Stereospecific Grignard reactions of cholesteryl 1-alkenesulfinate esters: Application of the Andersen Protocol to the preparation of non-racemic α,β-unsaturated sulfoxides

Rick R. Strickler, John M. Motto, Craig C. Humber, and Adrian L. Schwan

Abstract: Enantiomerically enriched α,β-unsaturated sulfinate esters of (–)-cholesterol undergo stereospecific substitutions at sulfur when treated in benzene at 6°C with Grignard reagents. Sulfoxides with ees of 85–99.5% are obtained when enantiopure sulfinates are used. The substitution reactions proceed with inversion of sulfur configuration. Enantiomerically pure cholesteryl (*E*)-2-carbomethoxyethenesulfinate is not a suitable reactant under the Grignard reaction conditions. It is suggested that the ester group induces unwanted reactions significantly lowering both the yield and sulfur stereogenicity.

Key words: sulfinate, sulfoxide, Grignard reagents, stereospecific, unsaturated.

Résumé : Lorsqu'on les traite avec des réactifs de Grignard, dans le benzène à 6 °C, les sulfinates α,β-insaturés énantiomériquement enrichis du (–)-chlolestérol subissent des réactions de substitution stéréospécifiques au niveau du soufre. Des sulfoxydes avec des ee de 95 à 99,5 % sont obtenus lorsqu'on utilise des sulfinates énantiomériquement purs. Les réactions de substitution se produisent avec inversion de configuration au niveau du soufre. Le (*E*)-2-carbométhoxyéthènesulfinate de cholestéryle énantiomériquement pur n'est pas un réactif approprié dans les conditions utilisées avec les réactifs de Grignard. Il est suggéré que le groupe ester induit des réactions indésirables qui abaissent de façon significative tant le rendement que la stéréogénicité au niveau du soufre.

Mots clés : sulfinate, sulfoxyde, réactifs de Grignard, stéréospécifique, insaturé.

[Traduit par la Rédaction]

Introduction

Enantioentriched sulfoxides can induce the introduction of carbon chirality into organic molecules by a number of means including carbanionic chemistry, Diels–Alder reactions and chiral ligand complexation (1–4). In these reactions it is the chirality at the sulfur center that plays a pivotal role in controlling the stereochemical outcome of the reaction. As such, a great deal of effort has gone into developing reliable and efficient methods for the synthesis of enantiopure sulfoxides. One mode of preparation of chiral sulfoxides that has enjoyed sustained popularity (4–7) is based on a protocol introduced by Andersen (8*a*). The original Andersen procedure involves treating a sulfinyl chloride with (–)-menthol to generate a diastereomeric mixture of menthyl sulfinate esters which, following a separation step, undergo organometallic substitution to afford enantiomerically pure sulfoxides (Scheme 1, R*OH = menthol). Since the original Andersen method was first introduced several improvements have been advanced. These typically involve the use of other chiral alcohols such as diacetone-D-glucose (DAG), (5*b*, 9) (1*R*,2*S*)-(–)-*trans*-2-phenyl-cyclohexanol (10), and cholesterol (7, 11). The majority of recent applications of this protocol have tended to employ either DAG (4, 5) or (–)-menthol (6).

To this point, the application of cholesterol to this chemistry has been focused on preparing methanesulfinate esters (11). The propensity of the large cholesteryl auxiliary to crystallize provided the driving force for the sulfinate separation by recrystallization and the eventual formation of enantiopure methanesulfinates and methyl sulfoxides (11). Our group has established a practical method for the synthesis of 1-alkenesulfinyl chlorides (12, 13) and while investigating their conversion to enantiopure α,β-unsaturated sulfinate esters, has found that cholesterol is a preferred chiral alcohol (14). The aptitude for cholesterol derivatives to crystallize provided a benefit no other alcohols could equal. In that investigation the first collection of optically active 1-alkenesulfinate esters was reported (eq. [1]) (14). As part of our continuing interest in this area we investigated the nucleophilic conversion of these α,β-unsaturated sulfinate esters to enantiopure or enriched α,β-

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Dedicated to Professor Don Arnold for his contributions to chemistry.

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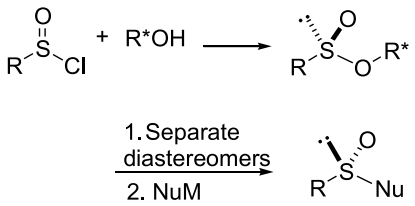
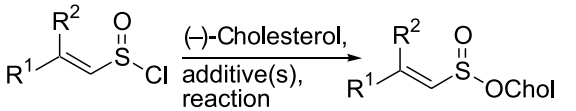
Scheme 1.



unsaturated sulfoxides, compounds that are well-established as useful sources of a variety of chiral derivatives (1, 15). Most of the existing chiral vinylic sulfoxide preparations either create the double bond after a chiral sulfoxide has been prepared, or treat a chiral arenesulfinate with a vinylic organometallic reagent (15*c*, 15*d*). No such syntheses have established the chirality once the C=C-S unit was already intact which is the strategy investigated by us. This paper reports the outcome of our investigation, a portion of which has already been communicated (7).

[1] 

Chol = (–)-cholesteryl

	R^1, R^2
1:	*t*Bu,H
2:	H, H
3:	Ph, H
4:	Ph, Cl
5:	CO_2Me, H

Results and discussion

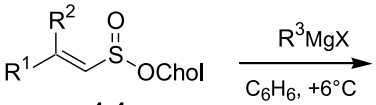
A synthetically useful organometallic displacement of the cholesteryl unit requires both high yield and maintenance of the stereogenicity at the sulfur. In work outlined in the preliminary communication (7), it was established using cyclohexyl analogs of the available enantioenriched sulfinate esters (14) that Grignard reagents (2 equiv) were readily found to be favored over organolithiums (16). To find the preferred conditions for maximum enantiomeric excesses, samples of [R_S]-(–)-cholesteryl (*E*)-3,3-dimethyl-1-butenesulfinate (**1**) possessing 88–100% optical purity were treated with *n*-BuMgCl under various conditions.[2] The results directed us to perform all subsequent substitution reactions in benzene (17) at 6°C where possible, although ethyl ether was the original solvent for such reactions (8*b*, 18).

Using the reaction conditions found in those preliminary experiments, the reactions of enantiopure or enantioenriched selected [R_S]- and [S_S]-sulfinates **1**–**4** with commercial and prepared Grignard reagents were proved to be efficient and chemoselective affording a wide variety of substituted α,β-unsaturated sulfoxides as outlined in Table 1 (eq. [2]). The enantiomeric excesses and the configurational assignments of the sulfoxides were determined using the chiral solvating agent [*R*]-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (19).[3] The sulfoxides possessing the highest ees arose from stereospecific reactions of sulfinates **1**, **3**, and **4**. Simple ethenyl sulfoxides could not be produced with high ee, since the precursor (–)-cholesteryl ethenesulfinate (**2**) could only be formed with des as high as 47% (14). Nevertheless, Grignard reactions of **2** still proceeded with high stereospecificity and yield when aromatic Grignard reagents were employed. Aliphatic Grignard reagents afforded somewhat lower yield and brought on losses of stereogenicity. Utilizing the availability of [S_S]-**1** (14) the corresponding Grignard reactions and the obtention of [R_S]-sulfoxides confirms the stereospecificity of the substitution pathway and eliminates the possibility of stereoconvergent Grignard reactions.

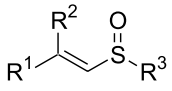
It was decided that the ^{1}H NMR – solvating agent method (19) of ee determination had a detection limit of 98% for samples that had only one set of peaks evident: the ^{1}H NMR of solvated **6f** shows the minor isomer and the ee of the sample of **6f** was found to be 98%. A closer inspection of the rotation data for **8b** further corroborates the detection limit, and hence the optical purity of the sulfoxides. The literature reports a value of $[\alpha]_D^{25}$ +166.0° ($CHCl_3$) for **8b** with 100% optical purity (20) while we obtained $[\alpha]_D^{25}$ +165.1° ($CHCl_3$) meaning our isolated sample of **8b** possessed an ee of 99.5%.

Successful 2-furyl Grignard reactions were obtained after several attempts and it was found that 2-furylMgBr generated in THF by the reaction of 2-furyllithium with $MgBr_2$-Et_2O (6*d*, 21) reacts with [R_S]-**1** in THF at –20°C in 78% yield and with >98% ee. Sulfoxides bearing the furyl group are important in organic synthesis and have been used in the synthesis of naturally occurring compounds (22). Also, noteworthy is that MeMgBr induced a 15% reduction in the measured ees of the sulfoxides obtained. Several repetitions and variations were performed but ees could not be improved and yields consistently ranged from 56 to 67%.

Many of the synthetic protocols for racemic and homo-

[2] 

1-4

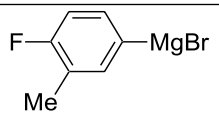
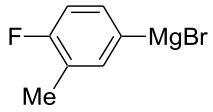


	R^1, R^2	R^3
6:	*t*Bu,H	**a**: *n*Bu
7:	H, H	**b**: *p*Tol
8:	Ph, H	**c**: 2-Furyl
9:	Ph, Cl	**d**: cC_6H_{11}
		e: Me
		f: *i*Pr
		g: 4-F-3-MePh
		h: $PhCH_2$
		i: *t*Bu
		j: $PhCMe_2CH_2$

chiral α,β-unsaturated sulfoxides introduce the double bond in the last stage of the preparation and sometimes lead to

[2] The reader is referred to the table of preliminary data presented in the communication (ref. (7)).
[3] In some cases, one can gain confirmation of the assigned sulfur configuration by comparison of the sample's optical rotation with literature values.

Table 1. Grignard reactions of optically enriched α,β-unsaturated sulfinates.

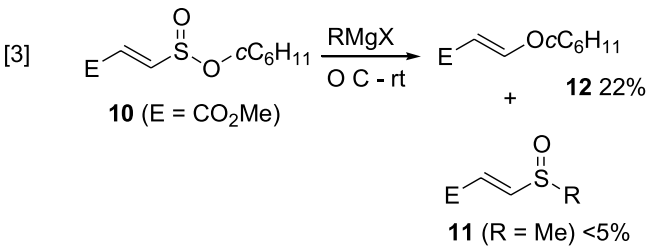
			Sulfoxide			
	Sulfinate and config.	Grignard reagent[a]	Structure	% Yield	$[\alpha]_D^{25}$[b]	%ee[c]
1	**2**: 42% [R_S]		**7g**	80	+153.4° (*c* 1.09)	41 [R_S]
2	**2**: 22% [S_S]		**7g**	83	–79.9° (*c* 1.42)	22 [S_S]
3	**2**: 22% [S_S]	*c*-$C_6H_{11}MgCl$	**7d**	42(63)[d]	–51.6° (*c* 0.32)	23 [S_S]
4	**2**: 42% [R_S]	*p*-TolylMgBr	**7b**	77(85)[d]	+136.3° (*c*, 1.08)[e]	42 [R_S]
5	**2**: 42% [R_S]	2-FurylMgBr[f]	**7c**	59	+72.3° (*c*, 0.83)	41 [R_S]
6	**2**: 36% [R_S]	$PhCMe_2CH_2MgCl$	**7j**	39	+43.0° (*c* 1.96)	28 [S_S]
7	**1**:100% [R_S]	*n*BuMgCl	**6a**	86	+130.7° (*c* 1.57)	>98 [S_S]
8	**1**:100% [R_S]	MeMgBr	**6e**	56–67	+238.2° (*c* 2.90)	85 to 86 [S_S]
9	**1**:100% [R_S]	*i*-PrMgCl	**6f**	85	+150.3° (*c* 1.95)	98 [S_S]
10	**1**:100% [R_S]	*c*-$C_6H_{11}MgBr$	**6d**	86	+61.4° (*c* 2.38)	>98 [S_S]
11	**1**:100% [R_S]	$PhCH_2MgBr$[g]	**6h**	78	+142.0° (*c* 1.31)	91 [S_S]
12	**1**:100% [R_S]	*p*-TolylMgBr	**6b**	86	+116.6° (*c* 1.41)[h]	94 [R_S]
13	**1**:100% [R_S]	2-FurylMgBr[f]	**6c**	78	+125.8° (*c* 1.69)	>98 [R_S]
14	**1**:71% [S_S]	*i*-PrMgCl	**6f**	76	–112.3° (*c* 1.53)	72 [R_S]
15	**1**:71% [S_S]	*c*-$C_6H_{11}MgBr$	**6d**	79	–41.4° (*c* 2.30)	71 [R_S]
16	**3**:42%[S_S]	*t*BuMgCl	**8i**	70	–46.6° (*c* 1.08)	41.5 [S_S]
17	**3**:100% [R_S]	*t*-BuMgCl	**8i**	70	+109.8° (*c* 0.96)	97 [R_S]
18	**3**:100% [R_S]	*i*-PrMgCl	**8f**	87	+116.7° (*c* 1.69)	91 [S_S]
19	**3**:100% [R_S]	c-$C_6H_{11}MgBr$	**8d**	62	+62.3° (*c* 1.61)	92 [S_S]
20	**3**:100% [R_S]	*n*-BuMgCl	**8a**	74	+62.1° (*c* 0.89)	n/d[i]
21	**3**:100% [R_S]	$PhCH_2MgBr$[g]	**8h**	56(87)[c]	–53.9° (*c* 1.04)	91 [S_S]
22	**3**:100% [R_S]	$PhCMe_2CH_2MgCl$	**8j**	81	+125.3° (*c* 0.64)	91 [S_S]
23	**3**:100% [R_S]	*p*-TolylMgBr	**8b**	76	+176.9° (*c*, 1.03)[j]	>98 [R_S]
24	**3**:100% [R_S]		**8g**	82	+152.0° (*c* 1.11)	95 [R_S]
25	**4**:86%[S_S]		**9g**	61	–49.5° (*c* 2.52)	86 [S_S]
26	**4**:85% [S_S]	*c*-$C_6H_{11}MgBr$	**9d**	73	–28.0° (*c* 1.17)	79 [R_S]

[a]Used 2 equiv of Grignard reagent unless otherwise noted. Reactions were performed in benzene at 6°C unless otherwise noted.
[b]Optical rotations were obtained in acetone, unless otherwise noted.
[c]Ees were determined using [*R*]-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol as an NMR solvating agent. See ref. (19).
[d]Yield in brackets is based on recovered starting material.
[e]Lit. (20) value +386° (ethanol, 94% [R_S]).
[f]Prepared from lithiated furanyl anion; see text and *Experimental* section for details.
[g]Experiment was done with 1 equiv of Grignard reagent.
[h]Lit. (23*d*) value +33° (acetone).
[i]Not determinable.
[j]$[\alpha]_D^{25}$ +165.1° (*c*, 1.03, $CHCl_3$) (lit. (20) value +166.0°; ($CHCl_3$, 100% [R_S])).

mixtures of double bond isomers (6*g*, 20, 23, 24). At no point were the sulfoxides obtained herein contaminated with any *cis*-isomer. Our protocol establishes the geometry of the double bond at a very early stage of the chemistry, and the double bond configuration is never jeopardized thereafter. In this regard we are demonstrating the stereospecific transfer of selected chiral alkenesulfinyl units, while maintaining the double bond geometry. Hence, the sulfinates represent the first usage of an intact chiral [RCH=CHSO]+ synthon.

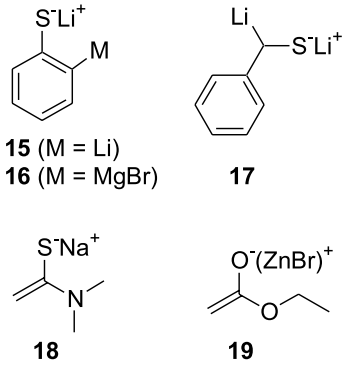
Reactions of cholesteryl (*E*)-2-carbomethoxyethene-sulfinate

Grignard reactions of optically pure sulfinate **5** proved troublesome. Under our established conditions little or no sulfoxide was observed. Hence, cyclohexyl (*E*)-2-carbomethoxyethenesulfinate (**10**) (12) was enlisted as a model compound for **5** to employ in an investigation of the behavior of this unique sulfinate. The reaction of **10** with MeMgBr (eq. [3]) typifies the results of several trials. Sulfoxide **11** could only be obtained in 0–20% yield and the reaction mixture always contained vinyl ether **12**. Changing to other organometallic species such as organolithium and organocerium reagents offered little improvement.

[3] 

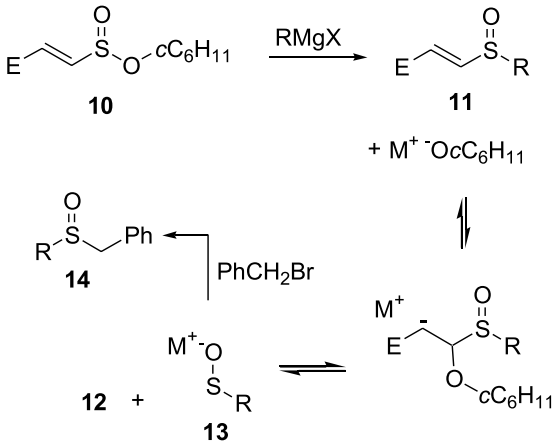
A mechanism to account for the observed results is offered in Scheme 2. It was felt that the sulfur substitution is indeed occurring, but the product is prone to counterattack by the displaced alkoxide. That attack occurs conjugate to the ester, the stronger electron-withdrawing group, and to conclude what appears to be an addition–elimination mechanism, a sulfenic acid anion (**13**) is released. To test this mechanism, sulfoxide **11** (R = $MeOC_6H_4CH_2$), the precursor of sulfinates **5** (14) and **10** (12), was treated with lithium cyclohexylate and the mixture was quenched with benzyl bromide to capture any reactive sulfenate (e.g., **13**). The observation of **12** as a reaction constituent and the isolation of **14** (R = $MeOC_6H_4CH_2$) in 47% purified yield from that mixture offer strong support for the proposed mechanism (Scheme 2).

A number of experiments were performed to see if the sulfoxide could be intercepted before the addition–elimination reaction took place. To this end, sulfinate **10** was treated with nucleophiles **15**–**19**. It was hoped that dianions **15** (25), **16**, and **17** (26) would effect sulfoxide formation and rapidly perform an intramolecular Michael addition. As an alternative strategy, it was suggested that **18** (5*d*) and **19** could achieve sulfoxide formation and the presence of a (thio)carbonyl group β to the sulfinyl unit would enhance the acidity of the intervening methylene hydrogens thereby providing the displaced alkoxide the recourse of deprotonation rather than Michael attack. None of these efforts provided significant sulfoxide and vinyl ether **12** was evident in the reaction mixtures.



Not completely discouraged, we pursued several reactions of **5** with Grignard reagents. Equation [4] depicts the best results that could be achieved, and although the low yields of sulfoxide **11** and of vinyl ether **20** were foreseen, the loss of sulfur stereochemistry was unexpected. The loss of sulfur chirality is presumably because of the presence of the conjugating carboxylic ester group. It has recently been shown (27) that the presence of a vinylic ester conjugating to a sulfinyl lone pair and the consequent mesomeric donation of that lone pair toward the ester leads to a reduced inversion barrier for the sulfinyl group. Based on this behavior, it follows that the sulfinyl group in a compound such as **11** exhibits increased electrophilicity at sulfur. Hence, a reasonable explanation for the loss of sulfur stereochemistry entails attack of **11** by excess Grignard agent, a pseudorotation step of the intermediate sulfurane at which time loss of stereogenicity occurs followed by release of one of the two carbon-based ligands. Alternatively, attack by previously released cholesteryloxy anion on **5** would bring about a similar outcome, as precedented by counterattack and racemization by thiolate on chiral thiosulfinates (28). However, control experiments have shown that racemization of **5** by cholesteryloxy anion is minimal.

Scheme 2.



[4] **5** $\xrightarrow[\text{conditions}]{\text{RMgX}}$ **11**: **a**, R = *n*Bu (31%, 51% ee); **b**, R = *p*Tol (25%, 21% ee) + **20**

Conclusions

Andersen, Mikolazcyk, and co-workers (11) have previously obtained optically pure cholesteryl [R_S]- and [S_S]-methanesulfinates in <5% yield. Although the behavior of cholesteryl ethenesulfinate would appear to be similar to those methanesulfinates, we were able to secure more substituted 1-alkenesulfinates in higher yield through recrystallization chemistry (14) and demonstrate in this paper that they are suitable 1-alkenesulfinyl transfer agents. Based on this observation, diastereomeric mixtures of cholesteryl sulfinate esters bearing large aryl and alkyl groups attached to sulfur may prove readily separable and hence worthy of investigation.

Those sulfinate esters that we have been able to secure undergo stereospecific substitution with inversion at sulfur yielding a range of α,β-unsaturated sulfoxides. The presence of a carbomethoxy group trans to the sulfinate ester creates significant unwanted reactions under Grignard treatment conditions. The method outlined herein is not limited to vinylic sulfoxides bearing only a *p*-tolyl group, the preparations of which have been amply demonstrated in the literature, buts allows for the preparation of a broader array of alkyl or aryl 1-alkenyl sulfoxides. It would appear that the collection of sulfoxides accessible by this protocol is only limited by the number of enantioenriched sulfinates available; we are currently exploring other means of pre-

paring a larger selection of enantiopure 1-alkenesulfinates.

Experimental

General

Our general experimental methods have been outlined in a previous publication (12). Unless noted below, all Grignard reagents were purchased as stock solutions from Aldrich. Optical rotation measurements were performed on an Autopol III automatic polarimeter.

Typical procedure for the conversion of optically enriched sulfinates 1–4 to sulfoxides

Diastereomerically pure cholesteryl 1-alkenesulfinate ester (**1**–**4**, 1 equiv) was dissolved in benzene (10 mL) and cooled to 6°C under N_2. After 10 min the Grignard reagent (commercially available stock solution; 1 to 2 equiv) was added dropwise. The reaction mixture was stirred until complete by TLC analysis (1 to 2 h) and then quenched with NH_4Cl (10 mL). The solution was diluted with EtOAc and the organic layer separated, washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The enantioenriched sulfoxides were isolated using silica gel flash chromatography, with EtOAc–hexanes as the eluent. Chemical yields, enantiomeric purities, and optical rotation data (in acetone) are presented in Table 1. All sulfoxides except **6c**, **7c**, **11a**, and **11b** were prepared by this protocol. Structural characterization of the sulfoxides follows.

*[R_S]-1-Ethenyl 4-methylphenyl sulfoxide (**7b**) (23c):*

^{1}H NMR (400 MHz) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.58 (dd, *J* = 16.4, 9.6 Hz, 1H), 6.19 (d, *J* = 16.4 Hz, 1H), 6.18 (d, *J* = 9.6 Hz, 1H), 2.41 (s, 3H).

*[S_S]-1-Ethenyl cyclohexyl sulfoxide (**7d**):*

Mp: 48–50°C. IR (CH_2Cl_2) (cm^{-1}): 3043, 2933, 2856, 1452, 1055. ^{1}H NMR (400 MHz) δ: 6.57 (dd, *J* = 16.5, 10.0 Hz, 1H), 6.07 (d, *J* = 16.5 Hz, 1H), 6.00 (d, *J* = 10.0 Hz, 1H), 2.57 (tt, *J* = 11.6, 3.6 Hz, 1H), 2.02–1.87 (m, 3H), 1.80–1.60 (m, 2H), 1.50–1.15 (m, 5H). ^{13}C NMR (100.6 MHz) δ: 138.6, 122.9, 60.2, 26.0, 25.5, 25.3, 24.2. MS (CI, NH_3) *m*/*z* (%): 159 ([M + 1]$^+$, 21), 108 (24), 91 (100), 90 (35), 74 (28), 73 (14). Anal. calcd. for $C_8H_{14}OS$: C 60.71, H 8.92; found: C 60.92, H 8.70.

*[R_S]-4-Fluoro-3-methylphenyl ethenyl sulfoxide (**7g**):*

IR (neat) (cm^{-1}): 3064, 3032, 2928, 1597, 1577, 1485, 1449, 1395, 1384, 1368, 1240, 1183, 1120, 1085, 1055, 1015, 986. ^{1}H NMR (400 MHz) δ: 7.48 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.42 (m, 1H), 7.14 (t, *J* = 8.8 Hz, 1H), 6.57 (dd, *J* = 16.4, 9.6 Hz, 1H), 6.20 (d, *J* = 16.4 Hz, 1H), 6.91 (d, *J* = 9.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100.6 MHz) δ: 162.9 (d, *J* = 250.6 Hz), 142.8, 138.1, 128.0 (d, *J* = 6.0 Hz), 126.9 (d, *J* = 18.5 Hz), 124.3 (d, *J* = 8.9 Hz), 120.6, 116.1 (d, *J* = 23.7 Hz), 14.5 (d, *J* = 3.2 Hz). MS (EI) *m*/*z* (%): 184 (M$^+$, 11), 157 (21), 141 (18), 137 (11), 136 (100), 135 (21), 110 (18), 109 (33), 108 (10), 107 (12), 97 (11), 83 (20), 59 (10), 57 (13), 45 (19). Anal. calcd. for C_9H_9FOS: C 58.68, H 4.92; found: C 58.77, H 5.02.

*[S_S]-Ethenyl 1-(2-methyl-2-phenylpropyl) sulfoxide (**7j**):*

IR (neat) (cm^{-1}): 3089, 3034, 2967, 2932, 1497, 1444, 1370, 1047. ^{1}H NMR (400 MHz) δ: 7.31–7.24 (m, 3H), 7.17–7.14 (m, 2H), 6.25 (dd, *J* = 16.4, 9.6 Hz, 1H), 5.92 (d, *J* = 16.4 Hz, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 2.89 (AB$_q$, *J* = 13.4 Hz, 2H), 1.16 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (100.6 MHz) δ: 146.7, 141.5, 128.5, 126.6, 125.6, 120.7, 70.0, 37.8, 29.9, 27.2. MS (EI) *m*/*z* (%): 209, (82), 133 (91), 91(100), 55(20). Anal. calcd. for $C_{12}H_{16}OS$: C 69.19, H 7.74; found: C 69.38, H 7.59.

*[S_S]-(E)-3,3-Dimethyl-1-butenyl 1-butyl sulfoxide (**6a**):*

IR (neat) (cm^{-1}): 2959, 2932, 2906, 2870, 1625, 1465, 1364, 1265, 1074, 1039, 971. ^{1}H NMR (400 MHz) δ: 6.45 (d, *J* = 15.4 Hz, 1H), 6.09 (d, *J* = 15.4 Hz, 1H), 2.70 (t, *J* = 7.7 Hz, 2H), 1.68 (m, 2H), 1.48 (m, 2H), 1.11 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz) δ: 151.1, 128.1, 53.8, 34.2, 28.8, 24.1, 22.0, 13.7. MS (EI) *m*/*z* (%): 188 (8), 171 (39), 132 (35), 118 (21), 117 (100), 115 (34), 101 (40), 99 (33), 97 (25), 85 (32), 84 (20), 83 (86), 79 (18), 74 (29), 71 (22), 69 (27), 67 (29), 65 (26), 59 (71), 57 (78), 56 (18), 55 (70), 53 (28), 51 (17). Anal. calcd. for$C_{10}H_{20}OS$: C 63.78, H 10.70; found: C 63.83, H 10.45.

*[R_S]-(E)-3,3-Dimethyl-1-butenyl 4-methylphenyl sulfoxide (**6b**) (29):*

^{1}H NMR (400 MHz) δ: 7.49 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 15.4 Hz, 1H), 6.11 (d, *J* = 15.4 Hz, 1H), 2.41 (s, 3H), 1.08 (s, 9H).

*[S_S]-(E)-3,3-Dimethyl-1-butenyl cyclohexyl sulfoxide (**6d**):*

IR (CH_2Cl_2) (cm^{-1}): 3029, 2935, 2855, 1622, 1474, 1463, 1451, 1365, 1264, 1055, 971. ^{1}H NMR (400 MHz) δ: 6.42 (d, *J* = 15.6 Hz, 1H), 6.04 (d, *J* = 15.6 Hz, 1H), 2.54 (m, 1H), 2.04 (m, 1H), 1.88 (m, 3H), 1.67 (m, 1H), 1.31 (m, 5H), 1.11 (s, 9H). ^{13}C NMR (100.6 MHz) δ: 152.2, 126.1, 60.5, 34.3, 28.9, 26.0, 25.6, 25.5, 25.3, 24.8. MS (EI) *m*/*z* (%): 214 (M$^+$, 8), 198 (19), 183 (32), 132 (100), 117 (78), 115 (27), 101 (48), 83 (88), 81 (19), 74 (20), 67 (26), 59 (41), 53 (17), 55 (85). Anal. calcd. for $C_{12}H_{22}OS$: C 67.23, H 10.34; found: C 67.08, H 9.93.

*[S_S]-(E)-3,3-Dimethyl-1-butenyl methyl sulfoxide (**6e**) (23d):*

^{1}H NMR (400 MHz) δ : 6.47 (d, *J* = 15.4 Hz, 1H), 6.17 (d, *J* = 15.4 Hz, 1H), 2.61 (s, 3H), 1.11 (s, 9H). MS (EI) *m*/*z* (%): 146 (M$^+$, 20), 131 (28), 130 (32), 117 (12), 115 (100), 83 (47), 81 (21), 71 (20), 58 (21), 57 (62), 53 (29), 51 (22). Anal. calcd. for: $C_7H_{14}OS$: C 57.49, H 9.65; found: C 57.45, H 9.52.

*[S_S]-(E)-3,3-Dimethyl-1-butenyl 2-propyl sulfoxide (**6f**):*

IR (neat) (cm^{-1}): 2961, 2932, 2905, 2868, 1628, 1475, 1463, 1365, 1266, 1062, 1024, 973. ^{1}H NMR (400 MHz) δ : 6.43 (d, *J* = 15.6 Hz, 1H), 6.01 (d, *J* = 15.6 Hz, 1H), 2.78 (m, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (100 MHz) δ: 152.3, 125.4, 51.7, 34.3, 28.9, 15.2, 14.6. MS (EI) *m*/*z* (%): 174 (M$^+$, 15), 158 (20), 143 (38), 132 (90), 117 (100), 115 (42), 101 (59), 99 (39), 83 (81), 74 (30), 67 (35), 65 (31), 59 (85), 57 (27). Anal. calcd. for $C_9H_{18}OS$: C 62.02, H 10.41; found: C 61.82, H 10.25.

*[S_S]-(E)-3,3-Dimethyl-1-butenyl benzyl sulfoxide (**6h**) (30):*
^{1}H NMR (400 MHz) δ: 7.25–7.23 (m, 3H), 7.16–7.13 (m, 2H), 6.12 (d, *J* = 15.5 Hz, 1H), 5.89 (d, *J* = 15.4 Hz, 1H), 3.89 (AB_q, *J* = 12.6 Hz, 2H), 0.90 (s, 9H).

*[R_S]-(E)-2-Phenylethenyl 1-butyl sulfoxide (**8a**):*
IR ($CDCl_3$) (cm^{-1}): 3084, 3030, 2961, 2933, 2875, 1615, 1494, 1467, 1070, 1039, 965. ^{1}H NMR (400 MHz) δ: 7.45 (m, 2H), 7.35 (m, 3H), 7.21 (d, *J* = 15.5 Hz, 1H), 6.82 (d, *J* = 15.5 Hz, 1H), 2.78 (m, 2H), 1.75 (m, 2H), 1.48 (m, 2H), 0.94 (t, *J* = 8 Hz, 3H). ^{13}C NMR (100.6 MHz) δ: 136.8, 133.8, 130.5, 129.6, 128.9, 127.6, 53.9, 24.0, 22.0, 13.7. MS (EI) *m*/*z* (%): 208 (4, M^+), 192 (53), 152 (31) 136 (17), 135 (72), 94 (100). Anal. calcd. for $C_{12}H_{16}OS$: C 69.19, H 7.74; found: C 68.98, H 7.61.

*[R_S]-(E)-2-Phenylethenyl 4-methylphenyl sulfoxide (**8b**) (23c):*
^{1}H NMR (400 MHz) δ: 7.58 (d, *J* = 6.8 Hz, 2H), 7.47–7.44 (m, 2H), 7.39–7.32 (m, 6H), 6.82 (d, *J* = 15.6 Hz, 1H), 2.41 (s, 3H).

*[S_S]-(E)-2-Phenylethenyl cyclohexyl sulfoxide (**8d**):*
Mp: 90 to 91°C. IR ($CDCl_3$) (cm^{-1}): 3088, 3055, 2936, 2857, 1449, 1263, 1253, 1234, 1167, 1159, 1032, 1015, 967. ^{1}H NMR (400 MHz) δ: 7.50–7.47 (m, 2H), 7.41–7.33 (m, 3H), 7.22 (d, *J* = 15.4 Hz, 1H), 6.81 (d, *J* = 15.4 Hz, 1H), 2.68 (tt, *J* = 11.8, 3.5 Hz, 1H), 2.09–1.96 (m, 2H), 1.91–1.87 (m, 2H), 1.73–1.70 (m, 1H), 1.55–1.40 (m, 2H), 1.40–1.15 (m, 3H). ^{13}C NMR (100.6 MHz) δ: 137.7, 134.0, 129.6, 128.9, 128.6, 127.5, 61.1, 26.1, 25.5 (2 C's), 25.3, 24.6. MS (EI) *m*/*z* (%): 234 (M^+, 2), 152 (100), 135 (25), 104 (22), 91 (12), 83 (13), 77 (12), 73 (22), 55 (50), 45 (20), 41 (28). Anal. calcd. for $C_{14}H_{18}OS$: C 71.75, H 7.74; found: C 71.73, H 7.32.

*[S_S]-(E)-2-Phenylethenyl 2-propyl sulfoxide (**8f**):*
Mp: 50–52°C. ^{1}H NMR (400 MHz) δ: 7.49–7.47 (m, 2H), 7.41–7.34 (m, 3H), 7.23 (d, *J* = 15.6 Hz, 1H), 6.78 (d, *J* = 15.6 Hz, 1H), 2.92 (septet, *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (100.6 MHz) δ: 137.9, 134.0, 129.6, 128.9, 127.9, 127.5, 52.3, 15.4, 14.5. IR ($CDCl_3$) (cm^{-1}): 3056, 2973, 2932, 1625, 1449, 1262, 1255, 1167, 1159, 1148, 1121, 1032, 1014, 967. MS (EI) *m*/*z* (%): 194 (M^+, 6), 152 (100), 135 (55), 134 (16), 104 (55), 91 (34), 77 (27), 73 (39), 51 (15), 45 (34), 43 (45), 41 (21). Anal. calcd. for $C_{11}H_{14}OS$: C 68.00, H 7.26; found: C 67.77, H 6.75.

*[R_S]-(E)-2-Phenylethenyl 4-fluoro-3-methylphenyl sulfoxide (**8g**):*
Mp: 58 to 59°C. IR ($CDCl_3$) (cm^{-1}): 3063, 3023, 3011, 2925, 1488, 1447, 1239, 1079, 1051, 1034. ^{1}H NMR (400 MHz) δ: 7.55–7.45 (m, 1H), 7.49–7.45 (m, 3H), 7.40–7.37 (m, 4H), 7.37 (d, *J* = 15.6 Hz, 1H), 7.14 (t, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100.6 MHz) δ: 162.9 (d, *J* = 250 Hz), 138.8 (broad), 136.2, 133.6, 132.7, 129.8, 128.9, 128.0 (d, *J* = 5.9 Hz), 127.3, 126.9 (d, *J* = 18.4 Hz), 124.3 (d, *J* = 9.0 Hz), 116.1 (d, *J* = 23.6 Hz), 14.6. MS (CI, NH_3) *m*/*z* (%): 261 ($[M + H]^+$, 100), 212 (23), 91 (6). Anal. calcd. for $C_{15}H_{13}SOF$: C 69.21, H 5.03; found: C 69.40, H 5.07.

*[R_S]-(E)-2-Phenylethenyl benzyl sulfoxide (**8h**) (31):*
IR ($CDCl_3$) (cm^{-1}): 3032, 2359, 1576, 1497, 1455, 1052, 965. ^{1}H NMR (400 MHz) δ: 7.34 (m, 10H), 7.11 (d, *J* = 15.5 Hz, 1H), 6.76 (d, *J* = 15.5 Hz, 1H), 4.09 (AB_q, *J* = 12.5 Hz, 2H). ^{13}C NMR (100.6 MHz) δ: 137.2, 133.8, 130.3, 129.8, 129.7, 129.4, 128.9, 128.8, 128.4, 127.6, 61.2.

*[R_S]-(E)-2-Phenylethenyl 1-(2-methyl-2-phenylpropyl) sulfoxide (**8j**):*
^{1}H NMR (400 MHz) δ: 7.31 (m, 10H), 7.10 (d, *J* = 15.4 Hz, 1H), 6.48 (d, *J* = 15.4 Hz, 1H), 3.14 (AB_q, *J* = 13.4 Hz, 2H), 1.71 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100.6 MHz) δ: 146.6, 135.5, 133.8, 131.3, 129.4, 128.8, 128.6, 127.5, 126.7, 125.7, 70.7, 37.8, 30.2, 27.2. IR ($CDCl_3$) (cm^{-1}): 3085, 3027, 2967, 2933, 2879, 1615, 1602, 1497, 1044, 1031, 965. Anal. calcd. for $C_{18}H_{20}OS$: C 76.01, H 7.09; found: C 76.22, H 7.10.

*[R_S]-(E)-2-Phenylethenyl 2,2-dimethylethyl sulfoxide (**8i**) (29):*
^{1}H NMR (400 MHz) δ: 7.46 (m, 2H), 7.35 (m, 3H), 7.21 (d, *J* = 15.5 Hz, 1H), 6.78 (d, *J* = 15.5 Hz, 1H), 1.28 (s, 9H).

*[R_S]-(Z)-2-Chloro-2-phenylethenyl cyclohexyl sulfoxide (**9d**):*
IR (neat) (cm^{-1}): 3058, 2933, 2855, 1625, 1594, 1489, 1454, 1296, 1066, 1063, 1030, 992. ^{1}H NMR (400 MHz) δ: 7.49–7.41 m, 3H), 7.39–7.36 (m, 2H), 6.73 (s, 1H), 2.18 (tt, *J* = 12.0, 3.6 Hz, 1H), 1.90–1.32 (m, 7H), 1.28–1.11 (m, 3H). ^{13}C NMR (100.6 MHz) δ: 142.4, 130.0, 129.5, 129.0, 128.4, 122.8, 56.7, 27.3, 25.7, 25.2 (2 C's), 21.5. MS (EI) *m*/*z* (%): 270 (50), 269 (M^+, 100), 188 (14), 186 (36), 185 (21), 83 (18), 55 (89), 54 (20). Anal. calcd. for $C_{14}H_{17}ClOS$: C 62.55, H 6.38; found: C 63.01, H 6.33.

*[S_S]-(Z)-2-Chloro-2-phenylethenyl 4-fluoro-3-methylphenyl sulfoxide (**9g**):*
IR (neat) (cm^{-1}): 3060, 2927, 1580, 1488, 1444, 1239, 1184, 1081, 1060. ^{1}H NMR (400 MHz) δ: 7.35–7.28 (m, 3H), 7.20 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.11 (s, 1H), 7.10–7.01 (m, 3H), 6.94 (t, *J* = 8.8 Hz, 1H). ^{13}C NMR (100.6 MHz) δ: 162.9 (d, *J* = 250.0 Hz), 147.4, 136.7, 129.4, 129.1, 129.0, 128.5, 128.1 (d, *J* = 6.1 Hz), 126.5 (d, *J* = 18.5 Hz) 124.6 (d, *J* = 9.0 Hz), 122.4, 115.7 (d, *J* = 23.8 Hz), 14.5 (d, *J* = 3.1 Hz). Anal. calcd. for $C_{15}H_{12}ClFOS$: C 61.12, H 4.10; found: C 61.32, H 4.24.

*Synthesis of [R_S]-2-furyl ethenyl sulfoxide (**7c**):*
n-BuLi (360 μL, 0.73 mmol) was added to a solution of furan (50 μL, 0.65 mmol) in dry ether (5 mL) at –20°C under N_2. After stirring for 20 min, $MgBr_2$ (180 mg, 0.98 mmol) dissolved in dry ether (5 mL) was added slowly with vigorous stirring over 20 min and then sulfinate [R_S]-**2** (301 mg, 0.65 mmol) in dry ether (5 mL) was added. After 1 h the reaction was quenched with NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Following flash chromatography (20% EtOAc – hexanes to elute cholesterol, 80% to elute sulfoxide) enantioenriched sulfoxide **7c** was isolated as an oil (42 mg, 59%). IR (neat) (cm^{-1}): 3117, 3039, 3010, 2952, 1600, 1550, 1456, 1453, 1370, 1220, 1165, 1066, 1051. ^{1}H NMR (400 MHz) δ: 7.64 (m, 1H), 6.95 (dd, *J* = 3.8, 0.4 Hz, 1H), 6.76 (dd, *J* = 16.4, 9.6 Hz, 1H), 6.53 (dd, *J* = 3.8, 2.0 Hz, 1H), 6.34 (d, *J* = 16.4 Hz,

1H), 6.11 (d, J = 9.6 Hz, 1H). ^{13}C NMR (100.6 MHz) δ: 137.4, 130.5, 130.2, 122.3, 116.4, 111.3. MS (EI) *m*/*z* (%): 142 (9), 126 (25), 115 (48), 99 (20), 97 (15), 94 (100), 83(15). Anal. calcd. for $C_6H_6O_2S$: C 50.69, H 4.25; found: C 50.77, H 4.42.

*Synthesis of [S_S]-(E)-3,3-dimethyl-1-butenyl 2-furyl sulfoxide (**6c**):*

As described for **7c**, *n*-BuLi (341 μL, 0.68 mmol), furan (40 μL, 0.57 mmol) in dry ether (5 mL), $MgBr_2$ (125.8 mg, 0.68 mmol) in dry ether (5 mL) were all brought together and enantiopure sulfinate [R_S]-**1** (295 mg, 0.57 mmol, 100% [R_S]) in dry ether (5 mL) was added. Work-up as for **7c** and flash chromatography (20% EtOAc – hexanes to elute cholesterol, 80% to elute sulfoxide) afforded enantioenriched sulfoxide **6c** as an oil (114.2 mg, 78%). Data for **6c**: IR (neat) (cm^{-1}): 3114, 2961, 2905, 2868, 1625, 1475, 1366, 1266, 1218, 1128, 1066, 1008, 970. ^{1}H (400 MHz) δ: 7.63 (m, 1H), 6.88 (d, J = 3.6 Hz, 1H), 6.66 (d, J = 15.4 Hz, 1H), 6.51 (dd, J = 3.6, 1.6 Hz, 1H), 6.35 (d, J = 15.4 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR (100.6 MHz) δ: 152.7, 151.7, 146.8, 125.9, 115.2, 111.3, 34.3, 28.7. MS (EI) *m*/*z* (%): 199 ([M + 1]$^+$, 6), 150 (51), 135 (69), 107 (11), 99 (15), 91 (10), 83 (17), 81 (16), 79 (15), 71 (14), 67 (11), 59 (22), 57 (57), 55 (82), 53 (17), 45 (32), 43 (37), 41 (100). Anal. calcd. for $C_{10}H_{14}O_2S$: C 60.57, H 7.12; found: C 60.69, H 7.06.

*Synthesis of (E)-[S_S]-2-carbomethoxyethenyl 1-butyl sulfoxide (**11a**):*

The reaction of sulfinate **5** (336 mg, 0.65 mmol, 100% [R_S]) with *n*-BuMgCl (388 μL, 0.78 mmol, as a 2 M solution in Et_2O) in anhydrous ether at –78°C generated vinyl ether by-product **20** (117 mg, 38%) as a solid after chromatography (20% EtOAc – hexanes). Enantioenriched sulfoxide **11a** was isolated as a solid (37 mg, 30%, 51% [S_S]) after additional chromatography (80% EtOAc – hexanes); mp: 53 to 54°C. $[\alpha]_D^{25}$ +120.6° (*c* 0.73, acetone). IR (cm^{-1}): 3030, 2959, 2932, 1719, 1621, 1292, 1223, 1146, 1041. ^{1}H NMR (400 MHz) δ: 7.58 (d, J = 15.0 Hz, 1H), 6.66 (d, J = 15.0 Hz, 1H), 3.81 (s, 3H), 2.87 (ddd, J = 13.2, 10.0, 5.8 Hz, 1H), 2.74 (ddd, J = 13.2, 10.0, 5.8 Hz, 1H), 1.81 (m, 1H), 1.69 (m, 1H), 1.48 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz) δ: 164.3, 149.7, 126.0, 52.6, 52.3, 24.0, 21.9, 6.6. MS (CI, NH_3) *m*/*z* (%): 191 ([M + 1]$^+$, 100), 175 (5.6), 151 (12), 141 (9), 135 (8), 121 (16), 107 (18), 57 (33). Anal. calcd. for $C_7H_{14}O_2S$: C 50.66, H 7.42; found: C 50.50, H 7.42.

*Synthesis of (E)-[R_S]-2-carbomethoxyethenyl 4-methylphenyl sulfoxide (**11b**) (23f):*

The reaction of sulfinate **5** (471.5 mg, 0.91 mmol, 100% [R_S] with *p*-tolMgBr (1.09 mL, 1.09 mmol, as a 1 M solution in Et_2O) in anhydrous ether warming from –78 to –40°C generated vinyl ether by-product **20** (76 mg, 18%) as a solid after chromatography (20% EtOAc – hexanes). Enantioenriched sulfoxide **11b** was isolated as a solid (50.5 mg, 25%, 21% [R_S]) after additional chromatography (80% EtOAc – hexanes). $[\alpha]_D^{25}$ +62.4° (*c* 0.22, acetone) (lit. (23*f*) value +421°) (acetone, >98% [R_S]). ^{1}H NMR (400 MHz) δ: 7.52 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 15.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 15.0 Hz, 1H), 3.77 (s, 3H), 2.47 (s, 3H).

*Characterization data for (–)-cholesteryl (E)-2-carbomethoxyethenyl ether (**20**):*

IR (CH_2Cl_2) (cm^{-1}): 2946, 2906, 2868, 2851, 1715, 1643, 1133, 959. ^{1}H NMR (400 MHz) δ: 7.55 (d, J = 12.4 Hz, 1H), 5.40–5.39 (m, 1H), 5.26 (d, J = 12.4 Hz, 1H), 3.84–3.76 (m, 1H), 3.69 (s, 3H), 2.38–2.35 (m, 2H), 1.01 (s, 3H), 0.91 (d, J = 6.5, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.68 (s, 3H), 2.09–0.80 (remaining peaks for cholesteryl skeleton, 26H). ^{13}C NMR (100.6 MHz) δ: 168.6, 161.7, 139.3, 123.1, 97.0, 82.3, 56.7, 56.1, 51.0, 50.0, 42.3, 39.7, 39.5, 38.5, 36.8, 36.6, 36.2, 35.8, 31.9, 31.8, 28.2, 28.1, 28.0, 24.3, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.8. MS (CI, NH_3) *m*/*z* (%): 471([M + H]$^+$, 37), 370 (29), 369 (100), 61 (13). Anal. calcd. for $C_{31}H_{50}O_3$: C 79.10, H 10.71; found: C 79.21, H 10.60.

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