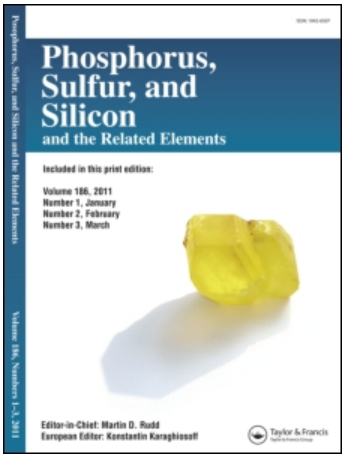

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STEREOCHEMISTRY OF THE ADDITION OF METALLATED SULFONAMIDES TO SUBSTITUTED CYCLOHEXANONES

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STEREOCHEMISTRY OF THE ADDITION OF METALLATED SULFONAMIDES TO SUBSTITUTED CYCLOHEXANONES

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Dedicated to Professor Dr. Manfred Hesse on the occasion of his 60th birthday

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The addition of α-metallated sulfonamides to cyclic ketones has been studied. Under kinetic control the axial attack of the lithium and the cerium reagents to 4-*tert*-butylcyclohexanone is preferred, whereas the stereochemical result is inverse when the metal is iron. High regio- and stereoselectivity of the addition of lithiated sulfonamides to (−)-*trans*-menthone (**3**) and (+)-(*R*)-pulegone (**4**) was observed, namely only 1,2-addition occurs affording the axial (with **3**) and equatorial (with **4**) hydroxysulfonamides **7** and **10**, resp. The reaction of phenylmethanesulfonamide reagents with **4** proceeds in 1,4 fashion. The configurations of the hydroxysulfonamides were established on the basis of NMR and X-ray analyses.

Key words: α-Metallated N,N-dialkylsulfonamides, 4-*tert*-butylcyclohexanone, menthone and pulegone, stereochemistry, absolute configuration, axial (equatorial) attack.

INTRODUCTION

Controlling the stereochemistry of addition of carbanions to cyclic ketones continues to be of theoretical[1] and synthetic[2–9] interest. Generally, the attack of small nucleophiles such as the hydride ion is preferentially axial,[2] whereas equatorial attack is favoured with Grignard type reagents.[3] On the other hand, axial attack is predominant if carbanions with insignificant steric requirements are employed.[10,11] The stereoselectivity can also be controlled by transmetallation of organolithium or Grignard compounds with transition metals, e.g. Ti,[5] Mn,[6] Fe[7] and Yb.[8] Organocerium[12] and organoiron (II)[13] regents are of increasing importance in organic synthesis, but their influence on the stereochemistry of the addition of nucleophiles to cyclic ketones has not been studied in detail. It must be noted that organoiron(II) reagents attack substituted cyclohexanones with unprecedented equatorial stereoselectivity.[7]

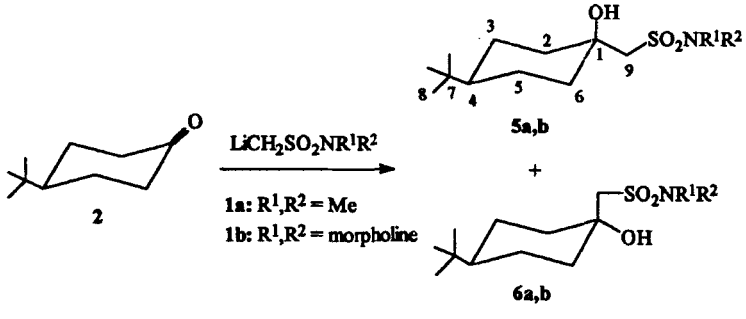
The stereochemistry of the addition of α-metallated sulfonamides to 4-*tert*-butylcyclohexanone has been studied recently.[14] In the case of methanesulfonamide reagents axial attack was always preferred regardless of the metal used (M = Mg, Li, Na). Thus it is of interest to determine if the use of Ce and Fe as metal counterions would influence the stereochemistry of this reaction?

In contrast to the addition of organometallic reagents to cycloalkanones, little is known about the stereochemistry of the addition of carbanions to cycloalkenones or alkenylcycloalkanones.[15]

We report herein the results of the addition of metallated sulfonamides (M = Li, Ce, Fe) to 4-*tert*-butylcyclohexanone (**2**), (−)-*trans*-menthone (**3**) and (+)-(*R*)-pulegone (**4**). Menthone[16] and pulegone[17] derivatives are of interest since they have been used as chiral auxiliaries and chiral precursors for asymmetric syntheses of natural products.[18]

RESULTS AND DISCUSSION

Addition of metal derivatives of sulfonamides **1a,b** to the cyclohexanone **2** yielded a mixture of isomeric alcohols **5a,b** and **6a,b** without any side reactions (Scheme I and Table I). The configuration of the diastereoisomeric β-hydroxysulfonamides **5b/6b** was assigned on the basis of their ^1H and ^{13}C NMR spectra, which were the same as these of **5a/6a**, previously assigned.[14] Thus, the signals for H C-9 for **5b** are shifted up-field, relative to the corresponding signals of **6b** and the observed ^{13}C-γ-effects are in agreement with the correlation $\delta_{C(9)ax} > \delta_{C(9)eq}$.[19] The following conclusions can be made from the results summarised in Table I: (1) the stereochemistry of the reaction depends on the metal counterion. Organocerium as well as lithium reagents caused axial attack, whereas the iron(II) metallated sulfonamide **1a** adds to **2** from the equatorial side (axial alcohol was favoured): (2) although the nature of organocerium reagents is unknown and has proved resistance to study[20] it can be seen that addition of $CeCl_3$ to $LiCH_2SO_2N(CH_3)_2$ has no or little influence on the stereoselectivity of the reaction studied (see Scheme I), but increases the reaction rate (compare entries 1 and 2, and 3 and 4, Table I): (3) it was shown,[7] that alkyl- and phenyliron(II) reagents add to substituted cyclohexanones solely from the equatorial side. The iron metallated sulfonamide **1a** showed the same tendency to equatorial attack, which lead to inversion of the stereochem-



SCHEME I

TABLE I

Addition of lithiated sulfonamides **1a, b** to 4-*tert*-butylcyclohexanone (**2**)[a]

Entry	Sulfonamide	Additive	Yield (%)[b]	Ratio 5 : 6[c]
1	1a	no	85 (73)	38 : 62[d]
2	1a	$CeCl_3$	96 (90)	35 : 65
3	1b	no	93 (85)	45 : 55
4	1b	$CeCl_3$	98 (89)	38 : 62
5	1a	$FeCl_2$	66 (59)	72 : 28
6	1a	$Fe(acac)_2$	60	68 : 32
7[e]	1a	$Fe(acac)_2$	63	68 : 32

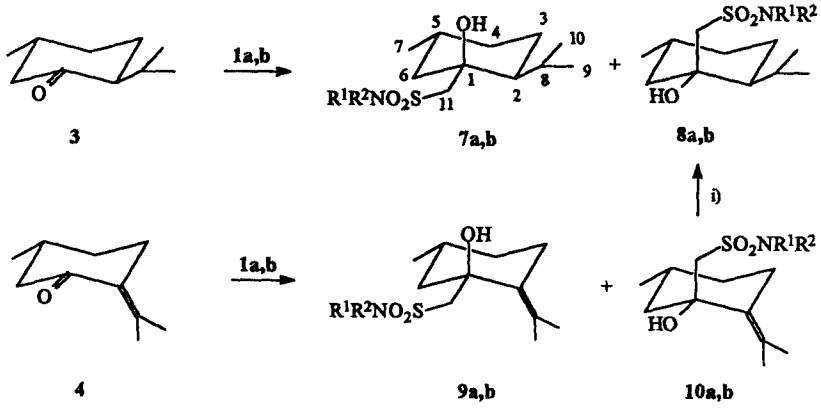
[a] The reactions were carried out at -50° for a 20 min.

[b] The numbers refer to conversion as determined by GC, those in parentheses to isolated yields.

[c] Determined by GC analysis of the crude reaction mixture.

[d] Reference 14.

[e] The reaction temperature was raised from - 50° to 0° within 3h.



SCHEME II

ical result (entries 5–7). In conclusion, by varying the metal used for the α-metallation of sulfonamides **1**, one can synthesise β-hydroxysulfonamides with either axial or equatorial OH groups, from the same starting sulfonamide.

In order to study the stereo- and regioselectivity of the reactions of metallated sulfonamides with substituted cyclohexanones, we examined the addition of these reagents to (−)-*trans*-menthone (**3**) and (+)-(*R*)-pulegone (**4**) (Scheme II). The

stereochemical outcome of the addition of allyl Grignard reagents to **4** was studied by Santelli and co-workers.[21] In many cases the authors detected only one diastereoisomer and the attack of the reagent proceeded in an axial fashion, which corresponded with the least-motion path.[11] (+)-(*R*)-pulegone was also used as a model compound in the study of 1,4-conjugated additions of different organometallics to enones.[11,22]

The results of the additions of α-lithiated sulfonamide **1** to (−)-*trans*-menthone (**3**) and (+)-(*R*)-pulegone (**4**) are summarised in Table II. As expected, the major isomer of the menthone adducts was the product of equatorial attack **7**, whereas the axial attack was preferred in the case of pulegone. The absolute configuration of the major diastereoisomer **7a**[23] was determined to be 1*S*, 2*S*, 5*R* by X-ray analysis (Figure 1) and therefore the configuration of its diastereoisomer **8a** should be 1*R*, 2*S*, 5*R*. The structure of the compound **7b** was elucidated by comparison of its spectroscopic data with those of **7a**. The pulegone adduct **10a** (major isomer) was converted by catalytic hydrogenation (1 atm, H_2/Pd/C, MeOH, 22°C) to the minor isomer **8a** of the menthone products, establishing that both have the same stereochemistry (Scheme II). The configuration of **8a** was also supported by its ^1H and ^{13}C NMR spectra, as well as by a GC analysis.[25] The different stereochemistry of the products of the addition of lithiated sulfonamides **1a,b** to (−)-*trans*-menthone and (+)-(*R*)-pulegone is presumably due to the different preferred conformations of these two ketones.

An examination of Table II reveals that the addition of **1** to **3** and **4** is highly diastereoselective. The menthone forms two adducts **7** and **8** in a 96/4 ratio with α-lithiated **1a**, whereas the pulegone gives **9** and **10** in a 3/97 ratio. The addition of **1b** to (−)-*trans*-menthone (**3**) and (+)-(*R*)-pulegone (**4**) proceeds with the same degree of selectivity (ratio **7/8** = 94/6 and **9/10** = 6/94).

When the addition of α-lithiated sulfonamide **1a** to **4** was carried out for a longer time and at higher temperatures (Table II, last entry) the ratio of axial/equatorial

TABLE II

Stereochemistry of the addition of lithiated sulfonamides **1a, b** to (−)-*trans*-mentone (**3**) and (+)-(*R*)-pulegone (**4**)[a]

	Addition to **3**		Addition to **4**	
Sulfonamide	**7/8**[b]	Yield (%)[c]	**9/10**[b]	Yield (%)[c]
1a	96/4	84 (70)	3/97	89 (83)
1b	94/6	64 (53)	6/94	90 (85)
1a[d]			11/89	49 (44)

[a] The reactions were carried out at -50° for a 20 min.

[b] Determined by GC analysis of the crude reaction mixture.

[c] The numbers refer to conversion as determined by GC, those in parentheses to isolated yields.

[d] The reaction temperature was raised from - 50° to 22° within 3.5h.

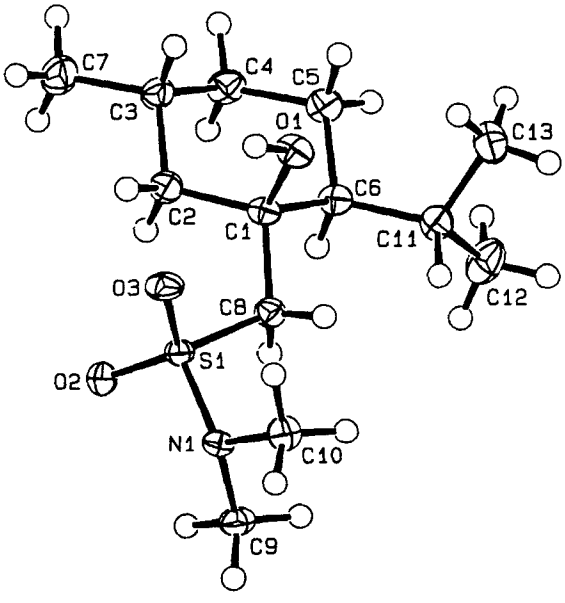


FIGURE 1 ORTEP diagram[24] of the molecular structure of **7a** (arbitrary numbering of the atoms).

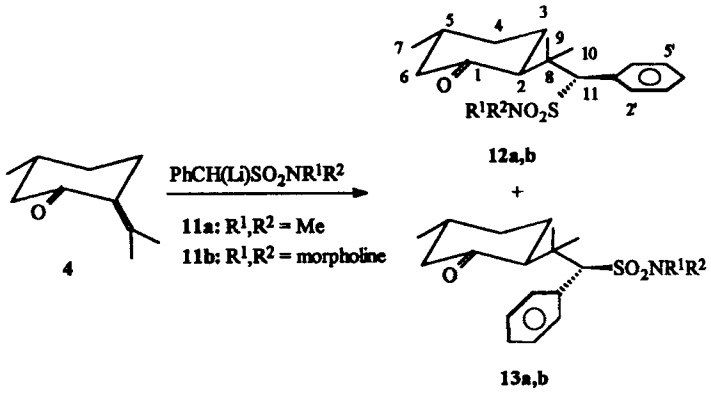
alcohols and the yield decreased, which indicated the reversibility of the reaction in these conditions.

The addition of lithiated sulfonamide **1** to (+)-(*R*)-pulegone (**4**) is highly regiostereoselective. No 1,4-addition products were detected either in the ^{1}H NMR spectra, or by GC analysis of the crude reaction mixtures. This result was in agreement with previous observations showing that the α-metallated methanesulfonamides behave as small and hard nucleophiles[26] and afford solely 1,2-addition products with α, β-unsaturated enones.[27]

In contrast, however, only 1,4-regioselectivity[28] was observed when α-metallated phenylmethanesulfonamides **11a,b** were added to (+)-(*R*)-pulegone (**4**) (Scheme III). The creation of the two new asymmetric centres (C-2 and C-11 in **12** and **13**) proceeds with very good at C-2 (ds = 89%) but with poor selectivity at C-11 (ds = 60%).

Surprisingly, in the case of (−)-*trans*-menthone (**3**), where only aldol addition could take place, no reaction with **11a** with either Li, or with Ce metallated sulfonamide was observed, although cerium is the metal of choice for obtaining a high level of 1,2-vs 1,4-addition.[12,29] The increased size and charge delocalisation of the nucleophile in the case of the α-lithiated sulfonamide **11a** could explain the formation of only, 1,4-addition products in the reaction with pulegone.

An attempt to determine the absolute configuration of **12a** and **13a** was made using CD spectroscopy. The CD curve of **12a** shows a weak negative Cotton effect at 190 nm and that of **13a** has weak positive effects at 314 and 309 nm. These effects can be associated with the n-π^* transition of the carbonyl chromophore. The π-π^* transitions of the phenyl chromophore are located for both compounds at 269, 263 and 216 nm. For **12a** the Cotton effects at 269 and 263 nm are negative



SCHEME III

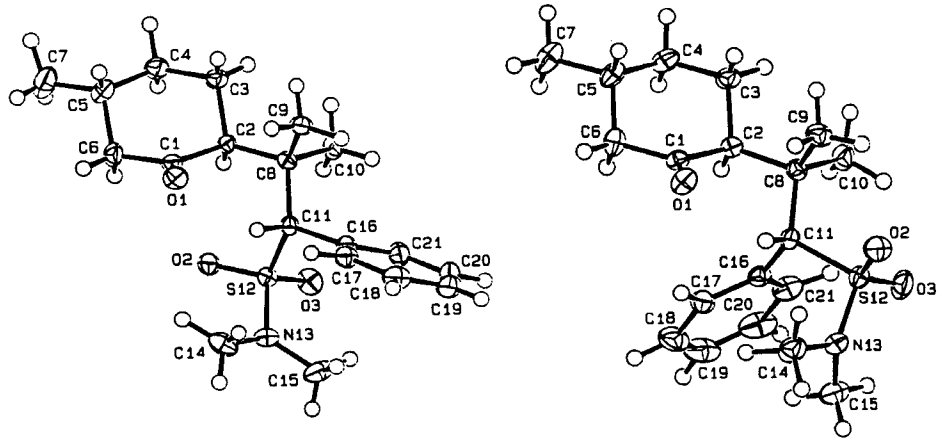


FIGURE 2 ORTEP diagram[24] of the molecular structure of **12a** (left) and **13a** (right) (arbitary numbering of the atoms).

and that at 216 nm is positive, whereas the effects for **13a** have opposite signs. From these data it can be concluded that the configuration at the stereogenic center bearing the phenyl group, C-11, of **12** must be the inverse of that of **13**, but from CD spectra alone it was not possible to assign the absolute stereochemistry of this center. Applying the octant rule[30] the stereochemistry of the C-2 stereogenic center in **12** or **13** could not be unambiguously determined, because of the limitations of the rule, e.g. availability of several low energy conformations and the presence of a long side chain bearing other chromophores, which would cause an additional through-space perturbation of the Cotton effects. From NMR experiments it was also not possible to determine the configuration at C-11, but the absolute configuration of compounds **12a** and **13A** could be elucidated by X-ray analyses[23] (see Figure 2), and confirmed our assumption that these compounds have different absolute configuration at C-11 stereogenic center, namely *R* and *S* for **12a** and **13a** respectively.

Detailed NMR experiments corroborated by force field calculations suggest that the conformation in chloroform corresponds to that in the solid state, which was

elucidated by the X-ray structure. Unambiguous assignment of all ^1H and ^{13}C signals in **12a** and **13a** was achieved by means of CH-correlation and homonuclear proton-proton NOE-measurements. In all phenylmethanesulfonamide addition products a fully hindered rotation of the phenyl ring is observed giving rise to non-broadened and well separated signals for all protons and carbons of the phenyl ring. In both **12a** and **13a** the proton at C-11 lies approximately in the plane of the phenyl ring and shows strong NOE to the proton in the phenyl ring, denoted as H-C-2′ (see Scheme III). The large differences in the proton chemical shifts of H-C-9, H-C-10 and H-C-2 in **12a** and **13a** are mainly due to the strong anisotropy effect of the fixed phenyl ring, which is differently oriented in both isomers. The NMR spectra of **12a** and **13a** allow the unambiguous determination of the chirality at C-2. Identical ^{13}C chemical shifts for C-4 and C-6 show that C-2 has the same configuration in both compounds. The C-2 proton in **12a** is clearly visible at 3.34 ppm as doublet of doublets with J = 4.4 and 12.4 Hz, which indicates that it occupies the axial position and therefore the configuration at C-2 is *S*.

EXPERIMENTAL

General: M.p.: on a Kofler hot stage apparatus, uncorrected. IR spectra were recorded on a Specord 75 in $CHCl_3$ soln; in cm^{-1}. ^1H (250.1 MHz) and ^{13}C NMR (62.9 MHz) were measured on Bruker WM-250; $CDCl_3$ soln; chemical shifts (δ) in ppm relative to TMS; coupling constants (J) in Hz. Signal multiplicity was determined from DEPT spectra. MS: on a Jeol D-300; reactant gas for CI MS: 2-methylpropane. Optical Rotations: Perkin-Elmer-241 polarimeter, measured at 22°. CD spectra were recorded on a Dichrograph Mark III (ISA, Jobin Yvon) instrument in CH_3CN soln; in nm ($\Delta\varepsilon$) TLC was performed on silica gel alu foils (60 F_{254}, Merck). Column chromatography (flash chromatography (FC)): silica gel 60 (230–400 mesh ASTM, Merck). GC separations were done on a Hewlett-Packard 5890 instrument using a SPB-1 capillary column (15 m) programmed at 10°/min, 100–300°; 0.7 bar N_2. All reactions were carried out in flame dried Schlenk flasks under Ar atmosphere. THF was distilled over $LiAlH_4$ prior to use. Soln. were dried over anh. $MgSO_4$.

1. Metallation of Sulfonamides **1** *and* **11**

1.1. M = Li: To a stirred soln. of LDA (2.4 mmol, prepared from n-BuLi (1.5 ml 1.6 M in hexane, 2.4 mmol) and 0.34 ml (2.4 mmol) of diisopropylamine in 2 ml of THF) at −40° 2.2 mmol of the corresponding sulfonamide in 5 ml of THF was added and the reaction mixture was stirred at −20° for 1 h.

1.2. M = $CeCl_2$: To a stirred suspension of $CeCl_3$ (2.1 mmol) in THF at −70°, the lithiated sulfonamide prepared according to 1.1 was added via syringe. The reaction mixture was stirred at −50° for 1 h.

1.3. M = Fe: Starting form $FeCl_3$: to a stirred soln of 370 mg (2.3 mmol) of $FeCl_3$ in 10 ml of THF at −70°, methyllithium (1.5 ml 1.6 M in Et_2O, 2.4 mmol) was added. The reaction mixture was stirred 1 h at −70° then lithiated sulfonamide **1a** was added via syringe and the whole mixture was stirred at the same temperature for 1 h. Starting from $Fe(acac)_2$[31]: to a stirred solution of 585 mg (2.3 mmol) of $Fe(acac)_2$ in 10 ml of THF at −78°, lithiated sulfonamide **1a**, prepared according to 1.1 was added via syringe and stirred for 1 h.

2. Addition of Metallated Sulfonamides to Substituted Cyclohexanones. General Procedure

To a stirred soln. of the organometallic reagents at −50°, 2 mmol of the corresponding ketone (**2**, **3** or **4**) in THF (2 ml) was added, the reaction mixture stirred for 20 min, acidified (pH ca 1) with HCl/H_2O (1:1), saturated with NaCl and diluted with 20 ml of Et_2O. The organic layer was separated, the water phase was extracted with either (2 × 20 ml), the combined organic phases washed to neutral reaction with brine, dried, evaporated and subjected to GC analysis. The crude products were purified by column chromatography.

2.1. 4-(1,1-Dimethylethyl)-1-(N-morpholinomethanesulfonamido)cyclohexan-1-ol (**5b/6b**): Following the General Procedure the lithiated sulfonamide **1b** was added to 4-*tert*-butylcyclohexanone (**2**) and after FC (hexane/ether = 1:1) the title compound was obtained in 85% yield as mixture of diastereoisomers (**5b/6b**) = **45/55**). Pure **6b** was obtained after recrystallization from $CHCl_3$/hexane. M.p.: 115–117°C. IR: 3530, 2940, 2860, 1400, 1340, 1330, 1260, 1160, 1120, 1070, 950, 625. ^{1}H NMR: 3.78(m, 5H, morpholino + OH); 3.25(m, 4H, morpholino); 3.12(s, 2H, C-9); 2.10(m, 2H); 1.79(m, 2H); 2.51(m, 3H); 1.09(m, 2H); 0.87(s, 9H, CH_3). ^{13}C NMR: 71.1(s, C-1); 66.4(t, 2C); 53.4(t, C-9); 47.5(d, C-4); 45.6(t, 2C); 38.4(t, C-2, 6), 32.2(s, C-7); 27.6(q, 3C, CH_3); 24.4(t, C-3, 5). CI MS: 320([M + 1]$^+$).

Data of **5b** (from a mixture with **6b**): ^{1}H NMR: 3.76(m, 5H, OH + 4H, morpholino); 3.22(m, 4H, morpholino); 2.97(s, 2H, C-9); 2.10(m, 2H); 1.79(m, 2H); 2.51(m, 3H); 1.09(m, 2H); 0.87(s, 9H, CH_3). ^{13}C NMR: 69.2(s, C-1); 66.4(t, 2C); 59.0(t, C-9); 47.5(d, C-4); 45.9(2C); 37.7(t, C-2, 6); 32.3(s, C-7); 27.6(q, 3C, CH_3); 22.0(t, C-3, 5).

2.2. (−)-(1S, 2S, 5R)-1-(N, N-Dimethylmethanesulfonamido)-5-methyl-2-(1-methylethyl)cyclohexan-1-ol (**7a**): According to the General Procedure, starting from **1a** and (−)-*trans*-menthone (**3**) and after FC (hexane/ether = 6:1) (−)-**7a** was obtained. Yield 84% $[\alpha]_D$ = −8.28;$[\alpha]_{546}$ = −16.75 (c = 0.56, $CHCl_3$). M.p.: 94–95°C ($CHCl_3$/hexane). IR: 3540, 2990, 1450, 1330, 1170, 1140, 960, 560, 530, 470. ^{1}H NMR: 3.36(d, *J* = 13.6, 1H, C-11); 2.89(d, *J* = 13.6, 1H, C-11); 2.88(s, 7H, OH + $N(CH_3)_2$); 2.18(m, 1H); 1.99(m, 1H); 1.81(m, 2H); 1.50(m, 3H); 1.25(m, 1H); 1.12(m, 1H); 0.95, 0.92, 0.90(3d, *J* = 6.4, 6.2, 6.0, 9H, CH_3). ^{13}C NMR: 73.8(s, C-1); 55.7(t, C-11); 50.5(d, C-2); 46.9(t, C-6); 37.4(q, 2C, $N(CH_3)_2$); 34.9(t, C-4); 27.7(d, C-5); 26.6(d, C-8); 23.5(q, C-7); 22.3(q, C-9); 20.4(t, C-3); 17.9(q, C-10). EI MS: 277(2, M$^+$·), 192(62), 155(12), 151(12), 150(12), 110(14), 95(33), 92(15), 81(28), 69(34), 55(28), 46(69), 45(100), 44(34), 43(24), 41(26).

2.3. Addition of the lithiated sulfonamide **1b** *to (−)-trans-methone* (**3**): By the reaction of (−)-menthone and **1b**, following the General Proceudre, the diastereoisomeric mixture of **7b/8b** (94/6) was formed in 53% yield (after FC: hexane/Et_2O = 3:1). These two diastereoisomers was separated by flash chromatography (hexane/Et_2O = 5/1).

2.3.1. (−)-(1S, 2S, 5R)-5-Methyl)-2-(1-methylethyl)-1-(N-morpholinomethanesulfonamido)cyclohexan-1-ol (**7b**): Yield = 50%. M.p.: 81–83°C (ether/hexane). $[\alpha]_D$ = −7.00; $[\alpha]_{546}$ = −12.40 (c = 0.5, $CHCl_3$). IR: 3570, 2930, 2860, 1450, 1340, 1330, 1300, 1260, 1160, 1150, 1120, 1070, 950, 560, 530, 480. ^{1}H NMR: 3.78(t, *J* = 4.7, 4H, morpholino); 3.35(d, *J* = 13.6, 1H, C-11); 3.25(t, *J* = 4.7, 4H, morpholino); 2.88(d, *J* = 13.6, 1H, C-11); 2.76(br.s, 1H, OH); 2.18(m, 1H); 1.97(m, 1H); 1.80(m, 2H); 1.56(m, 3H); 1.29(m, 1H); 1.14(m, 1H); 0.94, 0.92, 0.90(3d, *J* = 6.8, 6.8, 6.3, 9H, CH_3). ^{13}C NMR: 73.9(s, C-1); 66.4(t, 2C); 56.6(t, C-11); 50.4(d, C-2); 47.0(t, C-6); 45.7(t, 2C); 34.8(t, C-4); 26.6(d, C-5); 23.55(d, C-8); 23.5(q, C-7); 22.2(q, C-9); 20.4(t, C-3); 18.0(q, C-10). EI MS: 319(1, M$^+$·) 234(41), 155(12), 134(10), 110(12), 95(26), 88(45), 87(100), 86(33), 81(20), 69(24), 57(18), 56(20), 55(18), 43(18), 41(18).

2.3.2. (1R, 2S, 5R)-5-Methyl-2-(1-methylethl)-1-(N-morpholinomethanesulfonamido)cyclohexan-1-ol (**8b**): Yield = 3%. ^{1}H NMR: 3.78(t, *J* = 4.6, 4H, morpholino); 3.50(br.s, 1H, OH); 3.25(t, *J* = 4.6, 4H, morpholino); 3.22(d, *J* = 13.7, 1H, C-11); 3.04(d, *J* = 13.7, 1H, C-11); 2.40(m, 1H); 2.17(m, 1H); 1.73(m, 2H); 1.45(m, 4H); 1.13(m, 1H); 0.99, 0.92, 0.79(3d, *J* = 6.9, 6.4, 6.8, 9H, CH_3). CI MS: 320 ([M + 1]$^+$).

2.4. (+)-(1R, 5R)-1-(N, N-Dimethylmethanesulfonamido)-5-methyl-2-(1-methylethylidene)-cyclohexan-1-ol (**10a**): According to the General Procedure, starting from sulfonamide **1a** and (+)-(*R*)-pulegone (**4**) and after FC (hexane/Et_2O = 8/1) the adduct **10a** was obtained as colourless oil. Yield = 71%. $[\alpha]_D$ = +43.80; $[\alpha]_{546}$ = +56.47(c = 0.48, $CHCl_3$). IR: 3510, 2910, 1450, 1320, 1140, 960, 620, 560, 550, 480. ^{1}H NMR: 3.89(br.s, 1H, OH); 3.37(d, *J* = 13.6, 1H, C-11); 3.14(d, *J* = 14.1, 1H, C-11); 2.87(s, 6H, $N(CH_3)_2$); 2.75(m, 1H); 2.14(m, 1H); 2.06(d, *J* = 1.5, 3H, CH_3); 1.72(s, 3H, CH_3); 1.68(br.s, 4H); 1.38(m, 1H); 0.93(d, *J* = 6.2, 3H, CH_3). ^{13}C NMR: 131.0(s, C-2); 127.5(s, C-8); 75.9(s, C-1); 53.7(t, C-11); 48.6(t, C-6); 37.2(q, 2C, $N(CH_3)_2$); 34.4(t, C-4); 29.7(d, C-5); 28.4(t,C-3), 23.8(q, C-7); 22.1(q, C-9); 21.8(q, C-10). EI MS: 275(2, M$^+$·); 257(1, [M − 18]$^+$), 193(17), 154(12), 153(100), 149(38), 148(25), 114(12), 112(19), 93(27), 80(29), 69(19), 67(12), 60(21), 46(21), 45(29), 44(21), 43(35), 41(25).

2.5. (+)-(1R, 5R)-5-Methyl-2-(1-methylethylidene)-1-(N-morpholinomethanesfulfonamido)-cyclohexan-1-ol (**10b**): The addition of sulfonamide **1b** to **4** gave after FC (hexane/Et_2O = 4:1) **10b** in 85% yield. M.p.: 95–96°C ($CHCl_3$/hexane). $[\alpha]_D$ = +62.41; $[\alpha]_{546}$ = +80.68(c = 0.58, $CHCl_3$). IR: 3530, 2920, 1450, 1390, 1370, 1260, 1110, 950, 620. 560, 550, 480. ^{1}H NMR: 3.76(t, *J* = 4.7, 4H, morpholino); 3.75(s, 1H, OH); 3.38(d, *J* = 14.1, 1H, C-11); 3.25(t, *J* = 4.7, 4H, morpholino); 3.15(d, *J* = 14.1,

1H, C-11); 2.75(m, 1H); 2.15(m, 1H); 2.06(d, J = 1.1, 3H, CH_3); 1.73(s, 3H, CH_3); 1.68(br.s, 4H); 1.37(m, 1H); 0.94(d, J = 6.1, 3H, CH_3). ^{13}C NMR: 130.9(s, C-2); 127.6(s, C-8); 76.0(s, C-1); 66.3(t, 2C), 54.7(t, C-11); 48.6(t, C-6); 45.4(2C), 34.3(t, C-4); 29.7(d, C-5); 28.4(t, C-3); 23.8(q, C-7); 22.1(q, C-9); 21.7(q, C-10). EI MS: 317(1, $M^+\cdot$), 299(1, $[M - 18]^+$), 235(10, $[M - C_4H_8NO]^+$), 153(100), 149(31), 148(19), 107(12), 83(17), 70(21), 69(12), 67(10), 57(10), 56(10), 55(12), 43(19), 41(16).

2.6. Addition of sulfonamide **11a** *to (+)-(R)-pulegone* (**4**): Following the General Procedure, starting from 458 mg (2.3 mmol) of **11a** and 305 mg (2.0 mmol) of **4**, after FC (hexane/ether = 5:1) 315 mg (45%) of reaction products were obtained as a diastereoisomeric mixture (6.1:4.2:1:1.7). This mixture was separated by column chromatography (hexane/Et_2O = 10:1).

2.6.1. (−)-(1'R, 2S, 5R)-2-[2-(2, 2-Dimethyl-1-phenyl)-N, N-dimethylethanesulfonamido]-5-methylcyclohexanone (**12a**): First eluted diastereoisomer (180 mg): M.p.: 186–188.5°C (EtOH). $[\alpha]_D$ = −14.80(c = 0.76, $CHCl_3$): $[\alpha]_D$ = −13.48(c = 0.78, MeOH). IR: 2980, 2970, 1700, 1410, 1320, 1140, 970, 620, 580, 570, 490. ^1H NMR: 7.90(m, 1H, C-6'); 7.35(m, 3H, C-3', 4', 5'); 7.27(m, 1H, C-2'); 5.45(s, 1H, C-11); 3.34(dd, J = 4.4, 12.4, 1H, C-2); 2.34(s, 6H, $N(CH_3)_2$); 2.32(d, J = 6.8, 2H, C-6); 2.17(m, $1H_e$, C-3); 1.90(m, $1H_e$, C-4); 1.87(m, 1H, C-5); 1.44(m, $1H_a$, C-4); 1.41(m, $1H_a$, C-3); 1.30(s, 3H, C-10); 1.04(d, J = 6.2, 3H, C-7); 0.78(s, 3H, C-9). ^{13}C NMR: 213.7(s, C-1); 132.9(s, C-1'); 132.8(d, C-2'); 130.6(d, C-6'); 128.5(d, C-4'); 128.3(d, C-5'); 127.8(d, C-3') 68.9(d, C-11); 55.5(d, C-2); 52.2(t, C-6); 39.5(s, C-8); 37.4(q, 2C, $N(CH_3)_2$); 36.8(d, C-5); 34.9(t, C-4); 29.3(t, C-3); 22.27(q, C-7, 9); 22.13(q, C-10). EI MS: 351(2, $M^+\cdot$), 243(100, $[M - SO_2N(CH_3)_2]^+$), 235(21), 199(10), 169(17), 145(10), 143(12), 132(12), 131(46), 129(10), 117(19), 105(21), 92(10), 91(29), 81(17), 69(15), 55(16), 45(15), 44(12), 43(17), 42(10), 41(25). CD(1.379 × 10^{-3}M): 290.2(−0.54), 268.6(−0.26), 262.6(−0.17), 220.0(3.70), 216.2(3.99). 196.0(4.49).

2.6.2. (+)-(1'S, 2S, 5R)-2-[2-(2, 2-Dimethyl-1-phenyl)-N, N-dimethylethanesulfonamido]-5-methylcyclohexanone (**13a**): The second eluted diastereoisomer (130 mg) was obtained as one spot on TLC but it was a mixture of three diastereoisomers (GC-evidence). To these crystals 0.5 ml of Et_2O was added and the remaining solid filtered of to give 80 mg of (+)-**13a** as colourless crystals (one diastereoisomer). M.p.: 154–156°C. $[\alpha]_D$ = 0.00; $[\alpha]_{546}$ = +8.60; $[\alpha]_{365}$ = +14.84(c = 0.76, $CHCl_3$). $[\alpha]_D$ = 0.00; $[\alpha]_{546}$ = 0.00; $[\alpha]_{365}$ = +5.10(c = 0.45, MeOH). ^1H NMR: 7.86(m, 1H, C-6'); 7.33(m, 2H, C-3', 4'); 7.28(m, 1H, C-5'); 6.91(m, 1H, C-2'); 5.04(s, 1H, C-11); 2.40(s, 6H, $N(CH_3)_2$); 2.11(ddd, J = 2.3, 3.9, 12.2, 1H, C-6); 2.02(m, $1H_e$, C-3); 1.83(m, 2H, 1H, C-2 + $1H_e$, C-4); 1.80(m, 1H, C-5); 1.56(s, 3H, C-9); 1.43(m, $1H_a$, C-3); 1.42(t, J = 2.6, 1H, C-6); 1.37(s, 3H, C-10);1.10(m, $1H_a$, C-4); 0.89(d, J = 6.3, 3H, C-7). ^{13}C NMR: 212.6(s, C-1); 133.6(s, C-1'); 132.2(d, C-2'); 130.1(d, C-6'); 128.6(d, C-4'); 128.3(d, C-3'); 128.2(d, C-5'); 71.9(d, C-11); 57.2(d, C-2); 51.9(t, C-6), 40.3(s, C-8); 37.4(q, 2C, $N(CH_3)_2$); 36.1(d, C-5); 34.4(t, C-4); 27.5(t, C-3); 23.1(q, C-7); 22.4(q, C-9); 22.1(q, C-10). CD(1.646 × 10^{-3} M): 314.4(0.16), 309.4(0.17), 278.0(−0.02), 268.6(0.12), 261.8(0.14), 221.4(−6.94), 202.4(5.94), 194.6(12.46) 193.0(11.98).

2.7. Addition of the lithiated sulfonamide **11b** *to (+)-(R)-pulegone* (**4**): Analogeus to 2.6 from 554 mg (2.3 mmol) of **11b** and 305 mg (2.0 mmol) of **4** a mixture of diastereoisomers (10.3:6:1.7:1) 438 mg (56%) was obtained. This mixture was departed by column chromatography (hexane/Et_2O = 8:1):

2.7.1. (−)-(1'R, 2S, 5R)-2-[2-(2, 2-Dimethyl-1-phenyl)-N-morpholinoethanesfulfonamido]-5-methylcyclohexanone (**12b**): First eluted diastereoisomer (220 mg): M.p. 161–162°C. $[\alpha]_D$ = 0.00, $[\alpha]_{546}$ = 0.00, $[\alpha]_{365}$ = −10.36(c = 0.56, $CHCl_3$); $[\alpha]_D$ = 0.00, $[\alpha]_{546}$ = −1.56, $[\alpha]_{365}$ = −23.90(c = 0.71, MeOH). IR: 2960, 2930, 1700, 1450, 1340, 1330, 1260, 1150, 1110, 960, 630, 570, 490. ^1H NMR: 7.87(m, 1H, C-6'); 7.37(m, 3H, C-3', 4', 5'); 7.29(m, 1H, C-2'); 5.39(s, 1H, C-11); 3.44(m, 2H, morpholino); 3.31(m, 4H, morpholino); 2.93(m, 2H, morpholino); 2.47(br.s, 1H, C-2); 2.32(d, J = 9.0, 2H, C-6); 2.17(m, 1H); 1.92(m, 2H); 1.46(m, 2H), 1.29(s, 3H, C-10); 1.04(d, J = 6.2, 3H, C-7); 0.78(s, 3H, C-9). ^{13}C NMR: 213.7(s, C-1); 133.3(d, C-2'); 132.7(s, C-1'); 130.4(d, C-6'); 128.7(d, C-4'); 128.5(d, C-5'); 127.9(d, C-3'); 69.8(d, C-11); 66.7(t, 2C); 55.5(d, C-2); 52.2(t, C-6); 45.9(t, 2C); 39.6(s, C-8); 36.8(d, C-5); 34.9(t, C-4); 29.3(t, C-3); 22.34(q, C-7); 22.3(q, C-9); 22.1(q, C-10). EI MS: 393(1, $M^+\cdot$), 268(20), 243(69, $[M - SO_2NC_4H_8O]^+$), 242(12), 241(10), 237(28), 226(14), 225(67), 169(45), 153(12), 145(20), 143(26), 132(20), 131(100), 129(12), 117(26), 109(12), 105(37), 91(41), 87(26), 81(33), 69(18), 57(10), 56(30), 55(16), 43(14), 41(24). CD(1.114 × 10^{-3} M): 291.4(−0.64), 268.6(−0.33) 262.4(−0.23), 217.4(6.99), 203.6(2.25), 195.4(8.70).

2.7.2. (1'S, 2S, 5R)-2-[2-(2, 2-Dimethyl-1-phenyl)-N-morpholinoethanesulfonamido]-5-methylcyclohexanone (**13b**): Data for the major diastereoisomer from the diastereoisomeric mixture (8:1:1): ^1H NMR: 7.82(m, 1H, C-6'); 7.36(m, 2H, C-3', 4'); 7.29(m, 1H, C-5'); 6.93(m, 1H, C-2'); 4.98(s, 1H, C-11); 3.46(m, 2H, morpholino); 3.37(m, 4H, morpholino); 3.03(m, 2H, morpholino); 2.56(br.s, 3H);

2.14(m, 1H); 2.01(m, 2H); 1.82(m, 2H); 1.55(s, 3H, C-9); 1.36(s, 3H, C-10); 0.89(d, J = 6.3, 3H, C-7). ^{13}C NMR: 212.6(s, C-1); 133.3(s, C-1′); 132.4(d, C-2′); 129.9(d, C-6′); 128.8(d, C-4′); 128.4(d, C-3′, 5′); 72.8(d, C-11); 66.8(t, 2C); 57.1(d, C-2); 51.9(t, C-6); 45.8(t, 2C); 40.4(s, C-8); 36.0(d, C-5); 34.3(t, C-4); 27.7(t, C-3); 23.1(q, C-7); 22.4(q, C-9); 22.1(q, C-10).

3. (−)-(1R, 2S, 5R)-1-(N, N-Dimethylmethanesulfonamido)-5-methyl-2-(1-methylethyl)cyclohexan-1-ol (**8a**): 80 mg (0.29 mmol) of (+)-**10a** in 5 ml of abs. MeOH was hydrogenated with 5 mg 10% Pd/C at 22° and 1 atm. pressure of H_2. After 3h the hydrogenation was complete (TLC monitoring), the catalyst removed by filtration through celite and the solvent evaporated. The crude product was purified by column chromatography (hexane/Et_2O = 4/1) to yielded 68 mg (85%) of (−)-**8a**. M.p.: 117–119°C. $[\alpha]_D$ = −38.83; $[\alpha]_{546}$ = −49.22 (c = 0.77, $CHCl_3$). ^{1}H NMR: 3.63(s, 1H, OH); 3.23(d, J = 13.7, 1H, C-11); 3.02(d, J = 13.7, 1H, C-11); 2.87(s, 6H, $N(CH_3)_2$); 2.40(m, 1H); 2.19(m, 1H); 1.62(m, 4H); 1.36(m, 1H); 1.10(m, 2H); 1.00, 0.92, 0.79(3d, J = 6.9, 6.4, 6.9, 9H, CH_3). ^{13}C NMR: 74.1(s, C-1); 53.0(d, C-2); 49.8(t, C-11); 47.8(t, C-6); 37.4(q, 2C, $N(CH_3)_2$); 34.7(t, C-4); 30.4(d, C-5); 24.9(d, C-8); 24.6(q, C-7); 23.8(t, C-3); 22.1(q, C-9); 19.4(q, C-10). CI MS: 278($[M + 1]^+$).

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