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Free-radical cyclization of enantiomerically enriched 2-*p*-tolylthio derivatives of 2-allylcyclohexanones with Mn(III): asymmetric synthesis of bridged bicyclic ketones and thiochroman-3-ones†

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Abstract

Mn(III)-based oxidative intramolecular cyclization of enantiomerically enriched 2-allyl-2-(*p*-tolylsulfonyl)-cyclohexanone **4** and 2-allyl-2-(*p*-tolylsulfenyl)cyclohexanone **9** are reported. The observed chemoselectivity (reaction on the allylic double bond yielding bridged bicyclic ketones vs. reaction on the aromatic ring of the *p*-tolyl group affording thiochroman-3-ones) depends on the sulfur function (sulfone or thioether, respectively), which determines the electronic density of the *p*-tolyl ring and the conformational preferences of the starting compounds. The nature of the substituent at C-2 is related to the *endo*/*exo* selectivity of the cyclization as well as the regioselectivity in the formation of the enones.

1. Introduction

Bicyclo[3.3.1]nonan-9-one derivatives are interesting intermediates leading to natural and biologically valuable products,[1] novel bridged cyclic amino acids as pharmaceutical agents,[2] silaspiro compounds for liquid crystal composition,[3] etc. The problem of the synthesis of these compounds has recently been solved in an elegant way by Snider[4] making use of a Mn(III)-based oxidative free-radical cyclization[5] of 1-allyl-2-oxocycloalkanecarboxylate **1** yielding a readily separated mixture of three olefins (Scheme 1). The ester group controls the regioselectivity of the α-allylation of the cycloalkanone yielding the starting compound **1**. Concerning the cyclization step, the role of the ester group, which avoids the problems derived from the regioselectivity of the initially formed radical A, is evident, but its plausible influence

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† In memoriam, Professor J. de Pascual Teresa.

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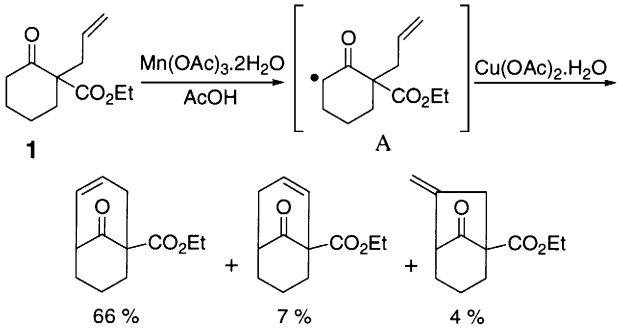
in the composition of the final olefin mixtures, achieved from its evolution with $Cu(OAc)_2 \cdot H_2O$, has not, so far, been clarified.



Scheme 1.

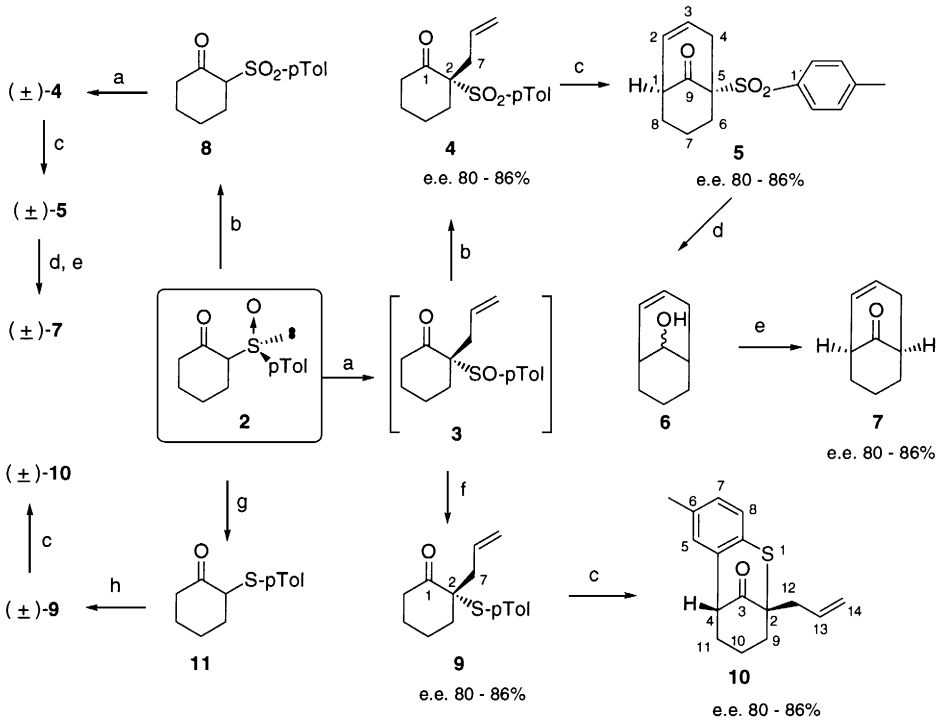
Some conclusions could be drawn from this problem by reproducing Snider's reaction sequence on substrates where the ester has been replaced by other functional groups able to stabilize enolates, thus also controlling the regioselectivity of the α-allylation. Additionally, in those cases where such groups were able to induce asymmetric α-alkylation, non-racemic bicyclo[3.3.1]nonan-9-one derivatives could be obtained. On the basis of the highly stereocontrolled methylation of enantiomerically pure β-ketosulfoxides,[6] we envisioned that the use of the sulfinyl group instead of the ester could be suitable for preparing enantiomerically enriched bicyclo[3.3.1]nonan-9-one derivatives. In this paper we report our studies concerning the reactions of 2-thio derivatives (sulfoxides, sulfones, and thioethers) of 2-allylcyclohexanones with $Mn(OAc)_3/Cu(OAc)_2$ under conditions similar to those reported by Snider (Scheme 2).

2. Results and discussion

The synthesis of compound **3**, used as the starting material in our experiments, was carried out from (*R*)-2-(*p*-tolylsulfinyl)-1-cyclohexanone **2**, previously reported by our research group,[7] by phase-transfer catalyzed alkylation.[8] The reaction afforded an 80:20 mixture of **3**[9] and the undesired *O*-allylation product. The ready pyrolytic elimination of the SOTol group from compound **3** hindered its isolation and complete characterization. When the crude product was treated under the Snider cyclization conditions, only decomposition products were obtained. These results indicated that the sulfinyl derivatives could not be used as the starting products of cyclizations due to their instability.

The in situ oxidation of the crude reaction mixture containing **3** (*m*-CPBA/CH_2Cl_2, 0°C) afforded the sulfone **4** (72%, isolated yield) which was isolated and characterized. Oxidative cyclization of **4** with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of $Cu(OAc)_2 \cdot H_2O$ in acetic acid at 90°C (conditions described by Snider) led to the bridged bicyclohexanone **5** (≥95% yield). The reductive elimination of the sulfone **5** with Na_2HPO_4-buffered sodium amalgam[10a] takes place with simultaneous reduction of the carbonyl group[10b] affording a 3:2 mixture of two isomers **6**, which was subsequently oxidized with PCC (CH_2Cl_2, rt) to give bicyclo[3.3.1]non-2-en-9-one **7**. Several syntheses of the bridged bicycloalkenone **7** have been reported[4c,11] due to its interest as an intermediate in the preparation of spiropyrans as photochromic substances.[12] To our knowledge, the method that we describe herein is the first asymmetric synthesis of this compound.

The structure of the compounds **4**–**6** and the complete assignment of ^1H and ^{13}C signals were unambiguously established by using ^1H and ^{13}C NMR spectra as well as the 2D NMR techniques:



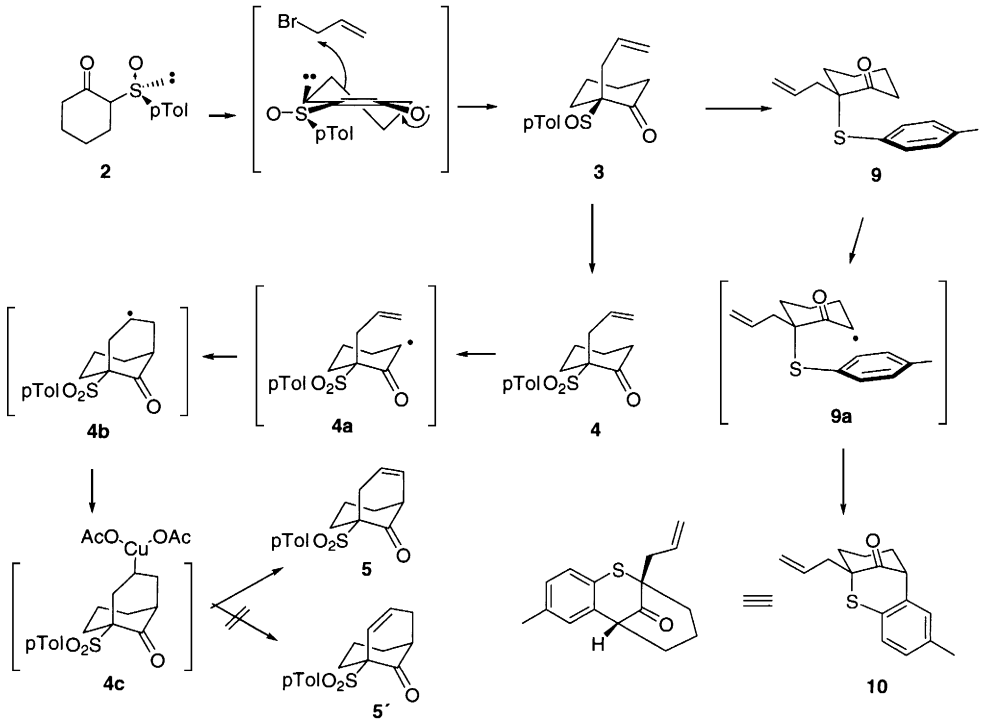
Scheme 2. (a) $PhCH_2N^+(Et)_3Cl^-$, allyl bromide, NaOH (50%), CH_2Cl_2, 0°C; (b) *m*-CPBA, CH_2Cl_2, 0°C; (c) 2 $Mn(OAc)_3 \cdot 2H_2O$, 1 $Cu(OAc)_2 \cdot H_2O$, AcOH, 90°C; (d) Na–Hg (6%), Na_2HPO_4, MeOH, rt; (e) PCC, silica gel, CH_2Cl_2, rt; (f) P_2I_4, CH_2Cl_2, rt; (g) $(CF_3CO)_2O$, NaI, –40°C, acetone; (h) NaH, allyl bromide, –40°C, DMF

^1H–^1H COSY, HMQC, HMBC, and NOESY. The structure of **7** was established by comparison with previously reported spectral data.[4c] Their enantiomeric excesses (see Scheme 2) were determined by chiral HPLC.[13] Racemic compounds **4**–**7**, required for chromatographic analysis, were synthesized as depicted in Scheme 2. The oxidation of sulfoxide **2** with *m*-CPBA in CH_2Cl_2 at 0°C yielded sulfone **8** (ca. 98%), which was transformed into allylated compound (±)-**4** under the same reaction conditions indicated for **3**. Compound (±)-**4** was further converted into (±)-**5** and (±)-**7**. Although the *ee* of compound **5** cannot be determined,[13] it must be similar to those of compounds **4** and **7.**

The most significant fact related to cyclization is the exclusive formation of the *endo* regioisomer **5**, in contrast with the mixture of compounds (two *endo*- and one *exo*-isomers) formed in the case of compound **1** (Scheme 1). Moreover, the reactivity of **4** (requiring 8 h to give **5** in 95% yield) is clearly higher than that of **1** (18 h, 75% yield). These facts suggest a significant role of the substituent at C-2 in the control of the composition of the reaction mixture. To verify the possible influence of the size of the substituent at C-2 in the course of these reactions, a study of thioether **9** was performed. Treatment of the crude reaction mixture containing **3** with diphosphorus tetraiodide[14] yielded sulfenyl compound **9** (70% isolated yield). The enantiomeric excess (86%) was determined by chiral HPLC,[13] and the configuration of the major enantiomer was unequivocally established as (*S*) by comparison of its specific rotation with that of an authentic sample of (*R*)-(+)-**9**.[15] This assignment allows us to establish the (*S*) configuration at C-2 for sulfoxide **3** and sulfone **4**. Unexpectedly, the reaction of (*S*)-**9** with $2Mn(OAc)_3 \cdot 2H_2O/Cu(OAc)_2 \cdot H_2O$ in acetic acid at 90°C afforded compound **10** (80% isolated yield and 86% *ee*) instead of the expected bicyclo[3.3.1]nonan-9-one (Scheme 2). The structures of compounds **9** and **10** were unambiguously determined from their ^1H and ^{13}C NMR spectra, as well as by 2D NMR techniques: ^1H–^1H COSY, HMQC, HMBC, and NOESY. Their enantiomeric excesses were determined by chiral HPLC.[13] Racemic

(±)-**9** and (±)-**10** were obtained as depicted in Scheme 2. Reduction of sulfoxide **2** with trifluoroacetic anhydride and sodium iodide[16] and further reaction of the resulting thioether **11** with sodium hydride and allyl bromide[17] yielded (±)-**9**, which was subsequently transformed into (±)-**10** under the condition indicated for *S*-(−)-**9**.

Taking into account previous observations in α-sulfinyl carbanion chemistry[18] we propose a plausible mechanism for these Mn(III)-mediated cyclizations, represented in Scheme 3. The stereoselective allylation of the starting sulfinyl cyclohexanone **2** must be a consequence of the steric differentiation of the diastereotopic faces of the enolate, due to the spatial arrangement adopted by its oxygens in order to minimize their electrostatic repulsion. This explanation was proposed to justify the highly stereoselective methylation of acyclic β-ketosulfoxide[6] and is in agreement with the above-mentioned predictions of (*S*) configuration at C-2 for the sulfoxide **3**. The sulfonyl group is clearly bulkier than the allyl one[19] and, therefore, will adopt an equatorial arrangement. This was unequivocally established by interpretation of the HMBC experiment.[20] The oxidation of **4** with Mn(III) yields intermediate **4a**, which reacts with the double bond mainly affording the *endo* radical **4b**[21] instead of the more congested five-membered *exo* radical. The increase in the size of the substituent could explain the observed improvement in the *endo/exo* selectivity, which explains why it was higher for sulfone **4** than for ester **1**. According to the results obtained by Kochi,[22] the formation of an alkylcopper(III) intermediate, such as **4c**, could be the following step in the reaction sequence, previous to the β-hydride elimination leading to (+)-(1*S*,5*S*)-5-(*p*-tolylsulfonyl)bicyclo[3.3.1]non-2-en-9-one **5**. The regioselectivity of this last step could be related to the allylic strain of the substituent at C-2, **5** always being favored with respect to **5′**. As the SO_2pTol group is bulkier than CO_2Et the evolution of sulfone **4** must be more selective (only **5** was detected) than that of ester **1** (66:7 mixture of regioisomers was formed, Scheme 1).



Scheme 3.

The formation of (−)-(2*S*,4*R*)-2-allyl-6-methyl-2,4-propanethiochroman-3-one **10** could be explained

by assuming that the conformation favored for compound **9** is that displaying the *p*-tolylsulfenyl group in an axial position. The smaller size of the sulfenyl group with respect to the alkyl one[19] would justify this conformational preference, which could be confirmed by the ^{1}H–^{1}H NOESY spectrum of compound **9**.[23] The axial arrangement of the *p*-tolylsulfenyl group prevents the attack of the α-carbonyl radical to the allylic double bond. Taking into account that the electrophilic character of the α-keto radical intermediate preferentially reacts with nucleophilic double bonds,[24] the intramolecular reaction of the radical center at **9a** (Scheme 3) with the electron enriched ring of its *p*-tolylsulfenyl group is not unexpected. A similar evolution of **4a** in the right conformation exhibiting the SO_2*p*Tol group in an axial arrangement would be unlikely, due to lower electronic density of the *p*-tolylsulfonyl ring.[25]

As a final conclusion, we have added to the knowledge on the chemoselectivity of the Mn(III)-based oxidative free-radical cyclization of unsaturated ketones. The different evolution of compounds **4** and **9** could be explained by assuming the conformation of the substrates and the different nucleophilic character of the double bonds acting as radical acceptors. The size of the substituent at C-2 could be related to the *endo/exo* selectivity of the cyclization, as well as the regioselective formation of the resulting olefins. Therefore, the different oxidation states (S, SO_2) of the sulfur atom have a definitive influence in the chemoselectivity of these intramolecular cyclizations, and the starting sulfinyl group is responsible for the enantiomeric excess of the final products. In summary, asymmetric synthesis of bicyclo[3.3.1]non-2-en-9-one and thiochroman-3-one derivatives has been developed.

3. Experimental

3.1. Materials and general procedure

Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using TMS as an internal reference. All reactions were monitored by TLC which was performed on precoated sheets of silica gel 60, and flash column chromatography was carried out with silica gel (230–400 mesh). Eluting solvents are indicated in the text. β-Ketosulfoxide **2** was prepared according to the described method.[7]

3.2. (−)-(2S)-2-Allyl-2-(p-toluenesulfonyl)cyclohexanone **4**

A solution of sulfoxide **2** (100 mg, 0.43 mmol), benzyltriethylammonium chloride (110 mg, 0.48 mmol), allyl bromide (59 mg, 0.48 mmol), and 50% NaOH (38 μL) in 7 mL of CH_2Cl_2 was stirred at 0°C for 1 h and 10% HCl was added. The layers were separated and the organic layer was washed with cold water. To this solution of sulfoxide **3** in CH_2Cl_2 at 0°C was added dropwise *m*-chloroperoxybenzoic acid (115 mg) in 2.5 mL of CH_2Cl_2. The mixture was stirred at 0°C for 2 h and then a saturated Na_2SO_3 solution was added. The organic layer was washed ($NaHCO_3$ solution), dried (anhydrous $MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel by eluting with hexane:ethyl acetate (4:1) gave 90.5 mg (72%) of **4** as a colorless oil. $[\alpha]_D^{20}=-163.3$ (*c* 0.5, $CHCl_3$), *ee* 80%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.64 (1H, qt, *J*=13.1, 3.8 Hz, H-5ax), 1.78 (1H, m, H-4eq), 2.04 (1H, ddd, *J*=15.3, 12.8, 4.3 Hz, H-3ax), 2.10 (1H, m, H-5eq), 2.13 (1H, m, H-7a), 2.35 (1H, tt, *J*=12.6, 3.7 Hz, H-4ax), 2.44 (3H, s, CH_3), 2.53 (1H, m, H-6eq), 2.62 (1H, ddt, *J*=13.5, 5.3, 1.6 Hz, H-7b), 2.70 (1H, ddd, *J*=15.3, 6.2, 3.8 Hz, H-3eq), 3.05 (1H, ddd, *J*=15.8, 13.0, 6.3 Hz, H-6ax), 5.01 (1H, br d, *J*=16.9 Hz, H-9t), 5.08 (1H, br d, *J*=10.1 Hz, H-9c), 5.43 (1H, m, H-8), 7.32 (2H, d, *J*=8.1 Hz, H-3′), 7.59 (2H, d, *J*=8.1 Hz, H-2′); ^{13}C NMR ($CDCl_3$) δ ppm: 21.42 (C-4), 21.64 (CH_3), 25.21 (C-5), 29.73 (C-3), 38.09 (C-7), 41.50 (C-6), 76.57

(C-2), 120.26 (C-9), 129.37 (C-3′), 130.18 (C-2′), 131.66 (C-8), 132.16 (C-4′), 145.27 (C-1′), 205.01 (C-1). Anal. calcd for $C_{16}H_{20}SO_3$: C, 65.73; H, 6.85. Found: C, 65.45; H, 6.61.

3.3. *(+)-(1*S*,5*S*)-5-(*p-*Toluenesulfonyl)bicyclo[3.3.1]non-2-en-9-one* ***5***

$Mn(OAc)_3 \cdot 2H_2O$ (720 mg, 2.68 mmol), $Cu(OAc)_2 \cdot H_2O$ (268 mg, 1.34 mmol), and β-ketosulfone **4** (391 mg, 1.34 mmol) were stirred in 20 mL of degassed glacial acetic acid at 90° C for 8 h under argon. The mixture was diluted with water and a 10% solution of $NaHSO_3$ was added. The resulting solution was extracted with CH_2Cl_2. The organic layer was washed (saturated $NaHCO_3$, brine), dried (Na_2SO_4), and evaporated in vacuo to give 350 mg (90%) of **5** as white solid, mp 169–171°C. $[\alpha]_D^{20}$=+13.2 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ ppm: 1.72 (1H, m, H-7a), 1.80 (2H, m, H-8), 2.04 (1H, m, H-7b), 2.18 (1H, m, H-6a), 2.36 (1H, m, H-6b), 2.45 (3H, s, CH_3), 2.75 (1H, ddd, *J*=18.4, 3.6, 1.5 Hz, H-4a), 2.93 (1H, dt, *J*=5.9, 2.9 Hz, H-1), 3.30 (1H, br d, *J*=18.4 Hz, H-4b), 5.58 (1H, m, H-2), 5.59 (1H, dt, *J*=9.6, 3.5 Hz, H-3), 7.98 (1H, d, *J*=8.3 Hz, H-2′), 7.99 (1H, d, *J*=8.3 Hz, H-3′);^{13}C NMR ($CDCl_3$) δ ppm: 17.46 (C-7), 21.61 (CH_3), 32.35 (C-8), 36.72 (C-6 and C-4), 49.06 (C-1), 72.99 (C-5), 126.46 (C-2), 127.83 (C-3), 129.15 (C-3′), 131.50 (C-2′), 133.11 (C-4′), 144.88 (C-1′), 205.59 (C-9). Anal. calcd for $C_{16}H_{18}SO_3$: C, 66.18; H, 6.24. Found: C, 66.13; H, 6.34.

3.4. *Bicyclo[3.3.1]non-2-en-9-ols* ***6***

To a solution of sulfone **5** (60 mg, 0.207 mmol) in MeOH (5 mL) were added Na_2HPO_4 (916 mg, 5.76 mmol) and powdered 6% Na–Hg (660 mg). The solution was vigorously stirred at room temperature for 48 h. Then the resulting Hg was decanted, and the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1% aqueous NaOH and brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to yield 20 mg (70%) of **6** as a 2:3 mixture of two isomers. **Major isomer**: ^{1}H NMR ($CDCl_3$) δ ppm: 1.24 (1H, m, H-8a), 1.30 (1H, m, H-6a), 1.35 (1H, m, H-7a), 1.62 (1H, m, H-7b), 1.87 (1H, m, H-8b), 1.92 (1H, m, H-6b), 2.00 (1H, m, H-5), 2.08 (1H, m, H-4a), 2.33 (1H, m, H-1), 2.51 (1H, m, H-4b), 3.94 (1H, t, *J*=3.2 Hz, H-9), 5.55 (1H, m, H-2), 5.81 (1H, dt, *J*=10.1, 3.6 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ ppm: 17.07 (C-7), 22.20 (C-8), 27.03 (C-6), 33.30 (C-5), 33.61 (C-4), 36.20 (C-1), 69.84 (C-9), 128.01 (C-2), 129.07 (C-3). **Minor isomer**: ^{1}H NMR ($CDCl_3$) δ ppm: 1.30 (1H, m, H-7a), 1.47 (1H, m, H-7b), 1.49 (1H, m, H-6a), 1.52 (2H, m, H-8), 1.62 (1H, m, H-6b), 1.83 (1H, m, H-4a), 2.10 (1H, m, H-5), 2.41 (1H, m, H-4b), 2.46 (1H, m, H-1), 3.68 (1H, dt, *J*=3.5, 1.2 Hz, H-9), 5.53 (1H, m, H-2), 5.97 (1H, dt, *J*=9.8, 3.4 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ ppm: 16.23 (C-7), 28.14 (C-4), 28.98 (C-8), 32.91 (C-6), 34.16 (C-5), 37.68 (C-1), 71.58 (C-9), 125.97 (C-2), 130.30 (C-3).

3.5. *(−)-(1*S*, 5*R*)-Bicyclo[3.3.1]non-2-en-9-one* ***7***

A solution of **6** (20 mg, 0.145 mmol) in 5 mL of dry CH_2Cl_2 was added to a stirring mixture of silica gel (55 mg) and pyridinium chlorochromate (55 mg, 0.25 mmol) containing 5 mL of dry CH_2Cl_2 in one portion at room temperature. The mixture of reaction was stirred for 2 h and finally diluted with dry diethyl ether (20 mL). The supernatant solution was decanted and evaporated at room temperature and atmospheric pressure. The brown residue was purified by silica gel column chromatography (CH_2Cl_2) to afford 10 mg of **7** (51%). $[\alpha]_D^{20}$=−13.3 (*c* 0.6, $CHCl_3$), *ee* 80%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.53 (2H, m, H-7), 1.88 (2H, m, H-6), 1.91 (2H, m, H-8), 2.46 (1H, ddd, *J*=18.5, 3.8, 1.4 Hz, H-4a), 2.58 (1H, m, H-5), 2.75 (1H, br dd, *J*=18.5, 7.3 Hz, H-4b), 2.85 (1H, m, H-1), 5.58 (1H, dddd, *J*=9.6, 6.0, 2.4, 1.7 Hz, H-2), 5.94 (1H, dt, *J*=9.6, 3.4 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ ppm: 16.93 (C-7), 33.21 (C-6), 36.89 (C-4

and C-8), 45.52 (C-5), 47.72 (C-1), 127.17 (C-2), 129.99 (C-3), 216.62 (C-9). The data are identical to those reported previously.[4c]

3.6. (±)-2-Allyl-2-(p-toluenesulfonyl)cyclohexanone **4**

(a) To a solution of sulfoxide **2** (74 mg, 0.31 mmol) in 5 mL CH_2Cl_2 at 0°C was added dropwise *m*-chloroperoxybenzoic acid (100 mg) in 3 mL of CH_2Cl_2. The mixture was stirred at 0° C for 2 h. After standard workup, ketosulfone **8** (75 mg, 96%) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$) δ ppm: 1.7–2.6 (m, 6H), 2.43 (s, 3H), 2.83 (m, 2H), 3.81 (t, *J*=5.0 Hz, 1H), 7.35 (d, *J*=8.3 Hz, 2H), 7.79 (d, *J*=8.3 Hz, 2H). (b) By a procedure identical to that described for preparation of **(−)-4**, the reaction of **8** (75 mg, 0.30 mmol), benzyltriethylammonium chloride (80 mg, 0.35 mmol), allyl bromide (43 mg, 0.35 mmol), and 50% NaOH (28 μL) in 5 mL of CH_2Cl_2 was stirred at 0° C for 1 h. After standard workup, (±)-**4** (78 mg, 89%) was obtained.

3.7. (±)-5-(p-Toluenesulfonyl)bicyclo[3.3.1]non-2-en-9-one **5**

By a procedure identical to that described for preparation of (+)-**5**, the reaction of (±)-**4** (22 mg, 0.075 mmol), $Mn(OAc)_3.2H_2O$ (40 mg, 0.15 mmol), and $Cu(OAc)_2.H_2O$ (15 mg, 0.075 mmol) in 3 mL of degassed glacial acetic acid afforded 20 mg of (±)-**5** (92%).

3.8. (−)-(2S)-2-Allyl-2-(p-toluenesulfenyl)cyclohexanone **9**

A solution of sulfoxide **2** (200 mg, 0.86 mmol), benzyltriethylammonium chloride (220 mg, 0.96 mmol), allyl bromide (118 mg, 0.96 mmol), and 50% NaOH (76 μL) in 15 mL of CH_2Cl_2 was stirred at 0° C for 1 h. The organic layer was washed with 10% HCl, cold water, and dried ($MgSO_4$). This solution was added in one portion to a stirred suspension of diphosphorus tetraiodide (245 mg, 0.43 mmol) in 1 mL of dry CH_2Cl_2 at room temperature under argon atmosphere. After 30 min the reaction mixture was quenched by adding water. The organic layer was separated, washed with an aqueous solution of sodium thiosulfate, dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography on silica gel by eluting with hexane:ethyl acetate (10:1) gave (−)-**9** (152 mg, 68%) as a colorless oil. $[\alpha]_D^{20}$=–290 (*c* 0.4, $CHCl_3$), *ee* 86%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.64 (1H, m, H-5a), 1.71 (1H, m, H-4a), 1.95 (1H, m, H-3a), 2.09 (1H, m, H-5b), 2.10 (2H, m, H-3b and H-4b), 2.31 (1H, m, H-6eq), 2.32 (2H, m, H-7), 2.33 (3H, s, CH_3), 3.38 (1H, ddd, *J*=14.6, 14.6, 6.2 Hz, H-6ax), 5.05 (1H, br d, *J*=16.8 Hz, H-9t), 5.10 (1H, br d, *J*=10.1 Hz, H-9c), 5.85 (1H, m, H-8), 7.10 (2H, d, *J*=8.1 Hz, H-3′), 7.22 (2H, d, *J*=8.1 Hz, H-2′); ^{13}C NMR ($CDCl_3$) δ ppm: 21.25 (CH_3), 21.42 (C-4), 26.83 (C-5), 36.48 (C-3), 37.65 (C-6), 39.60 (C-7), 60.07 (C-2), 118.28 (C-9), 126.53 (C-1′), 129.71 (C-3′), 133.97 (C-8), 136.29 (C-2′), 139.72 (C-4′), 207.01 (C-1). HMRS found *m/z*: 260.1234 (M^+); $C_{16}H_{20}SO$ requires: 260.1234.

3.9. (−)-(2S,4R)-2-Allyl-6-methyl-2,4-propanethiochroman-3-one **10**

By a procedure identical to that described for preparation of (+)-**5**, the reaction of (−)-**9** (50 mg, 0.19 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (102 mg, 0.38 mmol), and $Cu(OAc)_2 \cdot H_2O$ (38 mg, 0.19 mmol) in 5 mL of degassed glacial acetic acid at 90°C under argon for 36 h afforded 39 mg of (−)-**10** (80%) as a colorless oil. $[\alpha]_D^{20}$=–148.8 (*c* 0.5, $CHCl_3$), *ee* 86%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.63 (1H, m, H-10a), 2.01 (1H, m, H-9a), 2.09 (2H, m, H-11), 2.10 (1H, m, H-10b), 2.37 (1H, m, H-9b), 2.52 (3H, s, CH_3), 2.58 (2H, dd, *J*=7.5, 3.8 Hz, H-12), 3.56 (1H, br t, *J*=2.7 Hz, H-4), 5.15 (2H, m, H-14), 5.83 (1H, m, H-13), 6.70 (1H,

br s, H-5), 6.91 (1H, d, *J*=8.2 Hz, H-7), 6.95 (1H, d, *J*=8.2 Hz, H-8); ^{13}C NMR ($CDCl_3$) δ ppm: 18.07 (C-10), 20.71 (CH_3), 38.11 (C-11), 40.71 (C-12), 42.91 (C-9), 52.51 (C-4), 55.25 (C-2), 119.38 (C-14), 123.23 (C-8), 128.17 (C-7), 130.14 (C-5), 130.55 (C-4a), 132.21 (C-13), 134.47 (C-6), 137.51 (C-8a), 208.41 (C-3). HMRS found *m/z*: 258.1080 (M^+); $C_{16}H_{18}SO$ requires: 258.1078.

*3.10. (±)-2-Allyl-2-(*p*-toluenesulfenyl)cyclohexanone **9***

(a) A solution of trifluoroacetic anhydride (311 μL, 2.2 mmol) in acetone (1 mL) was added dropwise into a stirred suspension of sulfoxide **2** (103 mg, 0.43 mmol) and sodium iodide (195 mg, 1.31 mmol) in the same solvent (3 mL) at −40°C under argon atmosphere. The reaction mixture was stirred for 30 min at −40°C, and an excess of saturated aqueous Na_2SO_3 and Na_2CO_3 was added. Acetone was removed in vacuo, the aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo to provide compound **11** (88 mg, 93%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.6–2.4 (m, 6H), 2.31 (s, 3H), 2.92 (m, 2H), 3.78 (t, *J*=5.0 Hz, 1H), 710 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ ppm: 21.04 (CH_3), 22.40 (CH_2), 27.25 (CH_2), 33.73 (CH_2), 38.87 (CH_2), 56.91 (CH), 129.75 (2×CH), 132.68 (2×CH), 137.76 (C), 207.65 (C). (b) To a suspension of NaH (10 mg, 60% oil dispersion, 0.24 mmol) in 1 mL of dry DMF was added a solution of **11** (52 mg, 0.24 mmol) in 2 mL of dry DMF. The mixture was stirred at −40°C for 1 h under argon. Then allyl bromide (25 μL, 0.25 mmol) was added and the reaction mixture was stirred for 2 h at the same temperature. To this reaction mixture was added water and 10% HCl, and the solution was extracted with CH_2Cl_2. The organic layer was washed (brine), dried ($MgSO_4$), and evaporated in vacuo. Flash chromatography on silica gel by eluting with hexane:ethyl acetate (10:1) yielded (±)-**9** (76%).

*3.11. (±)-2-Allyl-6-Methyl-2,4-propanethiochroman-3-one **10***

By a procedure identical to that described for preparation of (+)-**5**, the reaction of (±)-**9** (33 mg, 0.125 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (67 mg, 0.25 mmol), and $Cu(OAc)_2 \cdot H_2O$ (25 mg, 0.125 mmol) was stirred in 4 mL of degassified glacial acetic acid at 90°C under argon for 36 h. After standard workup, compound (±)-**10** (25 mg, 78%) was obtained.

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13. HPLC analysis was performed with: (a) Chiral column Chiralpak AS (25 cm×0.46 cm) eluting with a mixture of *n*-hexane:isopropanol (90:10), flow rate=1.0 mL/min, detection 220 nm, retention times: (−)-**4**, *t*=9.1 min; (+)-**4**, *t*=11.2 min; (−)-**7**, *t*=8.6 min; (+)-**7**, *t*=12.0 min. (b) Chiral column Chiralcel OD (25 cm×0.46 cm) eluting with a mixture of *n*-hexane/isopropanol (99:1), flow rate=1.0 mL/min, detection 254 nm, retention times: (−)-**9**, *t*=4.7 min; (+)-**9**, *t*=5.2 min; (−)-**10**, *t*=5.4 min; (+)-**10**, *t*=7.7 min. (c) The *ee* of compound **5** could not be determined by chiral HPLC due to its insolubility in the eluting mixture.
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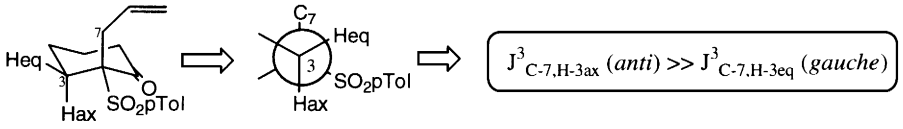
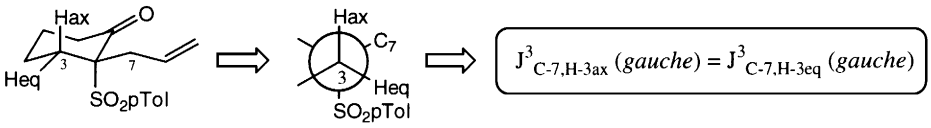
20. ^1H–^{13}C correlation experiment (HMBC) was optimized for observing $^3J_{CH}$≈8 Hz. The HMBC spectrum shows a large difference in the three-bond ^1H–^{13}C coupling constants between the C-7 (δ 38.09) and the protons H-3ax (δ 2.04, ddd, *J*=15.3, 12.8 and 4.3 Hz) and H-3eq (δ 2.70, ddd, *J*=15.3, 6.2 and 3.8 Hz). The three-bond correlation from H-3ax to C-7 (^3J≈8 Hz) typical of a disposition *anti* (Pretsch, E.; Clerc, T.; Seibl.; Simon W. *Tablas para la elucidación estructural de compuestos orgánicos por métodos espectroscópicos*; Alhambra, Madrid, 1989) and, additionally, the fact that no correlation was observed between H-3eq and C-7, allowed the unambiguous assignment of conformation I for compound **4**.



I



II

21. The formation of the more congested five-membered *exo* radicals would be difficult because of the size of substituent at C-2.

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23. The ^{1}H–^{1}H NOESY spectrum of compound **9** is in full agreement with the axial arrangement of the sulfenyl group, showing connectivities between the proton H-2′ and the protons H-4ax and H-6ax and also between the proton H-8 and the protons H-3ax and H-3eq.
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25. The different evolution of compounds **4** and **9** could be explained by assuming only the different nucleophilic character of the double bonds acting as radical acceptors (*p*TolS>allylic double bond>*p*TolSO$_2$) regardless of the conformational behavior of the substrates. Nevertheless, the fact that reaction time required for the complete evolution of compound **9** was larger (36 h) than that for **4** (8 h) suggests to us that this is not the case and other factors must be involved.