50:50 mixture of **24** and **25** was obtained. Purification by chromatography afforded **25** (5 mg, 0.020 mmol, 45%) and **24** (5 mg, 0.020 mmol, 45%) as white solids.

In an identical experiment with (+)-2-methoxy-2-phenylacetic acid **25** was obtained (10 mg, 0.020 mmol, 90%) as a white solid that was recrystallized from EtOAc/hexane. The ^{1}H NMR of the crude product showed **25** as a single diastereomer.

Data for **25**: R_f = 0.30 (100% EtOAc); mp 57 °C; $[\alpha]^{20}_D$ = +49.2 (*c* 0.65); ^{1}H NMR (300 MHz) δ 0.82 (t, *J* = 7.2 Hz, 3 H, Me-*n*-Bu), 1.14−1.47 (m, 5 H, *n*-Bu), 1.74 (m, 1 H), 2.41 (s, 3 H, Me-*p*-Tol), 2.49−2.57 (m, 2 H, H-5, H-7a), 3.29 (s, 3 H, OMe), 3.43 (d, *J* = 10.2 Hz, 1 H, H-3), 3.76 (dd, *J* = 8.8, 2.7 Hz, 1 H, H-1), 3.78 (d, *J* = 10.7 Hz, 1 H, H-3), 4.01 (dd, *J* = 8.7, 6.7 Hz, 1 H, H-1), 4.31 (s, 1 H, H_α), 5.11 (d, *J* = 3.2 Hz, 1 H, H-4), 6.44 (d, *J* = 4.1 Hz, 1 H, H-7), 7.27−7.39 (m, 7 H), 7.47 (d, *J* = 8.3 Hz, 2 H, *p*-Tol); ^{13}C NMR (75 MHz) δ 13.8 (Me-*n*-Bu), 21.4 (Me-*p*-Tol), 22.2, 28.8, 31.1, 39.1 (C-5), 48.3 (C-7a), 57.2 (OMe), 71.8 (C-4), 73.0 (C-1), 76.0 (C-3), 79.3 (C-3a), 81.7 (C_α), 125.0 (2 C), 126.9 (2 C), 129.1 (2 C), 129.4, 129.9 (2 C), 133.2, 136.3, 139.5, 141.4, 145.5, 169.1 (CO); IR (KBr) 3434, 2959, 2926, 2870, 1749, 1631, 1493, 1455, 1261, 1172, 1102, 1082, 1029, 808, 729, 697 cm^{-1}; MS (ES) *m*/*z* (%) 499 (100) $[M + H]^+$. Anal. Calcd for $C_{28}H_{34}O_6S$: C 67.44, H 6.87, S 6.43. Found: C 67.76, H 6.96, S 6.62.

Data for **24**: R_f = 0.25 (100% EtOAc); ^{1}H NMR (300 MHz) δ 0.73 (t, *J* = 7.1 Hz, 3 H, Me-*n*-Bu), 1.00−1.36 (m, 6 H), 2.24 (br s, 1 H, OH), 2.40 (s, 3 H, Me-*p*-Tol), 2.50 (m, 1 H, H-5), 2.88 (dtd, *J* = 7.3, 4.1, 1.5 Hz, 1 H, H-7a), 3.34 (s, 3 H, OMe), 3.57 (d, *J* = 9.8 Hz, 1 H, H-3), 3.76 (dd, *J* = 8.8, 4.4 Hz, 1 H, H-1), 3.82 (d, *J* = 9.8 Hz, 1 H, H-3), 4.17 (dd, *J* = 8.6, 7.4 Hz, 1 H, H-1), 4.66 (s, 1 H, H_α), 5.17 (d, *J* = 4.4 Hz, 1 H, H-4), 6.43 (dd, *J* = 4.1, 1.2 Hz, 1 H, H-7), 7.27 (d, *J* = 8.1 Hz, 2 H, *p*-Tol), 7.34 (m, 5 H), 7.42 (d, *J* = 8.3 Hz, 2 H, *p*-Tol). Anal. Calcd for $C_{28}H_{34}O_6S$: C 67.44, H 6.87, S 6.43. Found: C 67.17, H 6.95, S 6.28.

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Supporting Information Available: Experimental details and spectral data (^{1}H NMR and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.