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Synthesis of 4-Aminotropones from [(Sulfinyl or Sulfonyl)methyl]-Substituted *p*-Quinamines

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Abstract: An efficient synthesis of 4-aminotropones has been achieved in excellent yields by simple treatment of 4-amino-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienones (*p*-quinamines) with NaH. The method allowed regiocontrolled access to 3-methyl, 5-methyl- and 3,5-dimethyl-substituted derivatives starting from *p*-quinamines with adequate substituents at the cyclohexadienone moiety and/or at the carbon linked to the sulfur function. The *p*-quinamines in turn were easily accessible from *N*-Boc *p*-anisidines (Boc = *tert*-butoxycarbonyl) by electrochemical oxidation in MeOH to quinone imine monoketals, followed by addition of a α-lithium sulfinyl carbanion to the imino group, and ketal hydrolysis. Oxidation of the sulfoxide gave the sulfonyl-substituted *p*-quinamines that, upon basic treatment, behave similarly. The *p*-quinamine **55** and bis-*p*-quinamine **56**, resulting in the addition of the anion derived from dimethyl sulfone to the *p*-quinonimine ketal **14**, also gave the 4-aminotropone. The mechanism involves the initial formation of a α-sulfonyl carbanion, which intramolecularly attacks the cyclohexadienone giving a norcaradiene-like enolate intermediate, the evolution of which through a ring-expansion process, pushes off a methyl sulfinate anion or SO_2. This efficient process fulfils the criteria of atom economy. The introduction of a proline substituent in the nitrogen of the starting *p*-quinamine allowed the synthesis of an enantiopure 4-aminotropone, the asymmetric Diels–Alder reactions of which with maleimide occurred in a highly *endo* and π-facial diastereoselective manner.

Keywords: 4-aminotropones · Diels–Alder reactions · quinamine · quinonimine ketal · sulfones · sulfoxides

Introduction

The synthesis of tropone (cycloheptatrienone) and tropolone (2-hydroxytropone) derivatives is receiving increasing attention due to the presence of such heptacyclic systems[1] in a number of natural products, ranging from structurally simple monocyclic derivatives[2] to more complex norditerpenoids[3] and alkaloids.[4] Some of them are nowadays recognised as leading structures showing a wide range of biological properties, the pharmaceutical potential of which is demanding flexible synthetic approaches for the development of novel therapeutic analogues.[5]

Diels–Alder adducts derived from tropolones showing DNA-damaging properties have also been isolated from natural sources.[6] Several strategies have been applied up to now for the synthesis of the tropone ring. Since the pioneering work of Nozoe in 1951,[7] sequential transformations on cycloheptanone have allowed access to tropone itself as well as alternatively alkyl-substituted analogues, by using bromination–dehydrobromination processes and/or hydrogenolysis steps.

Starting from 1,2-cycloheptadione, tropolones were also available by this method, even in a regioselective manner by controlling the substitution in the starting product.[8] The tropinone, first synthesised in 1917 by Robinson,[9] could be transformed into tropone by Hofmann elimination followed by oxidation.[10] Nicolaou recently reported the synthesis of tropinone and tropone from cycloheptanol by using *o*-iodoxybenzoic acid (IBX) as the oxidant.[11] Aldol condensations between phthaldehyde and β-dicarbonyl derivatives gave rise to benzotropones.[12] Improved yields were achieved by using 2,3-bistrimethylsilyloxy-1,3-butadiene derivatives as the enol partners.[13]

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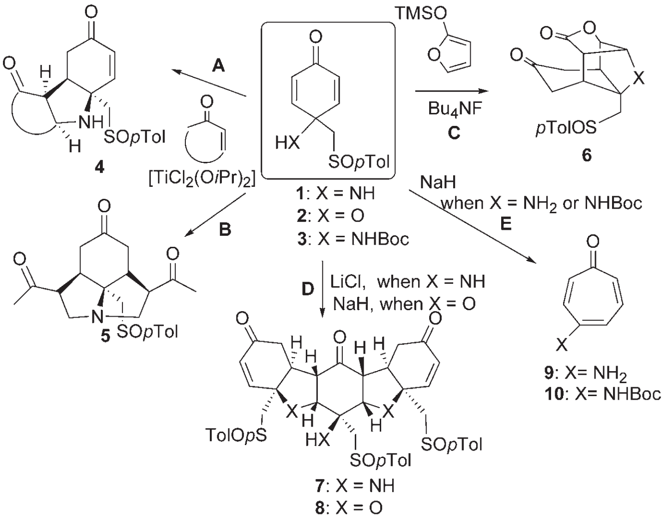
The direct formation of the seven-membered ring could be also achieved by using [4+3] cycloadditions. Thus, the $[Fe_2(CO)_9]$-promoted cycloaddition between α,α′-dibromoketones and 1,3-dienes led to 4-cycloheptenones which were latter transformed into tropones.[14] The [4+3] cycloadducts, resulting from the reaction of 1,3-haloketones and furan derivatives, evolved into tropones by dechlorination and ether-bridge cleavage with TMSOTf/Et_3N (TMSOTf = trimethylsilyl triflate).[15] Similarly, [4+3] cycloadditions between rhodium vinyl carbenoids[16] or α-methoxy-substituted oxyallyl derivatives and electron-rich dienes[17] allowed the direct construction of the seven-membered ring.

The ring expansion of a bicyclic system is among the most widely used strategies en route to substituted tropones and tropolones. Thus, upon a basic treatment, the bicyclic derivative proceeding from a [2+2] cycloaddition between cyclopentadiene and haloketenes[18] suffered a ring expansion leading to tropolones. The phototochemical [2+2] cycloaddition between a cyclopentenone and acetylene, followed by in situ electrocyclic cyclobutene ring opening, directly produced the seven-membered derivative.[19] Other cycloadditions followed by ring expansion that gave the cycloheptadienone skeleton include Diels–Alder reactions between *ortho*-quinones and alkynes[20] or between activated dienes and cyclopropene derivatives.[21] The Diels–Alder cycloadducts resulting from reactions between 3-hydroxypyridinium betaines and electron-poor olefins could be transformed into 4-substituted cycloheptatrienones after oxidation and chelotropic elimination of nitrosobenzene.[22] Adequately substituted bicyclo[4,1,0]heptacyclo-2,4-diene systems (norcaradiene) may undergo a ring-expansion process leading to tropones. The products resulting from the insertion of a dihalocarbene into an electron-rich aromatic ring[23] or a 1-methoxy-1,4-cyclohexadiene framework[24] evolve into tropones under different conditions. Other substituted carbenes[25] have been used with this aim.

Abstract in Spanish: *La síntesis de 4-aminotroponas se ha logrado en una única etapa y con excelentes rendimientos por tratamiento de 4-amino-4-[(*p*-tolilsulfinil)metil]-2,5-ciclohexadienonas (*p*-quinaminas) con NaH. Esta metodología permite acceder de forma regiocontrolada a 4-aminotroponas con sustituyentes metilo en distintas posiciones (3-, 5- y 3,5-) a partir de p-quinaminas adecuadamente sustituidas en el fragmento de ciclohexadienona y/o en el C-α respecto de la función de azufre. Las p-quinaminas precursoras son fácilmente accesibles a partir de* p-*anisidinas* N-*Boc protegidas por oxidación electroquímica en MeOH,* para *dar lugar a los monoacetales de quinonimina, seguida de adición de un α-litio sulfinil carbanión e hidrólisis del acetal. La oxidación del sulfóxido origina las sulfonil* p-*quinaminas que también se transforman en las 4-aminotroponas en presencia de NaH. La p-quinamina* ***55*** *y la bis-*p-*quinamina* ***56****, resultantes de la adición del anión derivado de la dimetil sulfona sobre el monoacetal de quinonimina* ***14****, también evolucionan a la 4-aminotropona en medio básico. El mecanismo del proceso implica la formación inicial de un α-sulfonil carbanión que ataca de forma intramolecular al fragmento de ciclohexadienona para dar un enolato intermedio con estructura de norcaradieno, que sufre la expansión del anillo con eliminación simultánea del anión metil sulfinato o de SO_2. Este proceso cumple los requisitos de economía de átomos que aumentan su interés sintético. La introducción de un resto de prolina en el nitrógeno de la* p-*quinamina de partida permite acceder a una 4-aminotropona enantiopura cuyas reacciones de Diels–Alder asimétricas con maleimida tienen lugar con una elevada selectividad endo y π-facial.*

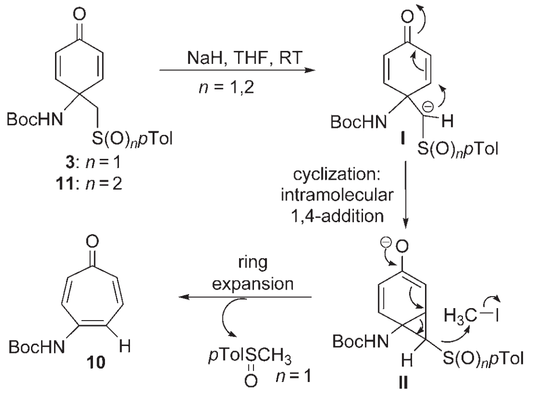
The formation of intermediate norcaradienes could also be achieved in an intramolecular way by irradiation of a lithiated benzamide,[26] 1,4-conjugate addition on a 2,5-cyclohexadienone 4-alkyl-substituted radical derivative[27] or Wagner–Meerwein rearrangement on a 1-methoxy-1,4-cyclohexadiene bearing a hydroxy methyl tosylate at C-3.[28] Under basic conditions, 4-halomethyl-substituted-2,5-cyclohexadienone oxime and 5-halomethyl-substituted cyclohexenones[29] also gave the tropones. The ring expansion of a 7-bromo-7-stannyl-substituted bicyclo[4,1,0]heptacyclo-2-ene allowed the synthesis of a 4-stannyl-substituted tropolone en route to colchicine analogues.[30]

In connection with a project directed to extend the synthetic applications of sulfoxides,[31] a systematic study on the behaviour of 4-amino-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienones (*p*-quinamines), such as **1** (Scheme 1), allowed us to establish that the β-amino sulfoxide moiety situated at C-4 increased the reactivity of the cyclohexadienone fragment towards intramolecular conjugate additions, being the ambident nature of the system essential to trigger a series of domino reactions.[32] Thus, a direct synthesis of hydroindolones or carbazolones **4** could be achieved in the titanium-promoted conjugate addition of the amino group of *p*-quinamine **1** to α,β-unsaturated ketones, which was followed by



Scheme 1. Synthetic applications of [(*p*-tolylsulfinyl)methyl]-*p*-quinamines **1** and **3** and *p*-quinol **2**.

an intramolecular 1,4-addition of the resulting enolate to the cyclohexadienone system. With acyclic enones, a highly stereoselective domino sequence involving two (Scheme 1, route A) or four conjugate additions (route B) occurred, leading to the azatricyclic framework **5**.[32a] Moreover, several polyheterocyclic cage compounds, such as **6** (X=NH),[32b] were stereoselectively synthesised by taking advantage of the reaction occurring between **1** and 2-trimethylsilyloxyfuran in the presence of Bu_4NF, which triggered a sequence of three conjugate additions affording **6** in a single step (Scheme 1, route C). A similar behaviour was observed for such reactions of the *p*-quinol derivative **2**. Both **1** and **2** behave like natural quinol metabolites, giving rise to a trimerisation process through a domino sequence of four conjugate additions (Scheme 1, route D).[32c] Thus, upon treatment of **1** with LiCl, the pentacyclic compound **7** (X=NH) was formed, whereas the analogue derivative **8** (X=O) resulted from *p*-quinol **2** in the presence of NaH (Scheme 1, route D). In both cases, four new bonds and eight stereogenic centres were formed in a single step. To complete the systematic study of the *p*-quinamine behaviour, we submitted compound **1** to a treatment with NaH. To our surprise, a rather different evolution was observed, with 4-amino cycloheptatrienone **9** detected (Scheme 1, route E). When the amino group of **1** was protected with a Boc group (Boc=*tert*-butoxycarbonyl), the NaH treatment gave rise to *N*-Boc-4-aminotropone **10** in an almost quantitative yield. We also showed that the ring expansion could take place from [(*p*-tolylsulfonyl)methyl]-*p*-quinamines. An inspection of the published work revealed that 4-aminotropones had only been synthesised in a stepwise manner from 4-aminotropolone sulphate[33] and 4-hydroxytropone.[34] The formation of *N*-Boc-4-aminotropone **10** was assumed to proceed from an initial α-sulfinyl carbanion **I**, resulting upon basic treatment of the *p*-quinamine **3**, which evolved to a norcaradiene-like intermediate **II**,[35,36] by an intramolecular 1,4-addition on the cyclohexadienone moiety. A subsequent elimination of the *p*-toluene sulfenate anion from this intermediate occurred with simultaneous ring expansion leading to **10** (Scheme 2). The sulfenate anion could be trapped with CH_3I forming methyl *p*-tolylsulfoxide. In agreement with this mechanism was also the fact that the [(*p*-tolylsulfonyl)methyl]-*p*-quinamine **11** behaved similarly. The efficiency of this new domino reaction, along with the lack of a general synthetic approach to 4-aminotropones, moved us to extend our methodology to the synthesis of alternatively substituted derivatives.

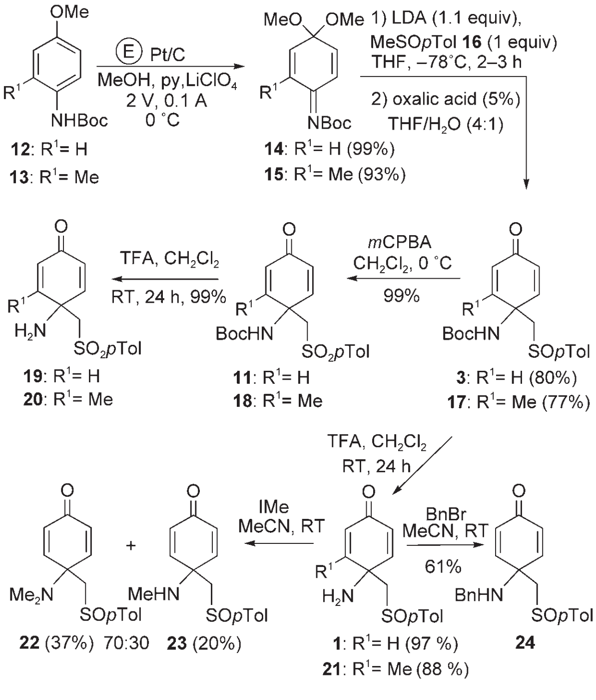


Scheme 2. Proposed mechanism for the formation of *N*-Boc-4-aminotropone **10** from *N*-Boc-[*p*-(tolylsulfinyl)methyl] and [*p*-(tolylsulfonyl)-methyl]-*p*-quinamines **3** and **11**.

We first focused on regioselective access to alkyl-substituted 4-aminotropones and then turned our attention to other analogues containing alternate nitrogen substituents. We now report the regioselective synthesis of new 4-aminotropones including enantiopure derivatives incorporating a proline amide, the asymmetric Diels–Alder reactions of which are studied. To our knowledge, this represents the first synthesis of an enantiopure 4-aminotropone. An important improvement of the synthesis, which allows significant atom economy, has been achieved by using $(CH_3)_2SO_2$ as the starting material. Our previous work is also discussed in full detail including results not described in our earlier communication.[37]

Results and Discussion

The general route devised to synthesize alternatively substituted *p*-quinamines started from *N*-Boc *p*-anisidine derivatives. In the case of [(*p*-tolylsulfinyl)methyl]-*p*-quinamine **1** and its *N*-Boc-protected derivative **3**, the starting material was *N*-Boc-*p*-anisidine **12** (Scheme 3), which was subjected to a controlled anodic oxidation in a single-cell apparatus by using a cylindrical 5 cm diameter × 5 cm 45 mesh Pt anode



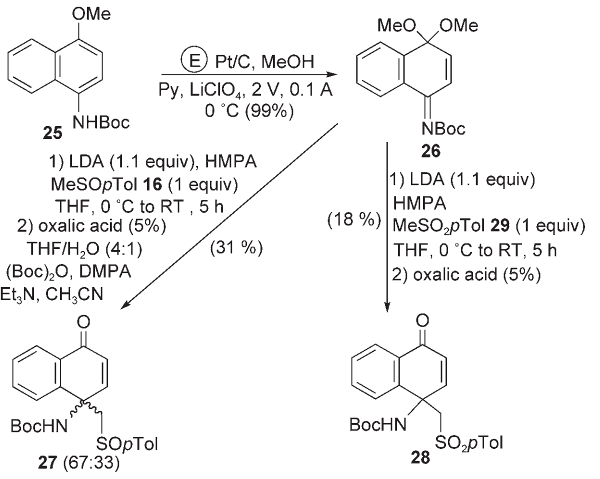
Scheme 3. Synthesis of *p*-[(*p*-tolylsulfinyl)methyl] or *p*-[(*p*-tolylsulfonyl)-methyl]-*p*-quinamines **1**, **3**, **11** and **17–24**.

and a carbon electrode situated inside as a cathode. The electrolysis, which was run in a methanol solution by using $LiClO_4$ as the electrolyte, a current efficiency of 0.1 A at 0 °C and by adding pyridine, afforded *N*-(*tert*-butoxycarbonyl)-4,4-dimethoxy-1-benzoquinonimine (**14**)[38] in a 99 % yield (Scheme 3).

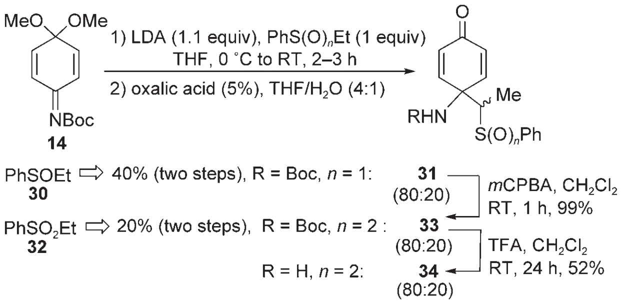
Addition of the lithium anion derived from methyl *p*-tolylsulfoxide **16** to the imine **14**, followed by ketal hydrolysis with aqueous oxalic acid gave the *p*-quinamine **3** in 80 % overall yield (Scheme 3). To evaluate the influence of the presence of a sulfoxide or a sulfone in the starting *p*-quinamines on the overall yield of the aminotropones, we planned to synthesize *p*-quinamines **11** and **19** (Scheme 3). Compound **11** was obtained from *m*CPBA (*meta*-chloroperbenzoic acid) oxidation of the sulfoxide **3** in 99 % yield. Removal of the *N*-Boc protecting group from **3** and **11** with TFA (TFA = trifluoroacetic acid) yielded the free NH_2 *p*-quinamines **1** and **19** in 97 and 99 % yield. The synthesis of 3-methyl-substituted sulfinyl derivative **17** was achieved as shown in Scheme 3, by following the above reaction sequence which started from *N*-Boc-2-methyl-*p*-anisidine **13**, after electrochemical oxidation (**15**, 93 %), α-lithium sulfinyl carbanion addition and ketal hydrolysis. *N*-Boc sulfinyl *p*-quinamine **17** was isolated as a mixture of diastereoisomers (77:23) in 77 % yield and was directly oxidised to the sulfone **18** (99 %). The free sulfonyl and sulfinyl amines **20** and **21** resulted in 99 and 88 % yield, respectively, by treatment of **18** and **17** with TFA. *N*-Alkyl-substituted *p*-[(*p*-tolylsulfinyl)-methyl]-*p*-quinamines (*N*,*N*-dimethyl- **22**, *N*-methyl- **23** and *N*-benzyl- **24**) were obtained by following established literature protocols[39] from the NH_2-free *p*-quinamine **1**, as depicted in Scheme 3, by simple treatment with the corresponding alkylating agent (MeI or BnBr) in acetonitrile.

The synthesis of the naphthoquinamine derivatives **27** and **28** was performed similarly. The electrochemical oxidation of *N*-Boc-1-methoxy-4-aminonaphthalene **25** quantitatively yielded the naphthoquinonimine monoketal **26**. Addition of the α-lithium anion derived from methyl *p*-tolylsulfoxide **16** to the imine group was followed by hydrolysis of the ketal group to give the desired 4-[(*p*-tolylsulfinyl)methyl]-4-naphthoquinamine **27** as a 67:33 mixture of C-4 epimers. This reaction proved to be difficult to reproduce due to the instability of **26**. After laborious experimentation, we could establish that the best results were achieved when freshly prepared **26** reacted with the lithium anion in the presence of HMPA (HMPA = hexamethylphosphoramide) at 0 °C. Under these conditions, after hydrolysis of the ketal group and protection of the free NH_2, naphthoquinamine **27** (67:33 mixture of epimers) could be isolated in 31 % yield by flash chromatography (Scheme 4).[40]

Due to the difficulties encountered to oxidize this sulfinyl derivative to the corresponding sulfone **28**, we tried the reaction of *N*-Boc-4,4-dimethoxy-1-naphthoquinonimine **26** with the lithium anion derived from methyl-*p*-tolylsulfone **29**. Although *p*-[(*p*-tolylsulfonyl)methyl]-*p*-naphthoquinamine (**28**) was obtained, we could never improve the low 18 % yield (Scheme 4). The synthesis of *p*-quinamines **31**, **33** and **34** with a methyl substituent α to the sulfur function was achieved as shown in Scheme 5 from the common *p*-quinonimine monoketal **14** precursor. The addition of the α-lithium carbanion derived from ethyl phenylsulfoxide **30** to **14** afforded, after acidic hydrolysis of the ketal group, compound **31** as a 80:20 mixture of epimers at the C-α sulfur, in 40 % yield (2 steps).

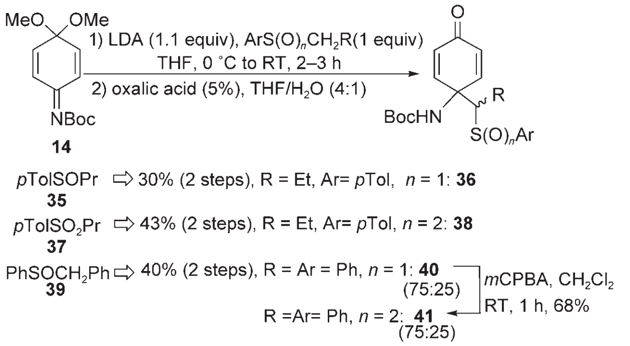


Scheme 4. Synthesis of *p*-[(*p*-tolylsulfinyl)methyl] and *p*-[(*p*-tolylsulfonyl)methyl]-*p*-naphthoquinamines **27** and **28**.



Scheme 5. Synthesis of *p*-[(1′-phenylsulfinyl or sulfonyl)ethyl]-*p*-quinamines **31**, **33** and **34**.

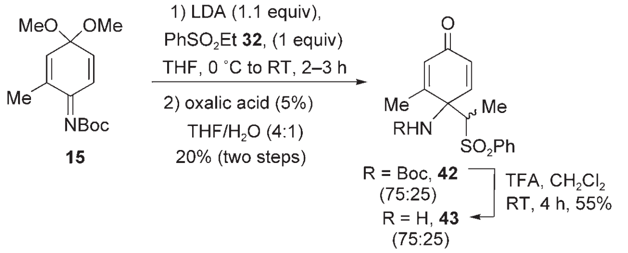
By starting from the lithium anion derived from ethyl phenyl sulfone **32**, the addition to the imine group of **14** gave the sulfonyl *p*-quinamine derivative **33**, also as a 80:20 mixture of epimers, in a lower 20 % yield. Compound **33** was also accessible by *m*CPBA oxidation of **31** in quantitative yield. Deprotection of the *tert*-butoxycarbonyl group led to NH_2-free *p*-quinamine **34** (80:20 mixture of epimers), as depicted in Scheme 5. The addition of the α-lithium carbanion derived from *p*-tolyl propyl sulfoxide **35** to the *p*-quinonimine monoketal **14** afforded, after acidic hydrolysis of the ketal group, compound **36**, which was isolated as a single diastereomer in 30 % yield (2 steps; Scheme 6). The sulfonyl *p*-quinamine derivative **38** resulted in a similar sequence from **14** and the anion derived from *p*-tolyl propyl sulfone **37** producing **38** in 43 % yield. Reaction of **14** with the lithium anion derived from benzyl phenyl sulfoxide **39** led to the



Scheme 6. Synthesis of *p*-[(1′-*p*-tolylsulfinyl or sulfonyl)propyl]-*p*-quinamines **36** and **38** and *p*-[(1′-phenylsulfinyl or sulfonyl)benzyl]-*p*-quinamines **40** and **41**.

p-quinamine **40** as a 75:25 mixture of epimers, after oxalic acid hydrolysis in 40 % yield. *m*CPBA oxidation of **40** gave rise to **41** in 68 % yield (Scheme 6).

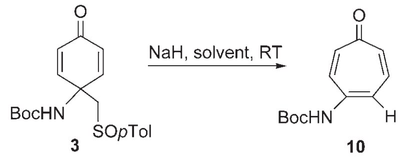
Finally, the synthesis of the *p*-quinamines **42** and **43**, bearing a double substitution at the cyclohexadienone moiety and at the carbon atom α to the sulfur function, was achieved by reaction between 2-methyl *p*-quinonimine monoketal **15**[38] and the α-lithium carbanion derived from ethyl phenylsulfone **32** under similar conditions (Scheme 7). In this case, the use of a lithium anion derived from PhSOEt did not give the addition on the imine group. The final *p*-quinamine **42** could be isolated in a 20 % yield (two steps) as a 75:25 mixture of epimers. Deprotection of the *tert*-butoxycarbonyl group of **42** led to the NH_2-free *p*-quinamine **43** in a 55 % yield. With the starting *p*-quinamines in hand, we checked their behaviour in the presence of a base to promote the synthesis of alternatively substituted 4-aminotropones.



Scheme 7. Synthesis of 3-methyl-*p*-[(1′-phenylsulfonyl)ethyl]-*p*-quinamines **42** and **43**.

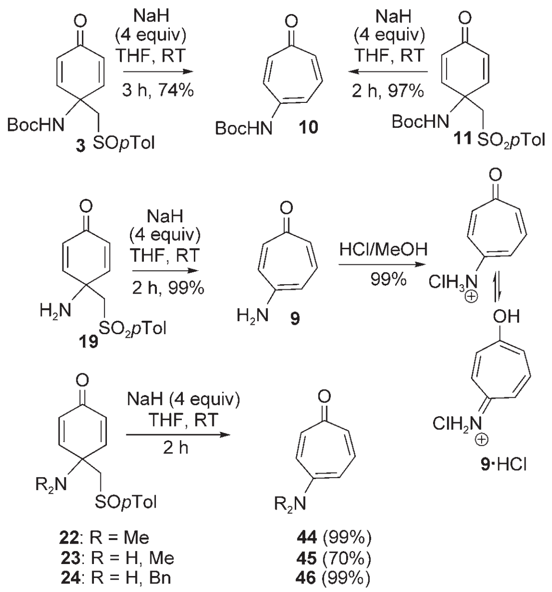
To establish the best conditions, we studied the reaction of the simplest *N*-Boc-[*p*-(tolylsulfinyl)methyl]-*p*-quinamine **3** in the presence of different bases, such as K_2CO_3, NaOH, NaH, LDA, KHMDS and LiHMDS, and by using different solvents or mixtures of solvents (H_2O, CH_3CN, THF, CH_2Cl_2). In all cases, we observed the formation of *N*-Boc-4-aminotropone **10**, but the conversion was highly dependent on the base chosen, the number of equivalents used and the solvent. Best conversions were achieved with NaH at room temperature, but the amount of base was critical to reach a useful yield. As shown in Table 1, when one equivalent of NaH was used in dry THF, only traces of *N*-Boc-4-aminotropone **10** were detected after 6 h (entry 1). By using two equivalents of NaH, a 54 % yield of **10** could be isolated after flash column chromatography (entry 2). When an excess of the base was added, working in THF, a 74 % yield of **10**[41] was isolated after 3 h at room temperature (4 equiv, entry 3). This was the best result as when other solvents were used in the presence of such an excess of the base (CH_2Cl_2, CH_3CN and toluene, entries 4–6) lower yields resulted.

Table 1. Reaction of **3** with NaH at room temperature in different solvents.



Entry	NaH [equiv]	Solvent	*t* [h]	Yield of **10** [%]
1	1	THF	6	traces
2	2	THF	2	54
3	4	THF	3	74
4	4	CH_2Cl_2	2	11
5	4	CH_3CN	2	21
6	4	toluene	2	33

We then used these conditions as the standard en route to alternatively substituted 4-aminotropones. As shown in Scheme 8, upon treatment with NaH (4 equiv) in THF at room temperature, the analogue *N*-Boc-*p*-[(*p*-tolylsulfonyl)-methyl] *p*-quinamine **11** evolved in a shorter time giving rise

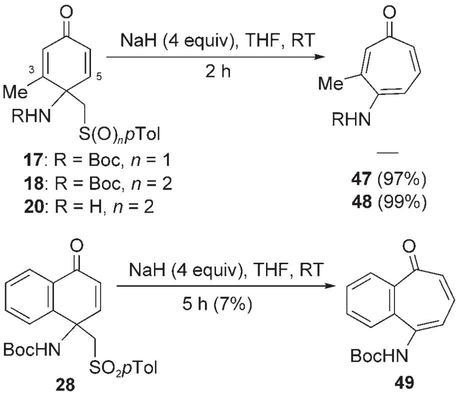


Scheme 8. Synthesis of 4-aminotropones **9**, **10** and **44**–**46** from *p*-[*p*-tolylsulfinyl)methyl]-*p*-quinamines **3** and **22**–**24** and *p*-[*p*-tolylsulfonyl)methyl]-*p*-quinamines **11** and **19**.

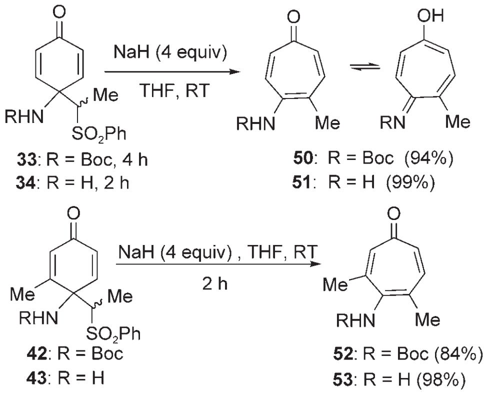
to the *N*-Boc-4-aminotropone **10** in an almost quantitative yield (97 %, Scheme 8). The better yield obtained from the sulfone bearing *p*-quinamine **11** was in agreement with the mechanism proposed in Scheme 2, as the best quality of the *p*-toluene sulfinate anion, namely its leaving-group ability, relative to the *p*-toluene sulfenate anion, which was lost from the analogue sulfoxide **3**, facilitated the ring-expansion step. The NH_2-free sulfonyl bearing *p*-quinamine **19** quantitatively yielded the free 4-aminotropone **9** (Scheme 8), which could be isolated pure by using a neutral silica gel for the column chromatography. The free amine proved to be highly sensitive to the air atmosphere and could only be indefinitely stored as the hydrochloride salt **9**·HCl which was obtained by treating **9** with a saturated solution of HCl (g) in MeOH (99 % yield).

The ^{13}C NMR spectrum of the final ammonium salt **9**·HCl showed two set of signals that were assigned to the tautomers represented in Scheme 8, resulting from tautomeric equilibrium with the 4-hydroxyiminotropone hydrochloride. The ring expansion was also proven to occur from [(*p*-tolylsulfinyl)methyl]-*p*-quinamines bearing alternate substitution at the nitrogen atom. Thus, as depicted in Scheme 8, the *N*,*N*-dimethyl-, *N*-methyl- and *N*-benzyl-substituted *p*-quinamines **22**, **23** and **24**, successfully afforded the corresponding *N*-substituted-4-aminotropones **44**, **45** and **46** in good to excellent yield (70–99 %).

On the contrary, *N*-Boc-3-methyl-[(*p*-tolylsulfinyl)methyl]-*p*-quinamine **17** remained unchanged upon treatment with NaH. Nevertheless, the *p*-tolylsulfonylmethyl-substituted analogue **18** gave the *N*-Boc-4-amino-3-methyltropone **47** in the presence of NaH in excellent yield (Scheme 9). The 4-amino-3-methyltropone **48**, with the free NH_2, could also be regioselectively obtained in an excellent yield from the corresponding 3-methyl-[(*p*-tolylsulfonyl)methyl]-*p*-quinamine (**20**). Once again, the results matched with the proposed mechanism, as the regioselective formation of **47** and **48** must be a consequence of the initial conjugate addition of the intermediate α-sulfonyl anion **I** (Scheme 2, $n=2$) derived from **18** or **20** to the more electrophilic unsubstituted conjugate position (C-5) of the cyclohexadienone moiety. *N*-Boc amino benzotropone **49** could also be obtained from the *N*-Boc-4-[(*p*-tolylsulfonyl)methyl]naphthoquinamine (**28**) under basic conditions, although in low yield (27 %). When the *p*-quinamines were substituted at the α-carbon atom with respect to the sulfur function with a methyl group, the sulfoxides were recovered unchanged upon treatment with the base, whereas the sulfones gave the ring expansion in good to excellent yields. Thus, *N*-Boc-4-amino-5-methyltropone **50** and the free-amine analogue **51** were accessible from 4-[(1′-phenylsulfonyl)ethyl]-*p*-quinamines **33** and **34** in 94 and 99 % yield, respectively (Scheme 10). Both **50** and **51** showed ^{13}C NMR spectra in $CDCl_3$ in which two sets of signals, assigned to the tautomeric equilibrium shown in Scheme 10, appeared in a 67:33 ratio. When the α-sulfur substituent was an ethyl group, no evolution was observed upon NaH treatment of both the sulfoxide **36**, and the sulfone **38**, with the 5-ethyl amino tropone not detected.

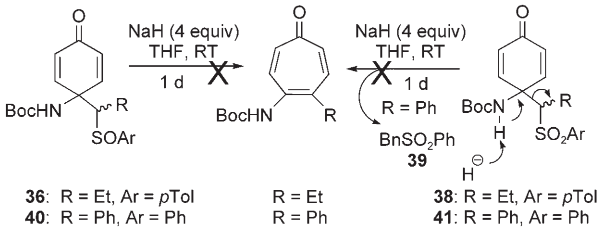


Scheme 9. Synthesis of 4-amino-3-methyltropones **47** and **48** and *N*-Boc-aminobenzotropone **49**.



Scheme 10. Synthesis of 4-amino-5-methyltropones **50** and **51**, and 4-amino-3,5-dimethyltropones **52** and **53**.

A similar result was obtained from 4-(1′-phenylsulfinyl)-phenyl-*p*-quinamine **40** and the sulfone **41**. In the reaction of **41** with NaH, traces of benzyl phenyl sulfone were detected in the crude reaction mixture. This could be a consequence of the formation of a nitrogen anion which could evolve through a retroaddition reaction to produce benzyl phenyl sulfone (Scheme 11). The results shown up to now have provided evidence that the synthesis of 4-aminotropones by basic treatment of [(*p*-tolylsulfinyl)methyl]-substituted *p*-quinamines is a general process when the 2,5-cyclo-

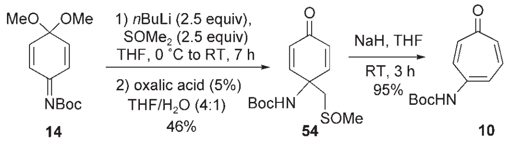


Scheme 11. Reaction of α-ethyl or phenyl-substituted *p*-quinamines **36**, **38**, **40** and **41** with NaH.

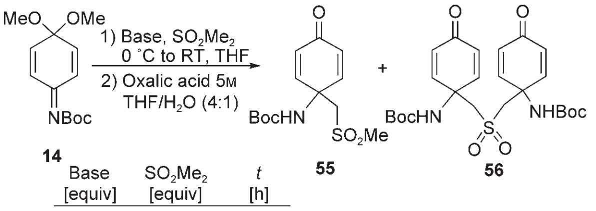
hexadienone moiety of the starting material was unsubstituted and the amine was protected as a Boc. When the starting *p*-quinamine had a free amine and/or a methyl substituent at the cyclohexadienone moiety and at *C*-α to the sulfur function, only the sulfones reacted in basic medium, opening a straightforward access to 4-aminocycloheptatrienones in excellent yields.

The final position of the methyl substituent at C-3 or C-5 of the tropone system can be directed by choosing adequate substitution in the starting materials. Considering all these results as well as the mechanism proposed in Scheme 2 for the formation of the 4-amino tropones, we reasoned that an alkyl sulfoxide or sulfone, instead of the aryl we had previously used, could behave similarly. The interest of changing the sulfur substituent stems on the possibility of using cheaper and commercially available compounds, such as a dimethyl sulfoxide or dimethyl sulfone, instead of methyl *p*-tolyl sulfoxide or the corresponding sulfone, as starting materials to synthesize the *p*-quinamine precursors.

To check the behaviour of an alkyl sulfoxide as a leaving group in the ring-expansion process, we chose to synthesize *p*-quinamine **54** bearing a methyl sulfoxide. Compound **54** was readily obtained from *p*-quinonimine monoketal **14** by addition of the α-lithium carbanion derived from dimethyl sulfoxide[42] generated with *n*BuLi as the base, followed by acidic hydrolysis of the ketal group (Scheme 12, 46 % yield, two steps). Subsequent treatment of a THF solution of **54** with NaH (4 equiv) afforded the *N*-Boc-4-aminotropone **10** in 95 % yield. In a similar reaction sequence, the *p*-[(methylsulfonyl)methyl]-*p*-quinamine **55** could be obtained from *p*-quinonimine monoketal **14** and the anion generated from dimethylsulfone with *n*BuLi, in almost quantitative yield (Scheme 13). When we swapped *n*BuLi with LDA (LDA = lithium diisopropylamide) as the base to produce the α-lithium carbanion of Me_2SO_2,[43] we obtained a mixture of compound **55** and the bis[*N*-(*tert*-butoxycarbonyl)-1′-amino-4′-oxo-2′,5′-cyclohexadienyl]dimethylsulfone (**56**) (bis-*p*-quinamine) which could be separated by column chromatography in 45 and 32 % yields, respectively. Both new *p*-quinamines **55** and **56** were used as the 4-aminotropone precursors. Thus, upon treatment of a THF solution of **55** with NaH, after 3 h at room temperature, *N*-Boc-4-aminotropone **10** was obtained in excellent yield (95 %; Scheme 14). The bis-*p*-quinamine derivative **56** behaved similarly, giving rise to a clean crude mixture in which the *N*-Boc-4-aminotropone **10** was the only product detected (96 % yield). In this case, the formation of **10** must arise from a double domino process, in which two intramolecular conjugate additions must give a double norcaradiene intermediate, such as **III**, the evolution of which through two ring-expansion processes, yielded the tropone derivative. The reaction gave almost pure **10** due to the formation of SO_2 as the only byproduct. Moreover, *N*-Boc-4-aminotropone **10** could also be directly obtained from the mixture of **55** and **56** in 95 % yield. The synthesis of aminotropone **10** from dimethyl sulfone and *p*-quinonimine ketal **14**, through the intermediate formation of bis-*p*-quinamine **56**, is an efficient process that fulfils the criteria of atom economy[44] as both carbon atoms of the methyl groups of the reactant appear in the product, and minimum waste (SO_2) is produced.

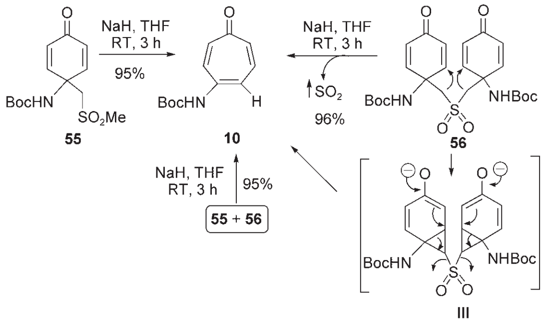


Scheme 12. Synthesis of *N*-Boc-4-aminotropone **10** from *p*-[(methylsulfinyl)methyl]-*p*-quinamine **54**.



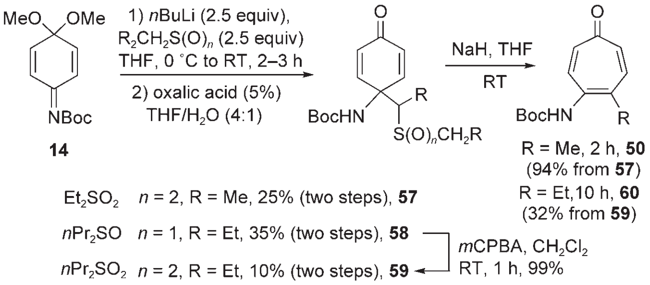
Base [equiv]	SO_2Me_2 [equiv]	*t* [h]	55	56
*n*BuLi 2.5	2.5	1	99 %	–
LDA 3	3	7	45 %	32 %

Scheme 13. Synthesis of *p*-[(methylsulfonyl)methyl]-*p*-quinamine and **55** and bis-*p*-quinamine **56**.



Scheme 14. Synthesis of *N*-Boc-4-aminotropone **10** from *p*-[(methylsulfonyl)methyl]-*p*-quinamine **55** or bis(*p*-quinamine)-substituted sulfone **56**.

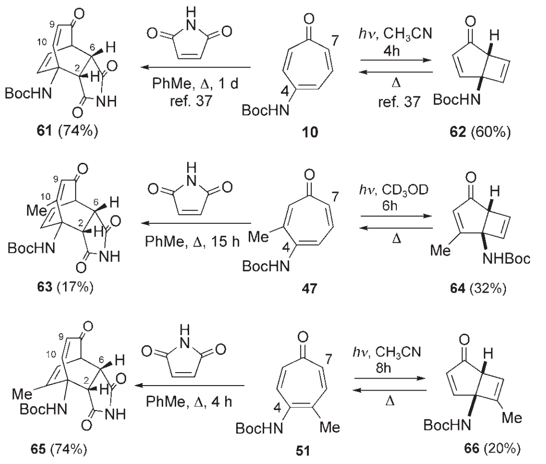
Although less efficient, the synthesis of **10** from the mixture of *p*-[(methylsulfonyl)methyl]-*p*-quinamines **55** and **56** was also economising atoms if compared with the analogue synthesis starting from *p*-tolylsulfoxide or *p*-tolylsulfone. Taking this into account, for the most efficient synthesis of **10** from **56**, we tried to improve the yield of bis-*p*-quinamine **56** by considering that it must arise from compound **55** through the formation of a new α-lithium sulfonyl carbanion reacting with a second equivalent of the *p*-quinonimine monoketal **14**. We thus repeated the reaction of **14** with the anion derived from dimethylsulfone by changing the conditions shown in Scheme 13, mainly the number of equivalents of LDA (up to 4), by using longer reaction times and/or substituting LDA with LHMDS (LHMDS = lithium hexamethyl disilazide). In spite of laborious experimentation, we could never improve the 32 % yield of **56** previously obtained. Other dialkylsulfoxides and sulfones were tested to evaluate the generality of this atom-economic tropone synthesis. Thus, reaction of the α-lithium carbanion resulting from treatment of diethylsulfone (Et_2SO_2) with *n*BuLi (2.5 equiv) with **14**, followed by ketal-group hydrolysis, gave the corresponding *N*-Boc-[(1′-ethylsufonyl)ethyl]-*p*-quinamine **57** in 25 % yield after column chromatography (Scheme 15). Treatment of a THF solution of **57** with NaH gave the desired *N*-Boc-4-amino-5-methyltropone **50** in excellent yield (94 %). Reaction of **14** with the α-lithium anion derived from nPr_2SO gave *N*-Boc-[(1′-propylsulfinyl)propyl]-*p*-quinamine **58** in 35 % yield. The synthesis of the *p*-quinamine sulfonyl analogue **59** by starting from nPr_2SO_2 and **14** gave a low yield (10 %).



Scheme 15. Synthesis of *N*-Boc-4-amino-5-alkyltropones **50** and **60** from alkylsulfinyl (or sulfonyl)-substituted *p*-quinamines **57**–**59**.

A much better yield of the sulfonyl derivative **59** was achieved by using *m*CPBA oxidation of **58** (99 % yield, Scheme 15). Upon treatment with NaH, the sulfinyl derivative **58** remained unaltered whilst the *N*-Boc-4-amino-5-ethyltropone **60** resulted from the sulfone **59** in 32 % yield. Up to now, the lack of an efficient method to synthesise 4-amino tropones had kept their reactivity unexplored. The preliminary studies we had carried out[37] on the reactivity of **10** had provided evidence that the 4-amino cycloheptatrienone system behaved as a diene through the C4–C7 fragment by reaction with maleimide giving the *endo* adduct **61** in a highly stereoselective manner (Scheme 16). Upon irradiation, *N*-Boc-4-aminotropone **10** suffered a 4π-electrocyclisation process giving rise to the *cis*-bicyclo[3.2.0]hepta-3,6-dien-2-one derivative **62**, with a protected bridged nitrogen function in a 60 % yield. Heating compound **62** (40 °C) promoted the reversible cyclobutene opening to regenerate **10** in 99 % yield (Scheme 16). Taking into account these results, we decided to extend the reactivity studies to the new 3-methyl- and 5-methyl-substituted *N*-Boc-4-aminotropones **47** and **50** we had synthesised.

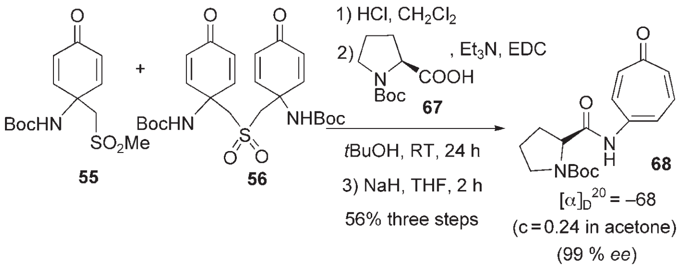
N-Boc-4-amino-3-methyltropone **47** reacted as a diene with maleimide in refluxing toluene to give adduct **63**, resulting from *endo* cycloaddition through the C-4–C-7 diene fragment, in a low 17 % yield. The similar reaction between the 5-methyl-substituted tropone **50** and maleimide, gave a much better yield (74 %) of the *endo* adduct **65**. This was expected on the basis of the activating effect of the methyl group situated at C-5 of the diene partner. The structure of both **63** and **65** was secured by NOESY experiments. The poor yield obtained from **47** could be due to the presence of the 3-methyl substituent existent in the cyclic diene which could be sterically hindering the *endo* approach of the maleimide.



Scheme 16. Diels–Alder reactions and 4π-electrocyclisations of *N*-Boc-4-aminotropones **10**, **47** and **50**.

When the 3,5-dimethyl-substituted tropone **52** was underwent reaction with maleimide under refluxing toluene, only a complex reaction mixture resulted. The photocyclisation of **47** and **50** also occurred upon irradiation of CH_3CN solutions, but the conversion of the starting materials was lower than that observed from the unsubstituted amino tropone **10**. The *cis*-*N*-Boc-1-amino-2-methylbicyclo[3.2.0]hepta-3,6-dien-2-one **64** and the 7-methyl-substituted analogue **66** were isolated in 32 and 20 % yields, respectively (Scheme 16). Taking into account the high *endo* selectivity achieved in these Diels–Alder reactions, as well as the presence of the amino group in the tropone core, we decided to extend our synthetic methodology to a novel enantiopure 4-aminotropone **68**, incorporating a proline unit in the amine function, and explore its asymmetric reactions. The synthesis of tropone **68** started from a 2:1 mixture of *p*-quinamines **55** and **56** the transformation of which into **68** occurred in a 56 % overall yield by following the reaction sequence summarised in Scheme 17. Thus, upon treatment of the mixture of **55** and **56** with concentrated HCl in CH_2Cl_2, cleavage of the *N*-*tert*-butoxycarbonyl groups was achieved, forming the hydrochlorides of the free *p*-quinamines. After evaporation to dryness, a solution of *N*-Boc-protected (*S*)-proline **67**, Et_3N and EDC was immediately added. The resulting crude mixture was washed with a diluted solution of HCl and evaporated to dryness before adding THF and NaH. After 2 h stirring at room temperature, enantiopure amide **68**[45] was isolated in 56 % yield (three steps; Scheme 17).

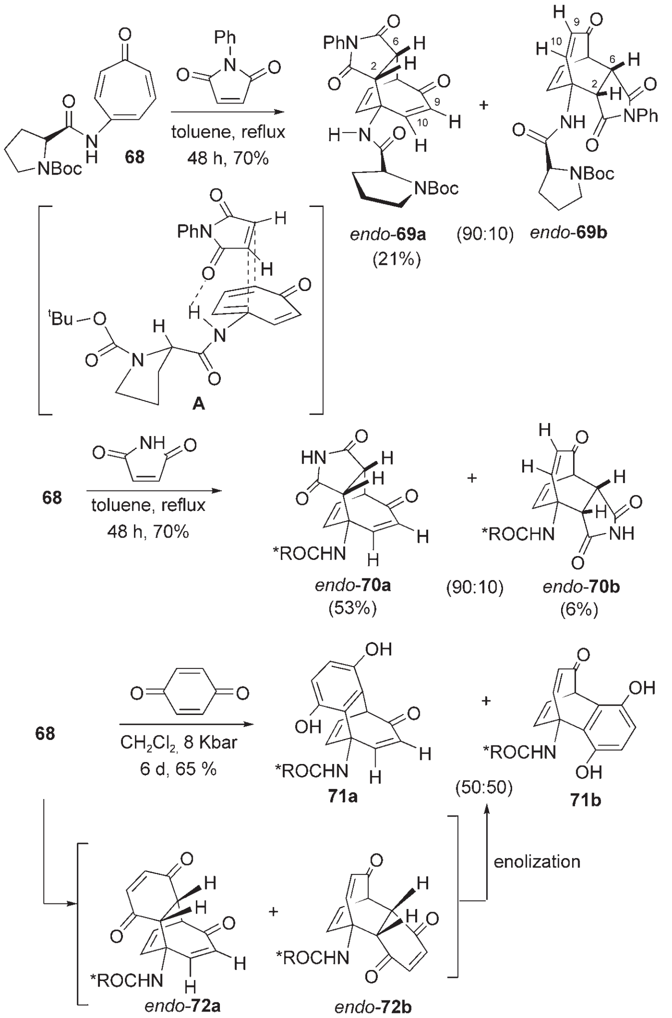
The Diels–Alder reaction of enantiopure (*S*)-aminotropone **68** with *N*-phenylmaleimide took place in refluxing toluene to give, after 48 h, a 90:10 mixture of diastereomeric



Scheme 17. Synthesis of enantiopure {(*S*)-4-amino-[1′-(*tert*-butoxycarbonyl)pyrrolidine]-2′-carboxamide}tropone (**68**) from sulfonyl-*p*-quinamines **55** and **56**.

endo adducts **69a** and **69b** that were separated by flash column chromatography. The major cycloadduct **69a** was thus obtained diastereomerically pure in 21 % yield, whereas a 50:50 mixture of **69a** and **69b** was obtained in a second fraction in 49 % yield. The overall yield of the cycloaddition was thus 70 % (Scheme 18).

The *endo* structure of both diastereomers was established on the basis of the ^{1}H NMR spectroscopic parameters obtained from the spectra registered at 353 K, as at room temperature, broad signals were observed. The values of the coupling constants and NOESY experiments were essential for such a structural assignment. The cross peaks observed between the hydrogens situated at C-2 and C-10 appearing at $\delta = 3.81$ and 7.14 ppm, respectively, and C-6 and C-9, $\delta = 3.46$ and 5.78 ppm, respectively, in the major diastereoisomer **69a** was evidence of their spatial proximity. Similar correlations were observed in the minor diastereomer **69b**. Moreover, the relative configuration of the major component **69a** was secured by X-ray diffraction (Figure 1).[46]



Scheme 18. Asymmetric Diels–Alder reaction of enantiopure **68**.

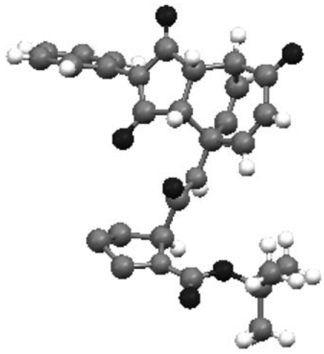
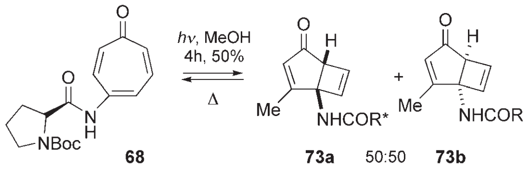


Figure 1. X-ray ORTEP of Diels–Alder adduct **69a**.

Taking into account the *S* absolute configuration of the proline moiety, the absolute configuration was established as (1*R*,2*R*,6*R*,7*S*) for **69a** and (1*S*,2*S*,6*S*,7*R*) for **69b**. Similar results were observed in the asymmetric Diels–Alder reaction of **68** with maleimide. The 90:10 mixture of *endo* adducts **70a** and **70b** could be separated in 53 and 6 % yields, respectively. The structures of both adducts were established by comparison of their NMR spectroscopic parameters with those of **69a** and **69b**. Contrary to our expectations, the cycloaddition of **68** with *p*-benzoquinone did not take place under thermal conditions (refluxing toluene). When the reaction between *p*-benzoquinone and **68** was carried out under high pressure conditions (8 Kbar), the cycloaddition occurred without selectivity giving rise to a 50:50 mixture of diastereomers **71a** and **71b** which must result from the cycloaddition and subsequent enolisation of the initially formed adducts **72a** and **72b** (Scheme 18). The high π-facial diastereoselectivity observed in the reactions of **68** with maleimide derivatives is noteworthy taking into account the structure of the enantiopure diene. The stereoselectivity could be explained on the basis of the transition state A shown in Scheme 18, in which hydrogen bonding between the carbonyl imide group of the dienophile and the amide hydrogen donor of the tropone could act as a transient tether favouring the *endo* approach which led to the major formation of **69a** and **70a** and facilitating the cycloaddition.

The lack of π-facial selectivity observed when *p*-benzoquinone was the dienophile suggested that the lower basicity of the quinonic carbonyl groups was hindering the formation of the intermolecular hydrogen bonding which was responsible for the high reactivity and diastereoselectivity observed with maleimide. Finally, irradiation of a MeOH solution of **68** also produced the 4π-electrocyclisation, yielding a 50:50 mixture of diastereomers **73a** and **73b** (Scheme 19). The polar hydroxylic solvent used for the electrocyclisation could contribute to the lack of diastereoselectivity observed.



Scheme 19. 4π-Electrocyclisation of **68**.

Conclusion

We have reported the regioselective synthesis of a series of substituted 4-aminoptropones by starting from *N*-Boc *p*-anisidines in three steps and good to excellent yields. The successful route involves the initial synthesis of 4-amino-4-[(arylsulfinyl)methyl]-2,5-cyclohexadienones or the analogues aryl or methyl sulfones by addition of an α-lithium sulfinyl or sulfonyl carbanion to the quinoneimine monoketal resulting in the electrochemical oxidation of the starting *N*-Boc *p*-anisidines. Our methodology provides a short and simple access to 4-amino tropones not accessible by other methods, through the basic treatment of the sulfinyl or sulfonyl *p*-quinamines, which triggers a one-pot, domino conjugate addition–ring expansion process. An optically pure amino tropone derivative, including a proline moiety is also described. The proline auxiliary delivers a high level of asymmetric induction in the Diels–Alder reaction with maleimide dienophiles, considering the distance of the chiral unit from the reactive centres.

Experimental Section

General: Melting points were obtained in open capillary tubes. ^{1}H NMR spectra were recorded at 500 or 300 MHz and ^{13}C NMR spectra were recorded at 125 or 75 MHz. All reactions were monitored by TLC, which was performed on precoated silica gel 60 F254 plates. Flash column chromatography was carried out with silica gel 60 (230–240 mesh). Diisopropylamine was used freshly distilled over KOH in each case. NaH was washed before use with several portions of hexane. Reagent quality solvents, such as THF, CH_3CN, CH_2Cl_2 and toluene, were dry purchased and kept under an argon atmosphere over activated 4 Å molecular sieves. Compounds **1**, **3**, **9**, **14**, **15**, **17**, **21**, **26**, **47**, **48**, **51**, **61** and **62** were synthesised as previously reported.[32,38]

General procedure for the synthesis of *p*-quinamines: **Method A**: A solution of *n*BuLi (2.6 M in hexanes, 1.1 equiv) was added dropwise to a solution of diisopropylamine in THF (0.5 M, 1.2 equiv) cooled to −78 °C. The resulting solution was stirred for 20 min. After this time, a solution of the corresponding sulfoxide or sulfone in THF (0.5 M, 1 equiv) at −78 °C was slowly added. After 30 min at this temperature, a solution of the corresponding *p*-benzoquinonimine ketal in THF (0.3 M 1.0 equiv) was added dropwise. The resulting solution was stirred at −78 °C (the reaction time is indicated in each case). The mixture was hydrolyzed with saturated NH_4Cl and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and the solvents were removed under reduced pressure. The resulting material was treated with a 5 % oxalic acid in a mixture of THF/H_2O 4:1. When the reaction was finished (reaction time is indicated), a saturated solution of $NaHCO_3$ was added and the aqueous phase was extracted with AcOEt (×3). The organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The obtained material was purified by flash column chromatography on silica gel. The eluents are indicated in each case.

General procedure for the oxidation of sulfoxides to sulfones: **Method B**: A solution of *m*CPBA (1.15 equiv) in CH_2Cl_2 (0.2 M) was slowly added to a solution of the corresponding sulfinyl *N*-Boc protected *p*-quinamine (1.0 equiv) in CH_2Cl_2 (0.2 M) cooled to 0 °C. The resulting mixture was stirred at 0 °C until no starting material could be detected by TLC (reaction time is indicated in each case). Then the organic phase was washed sequentially with $NaHSO_3$ 40 %, saturated $NaHCO_3$ and brine. The organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The final sulfone was purified by flash column chromatography on silica gel. The eluents are indicated in each case.

General procedure for the deprotection of Boc group: **Method C**: TFA (1.1 mmol, 10 equiv) was added at RT to a solution of the corresponding *N*-Boc-protected *p*-quinamine (0.11 mmol, 1 equiv) in CH_2Cl_2 (0.6 M). The resulting solution was stirred at RT for the time indicated in each case and then NaOH (2 N) was added at 0 °C until pH 12 was reached. The organic phase was extracted and washed with brine (×2). The organic extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude reaction was purified by flash column chromatography. Eluents are indicated in each case.

General procedure for the synthesis of 4-aminotropones from *p*-quinamines: **Method D**: NaH (4 equiv) at RT was added to a solution of the corresponding *p*-quinamine (1 equiv) in THF (0.2 M). The reaction was stirred under an argon atmosphere for the time indicated in each case. Then the mixture was diluted with CH_3CN and filtered over Celite. The solvents were removed under reduced pressure and the crude purified by flash column chromatography (eluents indicated in each case).

***N*-(*tert*-Butoxycarbonyl)-4-amino-3-methyl-4-[*p*-(tolylsulfonyl)methyl]-2,5-cyclohexadienone (18)**: Compound **18** was obtained by following method B from of *N*-(*tert*-butoxycarbonyl)-4-amino-3-methyl-4-[*p*-(tolylsulfinyl)methyl]-2,5-cyclohexadienone (**17**; 78 mg, 0.20 mmol, 1.0 equiv) as an orange solid in quantitative yield. Reaction time 1 h; eluent: hexane/AcOEt, 1:1; m.p. 132–134 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9H), 1.96 (s, 3H), 2.45 (s, 3H), 3.00–3.60 (AB system, $J = 13.9$ Hz, 2H), 6.11 (s, 1H), 6.23 (dd, $J = 10.1$, 1.8 Hz, 1H), 6.65 (brs, 1H), 7.25 (d, $J = 10.1$, 1H), 7.37–7.86 ppm (AA′BB′ system, $J = 8.3$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.6$, 21.7, 28.1 (3C), 56.7, 63.1, 80.9, 127.9 (2C), 128.2, 128.6, 130.3 (2C), 136.3, 146.0, 149.5, 153.8, 158.9, 184.5 ppm; MS (EI): *m*/*z* (%): 57 (83), 59 (30), 65 (30), 77 (16), 91 (98), 92 (27), 105 (11), 107 (23), 121 (47), 122 (54), 135 (12), 136 (44), 139 (13), 148 (16), 155 (19), 162 (27), 166 (21), 170 (13), 180 (100), 275 (10), 335 ppm $[M-56]^+$ (11); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{17}NO_5S$ $[M-tBu]^+$: 335.0827; found: 335.0843.

4-Amino-3-methyl-4-[*p*-(tolylsulfonyl)methyl]-2,5-cyclohexadienone (20): Compound **20** was obtained by following method C from **18** (40 mg, 0.10 mmol, 1 equiv) as a colourless oil in quantitative yield. Reaction time 5 h; eluent hexane/AcOEt, 3:1; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 1.82–1.98 (brs, 2H), 2.02 (s, 3H), 2.45 (s, 3H), 3.16–3.60 (AB system, $J = 13.9$ Hz, 2H), 6.05 (d, $J = 1.8$ Hz, 1H), 6.10 (dd, $J = 9.9$, 1.8 Hz, 1H), 7.22 (d, $J = 10.1$, 1H), 7.31–7.77 ppm (AA′BB′ system, $J = 8.5$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.7$, 21.6, 54.6, 63.6, 126.6, 127.9, 128.3, 130.1, 137.0, 145.5, 150.9, 158.7, 185.0 ppm; MS (EI): *m*/*z* (%): 65 (12), 83 (106), 91 (22), 107 (16), 121 (6), 135 (12), 136 (19), 291 $[M]^+$ (1); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{17}NO_5S$: 291.0929 $[M]^+$; found: 291.0928.

***N*,*N*-Dimethyl- and *N*-methyl-4-amino-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone (22) and (23)**: MeI (72 μL, 1.14 mmol, 6 equiv) was added to a solution of 4-amino-4-[*p*-(tolylsulfinyl)methyl]-2,5-cyclohexadienone (**1**) (50 mg, 0.19 mmol, 1 equiv) in CH_3CN (0.5 mL) under an argon atmosphere at room temperature and the resulting mixture was stirred for 3 d. The *N*-methylation products were obtained as a (70:30) mixture of **22** and **23**. The two *p*-quinamines were isolated separately as yellow oils with over 70% conversion after column chromatography (eluent: AcOEt/CH$_3$CN 6:1).

Compound **22**: Yield: 37% (20 mg); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.41 (s, 3H), 2.43 (s, 6H), 2.91–3.08 (AB system, J = 14.0 Hz, 2H), 6.38 (dd, J = 10.3, 1.8 Hz, 1H), 6.44 (dd, J = 10.3, 1.8 Hz, 1H), 6.97 (dd, J = 10.3, 3.3 Hz, 1H), 7.27 (dd, J = 10.3, 3.3 Hz, 1H), 7.29–7.53 ppm (AA′BB′ system, J = 8.3 Hz, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.4, 30.7, 58.2, 67.2, 123.9, 130.2, 130.6, 131.5, 140.7, 142.2, 150.6, 150.7, 185.0 ppm; MS (EI): *m*/*z* (%): 165 (28), 166 (27), 167 (22), 175 (13), 179 (15), 191 (10), 219 (20), 214 (10), 257 (10), 272 (10), 288 (34), 289 [M]$^+$ (100).

Compound **23**: Yield: 20% (11 mg); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.30 (s, 3H), 2.41 (s, 3H), 2.69–3.20 (AB system, J = 13.3 Hz, 2H), 6.34 (dd, J = 10.3, 1.8 Hz, 1H), 6.46 (dd, J = 10.3, 1.8 Hz, 1H), 6.88 (dd, J = 10.3, 3.0 Hz, 1H), 7.06 (dd, J = 10.3, 3.0 Hz, 1H), 7.27–7.56 ppm (AA′BB′ system J = 8.1 Hz, 4H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.4, 39.7, 60.6, 66.6, 123.9, 130.1, 130.4, 131.8, 141.4, 141.9, 147.3, 150.1, 184.7 ppm; MS (EI): *m*/*z* (%): 164 (12), 165 (14), 166 (12), 219 (27), 272 (11), 275 [M]$^+$ (17).

***N*-Benzyl-4-amino-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone (24)**: BnBr (53 μL, 0.44 mmol, 2 equiv) was added to a solution of **1** (58 mg, 0.22 mmol, 1 equiv) in CH$_3$CN (3 mL), under an argon atmosphere at RT. The resulting solution was stirred at RT for 3 d, then the solvent was removed at reduced pressure. The reaction crude was then purified by column chromatography to give **24** as a yellow solid in a 61% yield (47 mg). Eluent: hexane/AcOEt 4:1; m.p. 94–96 °C; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.36 (s, 3H), 2.70–3.18 (AB system, J = 13.3 Hz, 2H), 3.51–3.69 (AB system, J = 12.9 Hz, 2H), 6.28 (dd, J = 10.1, 2.0 Hz, 1H), 6.39 (dd, J = 10.1, 2.0 Hz, 1H), 6.92 (dd, J = 10.1, 3.2 Hz, 1H), 7.07 (dd, J = 10.1, 3.2 Hz, 1H), 7.17–7.32 (m, 5H), 7.28–7.53 ppm (AA′BB′ system, J = 8.3 Hz, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.4, 48.5, 57.9, 67.3, 123.9, 127.3, 128.0, 128.5, 130.1, 130.2, 131.0, 139.6, 140.6, 142.2, 150.9, 151.0, 185.0 ppm; MS (EI): *m*/*z* (%): 165 (28), 166 (25), 167 (20), 175 (38), 177 (20), 211 (10), 121 (36), 219 (21), 220 (16), 258 (12), 260 [M−91]$^+$ (5); HRMS (FAB+): *m*/*z*: calcd for C$_{14}$H$_{14}$NO$_2$S: 260.0745 [M−Bn]$^+$; found: 260.0675.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[*p*-(tolylsulfinyl)methyl]-4*H*-naphthalen-1-one (27)**: Compound **27** was obtained from *N*-(*tert*-butoxycarbonyl)-1,4-naphthoquinonimine dimethyl ketal (**26**) (435 mg, 1.45 mmol, 1 equiv), MeSOTol **16** (223 mg, 1.45 mmol, 1 equiv) and HMPA (1.7 mL, 8.70 mmol, 6 equiv) in THF (5 mL) by following method A. After 5 h stirring, the mixture was treated with Et$_3$N (36 μL, 0.25 mmol, 1 equiv), DMAP (12 mg, 0.1 mmol, 0.5 equiv) and di-*tert*-butyldicarbonate (270 mg, 1.23 mmol, 5 equiv) in refluxing CH$_3$CN (4 mL) for 5 d at RT, to reprotect the unprotected NH$_2$ residues. Compound **27** was finally isolated as a yellow oil in 31% yield as a (66:33) mixture of diastereoisomers. Eluent: hexanes/AcOEt 3:1; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.38 (s, 3H), 2.58–3.31 (AB system, J = 13.5 Hz, 2H), 6.37 (d, J = 10.1 Hz, 1H), 7.09 (d, J = 10.1 Hz, 1H), 7.24–7.65 (m, 5H), 7.72 (t, J = 6.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 8.20 ppm (d, J = 7.9 Hz, 1H); MS (EI): *m*/*z* (%): 57 (100), 59 (52), 63 (18), 65 (23), 75 (12), 77 (25), 91 (51), 92 (31), 102 (20), 127 (27), 128 (90), 139 (48), 140 (47), 156 (50), 172 [M−139]$^+$ (45); HRMS (EI): *m*/*z*: calcd for C$_{11}$H$_{10}$NO: 172.0762 [M−SO*p*Tol]$^+$; found: 172.0766.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[*p*-(tolylsulfonyl)methyl]-4*H*-naphthalen-1-one (28)**: Compound **28** was obtained from **26** (300 mg, 0.99 mmol, 1 equiv) and MeSO$_2$*p*Tol **29** (168 mg, 1.0 mmol, 1 equiv) as an orange oil in 18% yield (77 mg) by following a modified version of method A (the anion was formed at 0 °C, and the reaction was stirred at RT). Reaction time: 5 h; eluent: hexane/AcOEt 4:1; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.50 (s, 9H), 2.42 (s, 3H), 3.16–3.66 (AB system, J = 14.1 Hz, 2H), 6.45 (d, J = 10.5 Hz, 1H), 6.77 (brs, 1H), 7.28–7.74 (AA′BB′ system, J = 10.5 Hz, 4H), 7.41 (dd, J = 14.9, 1.4 Hz, 1H), 7.53 (dd, J = 7.8, 1.4 Hz, 1H), 7.59 (td, J = 7.1, 1.4 Hz, 1H), 7.72 (dd, J = 7.9, 1.4 Hz, 1H), 8.10 ppm (dd, J = 7.9, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.6, 28.0 (3C), 60.3, 66.5, 80.8, 125.0, 127.2 (2C), 127.9, 128.3, 128.4, 130.2, 130.5, 133.2 (2C), 136.4, 145.8, 149.9, 153.7, 183.4 ppm; MS (EI): *m*/*z* (%): 57 (100), 65 (26), 77 (18), 91 (69), 115 (17), 127 (18), 128 (57), 143 (17), 156 (34), 158 (97), 172 (52), 184 (37), 198 (21), 202 (58), 216 (67), 311 (10), 327 ppm.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(phenylsulfinyl)ethyl]-2,5-cyclohexadienone (31)**: Compound **31** was obtained from *N*-(*tert*-butoxycarbonyl)-*p*-benzoquinonimine dimethyl ketal (**14**) (300 mg, 1.19 mmol, 1 equiv) and EtSOPh **30** (189 mg, 1.18 mmol, 1 equiv) by following a modified version of method A (the anion was added at 0 °C and the reaction was stirred at RT). The product was produced as a (80:20) mixture of diastereoisomers in 40% yield (172 mg). Yellow oil; reaction time: 4 h; eluent: hexane/AcOEt 1:1; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.80 (d, J = 7.1 Hz, 3H), 1.48 (s, 9H), 3.60–3.79 (m, 1H), 5.51 (s, 1H), 6.32 (dd, J = 10.1, 2.0 Hz, 1H), 6.36 (dd, J = 10.1, 2.0 Hz, 1H), 7.13 (dd, J = 10.1, 3.3 Hz, 1H), 7.29 (dd, J = 10.1, 3.3 Hz, 1H), 7.45–7.59 ppm (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 4.2, 28.3 (3C), 58.1, 63.1, 81.1, 124.1, 129.2, 129.4, 130.7, 130.9, 141.7, 145.4, 146.7, 154.6, 184.6 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (14), 64 (13), 77 (19), 78 (30), 91 (21), 108 (16), 124 (14), 125 (28), 136 (21), 180 (50), 236 [M−125]$^+$ (2); HRMS (EI): *m*/*z*: calcd for C$_{13}$H$_{18}$NO$_5$: 236.1287 [M−SOPh]$^+$; found: 236.1283.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(phenylsulfonyl)ethyl]-2,5-cyclohexadienone (33)**: Compound **33** was obtained pure by following method B from *N*-(*tert*-butoxycarbonyl)-4-amino-4-[1′-(phenylsulfinyl)ethyl]-2,5-cyclohexadienone (**31**) (32 mg, 0.09 mmol, 1.0 equiv) as a yellow oil in 99% yield (33 mg). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.10 (d, J = 7.1 Hz, 3H), 1.48 (s, 9H), 3.77–3.89 (m, 1H), 6.35 (dd, J = 9.9, 2.0 Hz, 1H), 6.45 (dd, J = 9.9, 2.0 Hz, 1H), 6.51 (s, 1H), 7.01 (dd, J = 10.1, 3.3 Hz, 1H), 7.27 (dd, J = 10.1, 3.3 Hz, 1H), 7.51–7.73 (m, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.92 ppm (d, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.5, 28.2 (3C), 57.8, 62.1, 80.9, 128.6 (2C), 129.4 (2C), 129.5, 130.8, 134.3, 138.5, 145.0, 147.5, 154.3, 184.7 ppm; MS (EI): *m*/*z* (%): 55 (100), 59 (10), 77 (32), 78 (19), 91 (16), 105 (10), 108 (321), 109 (12), 136 (21), 151 (11), 161 (10), 169 (40), 180 (42), 321 ([M−56]$^+$, 1); HRMS (EI): *m*/*z*: calcd for C$_{15}$H$_{15}$NO$_5$S: 321.0671 [M−*t*Bu]$^+$; found: 321.0683.

4-Amino-4-[1′-(phenylsulfonyl)ethyl]-2,5-cyclohexadienone (34): Compound **34** was obtained from *N*-(*tert*-butoxycarbonyl)-4-amino-4-[1′-(phenylsulfonyl)ethyl]-2,5-cyclohexadienone (**33**) (42 mg, 0.11 mmol, 1.0 equiv) by following method C. The product was isolated as a white solid in 52% yield (16 mg) as a (80:20) mixture of epimers. Reaction time: 24 h; eluent: hexane/AcOEt 3:1; m.p. 128–130 °C (hexane/AcOEt); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.10 (d, J = 7.1 Hz, 3H), 2.27 (s, 2H), 3.42 (q, J = 7.1 Hz, 1H), 6.25 (dd, J = 10.1, 1.8 Hz, 1H), 6.30 (dd, J = 10.1, 1.8 Hz, 1H), 6.64 (dd, J = 10.2, 3.2 Hz, 1H), 7.43 (dd, J = 10.2, 3.2 Hz, 1H), 7.60 (d, J = 7.9 Hz, 2H), 7.65–7.73 (m, 1H), 7.93 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 12.2, 56.8, 65.9, 128.3, 128.5, 129.2, 129.4 (2C), 134.2, 138.9, 149.1, 150.0, 184.8 ppm; MS (EI): *m*/*z* (%): 57 (100), 65 (20), 67 (21), 69 (58), 71 (42), 77 (77), 78 (41), 79 (23), 81 (28), 83 (33), 85 (23), 91 (36), 95 (22), 97 (27), 105 (19), 107 (21), 121 (23), 135 (34), 136 (90), 148 (25), 208 (18), 277 [M]$^+$ (4); HRMS (EI): *m*/*z*: calcd for C$_{14}$H$_{15}$NO$_5$S: 277.0773 [M]$^+$; found: 277.0765.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(*p*-tolylsulfinyl)propyl]-2,5-cyclohexadienone (36)**: Compound **36** was obtained from **14** (276 mg, 1.09 mmol, 1 equiv) and PrSO*p*Tol (**35**) (200 mg, 1.09 mmol, 1 equiv) by following a modified version of method A (the anion was formed with 2 equiv of *n*BuLi and 1 equiv of PrSO*p*Tol, and the addition was carried out at 0 °C). The product was formed as a single diastereoisomer and as a white solid in 30% yield (130 mg). Reaction time: 2 h; eluent hexane/AcOEt 2:1; m.p. 128–130 °C (hexane/AcOEt); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.28 (t, J = 7.4 Hz, 3H), 0.92–1.11 (m, 1H), 1.46 (s, 9H), 1.84 (dq, J = 7.1, 7.1 Hz, 1H), 2.40 (s, 3H), 3.40–3.52 (m, 1H), 5.60 (brs, 1H), 6.34 (d, J = 9.0 Hz, 1H), 6.37 (d, J = 9.0 Hz, 1H), 7.11, 7.34 (dd, J = 10.5, 2.4 Hz, 2H), 7.22–7.47 ppm (AA′BB′ system, J = 8.1 Hz, 4H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.4, 14.9, 21.3, 28.2 (3C), 58.4, 70.2, 81.0, 124.0, 129.4, 129.9, 131.0, 138.0, 141.2, 145.7, 146.9, 154.5, 184.6 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (11), 65 (22), 77 (15), 79 (19), 91 (55), 92 (49), 105 (13), 121 (13), 123 (17), 133 (35), 134 (32), 139 (28), 140 (46), 149 (46), 193 (30), 194 (31), 205 (60), 249 (98), 279 (10), 316 (20), 330 [M−58]$^+$, 159.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(*p*-tolylsulfonyl)propyl]-2,5-cyclohexadienone (38)**: Compound **38** was obtained from **14** (253 mg, 1.00 mmol, 1 equiv) and $PrSO_2pTol$ **37** (200 mg, 1.00 mmol, 1 equiv) by following a modified version of method A (the anion was formed with 2.2 equiv of *n*BuLi, and the addition was done at 0 °C). The product was formed as an orange oil in 43 % yield (174 mg). Reaction time: 2 h; eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.3$ Hz, 3 H), 1.27–1.49 (m, 1 H), 1.42 (s, 9 H), 1.61–1.79 (m, 1 H), 2.47 (s, 3 H), 3.88–4.03 (m, 1 H), 6.34 (dd, $J = 10.1$, 1.6 Hz, 1 H), 6.42 (dd, $J = 10.1$, 1.6 Hz, 1 H), 6.70 (br s, 1 H), 6.98 (dd, $J = 10.3$, 3.0 Hz, 1 H), 7.28 (dd, $J = 10.3$, 3.0 Hz, 1 H), 7.34–7.82 ppm (AA′BB′ system, $J = 7.9$ Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.6$, 19.0, 21.7, 28.2 (3 C), 58.2, 65.2, 69.1, 125.4, 128.7, 129.9, 130.0, 131.1, 136.0, 144.9, 147.0, 154.9, 184.6 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (21), 65 (40), 77 (22), 91 (93), 92 (43), 106 (20), 108 (96), 109 (35), 133 (20), 134 (25), 139 (23), 148 (21), 150 (39), 176 (22), 183 (19), 194 (47), 208 (86), 250 (70), 405 $[M]^+$ (3); HRMS (EI): *m*/*z*: calcd for $C_{27}H_{27}NO_5S$: 405.1610 $[M]^+$; found: 405.1605.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(phenylsulfinyl)benzyl]-2,5-cyclohexadienone (40)**: Compound **40** was obtained from **14** (50 mg, 0.19 mmol, 1 equiv) and BnSOPh (**39**) (325 mg, 1.50 mmol, 1 equiv) by following a modified version of method A (the anion addition was formed at 0 °C and the reaction mixture stirred at RT). The product was formed as a (75:25) mixture of diastereoisomers and as a colourless oil in 40 % yield (253 mg). Reaction time: 5 h; eluent: hexane/AcOEt 2:1; mixture of diastereomers: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.51$ (s, 9 H), 1.59 (s, 9 H), 4.22 (s, 1 H), 4.24 (s, 1 H), 5.92 (dd, $J = 10.1$, 2.0 Hz, 1 H), 6.65 (dd, $J = 10.1$, 2.0 Hz, 1 H), 5.94 (dd, $J = 10.1$, 1.8 Hz, 1 H), 6.19 (dd, $J = 10.1$, 1.8 Hz, 1 H), 6.41 (dd, $J = 9.1$, 3.0 Hz, 1 H), 6.69 (dd, $J = 9.1$, 3.0 Hz, 1 H), 6.75 (dd, $J = 10.1$, 3.0 Hz, 1 H), 7.60 (dd, $J = 10.1$, 3.0 Hz, 1 H), 7.08–7.50 ppm (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.2$ (6 C), 58.3, 59.4, 64.9, 76.3, 80.2, 80.9, 123.7, 124.8, 127.2, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 129.2, 129.3, 130.3, 130.5, 131.6, 131.7, 132.2, 132.3, 141.6, 141.8, 144.1, 144.6, 148.1, 148.7, 153.9, 154.4, 184.1, 184.5 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (23), 65 (18), 77 (48), 78 (48), 83 (57), 85 (37), 91 (30), 105 (13), 125 (22), 126 (29), 153 (47), 167 (13), 196 (26), 222 (17), 241 (13), 242 (17), 297 $[M-126]^+$ (5); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{19}NO$: 297.1365 $[M-PhSO]^+$; found: 297.1360.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(phenylsulfonyl)benzyl]-2,5-cyclohexadienone (41)**: Compound **41** was obtained from **40** (141 mg, 0.33 mmol, 1 equiv, 75:25 mixture of diastereoisomers) by following method B. The product was formed as a yellow oil in 68 % yield (98 mg). Reaction time: 1 h; eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$ (s, 9 H), 3.75 (s, 1 H), 4.90 (br s, 1 H), 5.96 (dd, $J = 10.3$, 1.8 Hz, 1 H), 6.42 (dd, $J = 10.3$, 1.8 Hz, 1 H), 6.86 (dd, $J = 8.6$, 3.3 Hz, 1 H), 7.05 (dd, $J = 8.6$, 3.3 Hz, 1 H), 7.25–7.43 ppm (4 m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.2$ (3 C), 55.3, 58.3, 81.8, 114.0, 128.4 (2 C), 128.6 (2 C), 128.7 (2 C), 129.9 (2 C), 129.6, 133.6, 133.8, 138.0, 145.6, 147.5, 154.2, 157.4, 184.4 ppm; MS (EI): *m*/*z* (%): 55 (100), 67 (43), 69 (81), 71 (47), 72 (45), 79 (23), 81 (57), 83 (54), 85 (28), 93 (22), 95 (54), 97 (42), 107 (27), 109 (34), 111 (21), 123 (21), 135 (28), 153 (31), 241 (22), 261 (11), 266 (21), 272 (22), 280 (53), 288 (28), 298 $[M-141]^+$ (50); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{20}NO_3$: 298.14377 $[M-PhSO_2]^+$; found: 298.14511.

***N*-(*tert*-Butoxycarbonyl)-4-amino-3-methyl-4-[1′-(phenylsulfonyl)ethyl]-2,5-cyclohexadienone (42)**: Compound **42** was obtained from *N*-(*tert*-butoxycarbonyl)-2-methyl-*p*-benzoquinonimine dimethyl ketal (**15**) (479 mg, 1.76 mmol, 1 equiv) and $EtSO_2Ph$ (**32**) (486 mg, 1.76 mmol, 1 equiv) by following method A. The product was produced as a 75:25 mixture of diastereoisomers and as a yellow solid in 20 % yield (138 mg). Reaction time: 1.5 h; eluent: hexane/AcOEt 4:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.7$ Hz, 3 H), 1.39 (s, 9 H), 1.89 (s, 3 H), 3.29 (q, $J = 7.1$ Hz, 1 H), 6.19 (br s, 1 H), 6.41 (dd, $J = 10.3$, 1.8 Hz, 1 H), 7.19 (d, $J = 10.3$ Hz, 1 H), 7.34 (br s, 1 H), 7.59 (t, $J = 7.5$ Hz), 7.64–7.74 (m, 1 H), 7.90 ppm (d, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.8$, 18.3, 28.1 (3 C), 60.9, 62.9, 80.6, 128.5, 128.7, 129.4, 129.5, 130.6, 134.6, 145.8, 150.5, 153.6, 185.0 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (21), 77 (78), 91 (22), 122 (76), 148 (36), 166 (31), 170 (49), 176 (29), 194 (84), 335 $[M-56]^+$ (19); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{17}NO_5S$: 335.0825 $[M-tBu]^+$; found: 335.0811.

4-Amino-3-methyl-4-[1′-(pheylsulfonyl)ethyl]-2,5-cyclohexadienone (43): Compound **43** was obtained from **42** (75:25 mixture of diastereoisomers; 40 mg, 0.10 mmol, 1 equiv) by following method C. The reaction crude was purified by flash column chromatography by employing BondElut LRC-SCX cartridges and NH_3 in MeOH (2 N). Compound **43** was isolated as a (75:25) mixture of diastereoisomers and as a yellow oil in 55 % yield (16 mg). Reaction time: 4 h.

Major diastereomer: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.9$ Hz, 3 H), 1.99 (s, 3 H), 3.42 (q, $J = 7.1$ Hz, 1 H), 6.13 (br s, 1 H), 6.31 (dd, $J = 10.2$, 1.8 Hz, 1 H), 7.49 (d, $J = 10.2$ Hz, 1 H), 7.53–7.85 (m, 3 H), 7.94 ppm (d, $J = 6.7$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 11.8$, 18.6, 59.3, 65.3, 127.7, 128.5, 129.4, 129.5, 134.1, 139.0, 149.8, 158.5, 185.2 ppm

Minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (d, $J = 7.2$ Hz, 3 H), 2.17 (s, 3 H), 3.58 (q, $J = 7.1$ Hz, 1 H), 6.04 (br s, 1 H), 6.15 (dd, $J = 9.8$, 1.8 Hz, 1 H), 6.82 (d, $J = 10.2$ Hz, 1 H), 7.45–7.95 ppm (3 m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 10.3$, 19.5, 56.0, 65.1, 127.9, 128.3, 128.9, 129.1, 134.1, 138.5, 148.1, 159.5, 185.2 ppm; MS (EI): *m*/*z* (%): 77 (42), 94 (14), 122 (100), 149 (41), 150 (53), 291 $[M]^+$ (3); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{17}NO_3S$: 291.0929 $[M]^+$; found: 291.0925.

***N*-(*tert*-Butoxycarbonyl)-9-amino-5*H*-benzo[7]annulen-5-one (49)**: Compound **49** was obtained from **28** (45 mg, 0.11 mmol, 1.0 equiv) by following method D. The product was produced as a yellow oil in 27 % yield (8 mg). Reaction time: 5 h; eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$ (s, 9 H), 6.39–6.48 (m, 1 H), 6.67 (d, $J = 11.9$ Hz, 1 H), 7.02 (dd, $J = 11.9$, 8.4 Hz, 1 H), 7.63–7.75 (m, 2 H), 7.90 (dd, $J = 7.5$, 1.8 Hz, 1 H), 8.23 ppm (dd, $J = 6.8$, 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.2$ (3 C), 81.5, 117.9, 126.2, 127.9, 130.2, 130.8, 131.8, 132.5, 132.9, 134.4, 140.3, 153.0, 183.4 ppm; MS (EI): *m*/*z* (%): 57 (100), 143 (30), 169 (20), 215 (18), 271 $[M^+]$ (4); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{17}NO_3$: 271.1208 $[M]^+$; found: 271.1219.

***N*-(*tert*-Butoxycarbonyl)-4-amino-5-methyltropone (50)**: Compound **50** was obtained from *N*-(*tert*-butoxycarbonyl)-4-amino-4-[1′-ethylsulfonyl)-ethyl]-2,5-cyclohexadienone (**57**) (35 mg 0.1 mmol, 1.0 equiv) by following method D. The product was produced as a yellow oil in 94 % yield (25 mg). Reaction time: 5 h; eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.51$ (s, 9 H), 2.25 (s, 3 H), 6.27 (br s, 1 H), 6.79–7.10 (ABX system, $J_{AB} = 12.5$, $J_{AX} = 3.0$ Hz, 2 H), 6.91–7.73 ppm (ABX system, $J_{AB} = 13.3$, $J_{AX} = 2.8$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): two sets of signals are observed due to the tautomeric equilibrium: $\delta = 22.1$, 22.3, 28.2, (3 C), 28.3 (3 C), 81.9, 130.1, 132.1, 134.9, 135.0, 137.5, 137.9, 138.5, 138.6, 139.8, 140.3, 140.8, 141.0, 152.5, 153.6, 186.40, 186.44 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (13), 77 (14), 78 (11), 83 (19), 85 (12), 104 (14), 106 (18), 107 (35), 108 (14), 133 (10), 135 (16), 151 (19), 162 (13), 179 (15), 207 $[M]^+$ (13); HRMS (EI): *m*/*z*: calcd for $C_{13}H_{17}NO$: 235.1208 $[M]^+$; found: 235.1200.

***N*-(*tert*-Butoxycarbonyl)-4-amino-3,5-dimethyltropone (52)**: Compound **52** was obtained from **42** (40 mg, 0.10 mmol, 1 equiv) by following method D. The product was formed as a yellow oil in 84 % yield (21 mg). Reaction time 2 h: eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$ (s, 9 H), 2.27 (s, 3 H), 2.28 (s, 3 H), 6.00–6.09 (br s, 1 H), 6.80–7.09 (AB part of ABX system, $J_{AB} = 12.3$, $J_{AX} = 2.8$ Hz, 2 H), 6.98 ppm (X part of ABX system, $J_{AX} = 2.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.6$, 25.3, 28.2 (3 C), 81.0, 125.5, 138.8, 139.2, 139.4, 139.6, 141.4, 152.9, 186.1 ppm; MS (EI): *m*/*z* (%): 57 (100), 77 (12), 91 (10), 106 (12), 121 (21), 149 (17), 193 (18), 249 $[M]^+$ (1); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{19}NO_3$: 249.1365 $[M]^+$; found: 249.1355.

4-Amino-3,5-dimethyltropone (53): Compound **53** was obtained from **43** (16 mg, 0.06 mmol, 1 equiv) by following method D. The product was formed as a yellow oil in 98 % yield (9 mg). Reaction time 2 h: eluent: hexane/AcOEt 1:1; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3 H), 2.30 (s, 3 H), 4.32–4.47 (br s, 2 H), 6.54–7.11 (AB part of ABX system, $J_{AB} = 12.1$, $J_{AX} = 2.8$ Hz, 2 H), 7.19 ppm (X part of ABX system, $J_{AX} = 2.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 22.8$, 24.6, 117.7, 129.4, 137.7, 139.2, 142.3, 142.5, 184.7 ppm; MS (EI): *m*/*z* (%): 57 (30), 77 (30), 91 (17), 106 (77), 121 (100), 149 $[M]^+$ (42); HRMS (EI): *m*/*z*: calcd for $C_9H_{11}NO$: 149.0840 $[M]^+$; found: 149.0850.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[(methylsulfinyl)methyl]-2,5-cyclohexadienone (54)**: Compound **54** was obtained from **14** (50 mg, 0.19 mmol, 1 equiv) by following a modified version of method A (the anion was formed at 0 °C, with 2.5 equiv of *n*BuLi and 2.5 equiv of DMSO). The product was formed as a yellow oil in 46 % yield (25 mg). Reaction time: 7 h; eluent: hexane/AcOEt 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.66 (s, 3 H), 2.99–3.16 (AB system, *J* = 12.9 Hz), 6.03 (brs, 1 H), 6.29 (dd, *J* = 10.1, 1.8 Hz, 1 H), 6.34 (dd, *J* = 10.1, 1.8 Hz, 1 H), 7.07 (dd, *J* = 10.0, 3.0 Hz, 1 H), 7.23 ppm (dd, *J* = 10.0, 3.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.2 (3 C), 39.9, 54.2, 62.2, 80.9, 128.7, 129.6, 147.8, 148.8, 154.2, 184.3 ppm; MS (EI): *m*/*z* (%): 57 (100), 77 (16), 107 (23), 122 (18), 166 (44), 229 $[M-56]^+$ (15); HRMS (EI): *m*/*z*: calcd for $C_9H_{11}NO_4S$: 229.0409 $[M-t\text{Bu}]^+$; found: 229.0419.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[(methylsulfonyl)methyl]-2,5-cyclohexadienone (55)**: A solution of *n*BuLi (2.6 M in hexane, 2.7 equiv) was added dropwise to a solution of Me_2SO_2 (46 mg, 0.5 mmol, 2.5 equiv) in THF (1 mL) cooled to 0 °C. The resulting solution was stirred at 0 °C for 30 min and then a solution of **14** (50 mg, 0.19 mmol, 1.0 equiv) in THF (380 µL) was added. The resulting mixture was stirred at RT for 1 h to afford compound **55** as a yellow solid in 99 % yield (57 mg) after purification by flash column chromatography. Eluent: hexane/AcOEt, 1:1; m.p. 114–116 °C (AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H), 3.03 (s, 3 H,), 3.58 (s, 2 H), 5.82 (brs, 1 H), 6.34 (d, *J* = 9.5 Hz, 2 H), 7.27 ppm (d, *J* = 9.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (3 C), 42.6, 43.6, 53.1, 81.3, 129.1, 146.6, 154.3, 184.1 ppm; MS (APCI+): *m*/*z* (%): 122 (49), 166 (11), 202 (24), 246 (100), 247 (13), 302 $[M+1]^+$ (14); HRMS (ESI): *m*/*z*: calcd for $C_{13}H_{19}NnaO_5S$: 324.0882; found: 324.0880.

Bis[*N*-(*tert*-butoxycarbonyl)-1′-amino-4′-oxo-2′,5′-cyclohexadienyl]dimethylsulfone (56): A solution of *n*BuLi (2.6 M in hexanes, 1.4 mL, 3.3 equiv) was added dropwise to a solution of diisopropylamine (543 µL, 3.4 equiv) in THF (6.8 mL) cooled to −78 °C. After stirring for 20 min, a solution of Me_2SO_2 (107 mg, 1.14 mmol, 3.0 equiv) in THF (2.3 mL) was slowly added at −78 °C. After 30 min at this temperature, a solution of **14** (100 mg, 0.38 mmol, 1.0 equiv) in THF (1.3 mL) was added dropwise. The resulting solution was stirred for 7 h at RT to afford a mixture of the compounds **55** and **56** that was separated by flash column chromatography (hexane/AcOEt 1:1). Compound **55** and **56** were isolated as a yellow solid in 45 (52 mg) and 32 % (31 mg) yield, respectively.

*Compound **56***: M.p. 198–200 °C (AcOEt/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.66 (s, 4 H), 5.61 (brs, 1 H), 6.36 (d, *J* = 10.1 Hz, 2 H), 7.27 ppm (d, *J* = 10.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (3 C), 53.2, 60.3, 81.5, 129.4, 146.0, 154.3, 183.8 ppm; MS (FAB): *m*/*z* (%): 77 (23), 107 (31), 353 (33), 397 (100), 419 (13), 509 $[M+1]^+$ (28); HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{32}N_2NaO_8S$: 531.1777; found: 531.1771.

***N*-(*tert*-Butoxycarbonyl)-4-aminotropone (10)**: Compound **10** was obtained from *N*-(*tert*-butoxycarbonyl)-4-amino-4-[(methylsulfonyl)methyl]-2,5 cyclohexadienone (**55**) (60 mg, 0.2 mmol) by following method D. The product was isolated as pale-yellow crystals in 95 % yield (42 mg; eluent: hexane/AcOEt 1:1). Compound **10** was also obtained from bis[*N*-(*tert*-butoxycarbonyl)-1′-amino-4′-oxo-2′,5′-cyclohexadienyl] dimethyl sulfone (**56**) (170 mg, 0.14 mmol) by following method D in 96 % yield (29 mg). Reaction time: 2 h; eluent: hexane/AcOEt 1:1; m.p. 40–142 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 6.83 (dd, *J* = 11.9, 2.6 Hz, 1 H), 6.89 (brs, 1 H), 7.01–7.40 (ABXY system, J_{AB} = 12.9, J_{AX} = 2.6, J_{BY} = 2.2 Hz, 2 H), 7.12 ppm (dd, *J* = 12.1, 9.6 Hz, 1 H), 7.43 ppm (dd, *J* = 9.7, 2.0 Hz, 1 H); ^{1}H NMR (300 MHz, [D$_4$]MeOD): δ = 1.54 (s, 9 H), 6.83 (dd, *J* = 11.9, 3.0 Hz, 1 H), 7.05–7.50 (ABXY system, J_{AB} = 12.9, J_{AX} = 3.0, J_{BY} = 2.4 Hz, 2 H), 7.38 (dd, *J* = 11.9, 9.9 Hz, 1 H), 7.72 ppm (dd, *J* = 9.9, 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (3 C), 82.0, 118.6, 132.8, 136.6, 137.2, 142.0, 144.3, 152.0, 186.8 ppm; MS (EI): *m*/*z* (%): 57 (100), 93 (13), 121 (5), 148 (8), 221 $[M]^+$ (7); HRMS (EI): *m*/*z*: calcd for $C_{12}H_{15}NO_3$: 221.1051; found: 221.1057; elemental analysis calcd (%) for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33; found: C 65.05, H 6.47, N 6.20.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(ethylsulfonyl)ethyl]-2,5-cyclohexadienone (57)**: Compound **57** was obtained from **14** (50 mg, 0.19 mmol, 1 equiv) and Et_2SO_2 (61 mg, 0.5 mmol, 2.5 equiv) by following a modified version of method A (the anion was formed with 2.5 equiv of *n*BuLi and 2.5 equiv of Et_2SO_2). The product was isolated as an orange oil in 25 % yield (16 mg). Reaction time 2 h; eluent: hexane/AcOEt 4:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7.1 Hz, 3 H), 1.41 (s, 9 H), 1.42 (t, *J* = 8.7 Hz, 3 H), 2.93–3.18 (m, 2 H), 3.84 (q, *J* = 7.3 Hz, 1 H), 6.07 (brs, 1 H), 6.34 (dd, *J* = 10.1, 1.8 Hz, 1 H), 6.42 (dd, *J* = 10.1, 1.8 Hz, 1 H), 7.08 (dd, *J* = 10.3, 3.3 Hz, 1 H), 7.19 ppm (dd, *J* = 10.3, 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.4, 11.2, 28.2 (3 C), 48.3 (2 C), 58.7, 81.3, 129.6, 131.3, 144.4, 146.9, 154.4, 184.6; MS (EI): *m*/*z* (%): 57 (97), 108 (54), 180 (36), 275 (100), 329 $[M]^+$ (19); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{23}NO_5S$: 329.1297 $[M]^+$; found: 329.1308.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(propylsulfinyl)propyl]-2,5-cyclohexadienone (58)**: Compound **58** was obtained from **14** (50 mg, 0.19 mmol, 1 equiv) and Pr_2SO (66 mg, 0.50 mmol, 2.5 equiv) by following a modified version of method A (2.5 equiv of *n*BuLi and 2.5 equiv de Pr_2SO were employed, the anion addition took place at 0 °C). The product was formed as a mixture of diastereoisomers (75:25) and as a yellow oil in 35 % yield (20 mg). Reaction time: 3 h; eluent: hexane/AcOEt 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.5 Hz, 3 H), 1.09 (t, *J* = 7.5 Hz, 3 H), 1.43 (s, 9 H), 1.68–2.14 (3 m, 4 H), 2.47–2.61 (m, 1 H), 2.78–2.92 (m, 1 H), 5.25 (brs, 1 H), 6.35 (dd, *J* = 9.3, 2.0 Hz, 1 H), 6.38 (dd, *J* = 9.3, 2.0 Hz, 1 H), 7.05 (d, *J* = 9.3 Hz, 1 H), 7.24 ppm (d, *J* = 9.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 14.3, 15.7, 17.1, 28.2 (3C), 53.6, 57.9, 65.2, 81.0, 129.6, 129.7, 131.2, 132.0, 154.4, 184.5 ppm; MS (EI): *m*/*z* (%): 57 (100), 108 (37), 150 (22), 194 (24), 208 (13), 301 $[M^+-56]$ (%); HRMS (EI): *m*/*z*: calcd for $C_{13}H_{19}NO_5S$: 301.0983 $[M-t\text{Bu}]^+$; found: 301.0987.

***N*-(*tert*-Butoxycarbonyl)-4-amino-4-[1′-(propylsulfonyl)propyl]-2,5-cyclohexadienone (59)**: Compound **59** was obtained from **58** (10 mg, 0.03 mmol, 1 equiv) by following method B. The product was produced as a yellow oil in quantitative yield (9 mg). Reaction time: 1 h; eluent: hexane/AcOEt 1:1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.5 Hz, 3 H), 1.09 (t, *J* = 7.5 Hz, 3 H), 1.43 (s, 9 H), 1.81–2.00 (m, 4 H), 3.03 (t, *J* = 8.5 Hz, 2 H), 3.56–3.65 (m, 1 H), 5.80 (brs, 1 H), 6.37 (dd, *J* = 9.3, 2.0 Hz, 1 H), 6.41 (dd, *J* = 9.3, 2.0 Hz, 1 H), 7.25 ppm (d, *J* = 9.3 Hz, 2 H); MS (EI): *m*/*z* (%): 57 (100), 108 (37), 150 (22), 194 (24), 208 (13), 301 $[M-56]^+$ (7); HRMS (EI): *m*/*z*: calcd for $C_{13}H_{19}NO_5S$: 301.0983 $[M-t\text{Bu}]^+$; found: 301.0987.

***N*-(*tert*-Butoxycarbonyl)-4-amino-5-ethyltropone (60)**: Compound **60** was obtained from **59** (17 mg, 0.07 mmol, 1 equiv) by following method D. The crude reaction mixture was purified by flash column chromatography by employing BondElut LRC-SCX cartridges and NH_3 in MeOH (2 N), to afford compound **60** as a yellow oil in 32 % yield (5 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.6 Hz; ABX system, J_{AB} = 12.3, 3.0 Hz, 2 H), 6.74–7.02 ppm (dd, *J* = 12.9, 3.0 Hz, 2 H); MS (EI): *m*/*z* (%): 57 (100), 71 (14), 149 (13), 193 $[M-56]^+$ (25); HRMS (EI): *m*/*z*: calcd for C_8H_9NO: 193.0739 $[M-t\text{Bu}]^+$; found: 193.0732.

***N*-(*tert*-Butoxycarbonyl)-1-amino-10-methyl-3,5,8-trioxo-4-azatricyclo[5.3.2.0*2,6*]dodeca-9,11-diene (63)**: A solution of *N*-(*tert*-butoxycarbonyl)-4-amino-3-methyltropone (**47**) (54 mg, 0.23 mmol, 1 equiv) and maleimide (45 mg, 0.46 mmol, 2 equiv) in toluene (2 mL) was refluxed for 15 h. The solvent was evaporated under reduced pressure. The *endo* adduct **63** was obtained pure as a white solid after column chromatography in 17 % yield (13 mg). Eluent: AcOEt/hexane 1:1; m.p. 189–190 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, [D$_4$]MeOD): δ = 1.51 (s 3 H), 2.12 (s, 3 H), 3.36 (dd, *J* = 7.6, 1.4 Hz, 1 H), 3.50 (d, *J* = 8.5 Hz, 1 H), 3.74 (brd, *J* = 6.7 Hz, 1 H), 5.76 (brs, 1 H), 5.84 (brs, 1 H), 6.12 (dd, *J* = 8.9, *J* = 7.5 Hz, 1 H), 6.63 (d, *J* = 9.1 Hz, 1 H), 7.57 ppm (brs, 1 H); ^{13}C NMR (125 MHz, [D$_4$]MeOD): δ = 20.8, 22.7, 28.6 (3 C), 44.2, 53.5, 61.5, 81.4, 123.7, 126.0, 142.6, 156.9, 167.2, 172.0, 179.0, 194.4 ppm; MS (EI): *m*/*z* (%): 57 (100), 59 (16), 107 (33), 144 (29), 187 (23), 232 (34), 332 $[M]^+$ (1); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{20}N_2O_5$: 332.1372; found: 332.1379.

***N*-(*tert*-Butoxycarbonyl)-1-amino-2-methyl[3.2.0]hepta-2,6-dien-4-one (64)**: A solution of **47** (10 mg, 0.04 mmol, 1 equiv) in CD_3OD (500 µL) placed in a NMR tube was irradiated with a high pressure Hg lamp (150 W). The evolution of the reaction was checked by NMR spectroscopy. After 6 h, the reaction was completed. The solvent was eliminated under reduced pressure and the reaction mixture was purified by flash column chromatography (hexane/AcOEt 1:1), affording the bicyclic dienone **64** as a yellowish oil in 32 % yield (3 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 2.04, (d, *J* = 11.0 Hz, 3 H), 3.37 (s, 1 H), 5.30 (brs, 1 H), 5.77 (s, 1 H), 6.58–6.66 ppm (m, 2 H); ^{13}C NMR (125 MHz,

$CDCl_3$): $\delta = 14.8$, 28.2 (3C), 59.6, 69.2, 77.2, 128.7, 130.2, 141.3, 154.5, 203.0 ppm; MS (FAB): m/z (%): 136 (99), 149 (46), 181 (57), 236 $[M+1]^+$ (5); HRMS (FAB$^+$): m/z: calcd for $C_{13}H_{18}NO_3$: 236.1287 $[M+1]^+$; found: 236.1281.

N-(*tert*-Butoxycarbonyl)-1-amino-12-methyl-3,5,8-trioxo-4-aza-tricyclo[5.3.2.0*2,6*]dodeca-9,11-diene (65): A solution of N-(*tert*-butoxycarbonyl)-4-amino-5-methyltropone (**51**) (24 mg, 0.10 mmol, 1 equiv) and maleimide (20 mg, 0.20 mmol, 2 equiv) in toluene (2 mL) was refluxed for 4 h. The solvent was evaporated under reduced pressure. The *endo* adduct **65** was obtained as a white solid after column chromatography (hexane/AcOEt, 2:1) in a 74% yield (25 mg). M.p. 190–192 °C (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.49$ (s, 9H), 1.90 (s, 3H), 3.32 (dd, $J = 8.7$, 1.2 Hz, 1H), 3.65 (d, $J = 8.5$ Hz, 1H), 3.79 (ddd, $J = 7.7$, 2.2, 1.4 Hz, 1H), 5.75 (dd, $J = 11.2$, 2.4 Hz, 1H), 5.80 (d, $J = 2.4$ Hz, 1H), 6.85 (brs, 1H), 7.33 (d, $J = 11.7$ Hz, 1H), 8.53 ppm (brs, 1H); ^{13}C NMR (75 MHz $CDCl_3$): $\delta = 18.9$, 28.3 (3C), 42.9, 49.4, 52.9, 61.6, 80.7, 118.0, 126.0, 126.3, 149.1, 155.5, 175.6, 176.1, 192.1 ppm; MS (EI): m/z (%): 57 (100), 59 (20), 107 (33), 144 (61), 145 (26), 160 (19), 200 (19), 215 (55), 232 (24), 332 $[M]^+$ (1); HRMS (EI): m/z: calcd for $C_{17}H_{20}N_2O_5$: 332.1372 $[M]^+$; found: 332.1374.

N-(*tert*-Butoxycarbonyl)-1-amino-7-methyl[3.2.0]hepta-2,6-dien-4-one (66): A solution of **51** (16 mg, 0.07 mmol, 1 equiv) in CH_3CN (2 mL; previously deoxygenated) was irradiated with a high pressure Hg lamp (400 W) under an argon atmosphere at RT. An overheating in the reaction media should be avoided as the 4π-electrocyclic reaction is reversible at temperatures up to 25 °C. After 8 h, no starting material was detected by TLC. Then the solvent was eliminated in vacuo without heating. After column chromatography, the bicyclic dienone **66** was isolated as colourless oil in a 20% yield (3 mg). Eluent: hexane/AcOEt 4:1; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H), 1.79 (s, 3H), 3.20 (s, 1H), 4.96 (brs, 1H), 6.01 (d, $J = 4.9$ Hz, 2H), 6.10 (d, $J = 2.2$ Hz, 2H), 7.62 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 14.7$, 28.2 (3C), 56.1, 56.2, 68.7, 130.1, 130.3, 132.5, 141.2, 154.8, 204.6 ppm; MS (APCI+): m/z (%): 180 (100), 181 (10), 236 $[M+1]^+$ (46).

(S)-4-Amino-[1′-(*tert*-butoxycarbonyl)pyrrolidine]-2′-carboxamide tropone (68): An excess of HCl (37%, 1 mL) was added to a solution of **55** and dimer **56** (60:40 mixture, 300 mg) in CH_2Cl_2 (2 mL) at RT. After 2 h, the solvent was removed under reduce pressure and the resulting *p*-quinamine hydrochloride was used in the next step without further purification. To a solution of this hydrochloride in CH_2Cl_2 (5 mL) was added Et_3N, N-Boc-L-proline **67** (235 mg, 1.1 mmol) and EDC·HCl (210 mg, 1.1 mmol). The resulting solution was stirred at RT overnight. The CH_2Cl_2 solution was washed with HCl 10%, the organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The proline amide derivative obtained was directly used in the next step without further purification. The tropone **68** was obtained as a yellow solid in a 56% yield (179 mg, three steps) from the crude reaction mixture by following method D. Eluent: AcOEt/MeOH 10:1; m.p. 89–91 °C (AcOEt); $[\alpha]_D^{20} = -68$ ($c = 0.24$ in acetone); ^{1}H NMR (300 MHz, $[D_4]$MeOD): $\delta = 1.38$ (s, 9H), 1.88–2.36 (m, 4H), 3.38–3.58 (m, 2H), 4.12–4.34 (m, 1H), 6.90 (dd, $J = 12.2$, 2.8 Hz, 1H), 7.10 (dd, 1H, $J = 12.6$, 2.8 Hz), 7.38 (m, 1H), 7.50 (dd, $J = 12.9$, 2.0 Hz, 1H), 7.83 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.5$, 28.4 (3C), 29.7, 47.3, 60.7, 81.4, 120.4, 133.4, 137.0, 137.5, 141.9, 144.2, 170.8, 186.8 ppm; MS (EI): m/z (%): 57 (54), 70 (100), 114 (61), 121 (12), 149 (6), 318 $[M]^+$ (4); HRMS (EI): m/z: calcd for $C_{17}H_{22}N_2O_4$: 318.1579; found: 318.1577; HPLC (Daicel Chiralpack AD, 90:10 hexane/2-propanol): $ee > 99.5$% (ee = enantiomeric excess), 1.0 mL min^{-1}, $T = 25$ °C, $R_t = 26.5$ min.

N-(*tert*-Butoxycarbonyl)-1-amino(pyrrolidine-1-carboxylate)-3,5,8-trioxo-4-(phenyl)azatricyclo[5.3.2.0*2,6*]dodeca-9,11-diene (69): A solution of **68** (211 mg, 0.66 mmol, 1.0 equiv) and N-phenylmaleimide (137 mg, 0.79 mmol, 1.25 equiv) in toluene (2 mL) was refluxed for 48 h. The solvent was removed under reduced pressure. Adducts **69** were obtained as a mixture of *endo* cycloadducts (90:10) in 70% overall yield. After column chromatography (hexane/AcOEt, 1:1), only the major cycloadduct **69a** could be isolated as a pure diastereoisomer in 21% yield. White solid; m.p. 237–239 °C (CH_2Cl_2); $[\alpha]_D^{20} = +62$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, tetrachoroethane, 353 K): $\delta = 1.46$ (s, 9H), 1.85–1.91 (m, 2H), 2.13–2.16 (m, 2H), 3.46 (dd, $J = 8.7$, 1.4 Hz), 3.50–3.55 (m, 2H), 3.81 (d, $J = 8.7$ Hz, 1H), 4.04 (d, $J = 7.2$ Hz), 4.29–4.31 (m, 1H), 5.78 (dd, $J = 11.6$, 2.1 Hz, 1H), 6.15 (t, $J = 7.6$ Hz, 1H), 6.46 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 11.6$ Hz, 1H), 7.19–7.21 (m, 2H), 7.41–7.48 (m, 3H), 8.38 ppm (s, 1H); ^{13}C NMR (125 MHz, TCE, 353 K): $\delta = 24.2$, 28.5, 29.2, 41.2, 47.1, 47.6, 53.6, 59.0, 60.9, 80.3, 124.1, 126.2, 126.3, 129.2, 129.3, 131.3, 140.5, 155.8, 173.0, 174.5, 191.3 ppm; MS (FAB$^+$): m/z (%): 57 (79), 70 (96), 136 (72), 154 (100), 392 (100), 492 $[M^+-H]$ (84); HRMS (FAB$^+$): m/z: calcd for $C_{27}H_{30}N_3O_6$: 492.2134; found: 492.2132; HPLC (Daicel Chiralpack AD, 85:15 hexane/2-propanol): $ee > 99.5$%, 0.75 mL min^{-1}, $T = 25$ °C, $R_t = 100.3$ min.

Compound ***69b***: 50:50 mixture of **69a** and **69b**: ^{1}H NMR (500 MHz, tetrachloroethane, 353 K): only the signal of the NH appeared at a different chemical shift $\delta = 8.51$ ppm (s, 1H); ^{13}C NMR (125 MHz, tetrachloroethane, 353 K): $\delta = 25.4$, 28. (3C), 29.0, 41.4, 47.1, 47.4, 53.7, 59.0, 61.1, 80.4, 124.2, 126.4, 126.7, 128.8, 129.1, 131.6, 140.4, 156.0, 173.3, 174.6, 191.4 ppm.

N-(*tert*-Butoxycarbonyl)-1-amino(pyrrolidine-1-carboxylate)-3,5,8-trioxo-4-azatricyclo[5.3.2.0*2,6*]dodeca-9,11-diene (70): A solution containing **68** (100 mg, 0.31 mmol, 1.0 equiv) and maleimide (72 mg, 0.62 mg, 2.0 equiv) in toluene (2 mL) was refluxed for 24 h. The solvent was removed under reduced pressure to afford a mixture of *endo* cycloadducts (90:10). After column chromatography, the cycloadducts **70a** (white solid) and **70b** (yellowish oil) were isolated diastereomerically pure in 53 (168 mg) and 6% (8 mg) yields, respectively. Eluent: hexane/AcOEt 1:1.

Compound ***70a***: M.p. 128–130 °C (CH_2Cl_2); $[\alpha]_D^{20} = +41$ ($c = 0.7$ in acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H), 1.86–2.11 (m, 4H), 3.34 (d, $J = 8.6$ Hz), 3.49–3.55 (m, 2H), 3.63–3.75 (m, 1H), 3.89 (d, $J = 6.6$ Hz), 4.19–4.36 (m, 1H), 5.68 (d, $J = 10.8$ Hz, 1H), 6.06 (t, $J = 7.5$ Hz, 1H), 6.40 (t, $J = 11.6$ Hz, 1H), 7.07 (d, $J = 11.6$ Hz, 1H), 8.53 ppm (s, 1H); ^{13}C NMR (125 MHz, tetrachloroethane, 353 K): $\delta = 24.2$, 28.5, 29.17, 42.4, 47.1, 48.8, 53.2, 58.7, 61.1, 80.6, 124.2, 125.8, 135.0, 140.2, 155.8, 170.5, 173.4, 175.2, 175.4, 191.6 ppm; MS (EI): m/z (%): 57 (46), 70 (100), 114 (60), 170 (31), 415 (0.8) $[M]^+$; HRMS (EI): m/z: calcd for $C_{21}H_{25}N_3O_6$: 415.1743; found: 415.1740; HPLC (Daicel Chiralpack AD, 85:15 hexane/2-propanol): $ee > 99.5$%, 0.75 mL min^{-1}, $T = 25$ °C, $R_t = 28.9$ min.

Compound ***70b***: $[\alpha]_D^{20} = -45$ ($c = 0.1$ in acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9H), 1.68–2.25 (m, 4H), 3.37 (d, $J = 8.3$ Hz), 3.44–3.63 (m, 2H), 3.69–3.80 (m, 1H), 3.96 (d, $J = 7.9$ Hz), 4.28–4.42 (m, 1H), 5.74 (d, $J = 11.3$ Hz, 1H), 6.11 (t, $J = 7.9$ Hz, 1H), 6.41 (d, $J = 7.9$ Hz, 1H), 7.02–7.18 (m, 1H). 8.53 ppm (s, 1H); ^{13}C NMR (125 MHz, $[D_2]$tetrachloroethane, 353 K): $\delta = 24.2$, 28.5 (3C), 29.6, 42.3, 47.0, 48.5, 53.2, 58.7, 61.0, 80.4, 124.2, 126.0, 135.0, 140.4, 155.7, 170.1, 173.3, 174.6, 174.9, 191.3 ppm; MS (EI): m/z (%): 57 (35), 70 (100), 96 (25), 114 (32); HRMS (EI): m/z: calcd for $C_{21}H_{25}N_3O_6$: 415.1743; found: 415.1730; HPLC (Daicel Chiralpack AD, 85:15 hexane/2-propanol): $ee > 99.5$%, 0.75 mL min^{-1}, $T = 25$ °C, $R_t = 41.7$ min.

(S)-N-(*tert*-Butoxycarbonyl)-1,4-dihydroxy-8-oxo-8,9-dihydro-5*H*-5,9-ethenobenzo[7]annulen-5-pyrrolidine-1-carboxamide (71): A solution containing **68** (43 mg, 0.13 mmol, 1.0 equiv) and *p*-benzoquinone (25 mg, 0.23 mmol, 1.7 equiv) in CH_2Cl_2 (2 mL) placed in a teflon sealed tube was submitted to 8.5 Kbar for 6 d. After this time, the solvent was removed under reduced pressure and the crude reaction was purified by flash column chromatography to afford the cycloadduct **72** as a brownish solid and as a mixture of diastereomers (50:50) in 65% yield (36 mg). Eluent: hexane/AcOEt 1:1; ^{1}H NMR (500 MHz, $[D_4]$MeOD): $\delta = 1.38$ (s, 9H), 1.47 (s, 9H), 1.94–2.34 (m, 4H), 3.44–3.60 (m, 2H), 4.22–4.28 (m, 1H), 5.05–5.47 (m, 2H), 6.45–6.58 (m, 1H), 6.97–7.04 (m, 1H), 7.14–7.26 ppm (m, 1H); ^{13}C NMR (125 MHz, tetrachloroethane, 350 K): $\delta = 23.1$, 24.0, 27.2, 27.3, 30.8, 30.9, 46.5, 46.6, 54.7, 61.4, 61.6, 63.0, 63.1, 80.6, 80.6, 114.6, 116.0, 121.1, 121.3, 121.9, 125.1, 125.3, 125.6, 125.8, 142.8, 143.0, 143.2, 145.3, 145.4, 148.2, 154.6, 158.4, 158.5, 159.1, 173.5, 174.1, 190.4. 190.6 ppm; MS (EI): m/z (%): 57 (31), 70 (100), 96 (24), 114 (31), 184 (14), 212 (38), 229 (31), 426 $[M]^+$ (6); HRMS (EI): m/z: calcd for $C_{23}H_{26}N_2O_6$: 426.1790; found: 415.1786.

(S)-*tert*-Butyl 2-(4-oxobicyclo[3.2.0]hepta-2,6-dien-1-ylcarbamoyl)pyrrolidine-1-carboxylate (73): A solution of **68** (210 mg, 0.67 mmol, 1.0 equiv) in MeOH (20 mL) was irradiated with a high pressure Hg lamp (150 W) until the starting material could no longer be detected by NMR spectroscopy. The solvent was evaporated under reduced pressure, without heating the water bath and the resulting material was purified by flash column chromatography (hexane/AcOEt 1:1). Compound **73** was isolated as a yellow solid in 50% yield (107 mg) and as a (50:50) mixture of diastereoisomers. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 9H), 1.85–2.34 (m, 4H), 3.33 (d, $J = 3.9$ Hz, 1H), 3.38–3.50 (m, 2H), 4.06–4.35 (m, 1H), 5.95 (d, $J = 5.7$ Hz, 1H), 6.49 (s, 1H), 6.72 (s, 1H), 7.59 (d, $J = 5.7$ Hz 1H), 7.90 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 22.5$, 28.2 (3C), 28.4 (3C), 29.2, 29.6, 47.1, 47.2, 58.2, 58.3, 60.4, 60.6, 68.0 (2C), 80.4, 80.6, 130.8, 131.3, 138.8, 138.9, 143.1 (2C), 154.4, 155.3, 160.3, 160.4, 172.5, 172.6, 203.7, 203.8 ppm; MS (EI): m/z (%): 57 (67), 70 (100), 105 (10), 122 (11), 245 (83), 318 $[M]^+$ (0.1); HRMS (EI): m/z: calcd for $C_{17}H_{22}N_2O_4$: 318.1579; found: 318.1584; HPLC (Daicel Chiralpack AD, 90:10 hexane/2-propanol): dr: 1:1 (dr = diastereomeric ratio), $ee > 99.5\%$, 1.0 mL min^{-1}, $T = 25$ °C, $R_t = 9.3$, 13.3 min.

CCDC-247411 and CCDC-651134 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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[45] A 99% *ee* was determined for **68** by HPLC analysis, using commercially available chiral column Daicel Chiralpack AD, 90:10 hexane/2-propanol), 1.0 $\text{mL}\,\text{min}^{-1}$, $T = 25$ °C, $R_t = 26.5$ min: This required the synthesis of the racemic **68**.

[46] The structure of **69a** was determined by X-ray crystallographic analysis.

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