Stereoselective Synthesis of Heterocyclic Cage Compounds by Domino Conjugate Additions**

M. Carmen Carreño,* Carmen García Luzón, and María Ribagorda[a]

Dedicated to the late Professor Jesús H. Rodríguez Ramos

Abstract: Heterocyclic cage compounds have been stereoselectively synthesized from enantiopure [(S)*R*]-[(*p*-tolylsulfinyl)methyl]-*p*-quinols or their amine analogues and 2-(trimethylsilyloxy)furan in the presence of Bu_4NF. The method is particularly valuable not only because of the stereochemical control but also because the reactions occur in an experimentally simple one-pot procedure through a domino sequence of three consecutive conjugate additions. The intermediate 1,4-adducts could be isolated when the reaction was carried out in the presence of $BF_3 \cdot OEt_2$.

Keywords: 4-aminocyclohexa-2,5-dienones · cage compounds · domino reactions · heterocycles · *p*-quinols · sulfoxides

Introduction

Domino reactions leading to the stereoselective formation of carbon–carbon and carbon–heteroatom bonds have been the focus of intense studies.[1, 2] This interest stems from the possibility of rapid and economic preparation of structurally complex molecules from simple starting materials. The sequential formation of increasing number of bonds is favored when dense functionalization is present in such materials. For instance, 1,4-dien-3-one derivatives have been efficiently used to synthesize polycyclic systems through domino sequences including [3+2] cycloadditions with allylsilanes[3, 4] or successive Michael additions.[4b] Alkoxy substituted quinones and quinoneimines[5] reacted with styrenes in the presence of Lewis acids to form bridged compounds through domino cycloadditions that take advantage of the dienone fragment.

The 2,5-cyclohexadienone system present in *p*-quinols is a potential double Michael acceptor that has not been exploited in domino reactions. Enantiopure [(S)*R*]-[(*p*-tolylsulfinyl)-methyl]-*p*-quinols, which can be easily prepared by a method described by our laboratory,[6, 7] show the dienone fragment, as well as a sulfoxide, providing optical activity to the system, which bears a prochiral cyclohexadienone moiety. Such *p*-quinols have shown an excellent ability to direct the approach of dienes in Diels–Alder reactions[6] or organoaluminum derivatives in conjugate additions[7] by the face containing the OH. The efficiency of the hydroxy group in directing the face selectivity of 1,4-conjugate additions has also been pointed out in reactions of achiral *p*-quinol derivatives.[8] A logical extension of our work was to achieve consecutive diastereoselective conjugate additions to the dienone system in a single step. The potential usefulness of the sequential 1,4-adducts as building blocks for chiral targets prompted us to investigate such a process. We reasoned that the use of a nucleophile such as 2-(trimethylsilyloxy)furan,[9] which gives rise to a butenolide fragment on reaction with electrophiles[10] and can later act as a Michael acceptor,[11] could facilitate further transformation of the initial 1,4-adducts.

In this paper we report the achievement of a highly stereoselective synthesis of various tetracyclic cage compounds[12] bearing two heterocyclic rings through the reaction between [(S)*R*]-4-amino or 4-hydroxy-4-[(*p*-tolylsulfinyl)-methyl]cyclohexa-2,5-dienone derivatives and 2-(trimethylsilyloxy)furan. This combination provides a short and simple access to optically pure heterotetracyclic cage compounds not accessible by other methods through a one-pot, domino, triple conjugate addition process.

Results and Discussion

Enantiopure 4-amino-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienone [(S)*R*]-**7**[13] and the 3-methyl-substituted analogues **8** were easily accessible in high *ee* (>98%)[14a] by addition of α-lithiocarbanion derived from [(S)*R*]-methyl *p*-tolylsulfoxide[15] to quinoneimine monoacetals **1** and **2**[16] (Scheme 1). From the crude reaction mixture, hydrolysis of the acetal groups of **3** and **4** was effected with an aqueous

[a] Prof. M. C. Carreño, C. G. Luzón, M. Ribagorda
Departamento de Química Orgánica (C-I), Universidad Autónoma Cantoblanco, 28049 Madrid (Spain)
Fax: (+34) 91-397-3966
E-mail: carmen.carrenno@uam.es

[**] Supporting information for this article is available from the author.

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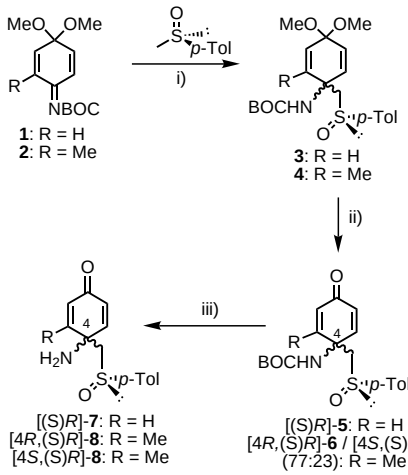
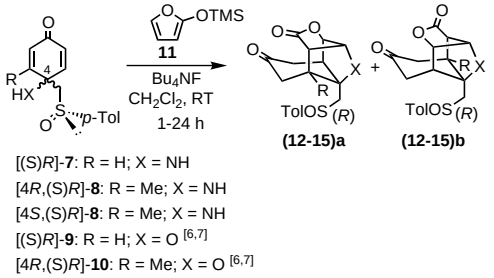


Scheme 1. Synthesis of 4-amino-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienones. i) LDA, THF, $-78\,^{\circ}C$; ii) oxalic acid, THF:H_2O, RT; iii) TFA, CH_2Cl_2, RT.

Table 1. Results of domino reactions of **7**–**10** with **11**.



	Starting material	R	X	Products (ratio)	Yield [%]
1	[(S)*R*]-**7**	H	NH	**12a**:**12b** (1:1)	67
2	[4*R*(S)*R*]-**8**	CH_3	NH	**13a**	56
3	[4*S*,(S)*R*]-**8**	CH_3	NH	**13b**	70
4	[(S)*R*]-**9**	H	O	**14a**:**14b** (1:1)	67
5	[4*S*,S)*R*]-**10**	CH_3	O	**15a**	67

solution of oxalic acid (10%) to afford *N*-Boc derivatives **5** and **6** in 80% and 82% overall yield, respectively. The latter was characterized as a 77:23 mixture of epimers at C-4. Diastereomers [4*R*,(S)*R*]-**6** and [4*S*,(S)*R*]-**6** could be separated by chromatography, and were isolated pure in 58% and 19% yield, respectively. N-Boc deprotection (TFA) of **5** and the major diastereomer [4*R*,(S)*R*]-**6** allowed the formation of compounds [(S)*R*]-**7** (97% yield) and [4*R*, (S)*R*]-**8** (99% yield), respectively. The minor epimer [4*S*,(S)*R*]-**8** could also be obtained pure by hydrolysis of [4*S*,(S)*R*]-**6** (88% yield).

The absolute configuration of the stereogenic amino-substituted carbons in diastereomers **8** could be assigned on the basis of a comparative analysis of their ^{1}H NMR parameters with those of [(S)*R*]-**7** and the *p*-quinols [(S)*R*]-**9**, [4*R*,(S)*R*]-**10** as well as the 3,5-dimethyl-substituted analogue whose structure had been already assigned.[6a, 7a] The most significant data correspond to the different chemical shifts observed for the substituents situated at the olefinic β-carbons (H and CH_3). In the cyclohexadienone moiety of the [4*S*,(S)*R*] epimer, the olefinic proton, which is situated on the unsubstituted double bond, appears more shielded than in the [4*R*,(S)*R*] diastereomers, whereas the methyl group is more shielded in the latter.[17]

Enantiomerically pure [(S)*R*]-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]cyclohexa-2,5-dienones **9** and **10** (Table 1) were prepared as previously described.[6, 7] The results of the reactions of **7**–**10** with 2-(trimethylsilyloxy)furan **11** promoted by Bu_4NF are given in Table 1. Under the conditions used (CH_2Cl_2, RT), amino-substituted derivative **7** is rapidly converted into a 1:1 mixture of two diastereomeric cage compounds **12a** and **b** in 67% total isolated yield (entry 1). Under the same conditions, asymmetrically substituted cyclohexadienone [4*R*,(S)*R*]-**8** afforded diastereomer **13a**[14b] exclusively (56% yield, entry 2), whereas epimer [4*S*,(S)*R*]-**8** was transformed stereospecifically into **13b** (70% yield, entry 3). The oxygenated derivative [(S)*R*]-**9** behaved similarly and gave rise to a 1:1 mixture of diastereomers **14a** and **b** (67% yield, entry 4), and the reaction of the 3-methyl substituted *p*-quinol [4*R*,(S)*R*]-**10** gave rise exclusively to **15a** (67% yield, entry 5). The transformation was faster when compounds **7** and **9**, which have an unsubstituted cyclohexadienone moiety, were allowed to react.

The structures of compounds **12**–**15** were characterized by different spectroscopic techniques. The ^{1}H NMR spectra feature similar chemical shifts and coupling constants for all the hydrogens of the cage moiety, except for the one situated at C-6[18] that supports an O (in compounds **14** and **15**) or NH substituent (in compounds **12** and **13**). The differences observed in chemical shifts of the CH_2SOTol AB system in diastereomers **13a**, **15a**, and **13b**, allowed the determination of their relative configurations. Such an assignment was confirmed in compound **13a**,[19] which was a crystalline solid and could be subjected to X-ray crystallographic analysis. Its absolute configuration was established by taking into account the *R* configuration of the starting sulfoxide. The most significant spectral data for the configurational assignment of **13a**, **13b**, and **15a** are displayed in Figure 1. The conformation around the CH_2–SO bond represented shows the disposition found for **13a** in the solid state (Figure 2), which is the most stable rotamer due to the anti disposition of the bulky *p*-tolyl substituent and the cage moiety. As can be seen, the AB system of **13a** appears at $\delta = 2.85$ and 3.27. A noticeable shielding effect of the sulfinyl oxygen situated anti

Abstract in Spanish: *La síntesis estereoselectiva de compuestos heterocíclicos con estructura de tipo jaula se ha descrito a partir de [(S)R]-[(p-tolilsulfinil)metil]-p-quinoles o sus análogos nitrogenados enantioméricamente puros y 2-(trimetilsililoxi)-furano. El proceso, que tiene lugar en una única etapa cuando se lleva a cabo en presencia de Bu_4NF, transcurre a través de una secuencia de reacciones dominó en la que se producen tres adiciones conjugadas. Además de un eficaz control de la estereoselectividad, el método permite aislar alguno de los intermedios de adición 1,4- cuando la reacción se lleva a cabo en presencia de $BF_3 \cdot OEt_2$.*

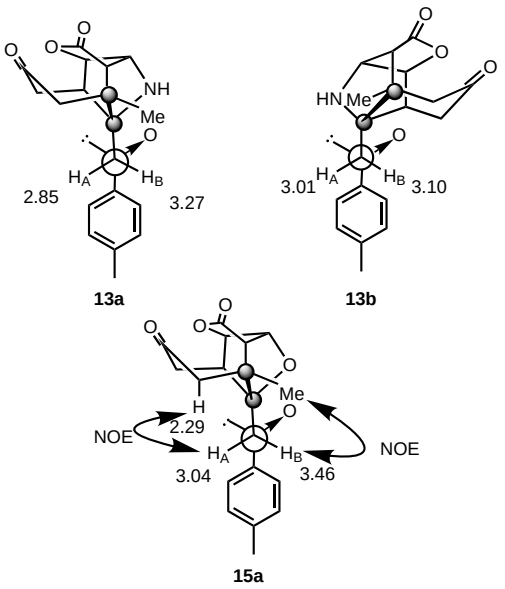


Figure 1. Significant spectral data for configurational assignment.

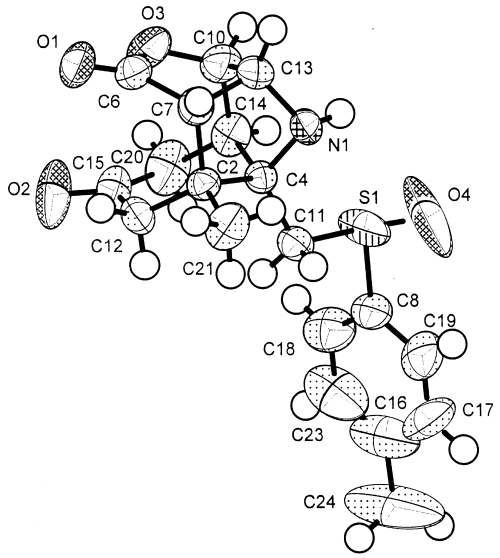
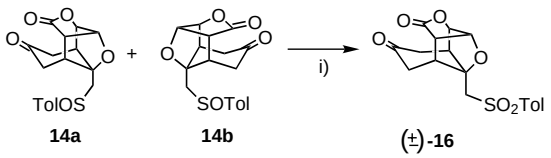


Figure 2. ORTEP plot of compound **13a**.

to H_A, appearing at $\delta = 2.85$,[20] is observed. Conversely, the deshielding observed for H_B ($\delta = 3.27$) must be a consequence of the 1,3-parallel disposition of the CH_3 group with respect to this hydrogen[21] together with the gauche conformation of the sulfinyl oxygen.[22] Confirmation of the absolute configuration of **13a** in this manner permitted reliable definition of the stereochemistry of the diastereomer **13b**, (Figure 1) whose CH_2–SO AB system appears much less differentiated ($\delta =$ 3.01 and 3.10). The shielding effect of the anti-sulfinyl oxygen on H_A is now attenuated by the gauche disposition of the NH and the 1,3-parallel methyl group, which do not affect H_B ($\delta =$ 3.10) and so H_B appears less deshielded than in **13a**. Comparison of these spectral features with those of **15a** allowed its configurational assignment, which was confirmed by NOESY experiments that displayed a NOE between H_B ($\delta = 3.46$) and the CH_3 group, whereas H_A ($\delta = 3.04$) presented a NOE with the axial hydrogen α to the carbonyl group of the cyclohexanone moiety ($\delta = 2.29$). The slight differences observed in the ^{1}H NMR data of diastereomers **12a** and **12b** or **14a** and **14b** did not allow unequivocal assignment of their configurations.

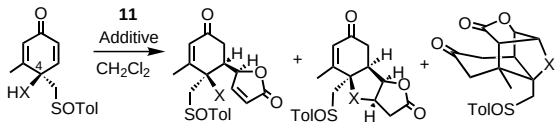
The diastereomeric relationship between **14a** and **14b** was confirmed by oxidation of a 1:1 mixture of **14a** and **14b** with *m*CPBA (83% yield) that gave a single racemic sulfone **16** (Scheme 2).



Scheme 2. Oxidation of **14a** and **14b** to sulfone **16**. i) *m*CPBA, CH_2Cl_2, 83%

The following experimental evidence allowed a mechanistic rationalization of the process. When *p*-quinol [4*R*,(S)*R*]-**10** was treated with 2-(trimethylsilyloxy)furan **11** in the presence of 1.5 equivalents of a mixture of $TiCl_4$ and $Ti(OiPr)_4$[23] instead of Bu_4NF to trigger the reaction (Table 2, entry 1), α,β-unsaturated lactone **17** was stereoselectively formed. Chromatographic purification of the crude mixture gave only 10% yield of pure **17** due to its transformation into the tricyclic derivative **18** (30% isolated yield), which resulted from an intramolecular stereoselective conjugate addition of the OH to the butenolide moiety of **17** in the presence of silica gel. When $BF_3 \cdot OEt_2$ was present in the reaction medium, [4*R*,(S)*R*]-**10** gave a 63:4:30 mixture of **17**, **18**, and **15a**, from which **17** and **18** were isolated in 30 and 34% yield after flash chromatography (Table 2, entry 2). These results suggested that **17** and **18** were the precursors of **15a**, which must be formed from **18** through a new intramolecular conjugate addition of the enolate derived from the lactone moiety to the methyl-substituted conjugate position of cyclohexenone **18**. Two mechanistic pathways could be envisaged to explain the

Table 2. Reaction of compounds **10** and **8** with **11**.



	Starting material	Additive (equiv)	T[a] [°C]	t [h]	Products[a] (ratios)	Yield [%]	Product[d]
1	[4*R*,(S)*R*]-**10**	$TiCl_4/Ti(OiPr)_4$ (1.5/1.5)	−78	6	**17**:**18**:**15a** (90:0:0)[b]	10 30	**17**[e] **18**
2	[4*R*,(S)*R*]-**10**	$BF_3 \cdot OEt_2$ (3)	RT	24	**17**:**18**:**15a** (63:4:30)[c]	30 34	**17**[f] **18**
3	[4*R*,(S)*R*]-**8**	$BF_3 \cdot OEt_2$ (3)	RT	24	**20**:**13a** (85:5)[b]	37	**20**

[a] Determined by ^{1}H NMR spectroscopy from the crude product. [b] 10% of **10** or **8** was detected. [c] 3% of **10** was recovered. [d] Yield after flash column chromatography. [e] Eluent: AcOEt. [f] Eluent: CH_3CN/CH_2Cl_2.

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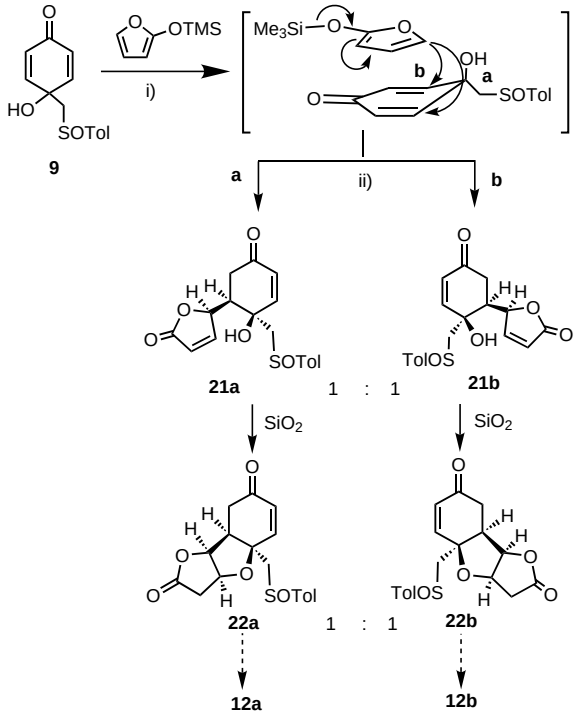
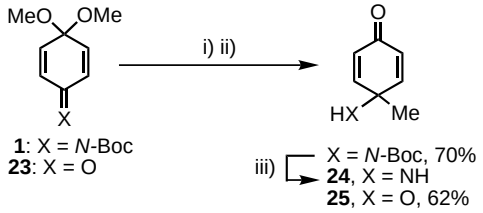
formation of compound **17**: an initial Diels–Alder cycloaddition followed by an acid-catalyzed rearrangement[24] or a 1,4-conjugate addition of 2-(trimethylsilyloxy)furan through its more nucleophilic position to the unsubstituted enone moiety of **10**. The former is unlikely since no Diels–Alder adducts were detected under any conditions. When the reaction of amino derivative [4*R*,(S)*R*]-**8** with **11** was run in the presence of $BF_3 \cdot OEt_2$ (Table 2, entry 3), an 85:5 mixture of tricyclic derivative **20** and the cage compound **13a** were formed, even though the conversion was not complete (10% of starting material was recovered). Although compound **19**, the nitrogen analogue of **17**, was not detected in this case, we can assume a similar transformation from **19**. Thus, once **19** has been formed, the higher nucleophilicity of the nitrogen facilitates its immediate attack on the α,β-unsaturated lactone moiety leading directly to **20** and **13a**. Compound **20** was isolated from this mixture in 40% yield. Although only 5% of **13a** was detected under these conditions, this is additional evidence of the intermediate formation of **19** and **20** en route to **13a**. All of these compounds were stereoselectively formed since only one diastereomer of each was detected.

When unsubstituted cyclohexadienone **9** was treated with **11** in the presence of $BF_3 \cdot OEt_2$ two diastereomers **21a** and **21b**, resulting from an initial conjugate addition, were formed in a 1:1 ratio (Scheme 3). After flash chromatography, a 1:1 mixture of tricyclic derivatives **22a** and **22b** could be isolated in a 50% yield. Although two diastereomers are formed as a consequence of the initial attack of 2-(trimethylsilyloxy)furan **11** to both prochiral conjugate positions of the unsubstituted cyclohexadienone, such a reaction is highly π-facially diastereoselective from the face of the OH group. Since cage compound **13a** was formed from **8** in the presence of $BF_3 \cdot OEt_2$ (Table 2, entry 3), we can assume that similar intermediates are formed when the reactions are carried out in the presence of Bu_4NF. Although compounds **21** and **12** were not detected in the reaction of **9** with **11** in the presence of Bu_4NF, similar intermediates must be formed en route to cage compounds **12a** and **12b**. Under these conditions, an initial Diels–Alder reaction is not possible since cycloadducts only rearrange in the presence of acids.[24]



Scheme 3. Sequential 1,4-additions in the reaction of **9** with **11**. i) **11**, CH_2Cl_2, −78 °C; ii) $BF_3 \cdot OEt_2$ (8 equiv), 5 h.

In order to know the role of the sulfoxide in the process, we decided to use *p*-quinamine **24** and *p*-quinol **25**, which lack such a group, in the reaction with **11** in the presence of Bu_4NF. Compound **24** was synthesized from *N*-Boc *p*-benzoquinone-imine dimethylacetal[16] **1** by addition of MeLi followed by hydrolysis of the acetal and *N*-Boc protecting groups (50% overall yield); see Scheme 4. Derivative **25**[8b] was obtained similarly from *p*-benzoquinone dimethylacetal[25] **23** by 1,2-addition of MeLi and hydrolysis of the acetal group, and isolated in a 62% overall yield.

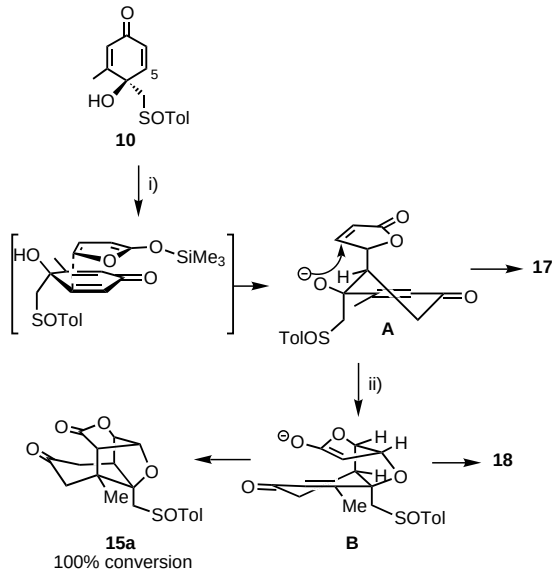


Scheme 4. Synthesis of compounds **24** and **25**. i) MeLi, THF, −78 °C; ii) oxalic acid, THF:H_2O; iii) TFA, CH_2Cl_2, RT, 71%.

When treated with 2-(trimethylsilyloxy)furan **11** in the presence of Bu_4NF/CH_2Cl_2, **24** and **25** gave only but-2-enolactone, whereas **7** and **9** were transformed in 1 h into cage compounds under the same conditions. This lack of reactivity, suggests that the sulfoxide plays an essential role in the process. The easy transformation of **7**–**10** into **12**–**15** under the experimental conditions used for these reactions (Bu_4NF/CH_2Cl_2), could only be due to the presence of the sulfoxide on the side chain at C-4, which must increase the electrophilicity of the cyclohexadienone framework. Thus, although this group is not directly involved in the transformations, it plays a double role: making the molecule optically active and increasing the reactivity of the cyclohexadienone framework. Although the experimental result is unequivocal, the origin of such increased reactivity is not evident.

Stereochemistry: The stereoselectivity of the overall process must be defined in the first 1,4-addition conjugate addition. The π-facial diastereoselectivity of this reaction on the cyclohexadienone fragment was the expected one according to previous results on *p*-quinol derivatives,[7, 8a] and was independent of the additive used to initiate the process. Steric effects are at the origin of the preferred attack of **11** on the face containing the OH of the cyclohexadienone system. The configuration of the stereogenic carbon of the lactone frag-

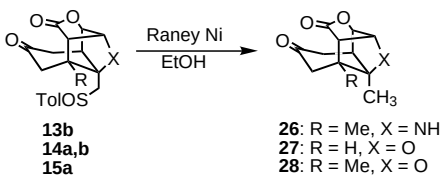
ment in **17** is consistent with the favored *endo* approach of 2-(trimethylsilyloxy)furan[26] to the enone, as shown in Scheme 5. This attack gives rise to intermediate **A**, whose



Scheme 5. Stereochemical course of domino conjugate additions. i) **11**, Bu_4NF, $CDCl_3$, RT; ii) Bu_4NF, $CDCl_3$.

protonation would yield **17**. Compound **17** was detected when this reaction was performed in a NMR sample tube ($CDCl_3$ as solvent). The preferred attack of 2-(trimethylsilyloxy)furan **11** on the more electrophilic C-5 conjugate position of 3-methyl-substituted cyclohexadienones **8** and **10** was also expected on the basis of its higher electrophilicity. The stereoselective 1,4-addition of the OH or NH_2 to the α,β-unsaturated lactone may be rationalized through the favored disposition of the π-systems, which results in the first reaction. As shown in Scheme 5 for intermediate **A**, a second conjugate addition to the butenolide led to the all-*cis* fused tricyclic intermediate **B**, which was observed in the NMR experiment as the protonated derivative **18**. Compound **18** was isolated when the reaction of **10** was carried out in the presence of $TiCl_4$/$Ti(OiPr)_4$ or $BF_3 \cdot OEt_2$ (Table 2). The concave geometry of intermediate **B** (Scheme 5) facilitates the attack of the enolized lactone fragment on the cyclohexenone from the face containing the oxygenated substituent. When these reactions are carried out in the presence of Bu_4NF, the formation of negatively charged intermediates must be responsible for the quick transformation observed. When $BF_3 \cdot OEt_2$ or $TiCl_4/Ti(OiPr)_4$ are in the medium, the role of the Lewis acids must be to activate the α,β-unsaturated systems for the Michael type additions through coordination to the C=O.

The elimination of the sulfoxide group is important for future applications of this methodology. This was quantitatively achieved in compounds **13b**, **15a**, **14a**, and **14b** upon reaction with Raney nickel, which gave optically pure compounds (−)-**26** (80%) and (+)-**28** (92%) and racemic derivative **27** (90%), respectively (Scheme 6).



Scheme 6. Raney Ni desulfurization of heterocyclic cage compounds.

Conclusion

A short and efficient asymmetric synthesis of a 7-aza-3-oxa or 3,7-dioxatetracyclo[6.4.0.$0^{2,6}$.$0^{5,9}$] skeleton from simple starting materials has been described. The method is based on the introduction of a homochiral *p*-tolylsulfinylmethyl substituent at C-4 of a *p*-quinol or *p*-quinamine, which significantly increases the acceptor character of the cyclohexadienone system. The available evidence suggests that a domino sequence of three conjugate additions occurs when a mixture of 2-(trimethylsilyloxy)furan and enantiomerically pure compounds is treated with Bu_4NF; this gives rise to the stereoselective formation of tetracyclic cage compounds in a one-pot reaction. The reactions described define a practical and unprecedented method resulting in the formation of complex structures with up to six stereogenic centers in a highly stereocontrolled manner.

Experimental Section

General: All reactions were monitored by TLC, which was performed on precoated silica gel $60F_{254}$ plates. Flash column chromatography was effected with silica gel 60 (230–240 mesh). ^1H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR were recorded at 50 or 75 MHz. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$. All NMR spectra were obtained in $CDCl_3$ at room temperature. HRMS were measured at 70 eV. All reagents were purchased from Aldrich and were used without further purification.

[(S)*R*]-*4*-(*tert*-Butoxycarbonyl)amino-4-[*p*-(tolylsulfinyl)methyl]cyclohexa-2,5-dienone (5): A solution of [(S)*R*]-methyl-*p*-tolylsulfoxide (1.6 g, 10 mmol, 1 equiv) in THF (15 mL) was added at −78 °C to a solution of LDA (1.2 equiv) in THF (20 mL). After 30 min of stirring, *N*-(*tert*-butoxycarbonyl)-*p*-benzoquinonemonoimine dimethylacetal (**1**)[16] (3.0 g, 12 mmol, 1.1 equiv) in THF (20 mL) was added at −78 °C. The mixture was stirred for 5 h. Hydrolysis was performed with saturated NH_4Cl, the residue was extracted with AcOEt, then the organic phase was dried (Na_2SO_4) and concentrated to dryness. The resulting ketal derivative **3** was dissolved in THF, then an aqueous solution of oxalic acid (10%) was added at RT. After 2 h, the solution was neutralized with saturated $NaHCO_3$ and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallized from AcOEt as a white solid. Yield: 3.0 g, 80%; m.p. 169–170 °C; $[\alpha]_D^{20} = +60.1$ ($c = 1$ in $CHCl_3$); ^1H NMR (300 MHz): $\delta = 7.51$–7.48 (AA′, 2H; Tol), 7.33–7.31 (BB′, 2H; Tol), 7.30 (dd, $J = 10.1$ and 3.1 Hz, 1H; H-3), 7.03 (dd, $J = 10.1$ and 3.1 Hz, 1H; H-5), 6.33 (dd, $J = 10.1$ and 1.9 Hz, 1H; H-2), 6.32 (s, 1H; NH), 6.23 (dd, $J = 10.1$ and 1.9 Hz, 1H; H-6), 3.01 (br s, 2H; CH_2SOTol), 2.39 (s, 3H; Tol), 1.42 (s, 9H; *t*Bu); ^{13}C NMR (75 MHz): $\delta = 184.3$ (CO), 154.2 (CO), 149.0 (C-3), 147.9 (C-5), 142.4 (C; Tol), 139.7 (C; Tol), 130.2 (2C; Tol), 129.4 (C-2), 128.7 (C-6), 123 (2C; Tol), 80.8 (C; *t*Bu), 65.6 (*C*H_2SOTol), 54.5 (C-4), 28.2 (3C; *t*Bu), 21.3 (Tol); elemental analysis calcd for $C_{19}H_{23}NO_4S$: C 63.13, H 6.41, N 3.88, S 8.87; found C 62.73, H 6.29, N 3.31, S 9.25.

[4*R*,(S)*R*] and [4*S*,(S)*R*] *4*-(*tert*-Butoxycarbonyl)amino-3-methyl-4-[*p*-(tolylsulfinyl)methyl]cyclohexa-2,5-dienone (6): A solution of [(S)*R*]-methyl-*p*-tolylsulfoxide (775.0 mg, 5.03 mmol, 1 equiv) in THF (15 mL),

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was added via cannula to a solution of LDA (1.2 equiv) at −78 °C in THF (20 mL). After 30 min of stirring, *N*-(*tert*-butoxycarbonyl)-2-methyl-*p*-benzoquinonmonoimine dimethylacetal **2**[16] (1.53 g, 5.7 mmol, 1.1 equiv) in THF (20 mL) was added at −78 °C. The mixture was stirred for 5 h. Hydrolysis was performed with saturated NH_4Cl, and the residue was extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. An aqueous solution of oxalic acid (10 %, 2 mL) was added at RT to the resulting acetal derivatives **4**, which were dissolved in THF (20 mL). After 2 h of stirring, the solution was neutralized with saturated $NaHCO_3$. The organic phase was extracted with AcOEt, dried (Na_2SO_4), and concentrated in vacuo to give a mixture of [4*R*,(S)*R*]-**6** and [4*S*,(S)*R*]-**6** (77:23, 82 % overall yield), which could be separated by column chromatography (hexane/AcOEt 4:1) to afford [4*R*,(S)*R*]-**6** (1.1 g, 58 % yield) and [4*S*,(S)*R*]-**6** (360 mg, 19 % yield) as white solids.

[4*R*,(S)*R*]-6: M.p. 136–137 °C; $[\alpha]_D^{20} = +60.1$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (200 MHz): 7.48–7.44 (AA′, 2H; Tol), 7.39 (d, $J = 11.2$ Hz, 1H; H-5), 7.29–7.26 (BB′, 2H; Tol), 6.91 (brs, 1H; NH), 6.39 (dd, $J = 11.2$ and 2.1 Hz, 1H; H-6), 6.07 (brs, 1H; H-2), 3.15 and 2.42 (AB system, $J = 13.3$ Hz, 2H; CH_2SOTol), 2.41 (s, 3H; Tol), 1.91 (d, $J = 1.6$ Hz, 3H; CH_3), 1.37 (s, 9H; *t*Bu); ^{13}C NMR (75 MHz): 184.7 (CO), 160.3 (CO), 154.1 (C-3), 150.6 (C-5), 142.9 (C; Tol), 140.1 (C; Tol), 129.9 (2C; Tol), 130 (CH), 127.8 (CH), 124.0 (2C; Tol), 80.78 (C; *t*Bu), 67.2 (CH_2SOTol), 57.7 (C-4), 28.4 (3C; *t*Bu), 21.7 (Tol), 18.8 (CH_3); elemental analysis calcd for $C_{20}H_{25}NO_4S$: C 63.97, H 6.71, N 3.73, S 8.54; found C 63.98, H 6.68, N 3.55, S 8.65.

[4*S*,(S)*R*]-6: M.p. 121–122 °C; $[\alpha]_D^{20} = +30$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz): 7.51–7.47 (AA′, 2H; Tol), 7.34–7.30 (BB′, 2H; Tol), 6.92 (d, 1H, $J = 10.2$ Hz; H-5), 6.63 (brs, 1H; NH), 6.24–6.15 (m, 2H; H-6 and H-2), 3.00, 2.80 (AB system, $J = 13.4$ Hz, 2H; CH_2SOTol), 2.39 (s, 3H; Tol), 2.21 (s, 3H; CH_3), 1.38 (s, 9H; *t*Bu); ^{13}C NMR (75 MHz): 184.7 (CO), 159.1 (CO), 154.0 (C-3), 151.1 (C-5), 142.0 (C; Tol), 139.2 (C; Tol), 129.5 (2C; Tol), 128.1 (CH), 127 (CH), 123.4 (2C; Tol), 80.6 (C; *t*Bu), 65.7 (CH_2SOTol), 57.3 (C-4), 27.7 (3C; *t*Bu), 21.2 (Tol), 19.2 (CH_3).

[(S)*R*]-4-amino-4-[*p*-(tolylsulfinyl)methyl]cyclohexa-2,5-dienone (7): TFA (10 equiv) was added to a solution of **5** (3 g, 8.3 mmol, 1 equiv) in CH_2Cl_2 (40 mL). The mixture was stirred at RT for 2 h, and an aqueous solution of NaOH (2 M) was added slowly at 0 °C until the pH was basic. The product mixture was extracted with AcOEt, and the combined organic phases were washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was recrystallized from AcOEt to afford a white solid. Yield: 2.1 g, 97 %; m.p. 162–163 °C; $[\alpha]_D^{20} = +146$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz): 7.54–7.50 (AA′, 2H; Tol), 7.35–7.31 (BB′, 2H; Tol), 7.15 (dd, $J = 9.6$ and 3.2 Hz, 1H; H-3), 6.99 (dd, $J = 9.6$ and 3.2 Hz, 1H; H-5), 6.27 (dd, $J = 9.6$ and 1.6 Hz, 1H; H-2), 6.19 (dd, $J = 9.6$ and 1.6 Hz, 1H; H-6), 3.10, 2.75 (AB system, $J = 13.4$ Hz, 2H; CH_2SOTol), 2.41 (s, 3H; Tol), 2.01 (brs, 2H; NH_2); ^{13}C NMR (75 MHz): 184 (CO), 151.0 (C-3), 150.8 (C-5), 142.2 (C; Tol), 140.3 (C; Tol), 130.1 (2C; Tol), 128.0 (C-2), 127.8 (C-6), 123.8 (2C; Tol), 67.2 (CH_2SOTol), 53.0 (C-4), 21.3 (Tol).

[4*R*,(S)*R*]-4-Amino-3-methyl-4-[*p*-(tolylsulfinyl)methyl]cyclohexa-2,5-dienone [4*R*,(S)*R*]-(8): TFA (10 equiv) was added to a solution of [4*R*,(S)*R*]-**6** (1.1 g, 2.9 mol, 1 equiv) in CH_2Cl_2 (50 mL). The mixture was stirred at RT for 1 h, then aqueous NaOH (2 M) was added slowly at 0 °C until the pH was basic. The mixture was extracted with AcOEt. The combined extracts were washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was recrystallized from AcOEt to afford a white solid. Yield: 694 mg, 87 %; m.p. 118–119 °C; $[\alpha]_D^{20} = +130$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz): 7.47–7.44 (AA′, 2H; Tol), 7.34 (d, $J = 10.1$ Hz, 1H; H-5), 7.30–7.28 (BB′, 2H; Tol), 6.25 (dd, $J = 10.1$ and 2 Hz, 1H; H-6), 6.04 (brs, 1H; H-2), 3.20, 2.65 (AB system, $J = 13.3$ Hz, 2H; CH_2SOTol), 2.36 (s, 3H; Tol), 1.99 (d, $J = 1.2$ Hz, 3H; CH_3), 1.95 (brs, 2H; NH_2); ^{13}C NMR (50 MHz): 184.9 (CO), 159.9 (C-3), 151.9 (C-5), 142.0 (C; Tol), 140.6 (C; Tol), 130.0 (2C; Tol), 127.4 (C-2), 127.2 (C-6), 123.7 (2C; Tol), 66.9 (CH_2SOTol), 55.1 (C-4), 21.2 (Tol), 18.5.

[4*S*,(S)*R*]-4-Amino-3-methyl-4-[*p*-(tolylsulfinyl)methyl]cyclohexa-2,5-dienone [4*S*,(S)*R*]-(8): Starting from [4*S*,(S)*R*]-**6** (360 mg, 0.96 mmol, 1 equiv) and following the procedure for the synthesis of [4*R*,(S)*R*]-**8**, the diastereomer [4*S*,(S)*R*]-**8** was obtained as a white solid. Yield: 262 mg, 99 %; m.p. 168–169 °C; $[\alpha]_D^{20} = +242$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz): 7.49–7.46 (AA′, 2H; Tol), 7.31–7.28 (BB′, 2H; Tol), 7.03 (d, $J = 10.6$ Hz, 1H; H-5), 6.16 (dd, $J = 10$ and 1.8 Hz, 1H; H-6), 6.13 (brs, 1H; H-2), 3.05, 2.93 (AB system, $J = 13.3$ Hz, 2H; CH_2SOTol), 2.39 (s, 3H), 2.13 (brs, 3H; CH_3), 1.83 (brs, 2H; NH_2); ^{13}C NMR (50 MHz): 184.9 (CO), 160.5 (C-3), 151.9 (C-5), 142.1 (C; Tol), 140.0 (C; Tol), 130.1 (2C; Tol), 128.2 (C-2), 127.3 (C-6), 123.9 (2C; Tol), 67.8 (CH_2SOTol), 52.9 (C-4), 21.3 (Tol), 18.3 (CH_3); HRMS (FAB+) calcd for $C_{15}H_{17}NO_2S$: *m/z*: 276.1061 $[M]^+$, found 276.1058.

[1*R*,2*R*,5*S*,6*R*,8*S*,9*R*,(S)*R*] and [1*S*,2*S*,5*R*,6*S*,8*R*,9*S*,(S)*R*]-8-[(*p*-tolylsulfinyl)methyl]-3-oxa-7-azatetracyclo [6.4.0.0^{2,6}.0^{5,9}]dodecane-4,11-dione (12a/12b): 2-(Trimethylsilyloxy)furan **11** (20.3 mg, 0.13 mmol, 1.2 equiv) and Bu_4NF (1 M in THF, 130 μL, 1.1 equiv) were sequentially added at RT to a solution of **7** (30 mg, 0.11 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 1 h of stirring, a saturated aqueous solution of NaCl was added. The solution was extracted with AcOEt, and the combined organic phases were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue, which was purified by column chromatography (CH_3CN/CH_2Cl_2 4:1). Compounds **12a** and **12b** were obtained as white solids as a 1:1 mixture of two diastereomers. Yield: 25.5 mg, 67 %; ^{1}H NMR (300 MHz): 7.59–7.56 (AA′, 2H; Tol, two diastereomers), 7.38–7.36 (BB′, 2H; Tol, two diastereomers), 4.80–4.79 (m, 1H; H-2, two diastereomers), 4.58–4.54 (m, 1H; H-6, two diastereomers), 3.36, 3.07 (AB system, $J = 14.1$ Hz, 2H; CH_2SOTol, one diastereomer), 3.32, 3.03 (AB system $J = 13.7$ Hz, 2H; CH_2SOTol, one diastereomer), 3.13 (brs, 1H; H-1, two diastereomers), 2.90–2.30 (m, 6H; two diastereomers), 2.46 (s, 3H; Tol, two diastereomers); ^{13}C NMR (75 MHz): 203.8 (CO; two diastereomers), 175.8 (CO), 175.7 (CO), 142.5 (Tol; two diastereomers), 140.1 (Tol; two diastereomers), 130.4 (2C, Tol; two diastereomers), 123.9 (2C, Tol; two diastereomers), 81.1 (C-2), 80.0 (C-2), 64.3 (C-8), 64.2 (C-8), 63.9 (CH_2SOTol; two diastereomers), 58.9 (C-6), 58.7 (C-6), 45.9 (C-5), 45.8 (C-5), 45.2 (C-1), 44.5 (C-1), 44.1 (C-9), 43.7 (C-9), 36.8 (C-12), 36.7 (C-10), 35.5 (C-12), 35.4 (C-10), 21.4 (Tol; two diastereomers); HRMS(EI) calcd for $C_{18}H_{19}NO_4S$: *m/z*: 345.1036, found 345.1034.

[1*R*,2*R*,5*S*,6*R*,8*R*,9*R*,(S)*R*]-9-Methyl-8-[(*p*-tolylsulfinyl)methyl]-3-oxa-7-azatetracyclo[6.4.0.0^{2,6}.0^{5,9}]dodecane-4,11-dione (13a): 2-(Trimethylsilyloxy)furan **11** (33.7 mg, 0.21 mmol, 1.8 equiv) and Bu_4NF (1 M in THF, 132 μL, 0.13 mmol, 1.1 equiv) were sequentially added at room temperature to a solution of [4*R*,(S)*R*]-**8** (32 mg, 0.12 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 24 h of stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue that was purified by column chromatography (CH_3CN/CH_2Cl_2 3:1) to give **13a** as a white solid. Yield: 24 mg, 56 %; m.p. 249–250 °C; $[\alpha]_D^{20} = +140$ ($c = 1.05$ in MeOH); ^{1}H NMR (200 MHz): 7.62–7.59 (AA′, 2H; Tol), 7.41–7.38 (BB′, 2H; Tol), 4.86 (dd, $J = 8.0$ and 4.9 Hz, 1H; H-2), 4.49 (brt, $J = 4.9$ Hz, 1H; H-6), 3.27, 2.85 (AB system, $J = 13.1$ Hz, 2H; CH_2SOTol), 3.03–2.93 (m, 1H; H-1), 2.70–2.49 [m, 3H; H-12$_a$, H-12$_e$, H-10$_e$), 2.43 (s, 3H; Tol), 2.32 (d, $J = 4.9$ Hz, 1H; H-5), 2.15 (part B of AB′ system, $J = 16.3$ Hz, 1H; H-10$_a$), 1.09 (s, 3H; CH_3); ^{13}C NMR (50 MHz): 204.1 (CO), 175.6 (CO), 142.5 (Tol), 139.9 (Tol), 130.3 (2C; Tol), 124.0 (2C; Tol), 82.0 (C-2), 66.3 (C-8), 63.1 (C-6), 56.5 (CH_2SOTol), 50.5 (C-5), 48.8 (C-9), 44.9 (C-1), 44.3 (C-10), 36.3 (C-12), 25.5 (CH_3), 21.4 (Tol).

[1*S*,2*S*,5*R*,6*S*,8*R*,9*S*,(S)*R*]-9-Methyl-8-[(*p*-tolylsulfinyl)methyl]-3-oxa-7-azatetracyclo[6.4.0.0^{2,6}.0^{5,9}] dodecane-4,11-dione (13b): 2-(Trimethylsilyloxy)furan **11** (37.5 mg, 0.24 mmol, 1.8 equiv) and Bu_4NF (1 M in THF, 156 μL, 1.2 equiv) were sequentially added at RT to a solution of [4*S*,(S)*R*]-**8** (37 mg, 0.13 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 24 h of stirring, a saturated aqueous solution of NaCl was added. Extraction was carried out with AcOEt, and the combined organic phases were dried (Na_2SO_4). Removal of the solvent in vacuo, afforded a crude product which was purified by column chromatography (CH_3CN/CH_2Cl_2 3:1) to give **13b** as a white solid. Yield: 33 mg, 70 %; m.p. 203–204 °C; $[\alpha]_D^{20} = +170$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (200 MHz): 7.58–7.55 (AA′, 2H; Tol), 7.38–7.35 (BB′, 2H; Tol), 4.84 (dd, $J = 8.0$ and 4.8 Hz, 1H, H-2), 4.52 (brt, $J = 4.8$ Hz, 1H; H-6), 3.10, 3.01 (AB system, $J = 13.1$ Hz, 2H; CH_2SOTol), 3.01–2.98 (m, 1H; H-1), 2.68–2.62 [m, 3H; H-12$_a$, H-12$_e$, H-10$_e$), 2.42 (s, 3H; Tol), 2.36 (d, $J = 4.8$ Hz, 1H; H-5), 2.16 (part B of AB′ system, $J = 16.0$ Hz, 1H; H-10$_a$), 1.09 (s, 3H; CH_3); ^{13}C NMR (75 MHz): 204.6 (CO), 175.5 (CO), 142.3 (Tol), 140.7 (Tol), 130.3 (2C; Tol), 123.8 (2C; Tol), 81.4 (C-2), 66.5 (C-8), 63.5 (C-6), 58.0 (CH_2SOTol), 51.7 (C-5), 48.9 (C-9), 45.7 (C-10), 45.0 (C-1), 36.3 (C-12), 25.6 (CH_3), 21.5 (Tol): HRMS(EI) calcd for $C_{19}H_{21}NO_4S$: *m/z*: 359.1191, found 359.1189.

[1*S*, 2*R*, 5*S*, 6*R*, 8*S*, 9*R*, (S)*R*] and [1*R*, 2*S*, 5*R*, 6*S*, 8*R*, 9*S*, (S)*R*]-8-[(*p*-Tolylsulfinyl)methyl]-3,7-dioxa tetracyclo[6.4.0.0^{2,6}.0^{5,9}]dodecane-4,11-

dione (14a/14b): 2-(Trimethylsilyloxy)furan **11** (167 mg, 1.07 mmol, 1.5 equiv) and Bu_4NF (1M in THF, 1.4 mL, 1.5 equiv), were sequentially added at RT to a solution of [(S)*R*]-**9** (270 mg, 1.03 mmol, 1 equiv), in dry CH_2Cl_2 (4 mL). After 1 h of stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue, which was purified by column chromatography (Hexane/AcOEt/CH_3CN 1:1:0.2) to give **14a**:**14b** as a white solid as a 1:1 mixture of two diastereomers. Yield: 239 mg, 67%; ^{1}H NMR (300 MHz): 7.60–7.57 (AA′, 2H; Tol, two diastereomers), 7.38–7.35 (BB′, 2H; Tol, two diastereomers), 5.45 (brt, 1H, J = 4.9 Hz; H-6, two diastereomers), 4.98–4.83 (m, 1H; H-2, two diastereomers), 3.39, 3.10 (AB system, J = 15 Hz, 2H; CH_2SOTol, two diastereomers), 3.19, 2.94 (m, 3H; two diastereomers), 2.75 (dd, J = 10 and 4.1 Hz, 2H; two diastereomers), 2.62–2.32 (m, 2H; two diastereomers), 2.42 (s, 3H; Tol, two diastereomers); ^{13}C NMR (75 MHz): 203.1 (CO), 174.1 (CO; two diastereomers), 174.0 (CO), 142.3 (Tol, two diastereomers), 140.5 (Tol, two diastereomers), 130.3 (2C; two diastereomers), 123.8 (2C; two diastereomers), 82.9 (C-8; two diastereomers), 81.8 (C-6; two diastereomers), 80.4 (C-2; two diastereomers), 60.4 (*C*H_2SOTol), 60.3 (*C*H_2SOTol), 46.8 (C-5), 45.4 (C-5), 45.3 (C-1), 45.0 (C-1), 44.0 (C-9), 42.7 (C-9), 36.8 (C-12; two diastereomers), 35.6 (C-10), 35.5 (C-10), 21.4 (Tol; two diastereomers); HRMS(EI) calcd for $C_{18}H_{17}O_5S$: *m/z*: 346.0871, found 346.0874.

[1*R*,2*R*,5*S*,6*R*,8*R*,9*R*,(S)*R*]-9-Methyl-3,7-dioxa-8-[(*p*-tolylsulfinyl)methyl]tetracyclo[6.4.0.0^{2,6}.0^{5,9}]dodecane-4,11-dione (15a): 2-(Trimethylsilyloxy)furan **11** (59.0 mg, 0.37 mmol, 1.8 equiv) and Bu_4NF (1M in THF, 228 μL, 1.1 equiv) were sequentially added at RT to a solution of [4*R*,(S)*R*]-**10** (60 mg, 0.21 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 24 h of stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases were dried (Na_2SO_4). Removal of the solvent in vacuo afforded a residue whose purification by column chromatography (CH_3CN/CH_2Cl_2 3:1) gave **15a** as a white solid. Yield: 52 mg, 67%; m.p. 228–229 °C; $[\alpha]_D^{20} = +237$ (c = 0.36 in $CHCl_3$); ^{1}H NMR (500 MHz): 7.62–7.61 (AA′, 2H; Tol), 7.41–7.40 (BB′, 2H; Tol), 5.39 (t, J = 5.02 Hz, 1H; H-6), 4.95 (dd, J = 7.9 and 4.9 Hz, 1H; H-2), 3.46–3.04 (AB system, J = 14.6 Hz, 2H; CH_2SOTol), 3.02–3.0 (m, 1H; H-1), 2.81 (part A of ABX system (H-12eq) and part A of AB system (H-10$_{eq}$)), J = 18.4 Hz, 2H), 2.69 (part B of ABX system (H-12$_{ax}$)), J = 18.3 and 6.2 Hz, 1H), 2.52 (d, J = 5.1 Hz, 1H; H-5), 2.47 (s, 3H; Tol), 2.29 (part B of AB system, J = 18.4, 1H; H-10ax), 1.18 (s, 3H; CH_3); ^{13}C NMR (75 MHz): 203.1 (CO), 174.1 (CO), 142.3 (Tol), 140.5 (Tol), 130.3 (2C; Tol), 124 (2C; Tol), 84.9 (C-8), 81.1 (C-6), 80.4 (C-2), 58.3 (*C*H_2SOTol), 51.8 (C-5), 50.1 (C-9), 45.1 (C-10), 44.2 (C-1), 36.4 (C-12), 25.4 (CH_3), 21.4 (Tol); HRMS(EI) calcd for $C_{19}H_{20}O_5S$: *m/z*: 360.1031, found 360.1029.

[1*S,2*R**,5*S**,6*R**,8*S**,9*R**]-8-[(*p*-Tolylsulfonyl)methyl]-3,7-dioxatetracyclo [6.4.0.0^{2,6}.0^{5,9}]dodecane-4,11-dione (16)**: A solution of *m*-chloroperoxybenzoic acid (50–70% *w/w*, 24 mg, 0.07–0.10 mmol, 1.4–2 equiv) in CH_2Cl_2 (10 mL) was added to a solution of a mixture of **14a** and **14b** (1:1, 18 mg, 0.052 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C. The reaction mixture was stirred for 1 h and then washed with saturated aqueous Na_2SO_3 and $NaHCO_3$. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by crystallization (AcOEt) to afford **16** as a white solid. Yield: 16 mg, 83%; m.p. 218–219 °C; ^{1}H NMR ([D$_6$]DMSO, 300 MHz): 7.81–7.78 (AA′, 2H; Tol), 7.43–7.40 (BB′, 2H; Tol), 5.28 (brt, J = 4.8 Hz, 1H; H-6), 4.78 (dd, J = 7.0 and 5.2 Hz, 1H; H-2), 4.26, 4.18 (AB system, J = 15.3 Hz, 2H; CH_2SO_2Tol), 2.8–2.6 (m, 6H), 2.40 (s, 3H; Tol), 2.32–2.24 (m, 2H); ^{13}C NMR ([D$_6$]DMSO, 75 MHz): 205.0 (CO), 175.2 (CO), 144.5 (Tol), 138.2 (Tol), 129.8 (2C; Tol), 128.0 (2C; Tol), 82.0 (C-8), 81.5 (C-6), 79.9 (C-2), 54.8 (*C*H_2SOTol), 44.3 (2C; C-5 and C-1), 43.3 (C-9), 36.8 (C-12), 35.4 (C-10), 21.2 (Tol).

[1*S*,2*R*,(S)*R*]-5-{2-Hydroxy-3-methyl-5-oxo-2-[(*p*-tolyl)sulfinyl]methyl}-3-cyclohexenyl}-2(5*H*)-furanone (17) and [3a*R*,4a*R*,8a*S*,8b*R*,(S)*R*]-5-Methyl-4a-[(*p*-tolylsulfinyl)methyl]-3a,8a,8b-tetrahydrofuro[3,2-b]benzofuran-2,7(3*H*, 4a*H*)-dione (18):

BF_3OEt_2: 2-(Trimethylsilyloxy)furan **11** (39.0 mg, 0.25 mmol, 1.5 equiv) and BF_3OEt_2 (68.5 mg, 0.48 mmol, 3 equiv) were sequentially added at RT to a solution of [4*R*,(S)*R*]-**10** (44.4 mg, 0.161 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 24 h of stirring, a saturated aqueous solution NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo to give a 63:4:30:3 mixture of **17**/**18**/**15a**/**10**. Purification by column chromatography (AcOEt) gave **17** as a pale yellow oil (yield: 18 mg, 30%) and **18** as a yellow oil (yield: 24 mg, 40%).

$TiCl_4/Ti(OiPr)_4$: $Ti(OiPr)_4$ (59.6 mg, 0.21, 1.5 equiv), $TiCl_4$ (39.8 mg, 0.21, 1.5 equiv), and 2-(trimethylsilyloxy)furan **11** (32.8 mg, 0.21 mmol, 1.5 equiv) were sequentially added at −78 °C to a solution of [4*R*,*R*(S)]-**10** (40 mg, 0.14 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 6 h stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo to give a 90:10 mixture of **17**/**18**/**15a**/**10**. Purification by column chromatography (AcOEt) gave **17** as a pale yellow oil (yield: 6 mg, 10%) and **18** as a yellow oil (yield: 18 mg, 30%).

Compound 17: ^{1}H NMR (300 MHz): 7.59–7.55 (AA′, 2H; Tol), 7.41–7.37 (BB′, 2H; Tol), 7.32 (dd, J = 5.9 and 1.6 Hz, 1H; H-4′), 6.06 (dd, J = 5.9 and 2.1 Hz, 1H; H-3), 5.84 (brs, 1H; H-4′), 5.80 (ddd, J = 4.3, 2.1 and 1.6 Hz, 1H; H-5), 5.58 (s, 1H; OH), 3.84–3.78 (m, 1H; H-1′), 3.20–3.80 (AB system, J = 13.9 Hz, 2H; CH_2SO_2Tol), 2.49–2.44 (m, 2H; H$_{eq/ax}$-6′), 2.44 (s, 3H; Tol), 2.07 (d, J = 1.6 Hz, 3H; CH_3); ^{13}C NMR (75 MHz): 193.7 (CO), 172.0 (CO), 162.3 (C-3′), 153.6 (C-4′), 143.3 (Tol), 138.5 (Tol), 130.6 (2C; Tol), 128.1 (C-4), 124 (2C; Tol), 122.5 (C-3), 81.8 (C-5), 74.3 (C-2′), 61.1 (*C*H_2SOTol), 45.2 (C-6′), 33.8 (C-1'), 21.5 (Tol), 18.8 (CH_3).

Compound 18: ^{1}H NMR (200 MHz): 7.52–7.48 (AA′, 2H; Tol), 7.36–7.32 (BB′, 2H; Tol), 6.04 (brs, 1H; H-6), 5.13 (t, J = 4.4 Hz, 1H; H-3a), 4.93 (brt, J = 4.8 Hz, 1H; H-8b), 3.24–2.90 (m, 4H), 2.86 (m, 3H), 2.42 (s, 3H), 1.98 (s, 3H; CH_3); ^{13}C NMR (75 MHz): 193.9 (CO), 173.7 (CO), 142.2 (Tol), 140.3 (Tol), 130.5 (C-6), 130.3 (2C, Tol), 124.0 (C-5), 123.9 (2C, Tol), 87.0 (C-3a), 82.6 (C-8b), 66.3 (*C*H_2SOTol), 56.7 (C-4a), 46.8 (C-8a), 37.1 (C-3), 33.5 (C-8), 21.4 (Tol), 18.1 (CH_3).

[3a*R*,4a*R*,8a*R*,8b*R*,(S)*R*]-5-Methyl-4a-[(*p*-tolylsulfinyl)methyl]-3a,4,4a,8,8a,8b-hexahydro-2*H*-furo[3,2-b]indole-2,7(3*H*)-dione (20): 2-(Trimethylsilyloxy)furan **11** (30.0 mg, 0.19 mmol, 1.2 equiv) and BF_3OEt_2 (68.1 mg, 0.48, 3 equiv) were sequentially added at RT to a solution of [4*R*,(S)*R*]-**8** (45.7 mg, 0.16 mmol, 1 equiv) in dry CH_2Cl_2 (0.5 mL). After 24 h of stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo to give a 85:5:10 mixture of **20**/**13a**/**8**. Purification by column chromatography (AcOEt) gave of **20** as a pale yellow oil. Yield: 22 mg, 37%; ^{1}H NMR (200 MHz): 7.53–7.50 (AA′, 2H; Tol), 7.38–7.35 (BB′, 2H; Tol), 5.92 (brs, 1H; H-6), 5.19 (t, J = 6.0 Hz, 1H; H-8b), 4.32 (brt, J = 6,2 Hz, 1H; H-3a), 3.30 (brt, J = 6.8 Hz, 1H; H-8a), 3.21, 3.69 (AB system, J = 13.9 Hz, 2H; CH_2SOTol), 3.0 (part A of AB system, J = 18.2 Hz, 1H; H-8), 2.76 (m, 2H; H-8 and H-3), 2.42 (s, 3H; Tol), 2.39 (part B of AB′ system, J = 17.0 Hz, 1H; H-3), 2.0 (d, J = 1.2 Hz, 3H; CH_3); ^{13}C NMR (50 MHz): 193.7 (CO), 175.3 (CO), 142.6 (Tol), 139.5 (Tol), 130.4 (2C; Tol), 128.9 (C-6), 125.3 (C-5), 123.8 (2C; Tol), 87.4 (C-8b), 64.8 (C-4a), 61.9 (*C*H_2SOTol), 55.8 (C-3a), 46.5 (C-8a), 37.8 (C-3), 33.8 (C-8), 21.4 (Tol), 19.0 (CH_3).

[1*S*,2*R*,(S)*R*]- and [1*R*,2*S*,(S)*R*]-5-{2-Hydroxy-5-oxo-2-[[*p*-tolylsulfinyl]-methyl}-3-cyclohexenyl}-2(5*H*)-furanone (21a/21b), and [3a*R*,4a*R*,8a*S*,8b*R*,(S)*R*]- and [3a*S*, 4a*S*, 8a*R*, 8b*S*,(S)*R*]-4a-[(*p*-tolylsulfinyl)methyl]-3a, 8a, 8b-tetrahydrofuro[3, 2-b]benzofuran-2, 7(3*H*,4a*H*)-dione (22a/22b): 2-(Trimethylsilyloxy)furan **11** (14.2 mg, 0.09 mmol, 1.2 equiv) and BF_3OEt_2 (86.3 mg, 0.60 mmol, 8 equiv) were sequentially added at RT to a solution of [(S)*R*]-**9** (20.5 mg, 0.076 mmol, 1 equiv) in dry CH_2Cl_2 (0.3 mL). After 5 h of stirring, a saturated aqueous solution of NaCl was added. Extractions were carried out with AcOEt, and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo to give a 1:1 mixture of **21a**:**21b**, which gave **22a**:**22b** after purification by column chromatography (AcOEt) as a pale yellow oil (yield: 13.1 mg, 50%).

Compound 21a/21b: ^{1}H NMR (200 MHz): 7.61–7.52 (m, 2H; Tol, two diastereoisomers), 7.41–7.32 (m, 2H; Tol, two diastereoisomers), 6.94 (d, J = 10.2 Hz, 1H; H-3′, two diastereoisomers), 6.19–6.08 (m, 1H; H-4, two diastereoisomers), 5.92 (d, J = 10.2 Hz, 1H; H-4′, two diastereoisomers), 5.73–5.68 (m, 1H; H-2, two diastereoisomers), 5.59–5.53 (m, 1H; H-5, two diastereoisomers), 3.43 and 2.12 (AB system, J = 14 Hz, 2H; CH_2SOTol), 3.39–3.23 (m, 1H; H-1′, one diastereoisomer), 3.25, 3.17 (AB system, J = 14 Hz, 2H; CH_2SOTol, one diastereoisomer), 2.78–2.73 (m, 1H; H-1′, one diastereoisomer), 2.58–2.29 (m, 2H; H-6′, two diastereoisomers), 2.42 (3H, Tol, two diastereoisomers).

Compound 22a/22b: ^{1}H NMR (200 MHz): 7.57–7.53 (AA′, 2H; Tol, one diastereoisomer), 7.56–7.51 AA′ 2H; Tol, one diastereoisomer), 7.37–7.33

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(BB′, 2H; Tol, two diastereoisomers), 6.73 (dd, $J = 10$ and 1.9 Hz, 1H; H-5, one diastereoisomer), 6.44 (dd, $J = 10.1$ and 1.9 Hz, 1H; H-5, one diastereoisomer), 6.23 (d, $J = 10$ Hz, 1H; H-6, one diastereoisomer), 6.02 (d, $J = 10.1$ Hz, 1H; H-6, one diastereoisomer), 5.18–5.12 (m, 1H; H-8b, two diastereoisomers), 4.95 (t, $J = 6.5$ Hz, 1H; H-3a, two diastereoisomers), 3.25, 2.98 (AB system, $J = 14$ Hz, 2H; CH_2SOTol), 3.91–3.85 (m, 1H; H-8a, one diastereoisomer), 3.40–3.03 (m, 1H; H-8a, one diastereoisomer), 3.08, 2.92 (ABX system, $J_{AB} = 13.5$ and $J_{BX} = 5$ Hz, 2H; two diastereoisomers, H-8), 2.78, 2.65 (ABX system, $J_{AB} = 17.1$, $J_{AX} = 5.7$ and $J_{BX} = 2$ Hz, 2H; two diastereoisomers, H-2), 2.41 (3H; Tol, two diastereoisomers); ^{13}C NMR (50 MHz): 194.1, 193.9, 174.0, 173.8, 146.3, 145.9, 142.1, 140.5, 140.4, 130.9, 130.4, 130.2, 123.8, 86.7, 86.4, 68.0, 47.0, 44.2, 37.5, 37.4, 33.6, 33.3, 21.3, 20.9.

***4*-(*tert*-Butoxycarbonyl)amino-4-methylcyclohexa-2,5-dienone (*N*-Boc-24)**: A solution of *N*-(*tert*-Butoxycarbonyl)-*p*-benzoquinoneimine dimethylacetal **1**,[16] (2.5 g, 9.4 mmol, 1 equiv) in THF (15 mL) was added via cannula to a solution of MeLi (1.6 M in diethyl ether, 6.7 ml, 10 mmol, 1.1 equiv) in THF (20 mL) at −78 °C. The mixture was stirred 5 h and then hydrolyzed with a saturated aqueous solution of NH_4Cl. The mixture was concentrated with AcOEt, and the organic phase dried (Na_2SO_4) and concentrated to dryness. The resulting acetal derivative was dissolved in THF, and then an aqueous solution of oxalic acid (10%) was added at RT. After 2 h of stirring, the solution was neutralized with saturated $NaHCO_3$ and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallized from AcOEt as a white solid. Yield: 1.5 g, 70%; m.p. 119 °C; ^{1}H NMR (200 MHz): 6.80 (d, $J = 9.8$ Hz, 2H; H-3 and H-5), 6.18 (dd, $J = 9.8$ and 1.6 Hz, 2H; H-2 and H-6), 1.34 (s, 3H; CH_3), 1.33 (s, 9H; *t*Bu); ^{13}C NMR (75 MHz): 185.1 (CO), 152.4 (2C), 127.8 (2C), 80.5 (C-4), 52.0 (C-*t*Bu), 28.1 (3C, *t*Bu), 26.8 (CH_3).

4-Amino-4-methylcyclohexa-2,5-dienone (24): TFA (10 equiv) was added to a solution of *N*-Boc-**24** (1.5 g, 6.7 mmol, 1 equiv) in CH_2Cl_2. The mixture was stirred at RT for 1 h, and NaOH (2 M) was added slowly at 0 °C until the pH was basic. The mixture was extracted with AcOEt. The combined extracts were washed with brine and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was crystallized from AcOEt to give an unstable white solid that must be used immediately after the synthesis. Yield: 585 mg, 71%; ^{1}H NMR (200 MHz): 6.75 (dd, $J = 10.1$ and 1.7 Hz; 2H), 5.98 (dd, $J = 10.1$ and 2.0 Hz; 2H), 1.51 (brs, 1H; NH), 1.26 (s; 3H); ^{13}C NMR (75 MHz): 185.2 (CO), 154.9 (2C), 126.2 (2C), 50.4 (C-4), 26.9 (CH_3).

4-Hydroxy-4-methylcyclohexa-2,5-dienone (25):[8b] Compound **25** was obtained by following the procedure used to synthesize *N*-Boc-**24** starting from *p*-benzoquinone dimethylacetal **23**[24] (600 mg, 1 equiv) in THF (15 mL) and MeLi (1.6 M in ether) (2.6 mL, 1.1 equiv), and allowing them to react for 3 h. The resulting acetal derivative was dissolved in THF, then an aqueous solution of oxalic acid (10%) was added at RT. After 1.5 h of stirring, the solution was neutralized with a saturated aqueous solution of $NaHCO_3$, followed by extraction with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (AcOEt/hexane 3:2) gave **25** as a light yellow oil. Yield: 302 mg, 62%; ^{1}H NMR (200 MHz): 6.83 (dd, $J = 8.4$ and 1.6 Hz, 2H; H-3 and H-5), 5.98 (dd, $J = 8.4$ and 1.8 Hz, 2H; H-2 and H-6), 1.39 (s, 3H, CH_3).

General method for desulfinylation: Activated Raney-Ni (1–2 equiv) was added at RT to a solution of the sulfinyl compound (1 equiv) in EtOH (0.2 M). The reaction was monitored by TLC. When the starting material could no longer be observed, the mixture was filtrated through Celite. Concentration of the filtrate in vacuo gave quantitative yield of the crude desulfinylated compound. Purification was done by recrystallization (the solvent is indicated in each case).

(1*S*,2*S*,5*R*,6*S*,8*S*,9*S*)-9,8-Dimethyl-3-oxa-7-azatetracyclo [6.4.0.0^{2,6}.0^{5,9}]-dodecane-4,11-dione (26): Compound **26** was obtained from **13b** (20 mg) by following the general method and purified by recrystallization (AcOEt/Hexane). Yield: 80%. $[\alpha]_D^{20} = -8.5$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (200 MHz): 5.22 (brt, $J = 4.8$ Hz, 1H; C-2), 4.81 (dd, $J = 6.6$ and 4.8 Hz, 1H; C-6), 2.69, 2.23 (AB system, $J = 18.7$ Hz, 2H; 2H-10), 2.65, 2.43 (ABX system, $J = 17.7$, 6.0, and 2.2 Hz, 2H; 2H-12), 2.31 (d, $J = 4.3$ Hz, 1H; H-5), 2.17–2.10 (m, 1H; H-1), 1.38 (s, 3H; C_8-CH_3), 1.09 (s, 3H; C_9-CH_3); ^{13}C NMR (75 MHz): 205.4 (CO), 176.3 (CO), 81.6 (C-2), 65.3 (C-8), 63.3 (C-6), 52.5 (C-5), 48.3 (C-10), 47.8 (C-9), 45.2 (C-1), 36.5 (C-12), 25.8 (CH_3), 14.8 (CH_3); HRMS calcd for $C_{12}H_{15}NO_3$ (M^+): *m/z*: 221.1051, found 221.1051.

(1*S,2*R**,5*S**,6*R**,8*S**,9*R**)-8-Methyl-3,7-dioxatetracyclo[6.4.0.0^{2,6}.0^{5,9}]-dodecane-4,11-dione (27)**: Compound **27** was obtained from a 1:1 mixture of **14a** and **14b** (60 mg) by following the general method and purified by crystallization (CH_2Cl_2/Hexane). Yield: 90%; m.p. 193–194 °C; ^{1}H NMR (200 MHz): 5.27 (brt, $J = 4.9$ Hz, 1H), 4.83 (dd, $J = 7.2$ and 4.8 Hz, 1H), 2.93 (dd, $J = 11.3$ and 4.8 Hz, 1H), 2.79–2.70 (m, 1H), 2.66 (t, $J = 2.0$ Hz, 1H; H-9), 2.56–2.40 (m, 3H), 2.29–2.23 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (75 MHz): 203.9, 174.8, 83.1, 81.0, 46.4, 45.6, 45.0, 37.3, 35.8, 17.8; HRMS(FAB+) calcd for $C_{11}H_{12}O_4$ $[M+1]^+$: *m/z*: 209.0813, found 209.0815.

(1*S*,2*R*,5*S*,6*R*,8*R*,9*R*)-8,9-dimethyl-3,7-dioxatetracyclo[6.4.0.0^{2,9}.0^{5,9}]dodecane-4,11-dione (28): Compound **28** was obtained from **15a** (40 mg) according to the general method and purified by crystallization (AcOEt/Hexane). Yield: 92%; m.p. 211–212 °C; $[\alpha]_D^{20} = +9$ ($c = 0.6$ in $CHCl_3$); ^{1}H NMR (200 MHz): 5.22 (brt, $J = 4.8$ Hz, 1H; H-6), 4.81 (dd, $J = 6.6$ and 4.8 Hz, 1H; H-2), 2.76–2.66 (m, 2H; H-10 and H-12), 2.49–2.41 (m, 2H; H-5 and H-12), 2.28–2.16 (m, 2H; H-1 and H-10), 1.51 (s, 3H; C_8-CH_3), 1.12 (s, 3H; C_9-CH_3); ^{13}C NMR (75 MHz): 204.4 (CO), 174.8 (CO), 85.2 (C-8), 81.1 (C-6), 80.6 (C-2), 52.0 (C-5), 48.5 (C-9), 47.5 (C-1), 45.3 (C-10), 36.5 (C-12), 25.6 (CH_3), 14.8 (CH_3); HRMS calcd for $C_{12}H_{14}O_4$ $[M]^+$: *m/z*: 222.0892, found 222.0891.

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