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Enantioselective synthesis of bridgehead hydroxyl bicyclo[2.2.2]octane derivatives via asymmetric allylindation

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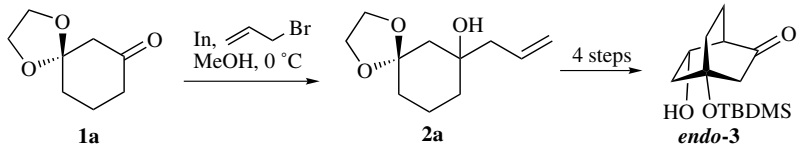
Abstract—A recent new strategy for the transformation of mono-dioxolane protected 1,3-cyclohexadione into bridgehead hydroxyl bicyclo[2.2.2]octane derivatives, based on allylindation followed by ozonolysis and intramolecular aldol addition, was modified to include asymmetric allylindation. This enabled the first enantioselective synthesis of (1*R*,4*R*,6*S*)-*endo*-4-(*tert*-butyl-dimethyl-silyl-oxy)-6-hydroxy-bicyclo[2.2.2]octan-2-one and (1*S*,4*S*,6*R*)-*endo*-4-(*tert*-butyl-dimethyl-silyloxy)-6-hydroxy-bicyclo[2.2.2]octan-2-one in high enantiomeric excess. Issues concerning the non-reproducibility of the asymmetric allylindation were also addressed.

1. Introduction

Enantiomerically pure bicyclo[2.2.2]octanes are useful chiral building blocks in asymmetric catalysis[1] and natural product synthesis.[2] Recently we reported a non-stereoselective synthesis of *rac-endo*-4-(*tert*-butyl-dimethyl-silyloxy)-6-hydroxy-bicyclo[2.2.2]octan-2-one **3** (Scheme 1),[3] which after oxidation yielded the corresponding diketone.

To obtain bicyclic hydroxyketones, such as **3**, in an enantiomerically pure state, the corresponding diketone can be asymmetrically reduced by Baker's yeast. Several examples have been reported in the literature on the bioreduction of bicyclo[2.2.2]octane-2,6-dione and analogues, giving mainly the *endo*-hydroxyketone in high enantiomeric excess.[4] In spite of this, it would be preferable to obtain the optically active hydroxyketone **3** directly, without the need for subsequent oxidation and Baker's yeast reduction. The first step in our synthesis towards **3** involves allylation of mono-protected 1,3-cyclohexadione **1a** to give **2a** (Scheme 1). Accordingly, an asymmetric version of this reaction would provide directly enantioenriched **3**.

The stereoselective introduction of an allyl group is often achieved by the use of allylic organometallic reagents in which the metal is coordinated to a chiral ligand.[5] For this purpose several different metals have been used with success. Since we employed indium for the non-asymmetric allylation of **1a**, we found it interesting to continue the development of an asymmetric version of this reaction using the same metal. Several examples of asymmetric allylindations, involving In(0), have already been described in the literature, in which the stereoselectivity has been achieved by employing substrate



1a **2a** ***endo*-3**

Scheme 1. Synthesis of *rac-endo*-**3** (see Ref. 3).

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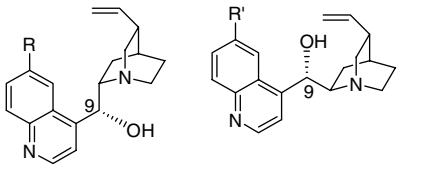
controlled processes,[6] catalytic asymmetric reactions,[7] or chiral reagents in stoichiometric amounts.[8] Most of these methods are exemplified by allylation of aldehydes, but a few also include ketones (mainly conjugated), hydrazones, and aldimines as substrates. The products are often obtained in high yields and ees.

For the asymmetric allylindation we became particularly interested in a procedure, which was described by Loh et al.[8d–f] They employed cinchona alkaloids (Fig. 1, structures **4a**–**4d**) as chiral promoters, which together with indium powder and different allylic bromides formed chiral non-racemic complexes. Unfortunately, the described methodology proved irreproducible in our hands, and, as will be discussed, extensive efforts had to be made in order to establish optimal and reproducible conditions.



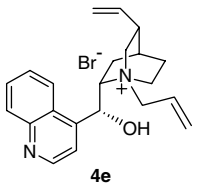
4a R=H, (-)-cinchonidine **4b** R'=H, (+)-cinchonine
4c R=OMe, (-)-quinine **4d** R'=OMe, (+)-quinidine

Figure 1. Structures of cinchona alkaloids.

Herein we report the optimization of the asymmetric allylation reaction employing In(0), together with cinchona alkaloids as chiral promoters. The improved protocol was subsequently applied to three different cyclohexanone derivatives, differing in the functionalization at the 3-position. Also, the first enantioselective synthesis of both enantiomers of bridgehead hydroxyl bicyclo[2.2.2]ocane derivative **3**, starting from optically active **2a**, is described.

2. Results and discussion

The literature procedure for the asymmetric allylindation consisted of mixing indium powder (2 equiv) and the chiral base (2 equiv) in a polar solvent, THF or DCM.[8e,f] In the case of THF, the solvent was distilled off three times to azeotropically remove water. After this, the allylic bromide (6 equiv) was added and stirring continued for approximately 1 h, after which a clear solution (the chiral complex) formed. Hexane was then added dropwise, and after adjustment of temperature, the carbonyl compound (1 equiv) was added. Initial attempts at the allylation of **1a** according to the above procedure, using allyl bromide together with (−)-cinchonidine **4a**, progressed nicely in both THF–hexane (3:1) and DCM–hexane (3:1). Compound **2a** was obtained in 79% ee and 85% yield at −78 °C.[9] However, on repeating the experiment, it frequently failed. Completely clear reaction mixtures were not obtained and the indium powder not consumed. This resulted in low ee's of **2a** (10–20%) while the yields were also somewhat reduced. In addition, we noticed that the reaction mixture changed character after approximately 30 min, when a new precipitate formed. ^{1}H NMR spectra of the precipitate indicated it to be the quaternary allylic ammonium salt **4e** (Fig. 2).



4e

Figure 2. Structure of quaternary allylic ammonium salt **4e**.

In fact, it is known from the literature that the quinuclidine nitrogen of the cinchona alkaloids can be quaternarized on reaction with an allylic halide in THF at rt.[10] Thus, salt formation seemed to be favored over the formation of the chiral complex.

Since sonication is known to activate metal surfaces and has been used to activate indium metal for different chemical transformations,[11] this method was tested for the complex formation, but did not lead to any improvements (neither when run in THF or DCM). We then tried to suppress the ammonium salt formation by adding equimolar amounts of allyl bromide with regard to the indium and chiral base (2 equiv), instead of excess amounts, but this also failed. In a study reported by Singaram et al.[8a] on the asymmetric allylindations of aldehydes using (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol as chiral promoter, they added 2 equiv of pyridine to the reaction mixture, and were able to increase both conversion and enantioselectivity. However, no progress in reproducibility was achieved by applying this methodology to our system.

We now began to suspect that water, present to some extent in the reaction mixture, might disturb the formation of the complex. The presence of water has been observed by others to be unfavorable in this kind of reaction.[7,8f] Azeotropically drying of the solids by distilling off the THF three times, as according to the literature procedure, did not seem to have any great effect on the complex formation. However, the addition of 4 Å MS to the reaction mixture did produce the chiral complex more frequently, but still not in a reproducible manner. This indicated the dryness of the reaction mixture to be an important factor. In fact, we noticed that the procedure for drying the THF also affected the complex formation. Drying of THF by passing it through an alumina column appeared to be preferable, in our hands, rather than distilling it from sodium/benzophenone.

Next, attempts were made to produce an allylic reagent with increased reactivity by performing a Finkelstein reaction in situ. This was done by adding either $Bu_4N^+{}^-I$ or NaI to the reaction mixture prior to the addition of the allyl bromide. In the case of NaI, the result was the same as before, that is no clear solution was obtained. However, in the case of $Bu_4N^+{}^-I$, a perfectly clear solution formed within 10 min, but unfortunately the allylic cinchonidinium salt **4e** formed after another

30 min. Because of these observations, we came to consider the complex formation to be dependent on the nature of the allylic reagent, and therefore the allyl bromide was exchanged for allyl iodide. Thus, when allyl iodide was added to a mixture of indium, **4a** and 4 Å MS in dry THF, a clear solution resulted within 2 min and the indium powder consumed after two more hours. This procedure was then tested repeatedly and finally proved to be reproducible, thus yielding **2a** with the same high ee (79%) and yield (87%) as before. Moreover, it was found that addition of hexane to the reaction mixture did not have any effect on the ee of **2a** and was thus excluded from subsequent reactions.

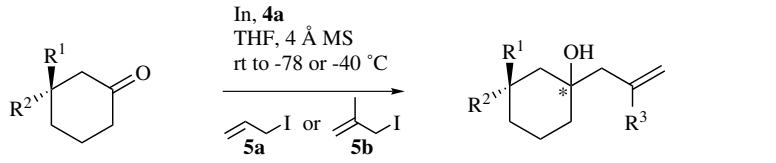
During our work, a study on a catalytic indium-mediated allylation of hydrazones was published by Cook et al.,[7] in which they were able to use reduced amounts of reagents (indium powder (1.1 equiv), chiral additive (1.1 equiv), allyl iodide (1.65 equiv)). When applying these same amounts to our system, the ee and yield of **2a** was the same as before (79% and 85%, respectively).[12]

To test the potential of the other cinchona alkaloids, allylation of **1a** was also performed with bases **4b**–**4d**, of which **4b** gave approximately the same high ee (78%) as **4a**, but the opposite enantiomer of **2a**. However, both **4c** and **4d** gave lower ees of **2a**, 55% and 50%, respectively. Furthermore, since it is unknown how indium and the allyl groups are coordinated to the cinchona alkaloids in the chiral complex, we found it interesting to elucidate the significance of the presence of the free hydroxyl group positioned at C9 in structures **4a**–**4d**. Thus, this position was acetylated[13] and the derivatives tested in the allylation reaction. Interestingly, all of them yielded racemic **2a**, showing the importance of the free 9-OH.

We also sought to address the importance of functionalization of the 3-position of compound **1a**. Thus, the asymmetric allylation was extended to include other 3,3-disubstituted derivatives of cyclohexanone; compound **1b**[14] bearing a dithiolane group, and compound **1c** having two methyl substituents at the 3-position. To investigate the effect of the bulkiness of the allylic reagent, we also included 3-iodo-2-methyl-propene **5b**[15] (Table 1). In these attempts, **4a** was used as a chiral additive since the complex formed faster with **4a** (2 h) than with **4b** (3 h). In the case of ketones **1b** and **1c**, the reactions were too slow at −78 °C and were therefore performed at −40 °C. The ees and yields obtained from the allylation of **1a** was superior, compared to both compounds **1b** and **1c**. Additionally, the bulkier allylic reagent **5b** resulted in products of both lower ees and yields in most cases.

Homoallylic alcohols (−)-**2a** and (+)-**2a** were then used for the synthesis of (−)-*endo*-**3** and (+)-*endo*-**3**, respectively (Scheme 2), which essentially followed the previously reported 'racemic' route.[3] The last step in the sequence consists of an aldol condensation, which, except for the *endo*-isomer, also provides the *exo*-isomer of **3** in a ratio of 85:15, respectively. Accordingly, (−)-**2a** led to the formation of (−)-*endo*-**3** and (+)-*exo*-**3** in 79% ee (for both) and (+)-**2a** gave (+)-*endo*-**3** and (−)-*exo*-**3** in 78% ee (for both). After a single recrystallization from petroleum ether, the ee of both (−)-*endo*-**3** and (+)-*endo*-**3** could be raised to >98%. Unfortunately, we were unable to find a suitable solvent system for the recrystallization of the *exo*-enantiomers.

Table 1. Results from the asymmetric allylation of ketones **1a**–**1c**

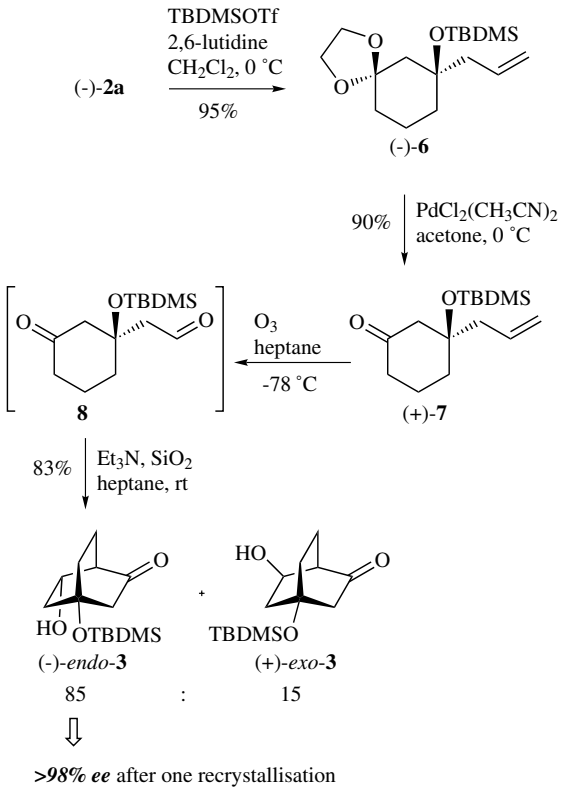


1a R^1,R^2 = -OCH_2CH_2O-
1b R^1,R^2 = -SCH_2CH_2S-
1c R^1,R^2 = Me

2a R^1,R^2 = -OCH_2CH_2O-, R^3 = H
2b R^1,R^2 = -OCH_2CH_2O-, R^3 = Me
2c R^1,R^2 = -SCH_2CH_2S-, R^3 = H
2d R^1,R^2 = -SCH_2CH_2S-, R^3 = Me
2e R^1,R^2 = Me, R^3 = H
2f R^1,R^2,R^3 = Me

Entry	Ketone	Allylic reagent	Product	*T* (°C)	ee (%)	Yield (%)[d]
1	**1a**	**5a**	**2a**	−78	79[b]	87
2[a]	**1a**	**5a**	**2a**	−78	78[b]	85
3	**1a**	**5b**	**2b**	−40	71[b]	58
4	**1b**	**5a**	**2c**	−40	54[c]	64
5	**1b**	**5b**	**2d**	−40	23[c]	30
6	**1c**	**5a**	**2e**	−40	37[b]	40
7	**1c**	**5b**	**2f**	−40	38[b]	31

[a] Compound **4b** was used as chiral promoter.
[b] Determined by GC.
[c] Determined by HPLC.
[d] Isolated yields.



Scheme 2. Synthesis of (−)-*endo*-**3** and (+)-*exo*-**3**. (+)-*endo*-**3** and (−)-*exo*-**3** were obtained from (+)-**2** according to the same procedure (see Ref. 3).

The possibility of producing larger amounts of optically active *endo*-**3** (and *exo*-**3**) in one reaction sequence was examined by performing the asymmetric indium allylation on 3 mmol scale (of **1a**). At this scale, successful complex formation required **4a** to be added in small portions over an extended period of time after the addition of allyl iodide. The ee of (−)-**2a** dropped to 68%, but to our satisfaction the yield was as high as before (85%), and the ee could still be raised to >98% by a single recrystallization from petroleum ether. In order to assign the absolute configuration of compounds **3** and their precursors (compounds **2a**, **6**, and **7**), the CD spectra of (−)-*endo*-**3** and (+)-*endo*-**3** were recorded and analyzed by applying the octant rule for the carbonyl chromophore.[16]

3. Conclusion

Reproducible conditions were developed for the asymmetric indium-mediated allylation, including **4a** or **4b** as chiral promoters, by exchanging allylic bromide for allylic iodide, and by adding 4 Å MS to the reaction mixture. Under these conditions, tertiary homoallylic alcohols **2a**–**2f** were obtained in moderate to good ees and yields. Furthermore, bicyclic hydroxyketones (−)-*endo*-**3**/(+)-*exo*-**3** (79% ee) and (+)-*endo*-**3**/(−)-*exo*-**3** (78% ee) were obtained in four steps, starting from (−)-**2** and (+)-**2**, respectively. The enantiomeric excess of the *endo*-enantiomers of **3** was further increased to >98% through a simple recrystallization from petroleum ether.

4. Experimental

4.1. General

Materials were obtained from commercial suppliers and used without further purification unless otherwise stated. Indium powder of quality: −100 mesh, 99.99%, was used. THF was dried by passing it through an argon pressurized column containing activated, neutral aluminum oxide and was stored over activated 4 Å MS under an atmosphere of argon. All moisture- and air-sensitive reactions were carried out under an atmosphere of dry argon using oven-dried glassware. Optical purities were analyzed by GC on a β-DEX 120 column (30 m, 0.25 mm i.d., 0.25 μm stationary phase) or by HPLC on an OD-H column (250 × 4.6 i.d., 5 μm). Optical rotations were measured at 22 °C and are given in 10^{-1} deg cm^2 g^{-1}. CD-spectroscopic analyses were measured at 22 °C. The NMR spectra were recorded at 400 MHz (^{1}H) and at 100 MHz (^{13}C) using benzene-d_6 (C_6H_6 δ 7.16 (^{1}H) and 128.0 (^{13}C)) as a solvent. The melting points were not corrected. Chromatographic separations were performed on normal phase silica gel 60 (0.035–0.070 mm). Thin-layer chromatography was performed on precoated TLC glass plates with silica gel 60 F_{254}, 0.25 mm. After elution, the TLC plates were sprayed with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL) and the compounds were visualized upon heating.

4.2. Representative procedure for asymmetric allylation of ketones 1a–1c

Allyl iodide **5a** or 3-iodo-2-methyl-propene **5b** (1.65 equiv) was added to a mixture of 4 Å MS (100 mg/1.5 mL THF), indium powder (1.1 equiv), and (−)-cinchonidine (1.1 equiv) in THF (1.5 mL/30 mg In) at room temperature under vigorous stirring. After approximately 5 min, a slightly yellow, clear solution resulted, and after two additional hours, the indium powder was consumed. The reaction mixture was cooled to −78 °C **1a** or −40 °C **1b** and **1c**. The ketone was then added dropwise, and stirring was continued for 12 h at the given temperature, whereafter the reaction was quenched by adding 0.1 M HCl aqueous solution. The water phase was extracted with EtOAc three times, the collected organic phases were washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The resulting homoallylic alcohols were purified by column chromatography.

4.3. (−)-(7*R*)-7-Allyl-1,4-dioxaspiro[4.5]decane-7-ol (−)-2a

Compound (−)-**2a** was obtained as a colorless oil in 87% yield and 79% ee. $R_f = 0.16$ (SiO_2, heptane–EtOAc 85:15). $[\alpha]_D^{22} = -19.7$ (*c* 1.69, EtOH); IR (NaCl) 3526, 3074, 2885, 1639 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 6.12 (ddt, $J = 17.1$, 10.1, 7.3 Hz, 1H), 5.11–5.03 (m, 2H), 3.99 (s, 1H), 3.40–3.27 (m, 4H), 2.32 (br dd_{AB}, $J = 7.0$ Hz, $J_{AB} = 13.7$ Hz, 1H), 2.21 (br dd_{AB}, $J = 7.5$ Hz, $J_{AB} = 13.0$ Hz, 1H), 1.89 (tq, $J = 3.7$,

13.5 Hz, 1H), 1.76 (td_{AB}, $J = 2.5$ Hz, $J_{AB} = 13.7$ Hz, 1H), 1.65–1.60 (m, 2H), 1.50 (d_{AB}, $J_{AB} = 13.7$ Hz, 1H), 1.47–1.42 (m, 1H), 1.33 (dt, $J = 4.4$, 13.2 Hz, 1H), 1.04 (dt, $J = 4.2$, 13.3 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 135.0, 117.3, 109.9, 72.2, 64.3, 63.9, 48.0, 43.9, 36.7, 35.0, 19.3. HRMS (FAB+): calcd for $C_{11}H_{19}O_3$ (M+H): 199.1334. Found: 199.1337. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.51; H, 9.23. GC (β-DEX 120, 140 °C isothermal) $t_{min} = 30.2$ min [(+)-enantiomer], $t_{maj} = 31.1$ min [(−)-enantiomer].

4.4. (+)-(7*S*)-7-Allyl-1,4-dioxaspiro[4.5]decane-7-ol (+)-2a

Compound (+)-**2a** was obtained as a colorless oil in 85% yield and 78% ee. $[\alpha]_D^{22} = +19.8$ (*c* 1.66, EtOH). GC (β-DEX 120, 140 °C isothermal) $t_{maj} = 30.2$ min ((+)-enantiomer), $t_{min} = 31.1$ min [(−)-enantiomer]. For other structural and analytical data, see compound (−)-**2a**.

4.5. (−)-7-(2-Methyl-allyl)-1,4-dioxaspiro[4.5]decane-7-ol 2b

Compound **2b** was obtained as a colorless oil in 58% yield and 71% ee. $R_f = 0.16$ (SiO_2, heptane–EtOAc 9:1). $[\alpha]_D^{22} = -13.9$ (*c* 0.90, $CHCl_3$); IR (NaCl) 3524, 2947, 2887 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 4.99–4.98 (m, 1H), 4.80–4.79 (m, 1H), 3.99 (s, 1H), 3.39–3.34 (m, 2H), 3.28–3.25 (m, 2H), 2.29 (d_{AB}, $J_{AB} = 13.2$ Hz, 1H), 2.16 (d_{AB}, $J_{AB} = 13.2$ Hz, 1H), 2.04 (s, 3H), 1.91–1.82 (m, 2H), 1.75–1.71 (m, 1H), 1.65–1.61 (m, 1H), 1.51–1.43 (m, 2H), 1.36 (dt, $J = 4.4$, 13.2 Hz, 1H), 1.03 (dt, $J = 4.2$, 13.4 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 143.4, 114.3, 110.0, 72.8, 64.3, 63.8, 51.2, 44.2, 37.3, 35.1, 25.0, 19.3. HRMS (FAB+): calcd for $C_{12}H_{19}O_3$ (M−H): 211.1334. Found: 211.1318. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.97; H, 9.43. GC (β-DEX 120, 140 °C isothermal) $t_{min} = 39.6$ min [(+)-enantiomer], $t_{maj} = 40.9$ min [(−)-enantiomer]. The absolute configuration was not determined.

4.6. (−)-7-Allyl-1,4-dithiaspiro[4.5]decane-7-ol 2c

Compound **2c** was obtained as a colorless oil in 64% yield and 54% ee. $R_f = 0.25$ (SiO_2, heptane–EtOAc 85:15). $[\alpha]_D^{22} = -10.8$ (*c* 1.30, $CHCl_3$); IR (NaCl) 3456, 2932, 2860 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 5.91–5.80 (m, 1H), 5.04–4.95 (m, 2H), 2.77–2.69 (m, 4H), 2.47 (s, 1H), 2.18 (td_{AB}, $J = 2.4$ Hz, $J_{AB} = 14.4$ Hz, 1H), 2.16–2.12 (m, 1H), 2.05–1.99 (m, 3H), 1.90 (d_{AB}, $J_{AB} = 14.4$ Hz, 1H), 1.69 (dt, $J = 3.5$, 13.0 Hz, 1H), 1.55–1.50 (m, 1H), 1.43–1.39 (m, 1H), 0.96 (dt, $J = 4.0$, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 134.1, 118.2, 71.9, 66.7, 50.9, 48.7, 43.0, 39.1, 37.4, 36.3, 21.8. HRMS (FAB+): calcd for $C_{11}H_{18}OS_2$ (M): 230.0799. Found: 230.0795. Anal. Calcd for $C_{11}H_{18}OS_2$: C, 57.35; H, 7.87. Found: C, 57.41; H, 7.81. HPLC (95:5 hexane–2-propanol, 0.5 mL/min, 254 nm) $t_{maj} = 20.6$ min [(−)-enantiomer], $t_{min} = 28.0$ min [(+)-enantiomer]. The absolute configuration was not determined.

4.7. (−)-7-(2-Methyl-allyl)-1,4-dithiaspiro[4.5]decane-7-ol 2d

Compound **2d** was obtained as a colorless oil in 30% yield and 23% ee. $R_f = 0.09$ (SiO_2, heptane–EtOAc 95:5). $[\alpha]_D^{22} = -2.7$ (*c* 1.08, $CHCl_3$); IR (NaCl) 3462, 2934, 2860 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 4.89–4.88 (m, 1H), 4.72–4.71 (m, 1H), 2.76–2.69 (m, 4H), 2.52 (s, 1H), 2.24 (td_{AB}, $J = 2.4$ Hz, $J_{AB} = 14.3$ Hz, 1H), 2.20–2.14 (m, 1H), 2.08–1.94 (m, 3H), 1.90 (d_{AB}, $J_{AB} = 14.3$ Hz, 1H), 1.83 (s, 3H), 1.70 (dt, $J = 3.6$, 13.1 Hz, 1H), 1.59–1.56 (m, 1H), 1.44–1.39 (m, 1H), 0.93 (dt, $J = 4.0$, 13.4 Hz, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.6, 114.8, 72.3, 66.7, 51.9, 51.3, 43.0, 39.1, 37.3, 36.7, 25.2, 21.8. HRMS (FAB+): calcd for $C_{12}H_{20}OS_2$ (M): 244.0956. Found: 244.0953. Anal. Calcd for $C_{12}H_{20}OS_2$: C, 58.97; H, 8.25. Found: C, 58.85; H, 8.18. HPLC (95:5 hexane–2-propanol, 0.5 mL/min, 254 nm) $t_{maj} = 17.3$ min [(−)-enantiomer], $t_{min} = 20.9$ min [(+)-enantiomer]. The absolute configuration was not determined.

4.8. (−)-1-Allyl-3,3-dimethyl-cyclohexanol 2e

Compound **2e** was obtained as a colorless oil in 40% yield and 37% ee. $R_f = 0.16$ (SiO_2, heptane–EtOAc 95:5). $[\alpha]_D^{22} = -0.3$ (*c* 1.13, $CHCl_3$); IR (NaCl) 3462, 2934, 2866 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 5.81–5.71 (m, 1H), 5.05–4.96 (m, 2H), 1.97–1.94 (m, 2H), 1.89–1.80 (m, 1H), 1.46–1.32 (m, 3H), 1.30–1.25 (m, 1H), 1.20 (s, 3H), 1.04–0.97 (m, 3H), 0.87 (s, 3H), 0.69 (s, 1H); ^{13}C NMR (100 MHz, benzene-d_6) δ 134.3, 118.4, 71.4, 50.1, 49.1, 39.7, 37.5, 34.3, 30.9, 27.3, 18.9. HRMS (FAB+): calcd for $C_{13}H_{25}OSi$ (M+$SiMe_2$): 225.1675. Found: 225.1673. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.38; H, 12.08. GC (β-DEX 120, 140 °C isothermal) $t_{maj} = 7.1$ min [(−)-enantiomer], $t_{min} = 7.4$ min [(+)-enantiomer]. The absolute configuration was not determined.

4.9. (+)-3,3-Dimethyl-1-(2-methyl-allyl)-cyclohexanol 2f

Compound **2f** was obtained as a colorless oil in 31% yield and 38% ee. $R_f = 0.04$ (SiO_2, heptane–EtOAc 98:2). $[\alpha]_D^{22} = +1.4$ (*c* 1.32, $CHCl_3$); IR (NaCl) 3555, 3489, 2947 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6) δ 4.88–4.87 (m, 1H), 1.72 (br s, 1H), 1.94 (q, $J = 12.7$ Hz, 2H), 1.89–1.80 (m, 1H), 1.73 (s, 3H), 1.50–1.41 (m, 1H), 1.39–1.32 (m, 3H), 1.22 (s, 3H), 1.04–0.97 (m, 3H), 0.90 (s, 1H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, benzene-d_6) δ 142.8, 114.8, 71.6, 53.1, 49.8, 39.6, 38.0, 34.6, 30.9, 27.1, 25.4, 19.0. HRMS (FAB+): calcd for $C_{14}H_{27}OSi$ (M+$SiMe_2$): 239.1831. Found: 239.1841. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.88; H, 12.19. GC (β-DEX 120, 140 °C isothermal) $t_{maj} = 8.9$ min [(+)-enantiomer], $t_{min} = 9.1$ min [(−)-enantiomer]. The absolute configuration was not determined.

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