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Selective ruthenium-catalyzed epimerization of chiral *sec*-alcohols

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ABSTRACT

Extension of secondary alcohol racemization catalyzed by homogeneous half-sandwich ruthenium complexes to the epimerization of natural products containing additional non-functionalized stereocenters has been investigated. Ruthenium-catalysed epimerization of the *sec*-alcohols (−)-menthol, (−)-isopulegol, (+)-borneol, (+)-fenchol and cholesterol under mild reaction conditions and low catalyst loadings (2 mol%) provides rapid access to their less abundant diastereoisomers (+)-neomenthol, (+)-neoisopulegol, isoborneol, beta-fenchol and epicholesterol in admixture with the parent diastereomers in ratios ranging from 1:4.9 to 1:2.4 (epimer:parent).

1. Introduction

Configurational interconversion of secondary carbinol based stereogenic centers takes place in the presence of some transition metal catalysts, for example homogeneous half-sandwich ruthenium complexes [1–6]. Such processes have particular relevance for dynamic kinetic resolution (DKR) of *sec*-alcohols, where often a homogeneous ruthenium catalyst used for *in situ* alcohol racemization in the presence of a resolving enzyme, such as CAL-B, enables the shift from conventional kinetic resolution to DKR providing, in optimal cases, chiral products in up to 100% yields and enantiomeric excesses [7–11]. Thus, with highly active racemization catalysts under optimized reaction conditions, short reaction times together with excellent selectivities and yields can be reached. In such processes, utilizing homogeneous half-sandwich ruthenium catalysts, the racemization of *sec*-alcohol stereocenters has been shown to involve an oxidation-reduction (dehydrogenation-hydrogenation) sequence, where hydrogen transfer from ruthenium to a coordinated ketone, initially formed by β-hydride elimination of the *sec*-alcohol derived ruthenium alkoxide, takes place with equal probabilities from both enantiofaces of the C=O bond resulting in efficient configurational interconversion [12–14].

In the present work, we have investigated the potential extension of *sec*-alcohol racemization catalyzed by homogeneous half-sandwich ruthenium complexes to the epimerization of *sec*-carbinol natural products containing additional non-functionalized stereocenters (Scheme 1). In such cases, only the hydroxyl containing stereocenter is expected to interconvert in the presence of the ruthenium catalyst, making the epimerization processes essentially analogous to racemization.

Related epimerization reactions have been reported for some saccharides catalyzed by homogeneous half-sandwich ruthenium complexes [15], for terpenoids by homogeneous and heterogeneous catalyst systems [16,17], and for steroid type structures by homogeneous half-sandwich rhenium catalyst [17].

In both resolution processes and chemical or enzymatic synthesis, undesired stereoisomers are frequently formed as byproducts, requiring separation and/or recycling. The development of new benign, selective and efficient epimerization processes is, therefore, valuable in improving the overall efficiencies of synthetic strategies [17]. Further, such processes may also have industrial significance as demonstrated here by the homogeneously catalyzed epimerization of menthol, which at least in theory could be applied for epimerization of the undesired stereoisomer in the synthetic production of (−)-menthol [16]. Moreover, in principle, such inversions of single stereocenters in chiral compounds containing multiple stereogenic centers could potentially be utilized for conversion of inexpensive starting materials into diastereomeric mixtures from which more valuable compounds could be isolated by conventional separation techniques, provided that the resulting equilibrium mixture contains sufficient amounts of the desired, rare stereoisomer. Ideally, such processes could be envisioned to become dynamic (similar to DKRs) in the presence of a suitable enzyme catalyst. In theory, catalytic epimerization processes could even be applied in multistep total syntheses of complex natural products, where other efficient methods for obtaining the desired

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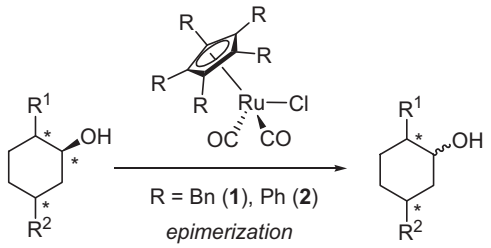


Scheme 1. Proposed epimerization of *sec*-alcohol natural products with half-sandwich ruthenium catalysts **1** and **2**.

configuration of a *sec*-alcohol based stereocenter prove inapplicable.

2. Materials and methods

All glassware was oven dried and cooled in desiccator over phosphorous pentoxide prior to use. All starting materials and solvents, except cholesterol, were purified by removal of possible water traces originating from storage at ambient conditions. Potassium *tert*-butoxide (*t*-BuOK) was sublimated in vacuum prior to use. Tetrahydrofuran (THF) was distilled directly from sodium/benzophenone ketyl under argon. The chiral alcohols (−)-menthol [(*R*)-**3**] (>99%, Fluka AG, Buchs, Switzerland), (−)-isopulegol [(*R*)-**4**] (>99%, SAFC Supply Solutions, St. Louis, USA), (+)-borneol [(*S*)-**5**] (>98%, Naarden International), (+)-fenchol [(*R*)-**6**] (>95%, Fluka AG, Buchs, Switzerland) and cholesterol [(*S*)-**7**] (99%, SigmaChemicals, St. Louis, MO, USA) were all obtained from commercial sources. Of the starting materials, (−)-menthol was recrystallized from chloroform and (+)-borneol was predried over 4 Å molecular sieves in stock solution (THF) for >24 h prior to use, (−)-isopulegol was redistilled under dry conditions (Ar atmosphere) and stored in a glovebox. Epimerization catalysts **1** and **2** were prepared as described in the literature with spectroscopic data identical to those reported previously [6,11].

In a typical epimerization experiment, 20 μmol of the corresponding catalyst was dissolved in THF (2 mL) and transferred to a Schlenk tube. A magnetic stirring bar and 0.25 M solution of *t*-BuOK in THF (100 μL, 25 μmol) were added. Activation time for the catalyst was 20 min, during which the tube was closed with a stopper and removed from the glovebox. Next, 2 mL of a 0.50 M stock solution of the starting material (1 mmol) was added to the Schlenk tube. The reaction mixture was stirred at 23 °C and samples were taken either through a rubber septa or counter gas flow using a degassed syringe and needle. The product distribution was monitored by GC, GC/MS and/or NMR spectroscopy. Samples of the reactions were filtered though a small pad of silica in order to quench the reaction after which the sample was diluted and directly analyzed. The GC apparatus used was Agilent Technologies 6850 GC equipped with a HP-1 column (30.0 m × 320 μm × 0.25 μm), H_2 as a carrier gas, and FID detector. The GC/MS apparatus used was Agilent Technologies 7890 A GC equipped with 5975C MS detector (EI), HP-5MS column (30 m × 250 μm × 0.25 μm) and He as a carrier gas. The NMR spectra of the compounds were recorded on a Bruker Avance 600 MHz NMR spectrometer equipped with a BBI-5 mm-Zgrad–ATM probe at 25 °C operating at 600.13 MHz for ^{1}H and 150.92 MHz for ^{13}C using TMS (0.00 ppm) or $CDCl_3$ (7.26 ppm) ^{1}H NMR signals as reference. Isolation of the products was performed by column chromatography using CH_2Cl_2-hexane mixture as the eluent. The isolated yields of reaction products (+)-neomenthol [(*S*)-**3**] and (+)-neoisopulegol [(*S*)-**4**] were 32 mg (20%) and 10 mg (6%), respectively.

3. Results and discussion

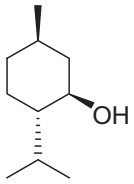
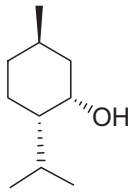
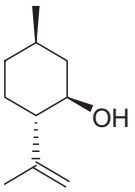
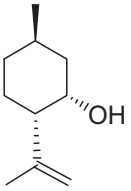
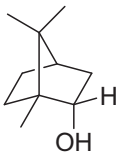
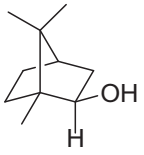
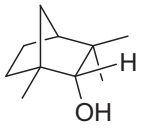
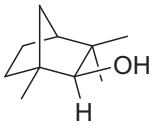
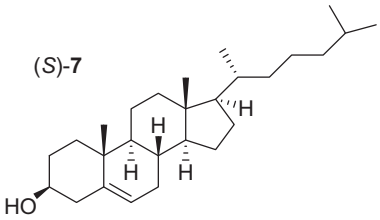
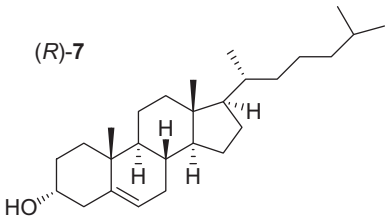
Production of pharmaceutically useful, otherwise desired or expensive stereoisomers of natural or non-natural products by simple-to-operate, cost effective and rapid catalytic methods is an appealing approach. In this work, two previously disclosed highly active homogeneous ruthenium catalysts, dicarbonylchloro(pentabenzylcyclopentadienyl)ruthenium (**1**) [11] and dicarbonylchloro(pentaphenylcyclopentadienyl)ruthenium (**2**) [6], were used for epimerization of (−)-menthol [(*R*)-**3**] and (−)-isopulegol [(*R*)-**4**]. Further, three other structurally different natural products, (+)-borneol [(*S*)-**5**], (+)-fenchol [(*R*)-**6**] and cholesterol [(*S*)-**7**] were epimerized using catalyst **1**. The results of the epimerization reactions are collected in Table 1. For the sake of clarity, the stereochemical descriptors used here for the chiral alcohols refer to the hydroxyl group containing stereocenters only, expected to undergo epimerization in the presence of the ruthenium catalysts, with the descriptors for the configurationally stable stereocenters being omitted. All starting materials employed in this work are biologically active or otherwise useful for various commercial applications. For example, the global demand for menthol, obtained both by synthetic processes and isolation from natural sources, and used in e.g., toothpaste, dietary products and cough drops, exceeds 20,000 metric tons per year [18]. Nevertheless, also the non-natural or naturally occurring rare stereoisomers exhibit in some cases useful and desirable properties with potential applications [19–21]. In addition, various terpenoid-type compounds have been shown to possess interesting biological activities, including anti-inflammatory, antitumor, induced apoptosis and other potential applications in cancer treatment [22–25]. The production or isolation of the rare stereoisomers is, however, seldom trivial due to their low abundance, difficult isolation or complex and expensive synthetic processes.

The configurational inversion of the C*(H)(OH) stereocenter in the readily available natural products (*R*)-**3** and (*R*)-**4** under mild reaction conditions and low catalyst loadings (2 mol%) would ideally provide rapid catalytic access to the rare diastereomeric terpenoids (*S*)-**3** and (*S*)-**4**. In the initial epimerization experiments with (*R*)-**3** and (*R*)-**4** using the pentabenzyl(cyclopentadienyl)ruthenium complex as the catalyst, diastereomeric mixtures of (*R*)-**3**/(*S*)-**3** and (*R*)-**4**/(*S*)-**4** were indeed obtained in 3:1 and 6:1 ratios, respectively, within a few hours. The first experiments were carried out under strictly anhydrous atmosphere in a glove box at ambient temperature, ensuring inert (water and oxygen free) reaction conditions. In these reactions, the diastereomeric ratio reached remained unchanged for 18 h. For demonstration of the proof-of-concept, the more expensive, minor diastereomers were then separated and purified by conventional column chromatography in 40–80% yields, based on their concentrations in the reaction mixtures (for details, see Section 2).

In a closer comparison of the catalysts **1** and **2** for epimerization, the latter was found to be less efficient, providing with both starting materials (*R*)-**3** and (*R*)-**4** diastereomeric mixtures of (*R*)-**3**/(*S*)-**3** and (*R*)-**4**/(*S*)-**4** in 89/11 and 93/7 ratios, respectively, after 23 h (Table 1, entries 2 and 4). Furthermore, the longer reaction times with catalyst **2** for starting materials (*R*)-**3** and (*R*)-**4** resulted in cloudy reaction mixtures, likely due to the poor overall solubility of catalyst **2** in common organic solvents as compared to **1**. Thus, for further experiments, catalyst **1** was selected, providing in all cases fast and selective epimerizations. Epimerization of (−)-menthol in the presence of **1** as a function of time is displayed in Fig. 1, demonstrating the equilibrium mixture obtained, evident from analysis of the shapes of the reaction concentration profiles after prolonged reaction time.

For broadening of the substrate scope, other readily available secondary alcohols (+)-borneol [(*S*)-**5**], (+)-fenchol [(*R*)-**6**] and

Table 1
Epimerization reactions of the naturally occurring chiral alcohols **3**–**7** in the presence of ruthenium catalyst **1** or **2** (2 mol%) and *t*-BuOK (2.5 mol%) in THF at 23 °C.

Entry	Catalyst	Starting material	Epimer	Diastereomer ratio
1	**1**	(*R*)-**3** 	(*S*)-**3** 	(*R*)-**3**/(*S*)-**3** 75/25[a]
2	**2**			(*R*)-**3**/(*S*)-**3** 89/11[a]
3	**1**	(*R*)-**4** 	(*S*)-**4** 	(*R*)-**4**/(*S*)-**4** 84/16[a]
4	**2**			(*R*)-**4**/(*S*)-**4** 93/7[a]
5	**1**	(*S*)-**5** 	(*R*)-**5** 	(*S*)-**5**/(*R*)-**5** 71/29[b]
6	**1**	(*R*)-**6** 	(*S*)-**6** 	(*R*)-**6**/(*S*)-**6** 82/18[b]
7	**1**	(*S*)-**7** 	(*R*)-**7** 	(*S*)-**7**/(*R*)-**7**[c] 78/22[b]

[a] Reaction time 23 h.
[b] Reaction time 21 h.
[c] Catalyst loading 7 mol%.

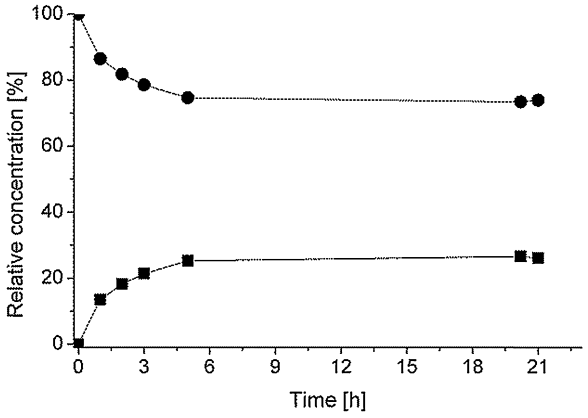


Fig. 1. Epimerization of (−)-menthol (●) producing (+)-neomenthol (■) with **1** (2 mol%) at 23 °C.

cholesterol [(*S*)-**7**] from the chiral pool were investigated using **1** as the epimerization catalyst. In all cases, stable concentration profiles similar to those shown in Fig. 1 were observed after few hours of reaction, although all reactions were continued for 23 h in order to ensure that true equilibrium values were reached. Here, for menthol and isopulegol 75/25 and 84/16 epimer ratios for (*R*)-**3**/(*S*)-**3** and (*R*)-**4**/(*R*)-**4**, respectively, were observed after 23 h (Table 1, entries 1 and 3). For borneol and fenchol, 71/29 and 82/18 ratios of (*S*)-**5**/(*R*)-**5** and (*R*)-**6**/(*S*)-**6**, respectively, were obtained (Table 1, entries 5 and 6). Finally, for cholesterol the epimerization with **1** provided, after 21 h, a 78/22 ratio of cholesterol (*S*)-**7** and epicholesterol (*R*)-**7** (Table 1, entry 7). In this case, slightly higher catalyst loading (7 mol%) was employed due to the smaller amount of starting material applied in the reaction.

Turnover frequency values (*TOF* = [mol of converted alcohol] [mol of Ru]$^{-1}$ [s]$^{-1}$) were then calculated for the reproduced reactions performed using catalyst **1** at 23 °C. As expected, (−)-menthol exhibited the highest TOF value, 0.003 s^{-1} (60 min sample). Both (+)-borneol and (−)-isopulegol (60 min samples) exhibited lower TOF values, 0.0015 s^{-1} and 0.00029 s^{-1},

respectively. The evidently lower TOF value for (−)-isopulegol could possibly be a consequence of the double bond present in the starting material. Conclusively, the equilibria for the epimerization reactions were reached within a reasonable reaction time, after approximately 5 h, being sufficiently fast and resulting in a viable process at low catalyst loading.

Heterogeneously catalyzed epimerizations of terpenoids have been studied earlier [16,26]. A drawback with the heterogeneous catalyst systems is, however, the formation of oxidized menthone intermediate, resulting in isomenthol which lowers the selectivity of the epimerization process. In the present work employing homogeneous Ru-based epimerization catalysts, byproducts, including isomenthol diastereoisomers potentially originating from keto-enol tautomerization of menthone, were not observed within the limits of GC detection. Moreover, for (−)-menthol, the utilization of an oxidation-reduction sequence forming (+)-neomenthol, (+)-isomenthol and (+)-neoisomenthol diastereomers has been reported earlier [27]. In addition, oxidation combined with selective reduction has been demonstrated for camphor [28,29]. An obvious advantage with the selective catalytic epimerization with homogeneous catalysts, such as **1**, is the one step reaction without the need for isolation of reaction intermediates, combined with fully selective epimerization reaction without detectable formation of side products.

Here, it can be emphasized that epimerizations of diastereoisomers are unlikely to produce equal amounts of the two stereoisomers, in contrast to what would be the case with two enantiomers using achiral catalysts. The thermodynamic equilibrium for epimerization reactions will be shifted toward the thermodynamically more stable diastereoisomer, which, in turn, is depending on the molecular structure and its interactions with the surrounding reaction media and the catalyst. In all five cases studied here, the predominantly formed diastereoisomer is the same as the more abundant one found in Nature. The inspiring and impressive ability of Nature to synthesize single stereoisomers in high selectivity is well documented, exemplified by the biosynthesis of menthol [30]. Interestingly, formation of the chemically least stable chiral center, containing the hydroxyl group, is the last step in menthol biosynthesis. Moreover, two different enzymes are involved in reduction of the menthone precursor yielding both (−)-menthol (in large excess) and (+)-neomenthol, respectively [30,31]. Furthermore, Nature has the ability to perform an additional separation of the two diastereoisomers formed by using specific transferase enzymes [31].

Finally, some epimerization experiments at slightly elevated temperature (50 °C) were performed using (*R*)-**3** as the starting material. The equilibrium concentrations at 50 °C [2.9:1, (*R*)-3:(*S*)-3] were, however, within experimental error similar to those obtained at 23 °C [3.0:1, (*R*)-3:(*S*)-3]. While the thermodynamic equilibrium constants would be expected to shift by changes in the reaction temperature, the increase here was incremental only and considerably higher temperatures, possibly in a pressurized reactor, would be required for further studying the influence of reaction conditions.

Equilibrium constants ($E_{neo\text{-}m}$) for (−)-menthol epimerization reactions carried out at different temperatures are presented in Table 2. The agreement of the $E_{neo\text{-}m}$ calculated for the (*R*)-**3**/(*S*)-**3** equilibrium (Table 2, entry 1 and 2) is satisfactory when compared with the literature values (Table 2, entry 3–5) from the related work by Etzold and co-workers [16]. Nevertheless, for complete characterization of the kinetic and thermodynamic aspects of the epimerization reactions further experiments would be needed.

Additionally, in earlier studies the mole fractions for (*R*)-**3**/(*S*)-**3** and (*S*)-**5**/(*R*)-**5** at equilibrium have been determined as 85.5/14.5 and 90.5/9.5, respectively [32]. These values were, however, measured for compounds in the gas phase at 500 K and are thus not directly comparable with the values obtained in present work.

Table 2
Equilibrium constants for the epimerization of (−)-menthol to (+)-neomenthol.

Entry	*T* [K]	$E_{neo\text{-}m}$
1	296	3.0
2	323	2.9
3	423	2.3[a]
4	448	2.0[a]
5	473	1.9[a]

[a] Ref. [16].

Notably, at least in principle, the epimerization processes studied here could also be converted into dynamic methods by combining the epimerization catalyst with a suitable (e.g., acylating) enzyme, in which case the reaction could possibly be shifted toward the selective formation and isolation of the energetically less stable diastereomer or its derivative. Alternatively, in a static fashion, the desired minor product can be separated and isolated from the initially formed equilibrium mixture, as demonstrated in the present work and the remaining major component re-epimerized by addition of a new batch of the ruthenium catalyst.

4. Summary and conclusions

The objective of this work was the selective epimerization of readily available chiral secondary alcohols from the chiral pool, (−)-menthol, (−)-isopulegol, (+)-borneol, (+)-fenchol and cholesterol into more valuable diastereomers by a simple to operate, rapid and cost efficient catalytic method. For such compounds, containing a single *sec*-carbinol stereocenter together with other non-functionalized stereogenic centers, the epimerization reactions closely resemble the catalytic racemizations of *sec*-alcohols employed in chemoenzymatic dynamic kinetic resolutions. The results obtained here using dicarbonylchloro(pentabenzylcyclopentadienyl)ruthenium as the epimerization catalyst demonstrate that for these naturally occurring chiral alcohols equilibrium mixtures of two diastereomers are rapidly formed at low catalyst loadings at ambient temperature. In two cases, with (−)-menthol and (−)-isopulegol, feasibility of isolation of the corresponding rare diastereoisomers (+)-neomenthol and (+)-neoisopulegol from the equilibrium mixtures was also demonstrated. Further development of the methodology described herein may provide inexpensive and practical catalytic routes, after diastereomer separation and purification or as a dynamic method in combination with a suitable enzyme catalyst, for conversion of inexpensive chiral pool starting materials into more valuable ones.

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