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Synthesis and dienophilic behavior of enantiomerically pure (*E*)-2-*p*-tolylsulfinylacrylonitrile derivatives†

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Abstract—The synthesis of (*E*)-3-formyl 2-sulfinylacrylonitrile **2** and its diethylacetal derivative **3**, as well as their behavior as dienophiles in reactions with cyclopentadiene are reported. The acetal **3** evolved with high π-facial selectivity under $Eu(fod)_3$ catalysis. The π-facial selectivity became almost complete after extended reaction times, which evidences that a retro Diels–Alder reaction occurs. The *endo*/*exo* selectivity (ca. 80:20) was only moderate. The reactivity of the aldehyde **2** was higher but its evolution was less stereoselective than that of **3**, the *endo*/*exo* product ratio observed being close to 1.

1. Introduction

The sulfinyl group has been shown to be an interesting chiral inductor in asymmetric Diels–Alder reactions due to its ability to differentiate between diastereotopic faces of neighboring double bonds.[1] Nevertheless, vinyl sulfoxides only exhibit good features as chiral dienophiles when additional activating groups are attached to the double bond in order to increase its dienophilic reactivity and simultaneously restrict the conformational mobility about the C–S bond, which also improves the stereoselectivity. In this sense, many electron-withdrawing groups have been inserted into vinyl sulfoxides, the alkoxycarbonyl ones (in both *cis* and geminal positions) being the most widely used.[1] However, in the last few years, the cyano group has been described as an even more interesting group regarding its effect in increasing the reactivity of vinyl sulfoxides and the stereoselectivity of their reactions. Therefore, (*Z*)-3-*p*-tolylsulfinylacrylonitriles have been reported by our research group as the best monoactivated vinyl sulfoxides in asymmetric Diels–Alder reactions.[2,3] They were found to react with cyclic and acyclic dienes, and with furan with complete regioselectivity and π-facial diastereoselectivity. Additionally, the *endo*-selectivity was very high and in some cases almost complete. The strong dipolar repulsion between the cyano and sulfinyl groups, which restricts the conformational equilibrium around the C–S bond, accounts for these results. The excellent features of these acrylonitriles with the SOTol and CN groups in a *cis* arrangement, led us to study the dienophilic behavior of a new family of compounds, 2-*p*-tolylsulfinyl acrylonitriles, bearing both functional groups at the same olefinic carbon, since the presumably strong dipolar interactions between both geminal groups suggested their highly stereoselective evolution in asymmetric Diels–Alder reactions. Herein, we report a synthetic sequence which affords the (*E*)-3-formyl and 3-diethoxymethyl substituted 2-sulfinylacrylonitriles (**2** and **3**, respectively), and the behavior of these compounds as dienophiles in their reaction with cyclopentadiene.

2. Results and discussion

Initially we focused our interest on the study of the simplest members of this family, 3-alkyl substituted 2-*p*-tolylsulfinylacrylonitriles. However, despite many attempts made to synthesize these compounds via Knoevenagel[4] or Peterson[5] reaction, the yields were rather low. Moreover, the preliminary Diels–Alder reactions performed with the so obtained acrylonitriles proved to be disappointing leading to sluggish complex mixtures, maybe due to their ready tendency to polymerize. These results drew our attention to the synthesis

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† Dedicated to the memory of Professor J. H. Rodríguez Ramos, a close friend and an outstanding chemist.

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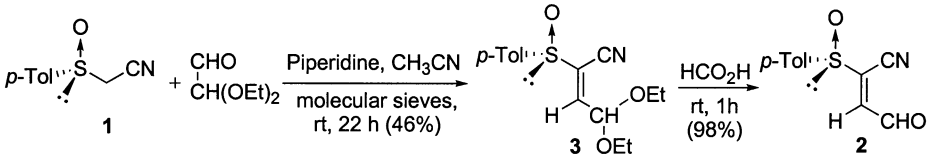


Scheme 1.

of 2-*p*-tolylsulfinylacrylonitriles bearing additional groups at C-3 capable of stabilizing the dienophile structure, such as the formyl group, which would also increase the dienophilic reactivity, and its corresponding diethylacetal which is presumably more stable.

The synthesis of the starting enantiomerically pure (*S*)-3-formyl and 3-diethoxymethyl 2-sulfinylacrylonitriles **2** and **3** was achieved following the sequence depicted in Scheme 1. It consisted initially of Knoevenagel condensation of 2,2-diethoxy ethanal (prepared by monoacetalization of glyoxal[6]) with (*R*)-cyanomethyl *p*-tolyl sulfoxide **1**[7] in the presence of a catalytic amount of piperidine in acetonitrile to give chiral vinyl sulfoxide **3** in 46% yield, which was almost quantitatively hydrolyzed into the corresponding formyl derivative **2** in the presence of an excess of formic acid. The enantiomeric purity (e.e. >98%) of **3** was determined by NMR by using enantiopure 2,2,2-trifluoro-1-(anthryl)ethanol[8] as the chiral solvating agent.

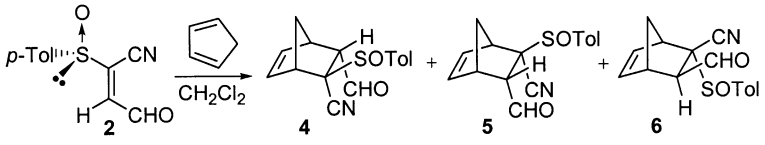
The results of the Diels–Alder reaction of dienophile **2** at different temperatures are collected in Table 1. Initially, all attempts to perform the cycloaddition reaction of **2** with cyclopentadiene at room temperature were unsuccessful because they afforded complex crude mixtures due to decomposition of the reactants. When we realized that this was the reason for the poor results (once we had observed that reaction conditions for **3** were milder), the reactions of **2** were performed at lower temperatures with the results indicated in Table 1 (entries 2 and 3). Complete transformation of the starting dienophile was detected after short reaction times. The observed π-facial selectivity was good but the *endo–exo* selectivity was scarce, neither of them experiencing any improvement on lowering the temperature (vide infra). These results could not be modified by acid catalysis, since **2** rapidly decomposed in the presence of Lewis acids.

The low stability of the resulting adducts prevented their chromatographic separation as well as their stereochemical assignment. Nevertheless, they could be identified by chemical correlation with the adducts derived from compound **3** (vide infra).

The results obtained in reactions of cyclopentadiene (excess) with the diethylacetal **3** in CH_2Cl_2 under thermal and catalytic conditions are collected in Table 2. All four possible adducts were formed under thermal conditions and their ratio was established from the ^1H NMR spectra of the reaction crudes (entry 1). The reaction evolved with good π-facial selectivity but moderate *endo*-selectivity. The addition of $ZnBr_2$ scarcely modified both the reactivity and the stereoselectivity (entries 2–4), whereas the use of BF_3 as the catalyst caused the decomposition of the starting material and/or the resulting adducts to afford a complex mixture (entry 5). The best results were obtained when the reactions were conducted in the presence of $Eu(fod)_3$ (entries 6–21). The number of equivalents of the catalyst had a small influence (entries 6–9), with a slight decrease in the *endo*/*exo* ratio at lower catalyst loadings. However, the π-facial selectivity, which was higher than that observed under thermal conditions, remained practically unaltered. Unexpectedly, both selectivities slightly decreased at 0°C (entry 10), but significantly increased at −20°C (entry 11), mainly the π-facial selectivity, which was almost complete under these conditions. A similar facial selectivity was observed under conditions of entry 12,[9] but the *endo* selectivity was slightly lower presumably as a consequence of the smaller number of equivalents of the catalyst.

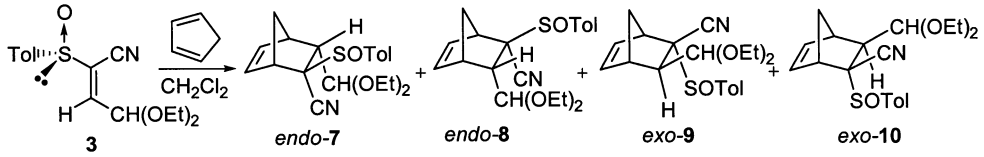
As the reaction times described in entries 11 and 12 were significantly longer than those in other cases studied, we decided to investigate the influence of this parameter on the composition of the crude reaction products. In the absence of any catalyst, the reactions

Table 1. Reaction of **2** with cyclopentadiene at different temperatures



Entry	*T* (°C)	*t* (h)	**4**/**5**/**6**	π-facial selectivity	*endo–exo* selectivity
1	20	0.5	Complex mixture		
2	−20	0.5	44/13/43	87/13	57/43
3	−78	1	42/13/45	87/13	55/45

Table 2. Reaction of **3** with cyclopentadiene under thermal and catalytic conditions



Entry	Lewis acid (equiv.)	T (°C)	t (h)	**7**/**8**/**9**/**10** ratio[a]	π-Facial selectivity	*endo*–*exo* Ratio
1		20	5	60/10/24/6	84/16	70/30
2	$ZnBr_2$ (3.0)	20	5	61/12/20/7	81/19	73/27
3	$ZnBr_2$ (4.0)	20	5	61/9/23/7	84/16	70/30
4	$ZnBr_2$ (3.0)	0	24	62/9/25/4	87/13	71/29
5	BF_3 (1.2)	20	1	Complex mixture		
6	$Eu(fod)_3$ (6.0)	20	1	74/3/17/6	91/9	77/23
7	$Eu(fod)_3$ (4.0)	20	1	73/3/18/6	91/9	76/24
8	$Eu(fod)_3$ (2.5)	20	1	70/4/21/5	91/9	74/26
9	$Eu(fod)_3$ (1.5)	20	1	68/4/24/4	92/8	72/28
10	$Eu(fod)_3$ (4.0)	0	5	64/6/24/6	88/12	70/30
11	$Eu(fod)_3$ (4.0)	−20	48	76/4/20/–	96/4	80/20
12	$Eu(fod)_3$ (1.5)	−20	24	70/0/28/2	98/2	70/30
13	$Eu(fod)_3$ (1.5)	rt	1.5	66/4/24/6	90/10	70/30
14	$Eu(fod)_3$ (1.5)	rt	17	62/8/26/4	88/12	70/30
15	$Eu(fod)_3$ (1.5)	rt	24	71/traces/23/6	94/6	71/29
16	$Eu(fod)_3$ (1.5)	rt	42	72/traces/22/6	94/6	72/28
17	$Eu(fod)_3$ (1.5)	rt	66	72/–/22/–	100/0	72/28
18	$Eu(fod)_3$ (1.5)	−20	17	73/3/21/3	94/6	76/24
19	$Eu(fod)_3$ (1.5)	−20	24	73/traces/23/4	98/2	73/27
20	$Eu(fod)_3$ (1.5)	−20	42	76/traces/24/traces	>98/<2	76/24
21	$Eu(fod)_3$ (1.5)	−20	66	74/–/26/–	100/0	74/26
22		40	3.5	59/13/22/6	81/19	72/28
23		40	45	62/8/23/7	85/15	70/30
24		40	68	61/6/25/8	86/14	67/33

[a] Determined by integration of well-separated signals on the ^1H NMR spectra of the reaction crudes.

conducted in refluxing CH_2Cl_2 (entries 22–24) did not show any clear variation in their results, with the reaction time exerting a small influence in the reaction course. However, in the presence of $Eu(fod)_3$ the adducts **8** and **10** completely disappeared from the reaction mixture as the reaction time was longer, which increased the π-facial selectivity. It became almost complete after 3 days and the adducts resulting from the *endo* and *exo* approaches of the cyclopentadiene to the same face of the dienophile were the sole products obtained under these conditions. This result suggested a thermodynamic equilibrium between the adducts as a consequence of a retro Diels–Alder process. The *endo*/*exo* ratio was moderate, increasing slightly as the temperature was lowered.

Only the adducts **7**, **8** and **9** could be isolated by flash column chromatography and were fully characterized. The ^1H NMR data of the fourth minor adduct **10** were deduced from the spectra of mixtures containing it. The absolute configuration and the *endo* structure of the major adduct **7** were unequivocally determined by X-ray diffraction analysis (Fig. 1).[10]

In order to assign the configuration of compound **8** it was transformed into the sulfone **11** by treatment with *m*-CPBA. When **7** was oxidized under similar conditions, the resulting sulfone exhibited an identical ^1H NMR spectrum,[11] which indicated that both compounds are enantiomers (**7** and **8** have the same configuration at the sulfinyl sulfur). This allowed us to unequivocally establish the stereochemistry of the adduct **8** as *endo* (Scheme 2). Sulfones **12**, resulting from the oxidation of **9** and **10**, showed different NMR parameters to those of **11**, which pointed to the fact that **9** and **10** were *exo* adducts. Finally, the stereochemistry of the major *exo* adduct **9** was tentatively assigned assuming that it resulted from attack of the diene to the same face resulting in the formation of the major *endo* adduct **7**. These stereochemical predictions were confirmed by ^1H NMR analysis, mainly by the NOE values observed[12] for the three isolated adducts **7**–**9** and the chemical shifts of the proton at C-3, which appear at higher field for compounds **8** and **10** than their respective isomers **8** and **10** (see Section 3), which may be due to the anisotropic effect of the aromatic ring (see Fig. 2).

The configurational assignment of the adducts **4**–**6** was established by independent hydrolysis of the isolated adducts **7**–**9** (previously characterized) with formic acid, to give the corresponding aldehydes (Scheme 3).

The stereochemical results observed in reactions of the acetal **3** can be explained by assuming the *endo* and *exo* approaches of cyclopentadiene to the less hindered

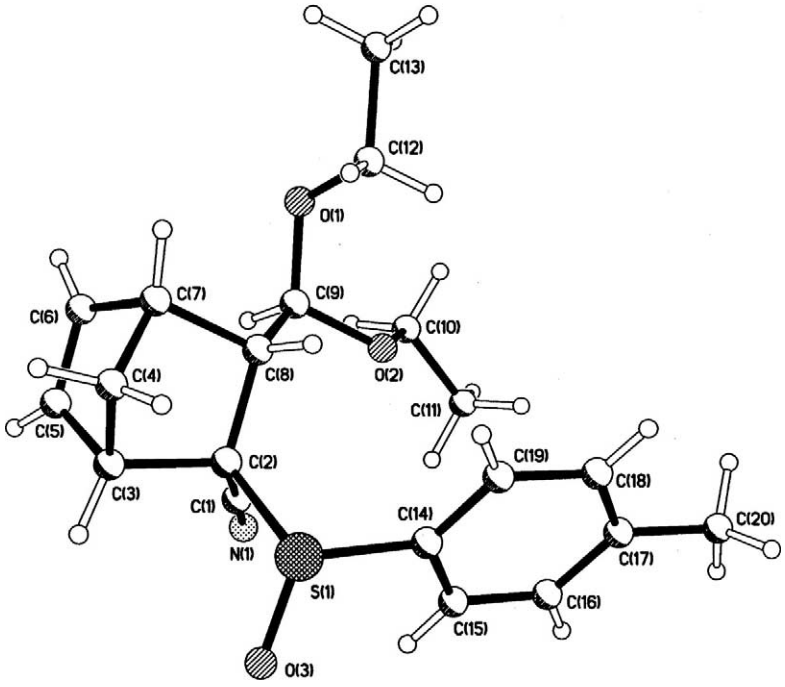
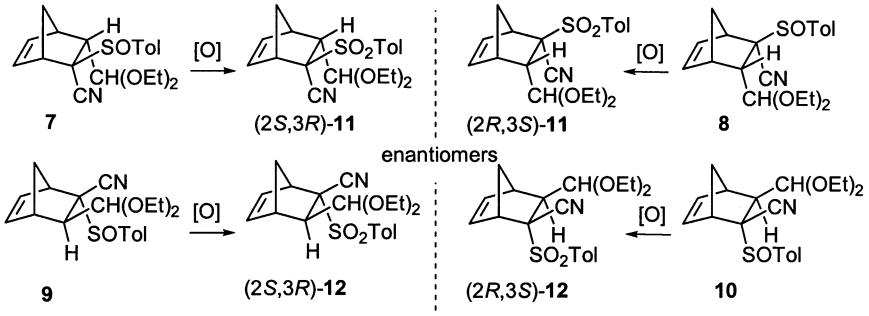


Figure 1. X-Ray structure for adduct *endo*-**7**.



Scheme 2.

lower face of the dienophile adopting the s-*trans* arrangement are favored (Fig. 2), yielding *endo*-**7** and *exo*-**9** adducts as the major products. A strong NOE (6.72) between the olefinic proton and the *ortho* protons of the *p*-tolyl group for compound **3** supports the preference of the conformation depicted in Fig. 2. In the absence of catalyst, it can be explained by assuming the stabilizing electrostatic interaction of the negatively charged sulfinyl oxygen and the positively charged nitrile carbon. The association of $Eu(fod)_3$ to the sulfinyl oxygen, strongly increasing its relative size, reinforce this preference from a steric point of view. Moreover, the higher stability of compounds *endo*-**7** and *exo*-**9**, which may be responsible for the complete π-facial selectivity observed under the conditions favoring a thermodynamic control, could be due to the interactions between the sulfinyl oxygen with the proton at C-3 destabilizing the adducts *endo*-**8** and *exo*-**10** (see Fig. 2) in conformations exhibiting the bulkier tolyl group in the sterically most favored arrangement. The higher δ shift of the protons at C-3 in the minor adducts (Fig. 2) supports the preference of the depicted rotamers with the sulfinyl oxygen deshielding such protons.

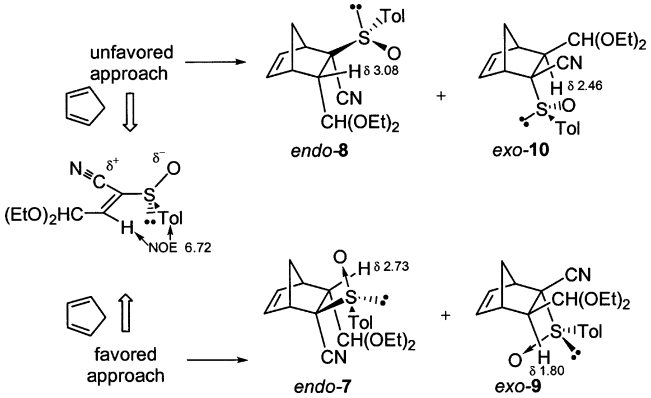
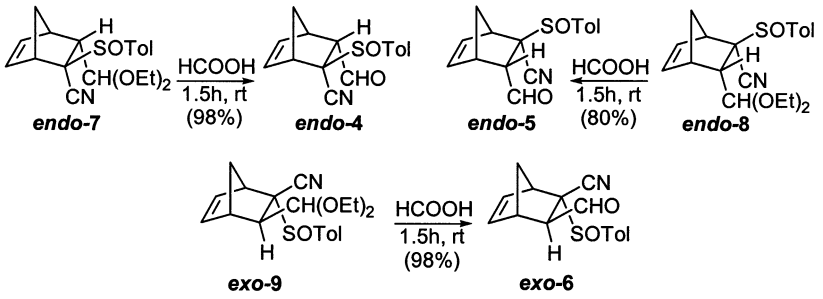


Figure 2. Favored approaches of the cyclopentadiene to the most stable rotamer of compound **3**.

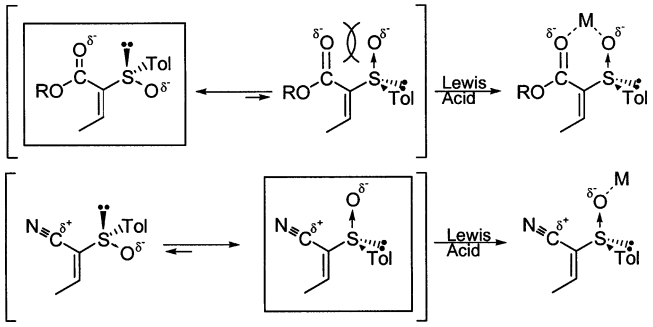


Scheme 3.

Finally, the low *endo*/*exo* selectivity observed in the reactions of compound **2** was completely unforeseen. Taking into account that the acetal **3** preferentially evolved into the *endo* adduct, we expected that changing the $CH(OEt)_2$ group to an aldehyde, with stronger *endo* orientating character, would increase the *endo*/*exo* ratio. The observed opposite result is not easy to explain, mainly after having looked unsuccessfully for evidence proving that a retro Diels–Alder process was also taking place in these reactions.[13]

It is interesting to compare these results with those obtained in the reactions of 2-*p*-tolylsulfinylacrylates.[14] The reactivity of the sulfinyl ester lacking alkyl substituents is similar to that of compound **3**. Bearing in mind the negative influence of the diethoxymethyl group on the reactivity (mainly due to its steric interactions with the diene), we can conclude that sulfinyl nitriles are more reactive than their alkoxycarbonyl counterparts. This conclusion is supported by the results obtained with 3-*p*-tolylsulfinyl butenolides[15] and their 5-alkoxy derivatives,[16] exhibiting a structure of 2-sulfinylacrylate with alkyl substituents at the double bond. These compounds were clearly less reactive than **3** and required several days or the use of high pressure for their reactions to reach completion. With respect to the stereoselectivity, nitriles and acrylates exhibit the opposite facial stereoselection in the absence of catalysts. As a consequence, the 2-*p*-tolylsulfinylacrylates evolve mainly through the electrostatically most stable conformations, with the sulfinyl oxygen in the s-*cis* arrangement,[14] whereas the corresponding nitriles evolve through the *s*-*trans* conformations shown in Fig. 2. In the case of acrylates and lactones, the use of ZnX_2 as catalysts led to inversion of the facial selectivity and strongly increased the reactivity as a consequence of the formation of a chelated species, whereas these effects are less significant in nitriles because chelated species can not form due to the linear structure of the cyano group (Scheme 4).

In summary, we have described the synthesis and Diels–Alder reactions of cyclopentadiene of the first hitherto reported enantiomerically pure 2-*p*-tolylsulfinyl acrylonitriles **2** and **3**. The reactivity of these compounds is clearly higher than that observed for the corresponding acrylates, and the π-facial selectivity is high and can become complete by increasing the reaction times, due to the occurrence of a retro Diels–Alder process, which leads to formation of the thermodynamically favored adducts. The *endo*/*exo* selectivity is moderate and similar to that observed from acrylates. The synthesis of other sulfinylacrylonitriles in order to improve the dienophilic features of the vinyl sulfoxides is currently in progress.



Scheme 4.

3. Experimental

3.1. General methods

All reactions were carried out in flame dried glassware under argon atmosphere. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM) and silica gel F_{254} plates were used for preparative TLC. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). NMR spectra were determined in $CDCl_3$ solutions unless otherwise indicated at 200 (or 300) and 50.3 (or 75.5) MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. All described compounds were over 97% pure by NMR analysis.

3.2. (2*E*,S_S)-4,4-Diethoxy-2-[(4-methylphenyl)sulfinyl]-but-2-enenitrile, 3

To a solution of **1**[7] (238 mg, 1.33 mmol, 1 equiv.) in anhydrous CH_3CN (10 mL) under argon, were sequentially added 4 Å molecular sieves (0.5 g), 2,2-diethoxy ethanal[6] (473 mg, 3.58 mmol, 2.7 equiv.) and piperidine (28 mg, 33 μL, 0.33 mmol, 0.25 equiv.). The resulting mixture was stirred for 22 h at room temperature. The mixture was filtered through a Celite pad and treated with 1% HCl (10 mL). The aqueous layer was extracted

with CH_2Cl_2 (2×30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated, then purified by flash chromatography (ethyl acetate–hexane 15:85), (yield 46%, orange oil); $[\alpha]_D$ +189.9 (*c* 1.0, chloroform); δ_H 7.58 and 7.36 (AA′BB′ system, 4H), 7.16 (d, 1H, *J* 5.2), 5.31 (d, 1H, *J* 5.2), 3.73–3.51 (m, 4H), 2.42 (s, 3H), 1.23 (t, 3H, *J* 7.0), 1.22 (t, 3H, *J* 7.0); δ_C 144.9 (2C), 143.6, 137.4, 130.4 (2C), 126.2, 125.2, 111.1, 98.1, 62.3, 62.2, 21.5, 14.9 (2C); IR: 2979, 2930, 2219, 1596, 1493, 1445, 1373, 1337, 1064, 811; MS (EI) 293 (10) M^+, 276 (12), 248 (10), 219 (30), 200 (62), 172 (16), 139 (89), 103 (100), 91 (44), 75 (86); HRMS (EI): $C_{15}H_{19}NO_3S$ requires 293.1086. Found: 293.1079.

3.3. (2*E*,(S_S)-2-[(4-Methylphenyl)sulfinyl]-4-oxobut-2-enenitrile, 2

To **3** (260 mg, 0.89 mmol, 1 equiv.) under argon was added formic acid (98%, 1.96 g, 1.6 mL, 42.66 mmol, 50 equiv.) and the resulting mixture was stirred for 1 h at room temperature. The mixture was treated with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2×40 mL) and the organic layer was treated with aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and evaporated (yield 98%, brown oil); $[\alpha]_D$ +510 (*c* 0.12, chloroform); δ_H 7.04 (d, 1H, *J* 7.0), 7.62 and 7.41 (AA′BB′ system, 4H), 7.38 (d, 1H, *J* 6.7), 2.45 (s, 3H); δ_C 185.7, 144.7, 142.0, 138.2, 135.7, 130.9 (2C), 125.4 (2C), 110.2, 21.6. IR: 3041, 2924, 2221, 1696, 1595, 1085, 811; MS (EI) 219 (3) M^+, 203 (3), 139 (100), 124 (26), 91 (73), 77 (22); HRMS (EI): $C_{11}H_9NO_2S$ requires 219.0354. Found: 219.0347.

3.4. Diels–Alder cycloadditions

3.4.1. Method A: Thermal conditions. To a solution of **2** or **3** (1 mmol) in CH_2Cl_2 (3 mL) was added cyclopentadiene (714 μL, 8 mmol). Reaction times and temperatures are indicated in Tables 1 and 2, respectively. When the reaction was complete, the crude mixture was concentrated, and the residue was purified by flash chromatography (ethyl acetate–hexane, 1:4).

3.4.2. Method B: In the presence of Eu(fod)$_3$. A solution of **3** (293 mg, 1 mmol) and Eu(fod)$_3$ (1.56 g, 1.5 mmol) in CH_2Cl_2 (4 mL), under argon, was stirred at room temperature for 1 h. Then cyclopentadiene (714 μL, 8 mmol) was added and the mixture was stirred at the temperature described in Table 2 for the time indicated in each case. Water (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×4 mL). The organic layer was washed with 10% HCl (10 mL), dried (Na_2SO_4), and concentrated.

3.4.3. Method C: In the presence of $ZnBr_2$. To a solution of **3** (293 mg, 1 mmol) in CH_2Cl_2 (4 mL) was added $ZnBr_2$ (675 mg, 3.0 mmol) in THF (0.5 mL) under argon, and the mixture was stirred at room temperature for 1 h. Then cyclopentadiene (714 μL, 8 mmol) was added and the reaction mixture was stirred at the temperature described in Table 2 for the time indicated in each case. Water (4 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×4 mL). The organic layer was dried (Na_2SO_4) and concentrated.

3.4.4. (1*S*,2*S*,3*R*,4*R*,S_S)-3-(Diethoxymethyl)-2-[(4-methylphenyl)sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *endo*-7. Prepared by reaction of **3** with cyclopentadiene following method B. It was purified by flash chromatography (ethyl acetate–hexane, 1:4) and crystallized from ethyl acetate–hexane (yield 59%), mp 82–83°C (white solid); $[\alpha]_D$ +35.1 (*c* 1.12, chloroform); δ_H 7.69 and 7.34 (AA′BB′ system, 4H), 6.47 (dd, 1H, *J* 3.0 and 5.7), 6.30 (dd, 1H, *J* 3.2 and 5.7), 3.96 (d, 1H, *J* 9.1), 3.62–3.45 (m, 4H), 3.25–3.15 (m, 1H), 3.11–3.06 (m, 1H), 2.73 (dd, 1H, *J* 3.2 and 9.1), 2.41 (s, 3H) 2.08 (dt, 1H, *J* 1.4 and 9.5), 1.56 (dt, 1H, *J* 1.6 and 9.5), 1.20 (t, 3H, *J* 7.1), 0.75 (t, 3H, *J* 7.1); δ_C 143.1, 140.6, 135.7, 135.1, 129.6 (2C), 126.3 (2C), 116.4, 103.8, 66.9, 64.5, 60.8, 50.1 (2C), 45.3, 45.2, 21.5, 15.5, 14.5; IR 3027, 2906, 2230, 1659, 1598, 1494, 1454, 1373, 1334, 1260, 1059, 814, 735; MS (EI) 359 (3) M^+, 220 (23), 174 (30), 139 (68), 118 (49), 91 (100), 66 (58); HRMS (EI): $C_{20}H_{25}NO_3S$ requires 359.1555. Found: 359.1547.

3.4.5. (1*R*,2*R*,3*S*,4*S*,S_S)-3-(Diethoxymethyl)-2-[(4-methylphenyl)sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *endo*-8. Prepared by reaction of **3** with cyclopentadiene following method B. It was purified by flash chromatography (ethyl acetate–hexane, 1:4) (yield 5%, oil); $[\alpha]_D$ +96.2 (*c* 0.5, chloroform); δ_H 7.64 and 7.32 (AA′BB′ system, 4H), 6.52 (dd, 1H, *J* 2.8 and 5.7), 6.34 (dd, 1H, *J* 3.0 and 5.7), 3.92 (d, 1H, *J* 8.5), 3.63–3.49 (m, 2H), 3.48–3.40 (m, 1H), 3.35–3.38 (m, 1H), 3.21–3.11 (m, 1H), 3.08–3.04 (m, 2H), 2.41 (s, 3H), 2.15 (dt, 1H, *J* 1.4 and 9.3), 1.48 (dt, 1H, *J* 1.6 and 9.3), 1.19 (t, 3H, *J* 7.1), 0.76 (t, 3H, *J* 7.1); δ_C 143.0, 141.4, 136.8, 134.9, 129.3 (2C), 126.5 (2C), 117.0, 103.3, 65.6, 64.2, 59.8, 53.3, 47.2, 45.1, 44.7, 21.5, 15.4, 14.5; IR 3064, 2978, 2928, 2228, 1676, 1597, 1454, 1374, 1152, 1060, 810; MS (EI) 359 (3) M^+, 220 (12), 174 (14), 139 (39), 118 (29), 91 (100), 66 (75); HRMS (EI): $C_{20}H_{25}NO_3S$ requires 359.1555. Found: 359.1549.

3.4.6. (1*R*,2*S*,3*R*,4*S*,S_S)-3-(Diethoxymethyl)-2-[(4-methylphenyl)sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *exo*-9. Prepared by reaction of **3** with cyclopentadiene following method B. It was purified by flash chromatography (ethyl acetate–hexane, 1:4) (yield 20%, oil); $[\alpha]_D$ +139.8 (*c* 1.07, chloroform); δ_H 7.65 and 7.32 (AA′BB′ system, 4H), 6.52–6.49 (m, 2H), 4.06 (d, 1H, *J* 6.9) 3.68–3.65 (m, 1H), 3.64–3.42 (m, 2H), 3.42–3.34 (m, 1H), 3.21–3.13 (m, 1H), 3.14–3.12 (m, 1H), 2.41 (s, 3H), 1.97 (dt, 1H, *J* 2.0 and 10.1), 1.80 (dd, 1H, *J* 2.0 and 6.9), 1.75 (dc, 1H, *J* 2.0 and 9.7), 1.82 (t, 3H, *J* 7.0), 0.71 (t, 3H, *J* 7.0); δ_C 143.2, 140.5, 136.7, 134.0, 129.5 (2C), 126.4 (2C), 116.9, 103.3, 70.0, 64.8, 62.6, 53.1, 48.0, 46.3, 44.7, 21.5, 15.3, 14.6; IR 2977, 2229, 1644, 1455, 1059, 811, 746. MS (EI) 359 (2) M^+, 220 (10), 174 (21), 154 (100) 139 (36), 126 (23), 91 (65), 75 (49); HRMS (EI): $C_{20}H_{25}NO_3S$ requires 359.1555. Found: 359.1547.

3.4.7. (1*S*,2*R*,3*S*,4*R*,S_S)-3-(Diethoxymethyl)-2-[(4-methylphenyl)sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *exo*-10. Prepared by reaction of **3** with cyclopentadiene following method B. It was obtained along with *endo*-**7** by flash chromatography (ethyl acetate–hexane, 1:4). Data deduced from an *endo*-**7**/*exo*-**10** mixture: δ_H 7.66 and 7.37 (AA′BB′ system, 4H), 6.53 (dd, 1H, *J* 3.2 and 5.6), 6.21 (dd, 1H, *J* 2.8 and 5.6), 4.58 (d, 1H, *J* 4.1), 3.86–3.45 (m, 5H), 2.89–2.87 (m, 1H), 2.46 (dd, 1H, *J* 2.0 and 4.2), 2.43 (s, 3H), 2.14–2.12 (m, 1H), 1.59 (dq, 1H, *J* 2.0 and 9.7), 1.21 (t, 3H, *J* 7.0), 1.20 (t, 3H, *J* 7.0); δ_C 143.1, 141.5, 135.7, 132.3, 129.5 (2C), 125.4 (2C), 116.4, 103.5, 69.6, 63.7 (2C), 51.9, 47.8 (2C), 43.8, 21.5, 15.2, 14.9.

3.5. Hydrolysis of diethoxymethyl cycloadducts into formyl cycloadducts; general procedure

A solution of adduct (1 mmol) and an excess of formic acid (2 mL) was stirred under argon at room temperature for 1.5 h. Water (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3×4 mL). The organic layers were combined and treated with aqueous $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4) and evaporated.

3.5.1. (1*S*,2*S*,3*R*,4*R*,S_S)-3-Formyl-2-[(4-methylphenyl)-sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *endo*-4. Obtained by reaction of *endo*-**7** with formic acid (yield 98%), mp 126–127°C (white solid); $[\alpha]_D$ +136.4 (*c* 0.26, chloroform); δ_H 8.93 (d, 1H, *J* 2.0), 7.73 and 7.40 (AA′BB′ system, 4H), 6.54 (dd, 1H, *J* 2.9 and 5.6), 6.39 (dd, 1H, *J* 3.2 and 5.6), 3.75 (d, 1H, *J* 1.5), 3.41–3.38 (m, 1H), 2.95 (t, 1H, *J* 2.3), 2.44 (s, 3H), 2.05 (d, 1H, *J* 10.0), 1.75 (d, 1H, *J* 10.3); δ_C 197.9, 144.3, 139.8, 135.5, 135.1, 130.2 (2C), 125.7, 125.1, 114.8, 67.5, 56.6, 49.8, 46.0, 45.3, 21.6; IR 2989, 2232, 1729, 1453, 1336, 1088, 1065, 818. MS (EI) 285 (3) M^+, 246 (1), 214 (2), 149 (2), 139 (46), 126(2), 116 (49), 91 (100), 77 (23), 66 (58). HRMS (EI): $C_{16}H_{15}NO_2S$ requires 285.0823 Found:. 285.0836.

3.5.2. (1*R*,2*R*,3*S*,4*S*,S_S)-3-Formyl-2-[(4-methylphenyl)-sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *endo*-5. Obtained by reaction of *endo*-**8** with formic acid (yield 80%, oil). It partially decomposed on purification. δ_H 8.99 (t, 1H, *J* 1.0), 7.68 and 7.39 (AA′BB′ system, 4H), 6.59 (dd, 1H, *J* 2.8 and 5.4), 6.34 (dd, 1H *J* 3.2 and 5.4), 3.57 (t, 1H, *J* 5.6), 3.45 (dd, 2H, *J* 1.4 and 3.2), 3.39–3.34 (m, 1H), 2.44 (s, 3H), 2.40 (d, 1H, *J* 11.5), 2.16 (dt, 1H, *J* 1.6 and 9.5); δ_C 198.4, 144.1, 141.3, 136.0, 135.6, 129.9 (2C), 125.6 (2C), 115.9, 65.7, 54.9, 51.9, 45.1, 44.3, 21.6.

3.5.3. (1*R*,2*S*,3*R*,4*S*,S_S)-3-Formyl-2-[(4-methylphenyl)-sulfinyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile, *exo*-6. Obtained by reaction of *exo*-**9** with formic acid; mp 132–133°C (white solid); $[\alpha]_D$ +273.4 (*c* 0.53, chloroform); δ_H 9.00 (s, 1H), 7.67 and 7.37 (AA′BB′ system, 4H), 6.56–6.49 (m, 2H), 3.78 (sp, 1H, *J* 1.6), 3.40 (sp, 1H, *J* 1.6), 2.42 (s, 3H), 2.22 (t, 1H, *J* 1.8), 1.88 (dq, 1H, *J* 1.8 and 10.1), 1.80 (dt, 1H, *J* 1.6 and 10.1); δ_C 196.8, 144.2, 139.7, 135.9, 134.2, 130.2, 125.4 (2C), 115.3, 69.3, 54.2, 53.4, 52.6, 47.5, 44.4, 21.5; IR 2924, 2230, 1728, 1083, 1062, 812. MS (EI) 285 (1) M^+, 214 (1), 149 (2), 139 (57), 126(2), 116 (35), 91 (100), 77 (25), 66 (89). $C_{16}H_{15}NO_2S$ requires 285.0823. Found: 285.0827.

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9. The ^{1}H NMR spectra of the crude product obtained under these conditions do not reveal the presence of compound **10**, but a small amount of it was isolated by chromatography—as a mixture of **7** and **10**—and therefore, it has been included in entry 12 (Table 2).
10. The authors have deposited the atomic coordinates for **7** with the Cambridge Crystallographic Data Centre (Deposit No. CCDC 188910). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
11. The reaction was carried out in an NMR tube in order to be monitored by ^{1}H NMR. A solution of 0.57 mmol of

m-CPBA in 0.3 mL of $CDCl_3$ was added into a solution of 0.38 mmol of adduct in 0.3 mL of $CDCl_3$ until the signals of the starting material were not observed by ^1H NMR. No sulfone was isolated. ^1H NMR are those deduced from the spectra of the reaction mixtures. **(1*S*,2*S*,3*R*,4*R*)-** and **(1*R*,2*R*,3*S*,4*S*)-3-(diethoxymethyl)-2-[(4-methylphenyl) sulfonyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile**, **11** were obtained from **7** and **8**, respectively: δ_H 7.87 and 7.35 (AA′BB′ system, 4H), 6.53 (dd, 1H, *J* 2.4 and 5.5), 6.38 (dd, 1H, *J* 3.2 and 5.5), 3.91 (d, 1H, *J* 8.9), 3.85–3.83 (m, 1H), 3.65–3.56 (m, 2H), 3.49–3.37 (m, 2H), 3.18–3.05 (m, 2H) 2.44 (s, 3H), 2.41 (d, 1H, *J* 9.7), 1.55 (d, 1H, *J* 9.5), 1.22 (t, 3H, *J* 7.1), 0.62 (t, 3H, *J* 7.1). **(1*R*,2*S*,3*R*,4*S*)-** and **(1*S*,2*R*,3*S*,4*R*)-3-(Diethoxymethyl)-2-[(4-methylphenyl) sulfonyl]bicyclo[2.2.1]hept-5-ene-2-carbonitrile**, **12** were obtained from **9** and **10**, respectively: δ_H 7.84 and 7.36 (AA′BB′ system, 4H), 6.48 (dd, 1H, *J* 3.4 and 5.7), 6.29 (dd, 1H, *J* 3.0 and 5.7), 4.44 (d, 1H, *J* 7.5), 3.73–3.49 (m, 4H), 3.42–3.25 (m, 2H), 3.15–3.10 (m, 1H), 2.56 (dd, 1H, *J* 2.2 and 7.5), 2.45 (s, 3H), 1.96 (d, 1H, *J* 9.7), 1.66 (d, 1H, *J* 9.7), 1.22 (t, 3H, *J* 7.1), 0.81 (t, 3H, *J* 7.1).

12. Double Pulsed Field Gradient Echo-DPFGS (Bruker DRX-500). NOE values for *endo*-**7**: 3.5% [C(3)H–C(7)H]; *endo*-**8**: 2.7% [C(3)H–C(7)H]; *exo*-**9**: 1.8% [C(3)H–C(5)H].
13. All reactions performed for longer reaction times or those consisting in treating any of the adducts **4–6** under the reaction conditions optimized for the cycloaddition, did not give any evidence of retro Diels–Alder reaction.
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