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Synthesis of a renewable hydroperoxide from (+)-norcamphor: influence of steric modifications of the bicyclic framework on asymmetric sulfoxidation

Alessandra Lattanzi,* Patrizia Iannece and Arrigo Scettri

Dipartimento di Chimica, Università degli Studi di Salerno, 84081 Baronissi (SA), Italy

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Abstract—A renewable tertiary hydroperoxide has been efficiently synthesized in 83% overall yield starting from commercially available (+)-*endo*-2-norborneol. This oxygen donor, derived from (+)-norcamphor, when employed in Ti(O*i*-Pr)$_4$-catalyzed sulfoxidations, proved to be considerably more reactive when compared to a previously reported camphor-derived hydroperoxide. Reduced steric hindrance of the new oxidant lowered the level of asymmetric induction achieved in the oxidation, but stereoconvergent kinetic resolution has been exploited to improve enantioselectivity. Excellent recovery (95%) of the tertiary alcohol at the end of the sulfoxidation provides a highly advantageous chiral resource saving protocol.
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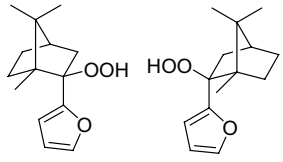
1. Introduction

Asymmetric oxidations, mediated by enantiopure alkyl hydroperoxides, represent an interesting area of research due to their potential use as stereoselective oxidants.[1] The main problem associated with their up to now limited employment, resides on the troublesome synthetic access. In fact, the most successful and general methodology involves the use of horse radish peroxidase (HRP), which allows enantiomerically pure secondary hydroperoxides to be obtained via kinetic resolution of racemic alcohols.[2] Although being useful for the synthesis of functionalized oxygen donors, this methodology fails in the preparation of enantiopure tertiary hydroperoxides. In general, tertiary hydroperoxides are the best oxidants to use in order to achieve the highest levels of enantioselectivity in asymmetric oxidations, as demonstrated in Sharpless allylic alcohols epoxidation and modified processes of this type.[3] Asymmetric syntheses of tertiary alkyl hydroperoxides have been reported exploiting as starting material compounds from the chiral pool. Aoki and Seebach[4] synthesized TADOOH hydroperoxide from TADDOL, which provides moderate to high enantioselectivity in the epoxidation of allylic alcohols,[5] sulfoxidation,[4] epoxidation of, β-unsaturated enones[4] and Baeyer–Villiger oxidation of bicyclic cyclobutane derivatives.[4]

We recently reported a facile synthesis of both enantiomers of renewable tertiary hydroperoxides (−)-*exo*-**1** and (+)-*exo*-**1** from easily available and inexpensive (*R*)- and (*S*)-camphor (Fig. 1).[6] These oxygen donors have been employed in the Ti(O*i*-Pr)$_4$-catalyzed epoxidation of allylic alcohols[6] and sulfoxidation[7] achieving up to 51% ee. In the oxidation of prochiral sulfides, reaction conditions were successfully modified in order to set up a catalytic [20% mol Ti(O*i*-Pr)$_4$] and chemoselective oxidative protocol.[7] Interestingly, for the first time, it was found that with the same oxidative system [Ti(O*i*-Pr)$_4$/(−)-*exo*-**1**], the kinetic resolution of racemic sulfoxides, under stoichiometric amounts of the metal catalyst, proved to be stereodivergent with respect to the sulfoxidation step.[7]



(-)-*exo*-**1** (+)-*exo*-**1**

Figure 1.

* Corresponding author. Tel.: +39-089-965370; fax: +39-089-965296; e-mail: lattanzi@unisa.it

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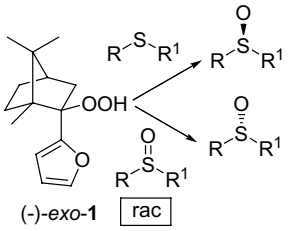


Figure 2.

Although this result prevented the well documented[8] synergic use of stereoconvergent kinetic resolution to improve the final enantiomeric excess of sulfoxides, the process is nonetheless suitable for application to access enantioenriched sulfoxides of opposite absolute configuration by means of the same chiral promoter (Fig. 2).

Thus, in consideration of the appreciable results obtained in the preparation and use of optically pure alkyl hydroperoxides of type **1**, we herein report the synthesis of a tertiary hydroperoxide, structurally modified in the bicyclic framework, and its employment in asymmetric sulfoxidation. Our aim is to synthesize an oxygen donor, which is easily accessible, suitable for recycling and more reactive than *exo*-**1**. Furthermore, it is interesting to investigate the impact of the structural modifications of the oxidant on the asymmetric induction with respect to the use of *exo*-**1**, with the intention of improving the performance of these compounds as stereoselective oxidants.

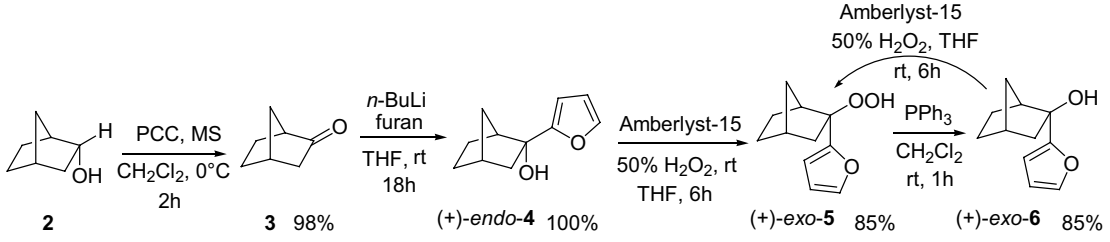
2. Results and discussion

The synthetic route was based on the previously reported two step sequence for (−)-*exo*-**1**,[6] involving 2-furyl lithium addition to (*R*)-camphor, which produced almost exclusively *exo*-furyl alcohol (*exo*/*endo*, 97/3) in 60% yield. The *exo*-furyl alcohol was treated with Amberlyst-15 and 50% aqueous H_2O_2 and furnished (−)-*exo*-**1** in 60% yield via stereospecific S_N1 reaction.

In our opinion a significant increase of reactivity in hydroperoxides of type **1** could have been achieved by reducing the steric hindrance in the bicyclic framework. Therefore, we envisaged the introduction of the hydroperoxy group at the C_2 position and with the correct stereochemistry of the norbornane skeleton, lacking the C_8, C_9 and C_{10} methyl groups of the camphor. (+)-*endo*-2-Norborneol **2** was chosen as the precursor of the required chiral starting material **3**, (+)-norcamphor. Some preliminary considerations were taken for the outcome of the 2-furyl lithium addition to norcamphor and the following hydroperoxidation step. It has been observed that 2-furyl lithium addition to norcamphor furnished the formation of *endo*-furyl alcohol, thanks to the exclusive attack of the organometallic reagent from the *exo*-face of ketone.[9] In order to obtain the tertiary *exo*-furyl hydroperoxide, the addition of H_2O_2 on the predictably stable[10] first formed 2-substituted norbornyl cation should have proceeded with epimerization at carbon 2. It has been documented that upon hydrolysis, esters of 2-substituted *exo*-norborneol as well as 2-substituted *endo*-norborneol exclusively yield the corresponding 2-substituted 2-*exo*-norborneol derivative.[11] Hence, on the basis of these findings, the hydroperoxidation should have furnished the desired *exo*-hydroperoxide.

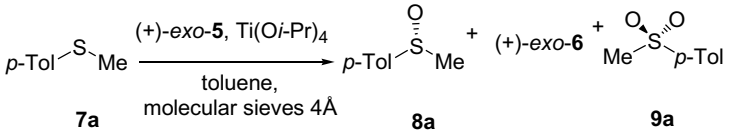
The oxidation[12] of **2** with PCC and molecular sieves at 0 °C in CH_2Cl_2 afforded in high yield (+)-norcamphor **3** (Scheme 1). Addition of 2-furyl lithium to (+)-norcamphor in THF at room temperature provided alcohol (+)-*endo*-**4** in quantitative yield.[9] The crucial hydroperoxidation step was carried out by employing the best reaction conditions optimized for the synthesis of (−)-*exo*-**1**. We observed complete epimerization at carbon 2, in fact, (+)-*exo*-**5** was isolated in high yield without any trace of side-products.[13] It is remarkable that this transformation furnished a selective access to (+)-*exo*-**5**, as it occurs via an intermediate 2-norbornyl cation, which is prone to undergo a Wagner–Meerwein rearrangement and hydride shifts.[14] Confirmation of epimerization was accomplished by reducing (+)-*exo*-**5** to alcohol (+)-*exo*-**6** and comparing its spectroscopic data with those of alcohol (+)-*endo*-**4**. Hydroperoxidation of (+)-*exo*-**6** performed under the same reaction conditions yielded exclusively (+)-*exo*-**5** thus supporting the literature.[11] Having in hand the targeted oxygen donor, some runs were performed on model methyl *p*-tolyl sulfide **7a** in the presence of Ti(O*i*-Pr)$_4$ (Table 1).

In order to compare the reactivity of hydroperoxide (+)-*exo*-**5** with respect to *exo*-**1**, the same reaction conditions[7] were employed (entry 1, 20% mol of metal catalyst in toluene at −20 °C). As expected, the sterically less encumbered hydroperoxide reacted faster and after a short period of time, (*R*)-sulfoxide **8a** and sulfone **9a** were isolated in comparable yields. The enantiomeric excess of **8a** was lower than the one reported[7] with the use of (+)-*exo*-**1**. The level of background oxidation, in



Scheme 1.

Table 1. Asymmetric sulfoxidation of **7a** by Ti(O*i*-Pr)$_4$/(+)-*exo*-**5**[a]



7a **8a** **9a**

Entry	*T* (°C)	Time (h)	Ti(O*i*-Pr)$_4$ (mol%)	Yield **8a**%[b]	Ee **8a**%[c]
1	−20	3.5	20	38 (38)	37
2	−20	23	—	—	—
3	−78	7	20	26 (5)	16
4	0	2.5	20	30 (34)	22
5	−20	1	20	35 (10)	23
6	−20	5.5	10	29 (5)	5
7	−20	2	50	38 (38)	38
8[d]	−20	5	50	35 (46)	40

[a] Molar ratios: (+)-*exo*-**5**/**7a** 1.2/1.
[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.
[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).
[d] Molar ratios: (+)-*exo*-**5**/**7a** 1.7/1.

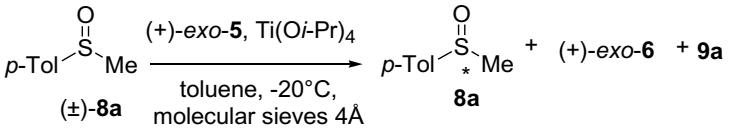
the absence of the metal catalyst, did not represent a competitive process as confirmed by entry 2. At −78 °C the reactivity decreased and a high chemoselectivity was observed; however the asymmetric induction was even lower than at −20 °C (entry 3). At 0 °C a similar result to that reported in entry 1 in terms of yield of **8a** and **9a** was obtained, but the sulfoxide was isolated with a decreased ee (entry 4). In order to better clarify the dependence of the enantioselectivity on the conversion to sulfone, the experiment for entry 1 was repeated, quenching the reaction after 1 h (entry 5). In this case, the overoxidation to **9a** was comparatively lower as well as the ee of **8a**. When using 10% mol of the metal catalyst, a chemoselective sulfoxidation occurred but with negligible asymmetric induction (entry 6). With 50% mol of Ti(O*i*-Pr)$_4$, the same result observed in entry 1 was accomplished in a shorter reaction time (entry 7). Increased amounts of the hydroperoxide produced a greater conversion of sulfoxide to sulfone while the best ee for **8a** was detected (entry 8).

Data reported in Table 1 clearly suggest that a stereoconvergent process of kinetic resolution takes place during the overoxidation of sulfoxide to sulfone. In fact, the enantioselectivity of **8a** improved with increasing conversion to **9a**. Several reports[8] on asymmetric sulfoxidation accounted for the synergic process of kinetic resolution mediated by the same chiral oxidative system and this has been used to enhance the ee of sulfoxides.[15] In substoichiometric loadings of Ti(O*i*-Pr)$_4$ (20% mol) with the less reactive (−)-*exo*-**1** hydroperoxide a negligible kinetic resolution of racemic **8a** occurred without selectivity ($S = 1$),[16] while a stereodivergent process was in act under stoichiometric loadings of the catalyst. We therefore set out to perform some runs on racemic **8a** with (+)-*exo*-**5** to gain a better insight into this oxidation (Table 2).

When using stoichiometric loadings of Ti(O*i*-Pr)$_4$ (entry 1), enantioenriched (*S*)-**8a** was isolated, whereas 50% mol or 20% mol of catalyst (entries 2–3) afforded enantioenriched (*R*)-**8a** with comparable selectivity. Although the calculated stereoselectivity factors *S* were small, indicating a poorly efficient kinetic resolution, under substoichiometric amounts of catalyst, the process proved stereoconvergent in the sulfoxidation step, thus rationalizing the findings in Table 1.

Data in Table 2 showed that the stereochemical preference in the kinetic resolution was reversed depending on

Table 2. Kinetic resolution of racemic **8a** by Ti(O*i*-Pr)$_4$/(+)-*exo*-**5**[a]



Entry	Time (h)	Ti(O*i*-Pr)$_4$(mol%)	Yield **8a**%[b]	Ee **8a**%[c,d]	*S*[e]
1	1	100	38	28 (*S*)	1.8
2	3.5	50	62	8 (*R*)	1.4
3	21	20	63	7 (*R*)	1.4

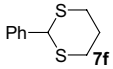
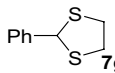
[a] Molar ratios: (+)-*exo*-**5**/**8a** 0.7/1.
[b] Isolated products after flash chromatography.
[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).
[d] Absolute configuration was determined by comparison with the $[\alpha]_D$ reported in the literature.
[e] Stereoselectivity factor calculated according to Ref. 16.

the Ti/(+)-*exo*-**5** ratio. Interestingly, in the asymmetric epoxidation of homoallylic alcohols, the enantiofacial preference was observed to be dependent on the Zr(O*t*-Bu)$_4$/enantiopure tartrate esters ratio.[17] The inversion of enantioselection was ascribed to the difference in structures of the zirconium complexes when generated by varied ratios of metal catalyst and chiral ligand. The same explanation could account for the observed opposite stereochemical preference in the kinetic resolution, as it is known that in solution different Ti-species can afford complex equilibria.[3]

On the basis of the preliminary studies on the reactivity of (+)-*exo*-**5**, some representative sulfides were oxidized, choosing reaction conditions where positive contribution of stereoconvergent kinetic resolution could be exploited [Ti(O*i*-Pr)$_4$/(+)-*exo*-**5** 0.5/2] (Table 3).

After short reaction times, preferentially enriched methyl aryl (*R*)-sulfoxides were isolated in moderate enantiomeric excess (entries 1–3), which were comparable to the values obtained by the use of *exo*-**1**. In the case of *p*-anisyl methyl sulfide, an improved ee was achieved for the corresponding sulfoxide with respect to the use of *exo*-**1**, while almost racemic sulfoxide **8e** was isolated (entry 4).[18] Electronic properties of the substituent on the aryl ring had noticeable effects on the *exo*-**1**/Ti mediated sulfoxidation and a decreased level of asymmetric induction was obtained with electron-withdrawing substituents on the aryl ring.[7] When employing compounds, which had two preexisting prochiral centres, complete diastereoselectivity was observed. 2-Phenyl-dithiane and dithiolane were chemoselectively oxidized in high yield to exclusively give *trans*-(1*S*,2*S*)-monosulfoxides with enantioselectivity comparable to that observed using *exo*-**1**, but with a better yield. It is worth noting that at the end of the oxidations, (+)-*exo*-**6** could be isolated by flash chromatography in 95% yield and recycled to access (+)-*exo*-**5**, thus providing a highly valuable chiral resource saving protocol. [19]

Table 3. Asymmetric sulfoxidation by Ti(O*i*-Pr)$_4$/(+)-*exo*-**5**/MS 4 Å[a]

Entry	Sulfide (R, R^1) **7**	Time (h)	Yield **8**%[b]	Ee **8**%[c,d]
1	**7a**	4	34 (55)	42 (*R*)
2	Me, Ph **7b**	5	30 (54)	38 (*R*)
3	Me, *p*-MeO-C$_6$H$_4$ **7c**	4	31 (63)	53 (*R*)
4	Me, *p*-Cl-C$_6$H$_4$ **7e**	3	52 (23)	5 (*R*)
5[e]	 **7f**	2	95	32 (*S*)[f]
6[e]	 **7g**	1.5	90	18 (*S*)[f]

[a] Molar ratios: (+)-*exo*-**5**/**7**/Ti(O*i*-Pr)$_4$ 2/1/0.5.
[b] Isolated products after flash chromatography. Number in parentheses refers to sulfone yield.
[c] Determined by HPLC analysis on chiral column (Daicel Chiralcel OB).
[d] Absolute configuration was determined by comparison with the $[\alpha]_D$ reported in the literature.
[e] Molar ratios: (+)-*exo*-**5**/**7** 1.1/1.
[f] Ee of *trans*-monosulfoxide was determined by ^{1}H NMR shift experiments with Eu(hfc)$_3$.

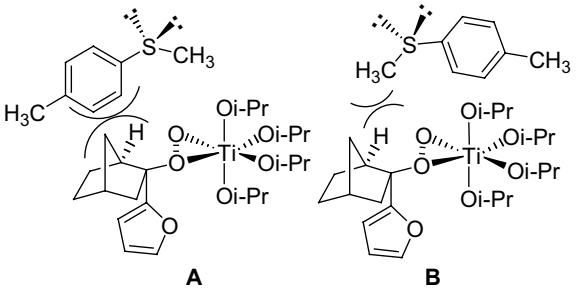


Figure 3.

By using hydroperoxide (+)-*exo*-**5**, derived from (+)-norcamphor, enantiomerically enriched (*R*)-sulfoxides were obtained, but with a lower degree of asymmetric induction in comparison to (+)-*exo*-**1**, derived from (*S*)-camphor.[7] The speculative models we proposed to explain the preferred formation of (*R*)-sulfoxides in Ti/(+)-*exo*-**1**-catalyzed oxygen-transfer process, would seem to account for the results achieved, even when using (+)-*exo*-**5** as oxidant (Fig. 3).

In this case, steric interactions of model sulfide **7a** approaching the electrophilically activated hydroperoxide in chiral Ti/(+)-*exo*-**5** complex, via pathways **A** and **B**, were inferior with respect to the chiral Ti/(+)-*exo*-**1** complex. In fact, when the sulfide attacked with the *pro*-(*S*) lone pair along the axis of the O–O bond in the Ti complex **A**, the tolyl group faced the hydrogen substituent at C$_1$ of the bicyclic system, instead of the C$_{10}$ methyl group of the camphor skeleton in (+)-*exo*-**1**. The sulfide, approaching with the *pro*-(*R*) lone pair along the axis of the O–O bond in Ti complex **B**, experiences a lower steric interaction of the methyl group facing the hydrogen at the C$_1$ position. A decreased preference for one of the two pathways and hence a lower enantioselectivity, is envisaged when using (+)-*exo*-**5**, although pathway **B** should be slightly favoured leading to the formation of enantioenriched (*R*)-sulfoxides.

Sulfoxides are known to coordinate to titanium,[20,3c] so in the case of the kinetic resolution, an intramolecular delivery of the oxygen by chelated hydroperoxide could be involved.[15] The stereochemical outcome of the kinetic resolution appears to be more difficult to rationalize, because species, which have different selectivities, are involved in the process as a function of the modified stoichiometric Ti/hydroperoxide ratios.

3. Conclusion

In conclusion, we have reported a simple and high yield synthesis of a tertiary enantiopure hydroperoxide starting from commercially available (+)-*endo*-2-norborneol. The most relevant transformation of the approach is the selective hydroperoxidation of the alcohol (+)-*endo*-**4** to yield hydroperoxide (+)-*exo*-**5** via a stereospecific S$_N$1 reaction. Less sterically encumbered (+)-*exo*-**5**, when employed in Ti-catalyzed sulfoxidation

under substoichiometric catalyst loadings, showed to be considerably more reactive than oxidant (+)-*exo*-**1** derived from (*S*)-camphor, but less enantioselective. Nonetheless, a concomitant process of kinetic resolution, stereoconvergent with the sulfoxidation step, was involved and has been exploited to improve the ee of the sulfoxides.[21] The stereochemical outcome of the kinetic resolution was dependent on the Ti/(+)-*exo*-**5** ratios, giving rise to catalytic species responsible for opposite stereocontrol. Recycling of the hydroperoxide proved to be a very efficient process, thanks to the excellent recovery of alcohol (+)-*exo*-**6** formed over the course of oxidation. It is worth pointing out that even though the approach to (+)-*exo*-**5** requires the additional oxidation of (+)-*endo*-2-borneol, the entire sequence is more advantageous than the two step route to (+) or (−)-*exo*-**1**, since all the steps, including the final recovery of the alcohol, are high yield and selective processes. The investigation on the impact of structural modifications on the bicyclic framework of hydroperoxide (+)-*exo*-**5**, allowed a better understanding of the steric motifs, which control the reactivity and the asymmetric induction of this new class of oxidants in metal-catalyzed sulfoxidation. This knowledge could be helpful in designing potentially more stereoselective hydroperoxides by tuning steric modifications. Finally we have demonstrated that it is possible to broaden the access to enantiomerically pure hydroperoxides, taking advantage from common compounds of the chiral pool. Further studies on the employment of (+)-*exo*-**5** as an oxygen donor in asymmetric oxidations are currently underway.

4. Experimental

4.1. Materials and general methods

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an argon atmosphere. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride under argon. CH_2Cl_2 and toluene were distilled from calcium hydride under argon. Petrol refers to the fraction of petroleum ether boiling in the range of 40–60 °C. Standard techniques were used in handling air sensitive reagents. All commercially available reagents were purchased from Aldrich and Fluka. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by 10% H_2SO_4/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). IR spectra were recorded as thin films unless stated otherwise. IR absorptions are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer at room temperature in $CDCl_3$ as the solvent. Chemical shifts (δ) are quoted in ppm relative to internal $CDCl_3$ δ 7.26 for ^1H NMR and $CDCl_3$ δ 77.0 for ^{13}C NMR. Coupling constants (J) are given in Hz. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excesses were determined by HPLC analysis on chiral column (Daicel Chiralcel OB column) with UV detection at 254 nm, *n*-hexane/2-propanol 8:2 as eluent and a flow rate of 0.5 mL/min for *p*-tolyl methyl sulfoxide, phenyl methyl sulfoxide, *p*-anisyl methyl sulfoxide, *p*-chlorophenyl methyl sulfoxide. Enantiomeric excesses for *trans*- 2-phenyl-[1,3]-dithiane-1-oxide and *trans*-2-phenyl-[1,3]-dithiolane-1-oxide were measured by ^1H NMR shift experiments with $Eu(hfc)_3$.[22] (+)-Norcamphor was obtained by oxidation of commercial (+)-*endo*-2-norborneol.[12]

4.2. (1*S*,2*R*,4*R*)-2-*endo*-Hydroxy-2-*exo*-(2′-furyl)-bicyclo-[2.2.1] heptane *endo*-4

n-BuLi (24 mL, 60 mmol, 2.5 M solution in hexane) was added dropwise to a solution of freshly distilled furan (3.5 g, 52 mmol) in anhydrous THF (20 mL) under an argon atmosphere at −20 °C. This mixture was stirred for 1 h at room temperature. A solution of (+)-norcamphor (1.9 g, 17.3 mmol) in anhydrous THF (10 mL) was added at 0 °C. The mixture was stirred at room temperature for 6 h. After this time, at 0 °C, the mixture was diluted with diethyl ether (50 mL) and quenched by slow addition of a saturated solution of ammonium chloride. The layers were separated and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried over sodium sulfate. The crude product was then filtered with Et_2O over a small pad of silica gel to give (+)-*endo*-**4**[9] as brown oil (3.07 g, 100%); (Found: C, 74.22; H, 7.88. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%); $[\alpha]_D^{24} = +1.5$ (*c* 0.81, $CHCl_3$); ν_{max}/cm^{-1} 3470 (O–H), 2954, 1729, 1451, 1284; δ_H (400 MHz) 7.36 (1H, dd, *J* 1.9, 0.8), 6.30 (1H, dd, *J* 3.2, 1.9), 6.18 (1H, dd, *J* 3.2, 0.8), 2.53–2.51 (1H, m), 2.28–2.21 (2H, m), 1.94 (1H, s), 1.64–1.58 (1H, m), 1.52–1.37 (5H, m), 1.31–1.20 (1H, m); δ_C (100.6 MHz) 160.0, 141.5, 109.8, 104.8, 77.1, 46.8, 43.9, 38.4, 36.8, 28.8, 21.6; *m*/*z* (EI) 178 (M^+, 100%), 161 (92), 150 (24), 132 (45), 110 (28), 95 (17), 81 (15).

4.3. (1*S*,2*S*,4*R*)-2-*exo*-Hydroperoxy-2-*endo*-(2′-furyl)-bicyclo-[2.2.1] heptane-*exo*-5

A solution of 50% aqueous H_2O_2 (1.2 mL, 22 mmol) and Amberlyst-15 (400 mg) were added at room temperature to a solution of (+)-*endo*-4 (400 mg, 2.2 mmol) in anhydrous THF (22 mL) under argon atmosphere. The mixture was stirred for 6 h at room temperature. The mixture was diluted with diethyl ether (20 mL) and washed with brine (3 × 20 mL). The organic phase was then dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, petrol/diethyl ether 90:10) to yield (+)-*exo*-5 (362 mg, 85%) as a dense orange oil; $[\alpha]_D^{26} = +36.4$ (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} 3400 (O–H), 2920, 2852, 1461, 1260, 1015; δ_H (400 MHz) 7.42 (1H, dd, *J* 1.7, 0.9), 7.32 (1H, br s), 6.39–6.35 (2H, m), 2.71–2.69 (1H, m), 2.40-2.38 (1H, m), 2.05–1.99 (1H, m), 1.92 (1H, d quint, *J* 9.9, 1.7), 1.82 (1H, dd, *J* 13.6, 2.7), 1.48–1.41 (2H, m), 1.30–1.26 (1H, m), 1.13-1.08 (1H, m), 0.95–0.89 (1H, m); δ_C (100.6 MHz) 154.5, 142.3, 109.9, 109.4, 90.3, 44.1, 39.9, 36.5, 36.2, 28.3, 23.6; *m*/*z* (EI) 194 (M^+, 5%), 178 (20), 161 (100), 110 (74), 95 (39), 81 (63).

4.4. (1*S*,2*S*,4*R*)-2-*exo*-Hydroxy-2-endo-(2′-furyl)-bicyclo-[2.2.1] heptane *exo*-6

Ph_3P (79 mg, 0.3 mmol) was added to a solution of (+)-*exo*-**5** (58 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) under argon atmosphere. The mixture was stirred at room temperature for 1 h. The solvent was then removed under vacuum while purification of the residue by flash chromatography (petrol/Et_2O, 90:10) gave (+)-*exo*-**6** (45 mg, 85%) as a white solid. (Found: C, 74.26; H, 7.83. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%); Mp 38.2–39.7 °C (from EtOH) $[\alpha]_D^{29} = +47.9$ (*c* 0.80, $CHCl_3$); ν_{max}/cm^{-1} 3480 (O–H), 2925, 1501, 1458, 1220; δ_H (400 MHz) 7.37 (1H, dd, *J* 1.6. 0.6), 6.30 (1H, dd, *J* 3.2, 1.6), 6.22 (1H, dd, *J* 3.2, 0.6), 2.49–2.46 (1H, m), 2.36–2.34 (1H, m), 2.01 (1H, br s), 1.99-1.95 (1H, m), 1.92 (1H, dd, *J* 13.2, 2.5), 1.78 (1H, dt, *J* 13.2, 3.5), 1.47–1.43 (1H, m), 1.36 (1H, dt, *J* 12.6, 4.4), 1.31–1.22 (1H, m), 1.09–1.06 (1H, m), 0.85–0.82 (1H, m); δ_C (100.6 MHz) 157.9, 141.8, 109.8, 106.1, 78.2, 48.4, 44.8, 36.7, 36.2, 27.8, 23.4; *m*/*z* (EI) 178 (M^+, 94%), 161 (100), 150 (20), 132 (82), 110 (40), 95 (23), 81 (20).

4.5. General procedure for asymmetric sulfoxidation

A solution of (+)-*exo*-**5** (100 mg, 0.515 mmol) in anhydrous toluene (2 mL) was added to a solution of Ti(O*i*-Pr)$_4$ (38 μL, 0.128 mmol) in anhydrous toluene (1 mL) and activated MS 4 Å (100%/wt based on the sulfide), under argon atmosphere at −20 °C. The mixture was stirred for 30 min at −20 °C and then a solution of sulfide **7** (0.257 mmol) in anhydrous toluene (0.5 mL) added. The reaction progress was monitored by TLC analysis. At the end of the reaction, water (120 μL) was added and the mixture stirred for 1 h at room temperature. After filtration of the mixture over Celite with ethyl acetate (40 mL), the solvent was evaporated under vacuum and the crude reaction mixture purified by flash chromatography (from petrol/diethyl ether mixtures 90:10 to pure ethyl acetate) to give (+)-*exo*-**6** (95% mol recovery with respect to **5**) and **8**.

4.6. General procedure for kinetic resolution

A solution of (+)-*exo*-**5** (100 mg, 0.515 mmol) in anhydrous toluene (2 mL) was added to a solution of Ti(O*i*-Pr)$_4$ (108 μL, 0.368 mmol) in anhydrous toluene (3 mL) and activated MS 4 Å (100%/wt based on the sulfoxide) under an argon atmosphere at −20 °C. The mixture was stirred for 10 min at −20 °C and then a solution of racemic sulfoxide (0.736 mmol) in 1.5 mL of dry toluene added. The reaction was monitored by TLC analysis. At the end of the reaction, water (390 μL) was added and the mixture stirred for 1 h at room temperature. After filtration of the mixture over Celite with ethyl acetate (50 mL), the solvent was evaporated under vacuum and the crude reaction mixture purified by flash chromatography (from petrol/diethyl ether mixtures 90:10 to pure ethyl acetate) to give (+)-*exo*-**6** (95% mol recovery with respect to **5**) and unreacted **8**.

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