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3-Alkyl-*p*-menthan-3-ol derivatives: synthesis and evaluation of their physiological cooling activity

Claudio Fuganti [a], Daniel Joulain [b], Francesco Maggioni [a], Luciana Malpezzi [c], Stefano Serra [a,*], Andrea Vecchione [c]

[a] *C.N.R. Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli 7, 20131 Milano, Italy*
[b] *Robertet S.A. 37 Avenue Sidi-Brahim, B.P. 52100, 06333 Grasse Cédex, France*
[c] *Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Via Mancinelli 7, 20131 Milano, Italy*

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ABSTRACT

Different 3-alkyl-*p*-methan-3-ol derivatives provide a strong physiological cooling effect with potential application as food and cosmetic additives. In order to investigate the influence of the chemical structure on the cooling sensation, the stereoselective syntheses of 29 different 3-alkyl-*p*-methan-3-ol derivatives were accomplished. All the compounds obtained are odorless and were evaluated by taste, considering two sensations: a cooling effect and bitterness. The results of this structure–activity relationship study highlight that compounds with a (1*R*,4*S*)-configuration are the isomers with the more intense cooling effect and lower bitterness. In addition, the structure of the 3-alkyl chain affected the latter properties. Increasing the chain length over two carbon atoms does not change the cooling power, but enhances the bitterness with the additional feature that the branched isomers are considerably more bitter than the linear ones. Overall, the 3-alkyl-*p*-menthan-3-ol isomers with the best quality in terms of high cooling power and low bitterness are (1*R*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol diastereoisomers (−)-**38** and (−)-**42**.

1. Introduction

A relevant topic in the flavor industry is the study of new substances that are able to impart a cooling or refreshing sensation to the skin or the mucous membranes. This physiological effect is not due to a change of temperature, but is caused by a specific interaction between the chemicals and the trigeminal nerve ending. Compounds showing these features have a wide range of applications, and have been employed as additives in a variety of products, such as foods, beverage, toothpaste, chewing gums, cosmetics, and tobacco. Historically, mint extracts and (−)-menthol **1** (Fig. 1) were the first cooling ingredients. The latter substances are still widely used since they have a definite refreshing effect, and are available at low cost both by extraction from plants or by chemical synthesis. In spite of this fact, the use of menthol holds some drawbacks, including high volatility, a strong mint odor, and a bitter and burning taste when used in high concentrations.

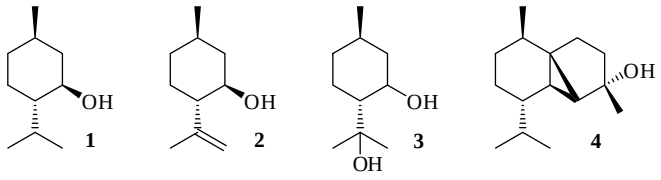

Figure 1. Examples of terpenes and sesquiterpene coolants with an oxygenated *p*-menthane framework.

Therefore, since the 1960s, many synthetic efforts have been focused toward the discovery of new substances with a powerful cooling effect, but without the above-mentioned drawbacks.[1–5] To this end, the following three main approaches have been investigated: the study of terpenes and sesquiterpenes with an oxygenated *p*-menthane framework; the use of menthol itself as a starting material for the preparation of new coolants with different chemical structures; and studies among compounds that are structurally unrelated to menthol. The first approach revealed that a number of terpene derivatives show the desired cooling effect, but few of them overcome the negative aspects of menthol. Some natural coolants are, for example, (−)-isopulegol **2**,[6] *p*-menthane-3,8-diol **3**[7] and the sesquiterpene (−)-cubebol **4**.[8] Otherwise, the second approach afforded a plethora of successful new derivatives, in which the hydroxyl group of menthol becomes part of an ester,[9–11] carbonate ester,[12] ketal[13] or ether[14,15] functionality (Fig. 2).

Moreover, the conversion of the C–O bond of menthol in a C–C bond gives an additional number of coolants of type **9**.[16,17] All of the aforementioned derivatives show a molecular weight much superior to menthol that decreases the volatility and increases the desired long-lasting cooling effect. The third approach

* Corresponding author. Tel.: +39 2 2399 3076; fax: +39 2 2399 3180.
E-mail address: stefano.serra@polimi.it (S. Serra).

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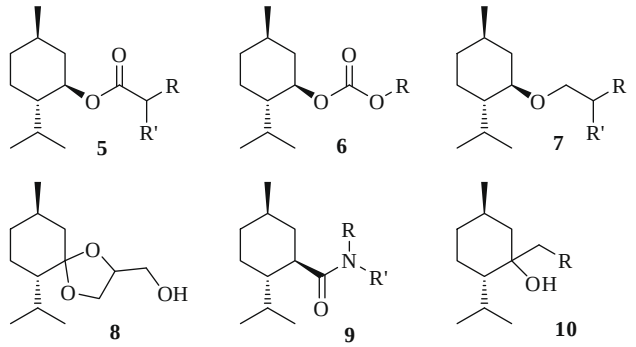


Figure 2. The best known classes of menthol derivatives used as cooling agents.

demonstrated that the presence of the *p*-menthane carbon skeleton is not mandatory for cooling properties.[18–22] Compounds **11**–**14** (Fig. 3) are artificial, non-menthol-based, products patented for the latter physiological effect, and lactone **14**[22] seems particularly effective.

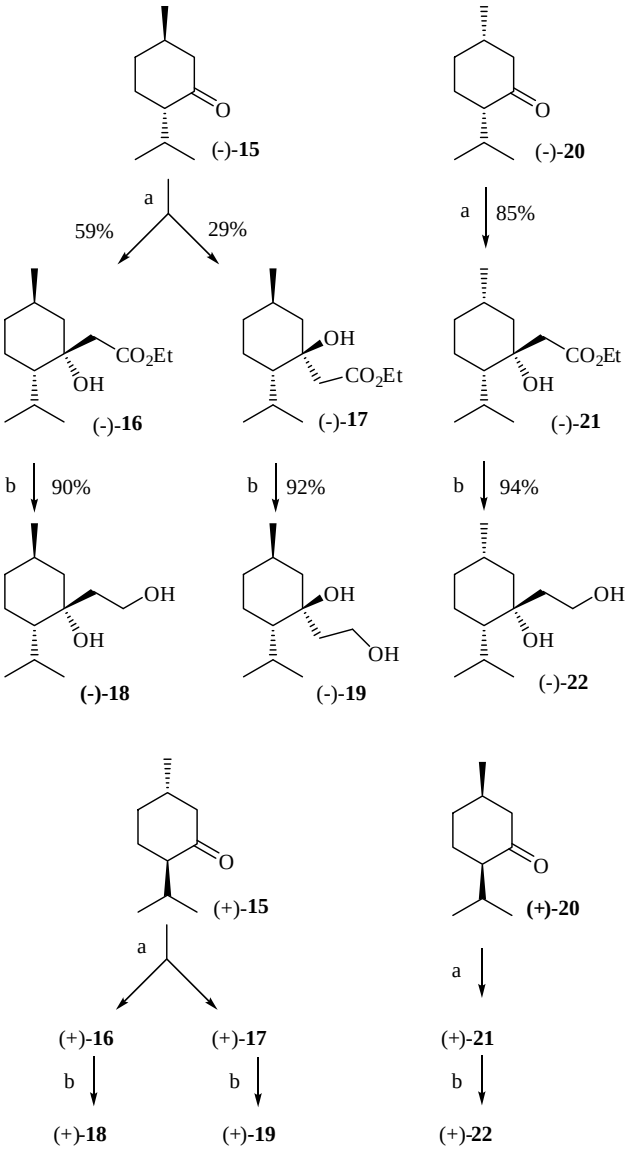
Overall, in spite of this abundance of cooling compounds, few of them are actually used industrially and with limits of concentration as **9** and **11**. The main limitations are due to the cost, the chemical stability and the volatility of the product. For instance, enantiopure (−)-isopulegol is odorless and tasteless but it shows high volatility, whereas **14** is easily hydrolyzed in aqueous conditions and gives side product with an unpleasant odor. Therefore, a successful coolant should be very stable, not volatile, without toxicity, and accessible from inexpensive starting materials.

During a program of enantioselective synthesis of *p*-menthane terpenes,[23–27] we envisaged that the 3-alkyl-*p*-methan-3-ol derivatives of type **10** could show all the latter features. Although the use of the latter class of substances as cooling agents has almost been neglected until now, our preliminary investigation provided successful results.[28] The preparation and use of one member of the aforementioned class of compounds, the 3-(2′-hydroxyethyl)-*p*-menthan-3-ol, were patented in 1976,[29] but the presence of a disagreeable bitter taste precluded its use. Otherwise, we found that a number of (1*R*,4*S*)-3-alkyl-*p*-methan-3-ol derivatives (including 3-(2′-hydroxyethyl)-*p*-menthan-3-ol) showed cooling effects without odor or taste. This discrepancy is due to the uncorrected evaluation of 3-(2′-hydroxyethyl)-*p*-menthan-3-ol obtained by the industrial process that consisted of a mixture of eight isomeric forms of the above-mentioned diol. Since regio- and enantiomeric composition greatly affected the properties of these compounds, their specific preparation is mandatory for a correct evaluation. Accordingly, we devised a stereospecific synthesis of the isomeric forms of 3-(2′-hydroxyethyl)-*p*-menthan-3-ol. Since a first evaluation demonstrated that only (1*R*,4*S*)-isomers possessed a suitable cooling activity with very low bitterness, we decided to exploit our synthetic pathway in order to prepare a number of new (1*R*,4*S*)-3-alkyl-*p*-methan-3-ol derivatives. Herein, we report a comprehensive study on the synthesis of the latter substances and on the evaluation of their cooling properties.

2. Results and discussion

2.1. Synthesis of the 3-(2′-hydroxyethyl)-*p*-menthan-3-ol isomers

As described in Section 1, the 3-(2′-hydroxyethyl)-*p*-menthan-3-ol was the first 3-alkyl-*p*-menthan-ol derivative that was used as a cooling agent.[29] This diol was obtained as a mixture of four or eight isomers depending on whether (−)-menthone or racemic menthone was employed, respectively. Both mixtures showed a



Scheme 1. Synthesis of 3-(2′-hydroxyethyl)-*p*-menthan-3-ol isomers from menthone isomers. Reagents and conditions: (a) Zn/$BrCH_2CO_2Et$/THF; (b) $LiAlH_4$/THF.

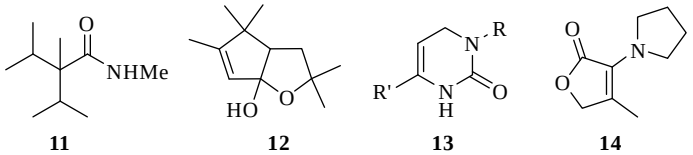


Figure 3. Representative cooling compounds structurally unrelated to menthol.

strong cooling effect associated with a disagreeable bitter taste. In order to investigate the influence of the stereochemistry on the bitterness and on the cooling properties of this type of diols, we devised a stereospecific synthesis of six of the eight isomeric forms of the 3-(2′-hydroxyethyl)-*p*-menthan-3-ol (Scheme 1). We selected the four isomeric forms of menthone as the starting materials, all available in high enantiomeric purity. More specifically, (−)-menthone is commercially available, whereas (+)-menthone and (+)-isomenthone were prepared by chromic oxidation[30] of (+)-menthol and (+)-isomenthol, respectively. Otherwise, (−)-isomenthone was obtained by catalytic hydrogenation ($Pd/BaSO_4$) of (+)-piperitone[31] that was obtained in turn from (+)-limonene following a previously developed procedure.[32,24] The 2′-hydroxyethyl moiety was introduced in two steps via Reformatsky reaction with ethyl bromoacetate, followed by reduction of the obtained hydroxy ester with $LiAlH_4$.

Accordingly, menthone isomers (−)- and (+)-**15** afforded the separable diastereoisomers (−)-**16**, (−)-**17**, and (+)-**16**, (+)-**17**, respectively, which after reduction gave diols (−)-**18**, (−)-**19**, and (+)-**18**, (+)-**19**, respectively. Isomenthone enantiomers (−)-**20** and (+)-**20** afforded (diastereoselectively) hydroxy esters (−)-**21** and (+)-**21**, respectively, that were finally reduced to diols (−)-**22** and (+)-**22**. The stereoselectivity of the Reformatsky reaction on menthone isomers had been previously reported[33], and the stereochemistry of compounds **16**, **17**, and **21** was tentatively assigned on the basis of spectroscopic studies. In order to unambiguously establish the configuration of the latter compounds, we carried out X-ray single-crystal analysis on diols, (−)-**18** and (−)-**22**. The molecular structures of **18** and **22** are illustrated in Figures 4 and 5, respectively (Section 4.3). Our synthetic path afforded six of the eight 3-(2′-hydroxyethyl)-*p*-menthan-3-ol isomers. The addition of different nucleophiles to the carbonyl functionality of isomenthone[34] exclusively afforded (1*SR*,3*RS*,4*SR*)-derivatives, and does not give access to the remaining (1*SR*,3*SR*,4*SR*)-isomers. Despite this limitation, we started with a preliminary, qualitative evaluation of the obtained isomeric forms. Four general aspects were observed:

(1) (1*R*,4*S*)-Isomers are more cooling than the corresponding (1*S*,4*R*)-enantiomers. It should be noted that the configuration at C(1) and C(4) of the latter more active compounds is the same as that of the natural (−)-menthol (1*R*,3*R*,4*S*), which is again the fresher menthol isomer.
(2) The isomers derived from menthone enantiomers are fresher than those prepared from isomentone enantiomers. Therefore, the *trans* relationship between C(1) methyl and C(4) isopropyl increases the cooling effect.
(3) The isomers derived from isomenthone showed a significant bitter taste. Therefore, the *cis*-relationship between C(1) methyl and C(4) isopropyl increases the bitterness.
(4) All the isomers are odorless.

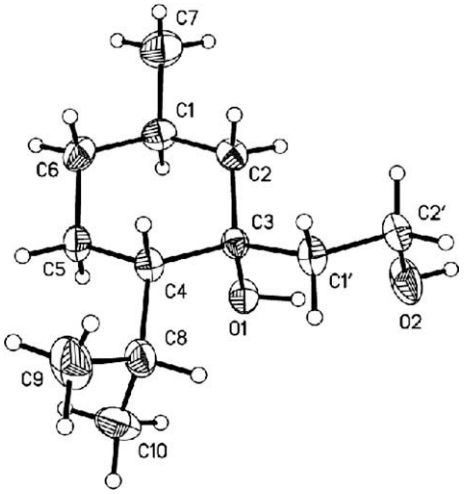


Figure 4. ORTEP drawing with numbering scheme of compound (−)-**18**.

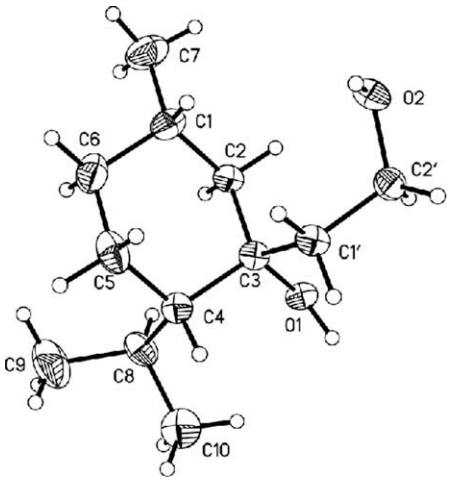
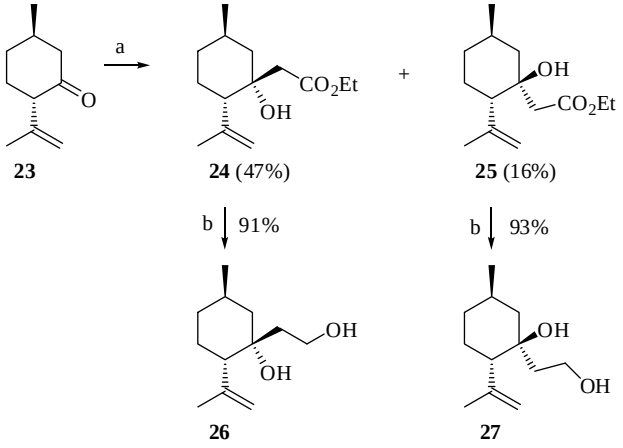


Figure 5. ORTEP drawing with numbering scheme of compound (−)-**22**.

2.2. Synthesis and evaluation of the 3-(2′-hydroxyethyl)-*p*-menth-8(9)-en-3-ol isomers and of some (1*R*,3*R*,4*S*)-3-(2′-hydroxyethyl)-*p*-menthan-3-ol derivatives

By taking advantage of the above-mentioned rules, we started with a more accurate and quantitative evaluation of the cooling properties of different 3-alkyl-*p*-menthan-3-ol compounds. In particular, we first made changes to the framework of (1*R*,4*S*)-3-(2′-hydroxyethyl)-*p*-menthan-3-ol in the hope of increasing the cooling properties. We selected some modifications of the above-mentioned compound by emulation of the chemical structures of the most successful commercial coolant with the *p*-menthane skeleton (Figs. 1 and 2). For instance, (−)-isopulegol **2** is more fresh than its saturated analog (−)-menthol **1**. Accordingly, we prepared 3-(2′-hydroxyethyl)-*p*-menth-8(9)-en-3-ol isomers **26** and **27** (Scheme 2).

We started from the easily available racemic isopulegone **23**, which was submitted to a Reformatsky reaction with ethyl



Scheme 2. Synthesis of (1*RS*,4*SR*)-3-(2′-hydroxyethyl)-*p*-menth-8(9)-en-3-ol isomers from isopulegone. Reagents and conditions: (a) $Zn/BrCH_2CO_2Et/THF$; (b) $LiAlH_4/THF$.

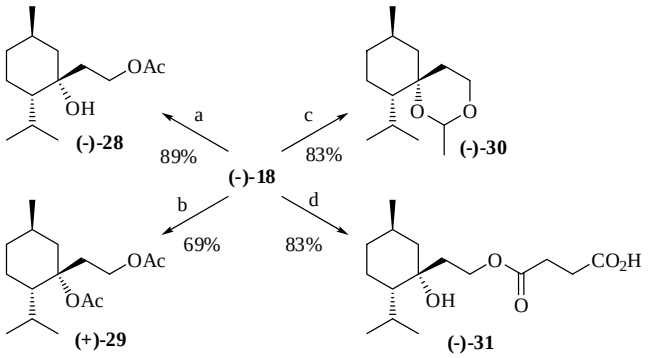
Table 1
Evaluation of the 3-alkyl-*p*-menthan-3-ol derivatives

Compound	Cooling effect	Bitterness
Session 1		
(−)-**18**	11	5
(−)-**19**	20	4
(+)-**34**	12	10
(+)-**44**	4	5
(−)-**35**	17	3
(+)-**47**	11	16
Session 2		
(−)-**18**	18	3
(−)-**38**	23	6
(−)-**42**	26	5
26	6	3
27	8	3
Session 3		
(+)-**29**	3	14
(−)-**28**	6	16
(−)-**31**	3	13
(−)-**30**	5	8
(−)-**37**	14	14
(−)-**19**	20	3
Session 4		
(+)-**44**	14	11
(−)-**52**	22	21
(+)-**53**	7	7
(−)-**19**	24	9
Session 5		
(+)-**36**	9	11
(−)-**35**	15	5
(−)-**19**	18	4
Session 6		
(−)-**50**	10	13
(−)-**51**	5	9
(−)-**54**	6	2
(−)-**55**	5	2
(+)-**46**	7	16
(−)-**48**	6	15
(−)-**40**	7	10
Menthyl-glyceryl ether	13	15

bromoacetate. The obtained hydroxy esters **24** and **25** were separated by chromatography, and then reduced with $LiAlH_4$ to give crystalline diols **26** and **27**, respectively. The latter compounds were evaluated in comparison with diols **18**, **38**, and **42** (Table 1, session 2). The results showed that the introduction of the double bond does not increase the cooling effect. Although compound **26** is racemic, its cooling power does not match that of its saturated analog **18**. Analogously, taking into account that a large number of commercially available cooling agents are menthol ester, succinic ester, or ketal derivatives, we used diol (−)-**18** as a starting material for similar derivatization. Following Scheme 3, the aforementioned diol was converted regioselectively in the monoacetate derivative (−)-**28** using acetic anhydride in pyridine and in the diacetate (+)-**29** by means of sodium acetate in refluxing acetic anhydride. Otherwise, treatment of (−)-**18** with acetaldehyde in the presence of catalytic PPTS or with succinic anhydride gave acetal (−)-**30** and acid-ester (−)-**31**, respectively. The evaluation of the latter four derivatives showed disappointing results. The functionalization of primary hydroxy group dramatically reduced the cooling effect, simultaneously increased the bitterness (Table 1, session 3).

2.3. Modification of the 3-alkyl chain of the (1*R*,4*S*)-3-alkyl-*p*-methan-3-ol derivatives

The modification of the 3-alkyl moiety was carried out via the following step in our study on the structure–activity relationship of the 3-alkyl-*p*-methan-3-ol derivatives. By setting up the

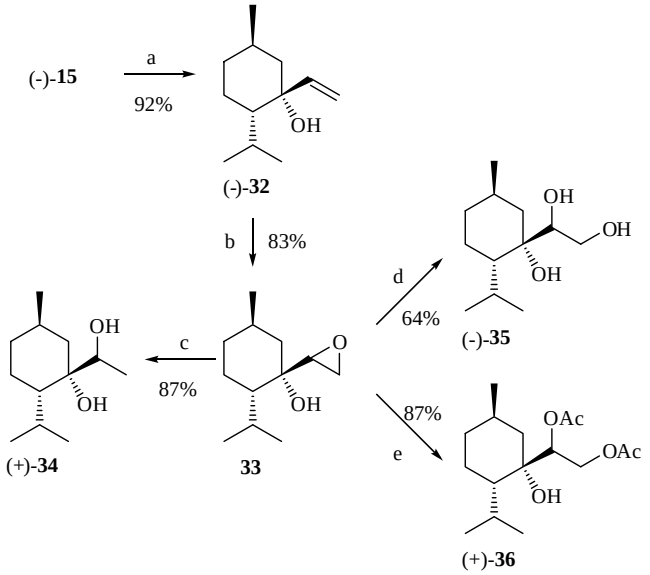


Scheme 3. Synthesis of some (1*R*,3*R*,4*S*)-3-(2′-hydroxyethyl)-*p*-menthan-3-ol derivatives. Reagents and conditions: (a) Ac_2O/Py; (b) Ac_2O/NaOAc, reflux; (c) $MeCHO/CH_2Cl_2$, PPTS cat.; (d) succinic anhydride, 110 °C.

aliphatic *p*-menthane ring with a (1*R*,4*S*)-configuration, we prepared different derivatives combining the following two strategies:

(a) Introduction of further hydroxy and/or ether groups.
(b) Change the length and/or nature of the alkyl moiety.

Again, the first approach involved the modification of the hydroxy-ethyl chain. According to Scheme 4, we prepared three 3-(1′-hydroxyethyl)-*p*-menthan-3-ol derivatives starting from (−)-menthone **15**. The addition of vinylmagnesium bromide to the latter ketone stereoselectively[34,35] gave the carbinol (−)-**32**, which was converted in the diastereoisomeric mixture of epoxide **33** by MCPBA oxidation. This compound was the starting material for the preparation of compounds **34**–**36**. Reduction of **33** with $LiAlH_4$ regioselectively gave diol (+)-**34** as a mixture of diastereoisomers. Otherwise, treatment of **33** with lithium hydroxide in water or with refluxing acetic anhydride in the presence of catalytic tributyl phosphine[36] afforded triol (−)-**35** or diacetate (+)-**36**, respectively, both as a mixture of diastereoisomers from which the major isomers were isolated by crystallization. Compounds (+)-**34** and (−)-**35** were evaluated and compared with diol (−)-**18** (Table 1, session 1). We observed that the shifting of hydroxyl group from the primary to secondary position increases bitterness, whereas the introduction of a secondary hydroxyl group keeping the primary



Scheme 4. The synthesis of some (1*R*,3*S*,4*S*)-3-(1′-hydroxyethyl)-*p*-menthan-3-ol derivatives. Reagents and conditions: (a) $CH_2CHMgBr$/THF; (b) MCPBA/CH_2Cl_2; (c) $LiAlH_4$/THF, reflux; (d) LiOH/H_2O, 50 °C; (e) Ac_2O, Bu_3P cat., reflux.

one unaffected significantly increased the cooling power with a decrease in bitterness. In addition, evaluation of diacetate (+)-**36** in comparison to triol (−)-**35** and diol (−)-**19** showed again that the esterification of primary and secondary hydroxyl groups increases the bitterness and decreases the cooling effect (Table 1, session 5).

Concerning the modification of the length of the 3-alkyl moiety, we first investigated its shortening to only one carbon atom. As shown in Scheme 5, we prepared the 3-hydroxymethyl derivatives **37**, **38**, and **40** starting from vinyl menthol (−)-**32**. Treatment of the latter compound with sodium acetate in refluxing acetic anhydride followed by reductive ozonolysis gave acetoxy alcohol (−)-**37**, whereas the direct reductive ozonolysis of (−)-**32** gave diol (−)-**38**. The same procedure was applied to the degradation of allyl ether **39**, which is in turn prepared by reaction of (−)-**32** with allyl bromide. The obtained diol (−)-**40** is of significant interest in our SAR study since it is an isomer of the well-known coolant, menthyl-glyceryl ether.[14] We prepared the diol (−)-**42**, which is the remaining diastereoisomeric form of diol (−)-**38**. Since the addition of different organometallic reagents to menthone stereoselectively gives carbinols with the axiol hydroxyl group,[33–35] we selected the addition of trimethylsilyl cyanide to (−)-**15** which afforded the cyanohydrin (−)-**41** with opposite diastereoselectivity.[37] The latter compound was then reduced stepwise. Reaction with DIBAH gave the corresponding hydroxy aldehyde that was treated with sodium borohydride to afford the suitable diol (−)-**42**. The evaluation of the obtained 3-hydroxymethyl derivatives showed the following interesting features:

The presence of a tertiary acetate in compound (−)-**37** increased the bitterness (in accordance with previous results), but did not reduce the cooling effect (Table 1, session 3).

Diols (−)-**38** and (−)-**42** gave a more intensive cooling effect than their homologues (−)-**18** and (−)-**19** (Table 1, session 2) although with a more pronounced bitterness. As described for the latter two 3-hydroxyethyl derivatives (Table 1, session 1), the isomer (−)-**38** shows a less intensive cooling effect than the isomer (−)-**42**.

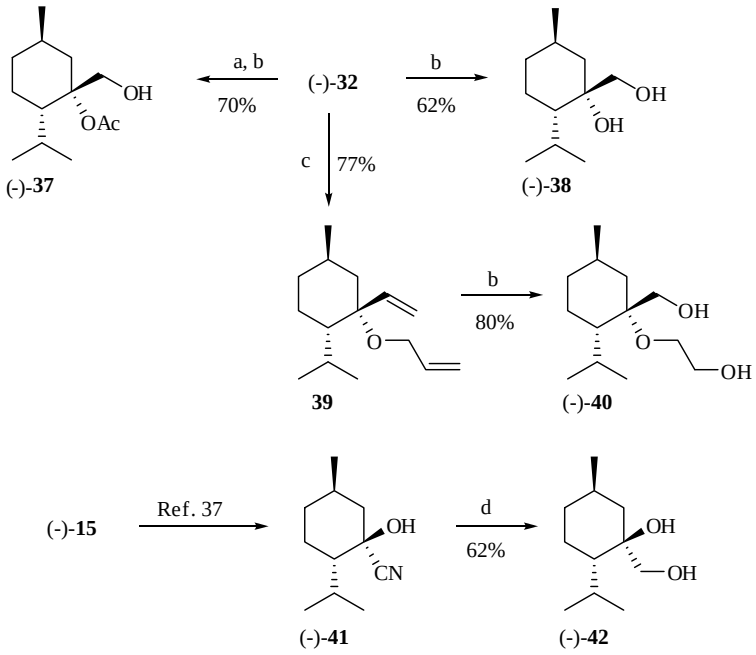
Diol (−)-**40** is less effective as a cooling agent than menthyl-glyceryl ether (Table 1, session 6), but shows inferior bitterness.

The synthesis of other 3-alkyl-*p*-methan-3-ol derivatives, in which the 3-alkyl moiety was increased in length and/or in nature, is described in Scheme 6.

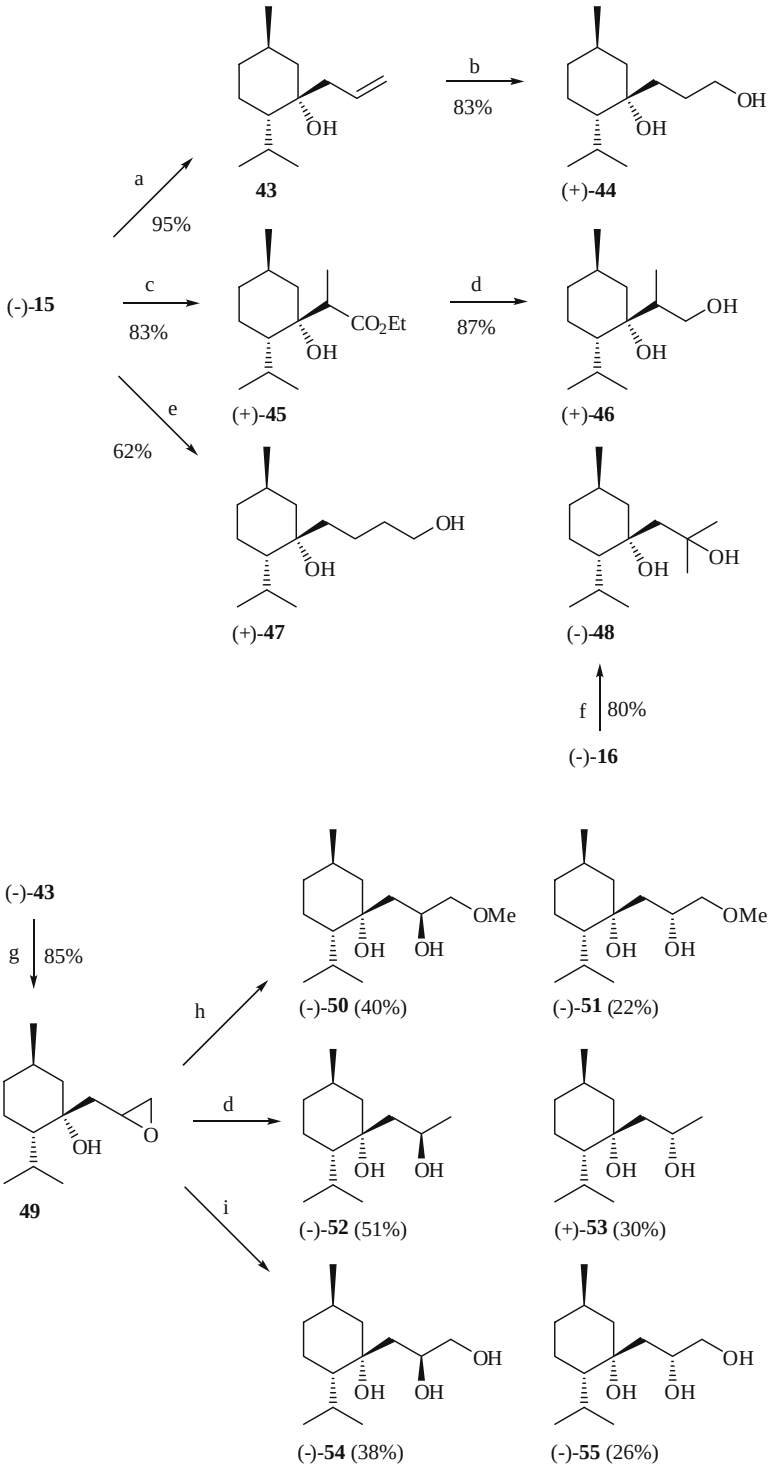
The addition of allylmagnesium bromide to (−)-menthone **15** stereoselectively gave the carbinol **43** that after hydroboration and oxidation afforded the 3-hydroxypropyl derivative (+)-**44**. The corresponding branched derivative (+)-**46** was obtained by Reformatsky reaction of (−)-menthone **15** and ethyl 2-bromopropionate, followed by $LiAlH_4$ reduction. Interestingly, the latter condensation proceeded with high stereoselectivity for both of the two new stereocenters, and ester (+)-**45** was isolated as a single isomer. Concerning the 3-hydroxybutyl derivatives, we prepared compounds (+)-**47** and (−)-**48**. The first, linear diol was synthesized by the addition of 4-benzyloxybutyl magnesium bromide[38] to (−)-menthone **15**, followed by the hydrogenation of the obtained carbinol. The second, branched diol was prepared by the addition of methylmagnesium iodide to ester (−)-**16**. Comparative evaluation of the above-mentioned compounds shows that increasing the chain length (Table 1, session 1) does not considerably change the cooling power, but enhances the bitterness. Moreover, branched isomers (Table 1, session 6) are considerably more bitter than the linear ones.

Carbinol **43** is the starting material for the synthesis of the hydroxylated 3-hydroxypropyl derivatives **50**–**55**. Indeed, oxidation of **43** with MCPBA afforded epoxide **49** as a mixture of diastereoisomers. The latter oxirane undergoes regioselective ring opening at the less-substituted position by means of different nucleophiles. LiOH in methanol, $LiAlH_4$ or LiOH in water afforded methyl ether (−)-**50** and (−)-**51**, diols (−)-**52** and (+)-**53**, or triols (−)-**54** and (−)-**55**, respectively. Since compound (−)-**52** is a crystalline product suitable for X-ray single-crystal analysis, we determined its molecular structure (Fig. 6, Section 4.3), and therefore its configuration which allowed us to also assign the configuration of the compounds **50**, **51**, **53**, **54**, **55**.

Evaluation of the latter six derivatives gave results with difficult interpretations. The couples of ethers and diols with the same configuration (−)-**50**/(−)-**52** and (−)-**51**/(+)-**53** (Table 1, sessions 4 and



Scheme 5. Synthesis of some (1*R*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol isomers and derivatives. Reagents and conditions: (a) Ac_2O/NaOAc, reflux; (b) (1) O_3/MeOH–CH_2Cl_2, −70 °C; (2) $NaBH_4$, rt; (c) NaH/THF/DMF, CH_2CHCH_2Br; (d) (1) DIBAH/toluene, −45 °C; (2) $NaBH_4$/MeOH, rt.



Scheme 6. Synthesis of some (1*R*,4*S*)-3-(hydroxypropyl/hydroxybutyl)-*p*-menthan-3-ol isomers and derivatives. Reagents and conditions: (a) CH_2CHCH_2MgBr/THF; (b) (1) $BH_3{\cdot}Me_2S$, 0 °C; (2) KOH/H_2O, 50 °C; (3) H_2O_2, rt; (c) Zn/$MeCHBrCO_2Et$/THF; (d) $LiAlH_4$/THF; (e) (1) $BnO(CH_2)_4MgBr$/ether; (2) H_2/AcOEt, Pd/C cat.; (f) MeMgI/ether; (g) MCPBA/CH_2Cl_2; (h) LiOH/MeOH; (i) LiOH/H_2O.

6) showed good and modest cooling power, respectively, but with a considerable bitterness.

Otherwise, triols (−)-**54** and (−)-**55** showed modest cooling power and a very low bitterness.

3. Conclusions

The present study on the synthesis and evaluation of the 3-alkyl-*p*-menthan-3-ol derivatives showed that the different members of this class of compounds suit the demanding requisites that are necessary to be a versatile cooling agent. Indeed, all the synthesized products are odorless, and many of these showed very good chemical stability in both acid and basic environments. Moreover, they are tasteless with the exception of the bitterness whose intensity ranges from very low to significant depending on the chemical structure of the 3-alkyl-*p*-menthan-3-ol derivative. Our structure–activity relationship study highlights that compounds with a (1*R*,4*S*)-configuration are the isomers with the more intense

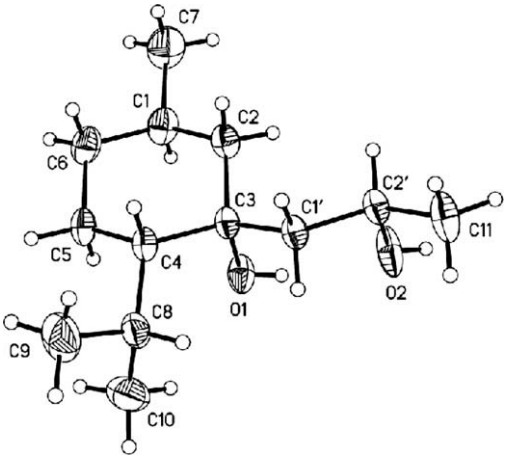


Figure 6. ORTEP drawing with numbering scheme of compound (−)-**52**.

cooling effect and lower bitterness. In addition, the structure of the 3-alkyl chain affected the latter properties. Different kinds of derivatizations of the hydroxyl group afforded compounds, which showed worse performances. An increase in the length of the chain over two carbon atom does not noticeably change the cooling power, but enhances the bitterness with the additional feature that branched isomers are considerably more bitter than the linear ones. Moreover, the isomers with the 3-hydroxy group in the equatorial position are fresher than the corresponding diastereoisomers suggesting that (1*R*,3*R*,4*S*)-configuration, the same as (−)-menthol, is necessary to obtain the best cooling effect. Overall, the 3-alkyl-*p*-menthan-3-ol isomers with the best quality in terms of high cooling power and low bitterness are (1*R*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol diastereoisomers. These isomers are prepared in a straightforward manner in only two steps from inexpensive (−)-menthone. In addition, their crystalline nature allows us to obtain them in high purity without demanding chromatographic separation. Together, all these aspects indicate that the latter 3-alkyl-*p*-menthan-3-ol isomers might be considered as successful coolants, whose use will have further expansion.

4. Experimental

4.1. General experimental

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All solvents and reagents were of commercial quality, unless otherwise stated. (−)-Menthone is a commercial product obtained by fractionation of *Mentha arvensis* essential oil. (+)-Isomenthone was prepared from commercially available (+)-isomenthol by chromic oxidation.[30] (+)-Menthone was prepared by chromic oxidation of (+)-menthol. (−)-Isomenthone was obtained by catalytic hydrogenation (Pd/$BaSO_4$) of (+)-piperitone.[31] The latter compound was prepared in two steps consisting in a photosensitized oxidation of (+)-limonene[32], followed by chromic oxidation of the obtained mixture of carbinols.[24] Racemic isopulegone was prepared by chromic oxidation of racemic isopulegol. 4-Benzyloxybutyl magnesium bromide was prepared from 4-benzyloxybutyl bromide according to a reported procedure.[38] TLC analyses were conducted using *Merck* Silica Gel 60 F_{254} plates. Column chromatography was performed over silica gel (70–230 mesh). GC–MS analyses: *HP-6890* gas chromatograph equipped with a 5973 mass detector, using a *HP-5MS* column (30 m × 0.25 mm, 0.25 μm firm thickness; *Hewlett Packard*) with the following temp. program 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1/30; t_R given in min: t_R(**16**) 19.55, t_R(**17**) 19.54, t_R(**18**) 18.39, t_R(**19**) 18.54, t_R(**21**) 18.58, t_R(**22**) 19.23, t_R(**24**) 18.71, t_R(**25**) 18.98, t_R(**26**) 18.79, t_R(**27**) 19.23, t_R(**28**) 20.05, t_R(**29**) 21.24, t_R(**30**) 15.86 and 15.94, t_R(**31**) 18.44, t_R(**34**) 16.20 and 16.30, t_R(**35**) 17.50, t_R(**36**) 22.08, t_R(**37**) 17.87, t_R(**38**) 15.58, t_R(**40**) 20.46, t_R(**42**) 16.38, t_R(**44**) 19.99, t_R(**45**) 19.74, t_R(**46**) 19.62, t_R(**47**) 21.04, t_R(**48**) 18.51, t_R(**50**) 20.86, t_R(**51**) 20.65, t_R(**52**) 18.43, t_R(**53**) 18.00, t_R(**54**) 21.78, t_R(**55**) 21.73; mass spectra: *m/z* (rel.%). Optical rotations: *Jasco-DIP-181* digital polarimeter. NMR spectra were recorded at rt on *Bruker-AC-250* spectrometer or on *Bruker-AC-400* spectrometer. ^1H and ^{13}C spectra were recorded at 250.1 or 400.1 MHz and at 100.6 or 62.8 MHz, respectively, using $CDCl_3$ as solvent, unless otherwise stated; chemical shifts in ppm rel. to internal $SiMe_4$ (=0 ppm), *J* values in hertz. IR spectra were recorded on a *Perkin–Elmer 2000 FT-IR* spectrometer; films; ν in cm^{-1}. Melting points were measured on a Reichert apparatus that was equipped with a Reichert microscope, and are uncorrected.

4.2. Syntheses and products characterization

A solution of (−)-menthone **15** (30.8 g, 0.2 mol) and ethyl bromoacetate (50 g, 0.3 mol) in dry THF (150 mL) was added dropwise under nitrogen to a heated and stirred suspension of activated zinc dust (30 g, 0.46 mol) in dry THF (250 mL). After starting the exothermic reaction, the heater was removed, and the addition of the reagents adjusted in order to ensure a gentle reflux. When the reaction settled down, the mixture was heated again for 1 h, and then cooled. The unreacted zinc was filtered under a Celite pad, and was washed with ethyl acetate (300 mL). The combined organic phase was washed in turn with 5% HCl aq (400 mL) and brine (100 mL), then was dried ($NaSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford the less polar hydroxy ester (−)-**16** (28.4 g, 59% yield) and the more polar hydroxy ester (−)-**17** (14.2 g, 29% yield).

The same procedure described above was applied to the Reformatsky reaction of the other menthone isomers and ethyl bromoacetate. Accordingly, (+)-menthone **15** (27 g, 175 mmol) afforded the less polar hydroxy ester (+)-**16** (24.1 g, 57% yield) and the more polar hydroxy ester (+)-**17** (12 g, 28% yield). When isomenthone **20** was used as a starting ketone, the reaction proceeded in a highly diastereoselective fashion affording hydroxy ester **21** as exclusive isomers. Accordingly, (−)-isomenthone (13 g, 84.3 mmol) afforded hydroxy ester (−)-**21** (17.3 g, 85% yield), and (+)-isomenthone (30 g, 194.5 mmol) afforded hydroxy ester (+)-**21** (39.6 g, 84% yield).

Data for (1R,3R,4S)-3-ethoxycarbonylmethyl-p-menthan-3-ol (−)-**16**: Colorless oil; $[\alpha]_D^{20} = -14.8$ (*c* 1, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 3516, 1713, 1458, 1397, 1371, 1326, 1298, 1193, 1026; ^1H NMR (400 MHz), δ 0.82–0.88 (m, 1H), 0.85 (d, 3H, *J* = 6.5 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 1.01–1.09 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.44–1.62 (m, 2H), 1.66 (dm, 1H, *J* = 13.4 Hz), 1.72–1.88 (m, 2H), 2.04 (m, 1H), 2.30 (d, 1H, *J* = 14.8 Hz), 2.79 (d, 1H, *J* = 14.8 Hz), 2.96 (br s, 1H), 4.18 (qd, 2H, *J* = 7.1 Hz); ^{13}C NMR (100.6 MHz), δ 14.2, 18.0, 20.6, 22.2, 23.6, 26.4, 27.7, 35.2, 44.7, 47.5, 50.1, 60.5, 73.7, 173.5; MS, *m/z* (%) 242 (M^+, $C_{14}H_{26}O_3$, 2), 227 (3), 224 (2), 197 (2), 186 (5), 157 (100), 137 (13), 130 (31), 111 (29), 95 (12), 81 (11), 69 (31), 55 (14).

Data for (1R,3S,4S)-3-ethoxycarbonylmethyl-p-menthan-3-ol (−)-**17**: Colorless crystals; mp 52–53 °C; $[\alpha]_D^{20} = -17.4$ (*c* 1, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3538, 1710, 1456, 1366, 1324, 1202, 1117, 1027; ^1H NMR (400 MHz), δ 0.79 (d, 3H, *J* = 6.7 Hz), 0.84–0.95 (m, 1H), 0.86 (d, 3H, *J* = 6.5 Hz), 0.99 (d, 3H, *J* = 7.1 Hz), 1.02–1.15 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.27–1.32 (m, 1H), 1.38–1.52 (m, 1H), 1.65 (dqd, 1H, *J* = 3.5, 13.6 Hz), 1.69–1.81 (m, 2H), 2.18 (m, 1H), 2.51 (dd, 1H, *J* = 1.5, 14.7 Hz), 2.64 (d, 1H, *J* = 14.7 Hz), 3.61 (s,

1H), 4.10–4.27 (m, 2H); ^{13}C NMR (100.6 MHz), δ 14.2, 19.1, 22.3, 23.6, 24.6, 25.0, 30.3, 34.9, 38.0, 48.6, 52.0, 60.6, 74.0, 173.5; MS, *m/z* (%) 242 (M^+, $C_{14}H_{26}O_3$, 1), 227 (2), 224 (1), 197 (2), 186 (5), 172 (4), 157 (100), 137 (13), 130 (29), 111 (26), 95 (11), 81 (9), 69 (28), 55 (13).

(1*S*,3*S*,4*R*)-3-Ethoxycarbonylmethyl-*p*-menthan-3-ol (+)-**16** and (1*S*,3*R*,4*R*)-3-ethoxycarbonylmethyl-*p*-menthan-3-ol (+)-**17** showed $[\alpha]_D^{20} = +15.0$ (*c* 1, $CHCl_3$) and $[\alpha]_D^{20} = +17.3$ (*c* 1, $CHCl_3$), respectively; IR, ^{1}H NMR, ^{13}C NMR, and MS data in accordance with those of (−)-**16** and (−)-**17**, respectively.

Data for (1S,3R,4S)-3-ethoxycarbonylmethyl-p-menthan-3-ol (−)-**21**: Colorless oil; $[\alpha]_D^{20} = -25.1$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 3515, 1714, 1458, 1371, 1323, 1219, 1187, 1030; ^{1}H NMR (400 MHz), δ 0.92 (d, 3H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 1.02 (d, 3H, *J* = 6.8 Hz), 1.06–1.19 (m, 1H), 1.21–1.38 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.39–1.56 (m, 3H), 1.57–1.70 (m, 1H), 1.71–1.81 (m, 1H), 2.01 (m, 1H), 2.45 (d, 1H, *J* = 15.3 Hz), 2.73 (d, 1H, *J* = 15.3 Hz), 3.42 (s, 1H), 4.10–4.22 (m, 2H); ^{13}C NMR (100.6 MHz), δ 14.2, 20.4, 21.7, 22.1, 25.1, 26.3, 28.7, 30.9, 43.2, 44.7, 48.5, 60.4, 74.4, 173.4; MS, *m/z* (%) 242 (M^+, $C_{14}H_{26}O_3$, 1), 227 (2), 224 (1), 197 (1), 186 (4), 172 (5), 157 (100), 139 (16), 130 (24), 111 (27), 95 (13), 81 (10), 69 (36), 55 (17).

(1*R*,3*S*,4*R*)-3-Ethoxycarbonylmethyl-*p*-menthan-3-ol (+)-**21** showed $[\alpha]_D^{20} = +25.6$ (*c* 2, $CHCl_3$); IR, ^{1}H NMR, ^{13}C NMR, and MS data in accordance with those of (−)-**21**.

Racemic isopulegone (40 g, 263 mmol) and ethyl bromoacetate (65 g, 389 mmol) were condensed by a Reformatsky reaction according to the procedure described for the preparation of (−)-**16** and (−)-**17**. Chromatography and purification afforded **24** (first eluted diastereoisomer, 29.5 g, 47% yield) and **25** (last eluted diastereoisomer, 10.2 g, 16% yield).

Data for (1RS,3RS,4SR)-3-ethoxycarbonylmethyl-p-menth-8(9)-en-3-ol **24**: Colorless oil; IR (film, cm^{-1}), ν_{max} 3511, 1713, 1636, 1373, 1339, 1231, 1186, 1095, 1023, 892; ^{1}H NMR (400 MHz), δ 0.84–1.04 (m, 2H), 0.87 (d, 3H, *J* = 6.7 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.39–1.46 (m, 1H), 1.71–1.81 (m, 2H), 1.79 (s, 3H), 1.82–2.01 (m, 3H), 2.22 (d, 1H, *J* = 15.6 Hz), 2.65 (d, 1H, *J* = 15.6 Hz), 3.37 (br s, 1H), 4.15 (q, 2H, *J* = 7.1 Hz), 4.74 (br s, 1H), 4.81 (br s, 1H); ^{13}C NMR (100.6 MHz), δ 14.1, 21.5, 22.2, 27.0, 27.4, 34.9, 44.7, 46.7, 53.9, 60.4, 72.0, 113.4, 147.4, 173.5; MS, *m/z* (%) 240 (M^+, $C_{14}H_{24}O_3$, 2), 222 (100), 207 (16), 179 (89), 166 (31), 157 (59), 134 (43), 123 (24), 109 (59), 95 (64), 81 (24), 69 (70), 55 (23).

Data for (1RS,3SR,4SR)-3-ethoxycarbonylmethyl-p-menth-8(9)-en-3-ol **25**: Colorless oil; IR (film, cm^{-1}), ν_{max} 3512, 1713, 1641, 1456, 1372, 1332, 1192, 1093, 1042, 891; ^{1}H NMR (400 MHz), δ 0.85–1.03 (m, 2H), 0.89 (d, 3H, *J* = 6.5 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.39–1.56 (m, 2H), 1.64 (ddd, 1H, *J* = 3.6, 3.8, 13.9 Hz), 1.72 (m, 1H), 1.76–1.90 (m, 1H), 1.89 (s, 3H), 2.12 (dd, 1H, *J* = 3.6, 13.2 Hz), 2.55 (s, 2H), 3.80 (br s, 1H), 4.16 (m, 2H), 4.66 (br s, 1H), 4.95 (br s, 1H); ^{13}C NMR (100.6 MHz), δ 14.1, 22.1, 25.8, 28.5, 30.0, 34.7, 37.6, 48.1, 53.0, 60.4, 73.5, 112.3, 147.4, 173.5; MS, *m/z* (%) 240 (M^+, $C_{14}H_{24}O_3$, 2), 222 (99), 207 (17), 179 (100), 166 (33), 157 (67), 134 (50), 123 (29), 109 (69), 95 (73), 81 (30), 69 (81), 55 (28).

Hydroxy ester (−)-**16** (15 g, 62 mmol) in dry THF (50 mL) was added dropwise and under nitrogen to a stirred suspension of $LiAlH_4$ (3 g, 79 mmol) in dry THF (150 mL). The reaction mixture was heated for 1 h at reflux then cooled to 0 °C, and quenched by dropwise addition of ethyl acetate (50 mL) followed by addition of 5% aqueous HCl (300 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (9:1 v/v) to afford pure diol (−)-**18** (11.2 g, 90% yield).

The same procedure described above was applied in the reduction of hydroxy esters (−)-**17**, (+)-**16**, (+)-**17**, (−)-**21**, (+)-**21**, **24**, and **25** to give diols (−)-**19** (92%), (+)-**18** (91%), (+)-**19** (89%), (−)-**22** (94%), (+)-**22** (92%), **26** (91%), and **27** (93%), respectively.

Data for (1R,3R,4S)-3-(2′-hydroxyethyl)-p-menthan-3-ol (−)-**18**: Colorless crystals; mp 80–82 °C; $[\alpha]_D^{20} = -16$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3378, 3295, 1074, 1030, 854; ^{1}H NMR (250 MHz), δ 0.77–0.98 (m, 2H), 0.90 (d, 3H, *J* = 6.5 Hz), 0.91 (d, 6H, *J* = 6.7 Hz), 1.03 (ddd, 1H, *J* = 12.9, 3.5, 2.0 Hz), 1.27–1.59 (m, 3H), 1.60–1.93 (m, 3H), 2.12–2.36 (m, 2H), 2.23 (br s, 2H), 3.70–3.83 (m, 1H), 3.99 (ddd, 1H, *J* = 14.5, 10.3, 4.1 Hz); ^{13}C NMR (62.8 MHz), δ 17.9, 20.3, 22.3, 23.6, 25.5, 27.7, 34.9, 40.8, 46.2, 50.0, 58.9, 75.2; MS, *m/z* (%) 200 (M^+, $C_{12}H_{24}O_2$, 1), 185 (1), 155 (15), 137 (6), 115 (100), 97 (20), 81 (13), 69 (28), 55 (13).

Data for (1R,3S,4S)-3-(2′-hydroxyethyl)-p-menthan-3-ol (−)-**19**: Colorless crystals; mp 84–86 °C; $[\alpha]_D^{20} = -33.4$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3308, 1157, 1071, 865; ^{1}H NMR (250 MHz), δ 0.80–1.06 (m, 2H), 0.85 (d, 3H, *J* = 6.7 Hz), 0.90 (d, 3H, *J* = 6.2 Hz), 0.98 (d, 3H, *J* = 6.7 Hz), 1.1 (m, 2H), 1.26–1.50 (m, 1H), 1.57–1.80 (m, 3H), 1.83–2.00 (m, 1H), 2.04–2.26 (m, 2H), 2.30 (s, 2H), 3.72–3.85 (m, 1H), 3.93 (ddd, 1H, *J* = 13.9, 10.8, 3.1 Hz); ^{13}C NMR (62.8 MHz), δ 19.4, 22.3, 24.0, 24.7, 24.8, 30.1, 32.4, 35.0, 46.9, 53.9, 59.1, 76.9; MS, *m/z* (%) 200 (M^+, $C_{12}H_{24}O_2$, 1), 185 (1), 155 (6), 137 (4), 129 (2), 121 (2), 115 (100), 97 (19), 88 (6), 81 (11), 69 (26), 55 (12).

(1*S*,3*S*,4*R*)-3-(2′-Hydroxyethyl)-*p*-menthan-3-ol (+)-**18** and (1*S*,3*R*,4*R*)-3-(2′-hydroxyethyl)-*p*-menthan-3-ol (+)-**19** showed $[\alpha]_D^{20} = +15.8$ (*c* 2, $CHCl_3$) and $[\alpha]_D^{20} = +32.5$ (*c* 2, $CHCl_3$), respectively; IR, ^{1}H NMR, ^{13}C NMR, and MS data in accordance with those of (−)-**18** and (−)-**19**, respectively.

Data for (1S,3R,4S)-3-(2′-hydroxyethyl)-p-menthan-3-ol (−)-**22**: Colorless crystals; mp 79–81 °C; $[\alpha]_D^{20} = -28.6$ (*c* 1, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3321, 3255, 1374, 1307, 1178, 1115, 1055, 1040; ^{1}H NMR (250 MHz), δ 0.95 (d, 3H, *J* = 6.9 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 1.06 (d, 3H, *J* = 6.6 Hz), 1.03–1.14 (m, 1H), 1.29–1.50 (m, 4H), 1.53–1.67 (m, 2H), 1.68–1.83 (m, 2H), 1.90–2.06 (m, 2H), 2.18 (s, 1H), 2.71 (br t, 1H, *J* = 4.9 Hz), 3.86 (m, 2H); ^{13}C NMR (62.8 MHz), δ 20.8, 22.1, 22.7, 25.4, 25.9, 29.0, 30.9, 41.0, 43.4, 48.2, 59.6, 77.1; MS, *m/z* (%) 200 (M^+, $C_{12}H_{24}O_2$, 1), 185 (2), 155 (15), 137 (8), 115 (100), 97 (23), 81 (17), 69 (31), 55 (15).

Data for (1R,3S,4R)-3-(2′-hydroxyethyl)-p-menthan-3-ol (+)-**22**: Colorless crystals; mp 80–82 °C; $[\alpha]_D^{20} = +28.2$ (*c* 1, $CHCl_3$); IR, ^{1}H NMR, ^{13}C NMR, and MS data in accordance with those of (−)-**22**.

Data for (1RS,3RS,4SR)-3-(2′-hydroxyethyl)-p-menth-8(9)-en-3-ol **26**: Colorless crystals; mp 73–74 °C; IR (Nujol, cm^{-1}), ν_{max} 3374, 1637, 1374, 1034, 948, 889, 856, 812; ^{1}H NMR (400 MHz), δ 0.85–1.00 (m, 2H), 0.91 (d, 3H, *J* = 6.5 Hz), 1.37–1.49 (m, 2H), 1.70–2.03 (m, 6H), 1.82 (s, 3H), 2.37 (s, 1H), 2.68 (m, 1H), 3.75 (m, 1H), 3.96 (m, 1H), 4.75 (s, 1H), 4.87 (br s, 1H); ^{13}C NMR (100.6 MHz), δ 22.3, 23.5, 27.5, 27.5, 34.8, 41.9, 45.0, 53.9, 59.1, 73.8, 112.6, 148.0; MS, *m/z* (%) 198 (M^+, $C_{12}H_{22}O_2$, 2), 180 (4), 165 (5), 153 (12), 136 (16), 128 (12), 115 (52), 110 (34), 95 (63), 81 (26), 73 (58), 69 (100), 55 (52).

Data for (1RS,3SR,4SR)-3-(2′-hydroxyethyl)-p-menth-8(9)-en-3-ol **27**: Colorless crystals; mp 70–71 °C; IR (Nujol, cm^{-1}), ν_{max} 3360, 1639, 1045, 972, 931, 889, 865; ^{1}H NMR (400 MHz), δ 0.92 (d, 3H, *J* = 6.5 Hz), 0.93–1.09 (m, 2H), 1.36–1.48 (m, 1H), 1.45–1.58 (m, 1H), 1.61–1.70 (m, 1H), 1.70–1.84 (m, 3H), 1.83 (s, 3H), 2.08 (dm, 2H, *J* = 12.9 Hz), 2.64 (s, 1H), 2.99 (m, 1H), 3.75 (m, 1H), 3.89 (m, 1H), 4.76 (s, 1H), 4.99 (br s, 1H); ^{13}C NMR (100.6 MHz), δ 22.3, 23.6, 28.1, 29.9, 33.7, 34.7, 45.6, 55.5, 59.3, 75.3, 114.0, 146.1; MS, *m/z* (%) 198 (M^+, $C_{12}H_{22}O_2$, 2), 180 (3), 165 (6), 153 (13), 136 (14), 128 (12), 115 (50), 110 (32), 95 (65), 81 (26), 73 (59), 69 (100), 55 (58).

A sample of (−)-**18** (2.5 g, 12.5 mmol) was dissolved in pyridine (10 mL) and acetic anhydride (2 mL, 21 mmol). The solution was set aside at rt overnight, and then the solvent was removed at re-

duced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford pure (1*R*,3*R*,4*S*)-3-(2′-acetoxyethyl)-*p*-menthan-3-ol (−)-**28** (2.7 g, 89% yield) as a colorless oil; $[\alpha]_D^{20} = -2.9$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 3523, 2951, 1738, 1459, 1367, 1242, 1156, 1034; ^1H NMR (250 MHz), δ 0.75–0.84 (m, 1H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 6H, *J* = 7.2 Hz), 0.97–1.12 (m, 2H), 1.32–1.60 (m, 3H), 1.64 (s, 1H), 1.65–1.84 (m, 2H), 1.92 (m, 2H), 2.10 (s, 3H), 2.07–2.22 (m, 1H), 4.18 (t, 2H, *J* = 7.5 Hz); ^{13}C NMR (62.8 MHz), δ 18.0, 20.4, 21.0, 22.3, 23.5, 25.7, 27.8, 34.9, 39.0, 46.8, 49.0, 61.2, 74.0, 171.0; MS, *m/z* (%) 242 (M^+, $C_{14}H_{26}O_3$, 1), 227 (1), 182 (3), 167 (5), 155 (23), 137 (8), 125 (9), 115 (15), 97 (100), 81 (16), 69 (19), 55 (15).

A sample of (−)-**18** (2 g, 10 mmol) was dissolved in acetic anhydride (20 mL), and treated with anhydrous sodium acetate (1 g, 12 mmol). The mixture was stirred at reflux for 8 h, then cooled and quenched by addition of crushed ice (100 g) and diethyl ether (100 mL). The organic phase was separated and washed in turn with water, saturated $NaHCO_3$ aq, and brine, then was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford pure (1*R*,3*R*,4*S*)-3-(2′-acetoxyethyl)-*p*-menthan-3-ol acetate (+)-**29** (1.95 g, 69% yield) as a colorless oil; $[\alpha]_D^{20} = +10.9$ (*c* 1.5, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 2954, 1740, 1451, 1370, 1245, 1227, 1142, 1033, 1018; ^1H NMR (250 MHz) δ 0.76–1.16 (m, 2H), 0.86 (d, 3H, *J* = 6.4 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 1.37–1.60 (m, 3H), 1.68–1.83 (m, 1H), 1.96–2.27 (m, 3H), 1.99 (s, 3H), 2.04 (s, 3H), 2.67–2.82 (m, 2H), 4.07 (t, 2H, *J* = 7.4 Hz); ^{13}C NMR (62.8 MHz) δ 17.6, 20.3, 20.9, 22.1, 22.3, 23.4, 25.9, 28.0, 34.6, 34.7, 41.3, 48.7, 60.8, 86.0, 170.0, 170.9; MS, *m/z* (%) 242 (1), 197 (4), 182 (6), 164 (100), 155 (44), 137 (21), 121 (57), 109 (16), 97 (56), 81 (31), 69 (24), 55 (32).

A solution of (−)-**18** (2 g, 10 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and treated under stirring with acetaldehyde (10 mL) and pyridinium *p*-toluene-sulfonate (0.1 g, 0.4 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched by addition of satd aq $NaHCO_3$ solution (50 mL). The organic phase was separated, dried over Na_2SO_4, and evaporated. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford (1*R*,3*R*,4*S*)-3-(2′-hydroxyethyl)-*p*-menthan-3-ol methyl ketal = (6*R*,7*S*,10*R*)-7-isopropyl-2,10-dimethyl-1,3-dioxaspiro[5.5]undecane (−)-**30** (1.6 g, 83% yield, 8:1 mixture of diastereoisomers by GC analysis) as a colorless oil: $[\alpha]_D^{20} = -27.0$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 2952, 1457, 1403, 1251, 1164, 1124, 954, 836; ^1H NMR (*major diastereoisomer*, 250 MHz) δ 0.48–0.62 (m, 1H), 0.77–1.01 (m, 3H), 0.87 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.8 Hz), 1.23 (d, 3H, *J* = 4.9 Hz), 1.36–1.49 (m, 1H), 1.49–1.69 (m, 2H), 1.70–1.81 (m, 1H), 2.10–2.32 (m, 1H), 2.38 (dt, 1H, *J* = 12.8, 6.0 Hz), 2.58 (ddd, 1H, *J* = 14.0, 4.9, 2.5 Hz), 3.82–4.15 (m, 2H), 4.88 (q, 1H, *J* = 4.9 Hz); ^{13}C NMR (*major diastereoisomer*, 62.8 MHz) δ 18.3, 20.0, 21.6, 22.4, 23.8, 25.6, 26.6, 30.6, 35.4, 39.6, 50.4, 62.3, 74.9, 91.5; MS, *m/z* (*major diastereoisomer*, %), 197 (2), 182 (5), 167 (11), 156 (5), 141 (100), 125 (21), 114 (35), 97 (84), 83 (15), 69 (40), 55 (29), 41 (22).

A mixture of (−)-**18** (2 g, 10 mmol) and succinic anhydride (1 g, 10 mmol) was stirred at 110 °C for 1 h. After cooling, the crude product was purified by chromatography eluting with hexane/ethyl acetate (6:4 v/v) to afford acid (1*R*,3*R*,4*S*)-3-(2′-carboxypropionyloxy-ethyl)-*p*-menthan-3-ol (−)-**31** (2.5 g, 83% yield) as a white powder; mp 109–110 °C; $[\alpha]_D^{20} = -4.2$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3513, 1720, 1213, 1158, 1010; ^1H NMR (250 MHz) δ 0.75–0.97 (m, 1H), 0.87 (d, 3H, *J* = 6.4 Hz), 0.90 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.9 Hz), 0.97–1.12 (m, 2H), 1.20–2.24 (m, 8H), 2.56–2.76 (m, 4H), 4.21 (t, 2H, *J* = 8.4 Hz), 5.50–7.90 (br s, 2H); ^{13}C NMR (62.8 MHz) δ 17.9, 20.3, 22.3, 23.5, 25.6, 27.8, 28.8, 28.9, 34.8, 38.8, 46.7, 48.9, 61.5, 74.4, 172.2, 177.5; MS, *m/z* (%) 200, 171, 157, 143, 138, 129, 115, 97, 85, 78, 73, 67, 60, 55.

Vinylmagnesium bromide (335 mL of 1.2 M solution in THF) was added under nitrogen to a cooled (−20 °C) and stirred solution of (−)-menthone **15** (54 g, 0.35 mol) in dry THF (250 mL). The reaction mixture was stirred for 2 h at rt, then cooled to 0 °C and quenched by the careful addition of saturated NH_4Cl aq (400 mL). The organic phase was separated, and the aqueous layer extracted with diethyl ether (2 × 150 mL). The combined organic phases were washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue (59 g, 92% yield) consisted of alcohol (−)-**32** (94% of the mixture by GC analysis), and was used in the next steps without further purification.

At 0 °C, 3-chloroperbenzoic acid (27.6 g of a 75% wet acid, 0.12 mol) was added portionwise to a sample of vinyl menthol (−)-**32** (18.2 g, 0.1 mol) in CH_2Cl_2 (250 mL). The mixture was stirred for 2 h, and then the 3-chlorobenzoic acid formed was filtered off over a Celite pad. The clear solution obtained was washed with 5% aq Na_2SO_3 soln (100 mL) and satd aq $NaHCO_3$ soln (200 mL), dried over Na_2SO_4, and evaporated. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford epoxide **33** (16.5 g, 83% yield, 77:23 mixture of diastereoisomers by GC analysis) as an oil that crystallized on standing.

Epoxide **33** (5 g, 25.2 mmol) in dry THF (30 mL) was added dropwise and under nitrogen to a stirred suspension of $LiAlH_4$ (1.9 g, 50 mmol) in dry THF (100 mL). The reaction mixture was heated for 3 h at reflux, then cooled to 0 °C and quenched by dropwise addition of ethyl acetate (50 mL) followed by the addition of 5% aqueous HCl (300 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (2 × 80 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (4:1 v/v) to afford pure (1*R*,3*S*,4*S*)-3-(1′-hydroxy-ethyl)-*p*-menthan-3-ol (+)-**34** (4.4 g, 87% yield, 75:25 mixture of diastereoisomers by GC analysis) as a colorless oil: $[\alpha]_D^{20} = +11.7$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max} 3425, 1454, 1368, 1092, 1016, 942, 893, 878, 844, 810; ^1H NMR (250 MHz) δ 0.79–0.96 (m, 12.5H), 0.98–1.18 (m, 1.25H), 1.12 (d, 0.75H, *J* = 6.6 Hz), 1.22 (d, 3H, *J* = 6.6 Hz), 1.34–1.81 (m, 7.5H), 1.91 (br s, 2.5H), 1.90–2.08 (m, 0.25H), 2.42 (m, 1H), 3.79 (1H, q, 1H, *J* = 6.6 Hz), 4.08 (q, 0.25H, *J* = 6.6 Hz); ^{13}C NMR (*major diastereoisomer*, 62.8 MHz) δ 17.0, 18.0, 20.5, 22.4, 23.2, 25.6, 28.1, 34.9, 43.4, 45.4, 73.6, 76.7; MS (*major diastereoisomer*), *m/z* (%) 200 (M^+, $C_{12}H_{24}O_2$, 1), 182 (1), 167 (1), 155 (100), 137 (40), 111 (11), 95 (49), 81 (82), 69 (25), 55 (19), 43 (20).

A solution of epoxide **33** (5.9 g, 29.8 mmol) in THF (60 mL) was treated under stirring with a solution of LiOH (3.6 g, 0.15 mol) in water (20 mL). The mixture was heated at 50 °C for 5 h, then concentrated at reduced pressure and diluted with ether (100 mL) and water (50 mL). The organic phase was separated, and the aqueous layer extracted with diethyl ether (2 × 60 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (7:3 v/v) to afford pure (1*R*,3*S*,4*S*)-3-(1′,2′-dihydroxy-ethyl)-*p*-menthan-3-ol (−)-**35** (4.1 g, 64% yield, 9:1 mixture of diastereoisomers by NMR analysis) as a colorless oil. The latter oil was crystallized from hexane at −20 °C to give (−)-**35** as a single diastereoisomer (stereochemistry at 1′ not determined): mp 34–36 °C; $[\alpha]_D^{20} = -14.6$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3383, 1065, 1032, 984, 896; ^1H NMR (250 MHz) δ 0.70–1.10 (m, 3H), 0.80 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.7 Hz), 0.92 (d, 3H, *J* = 6.7 Hz), 1.2–1.9 (m, 9H), 3.29 (dd, 1H, *J* = 6.6, 4.2 Hz), 3.71 (dd, 1H, *J* = 12.0, 7.0 Hz), 3.88 (m, 1H); ^{13}C NMR (62.8 MHz) δ 18.3, 21.8,

23.0, 23.8, 25.6, 30.4, 33.5, 38.2, 45.8, 60.9, 61.1, 65.6; MS, *m/z* (%) 198 (M^+-18, $C_{12}H_{24}O_3-H_2O$, 2), 183 (100), 167 (3), 155 (20), 139 (64), 125 (25), 111 (26), 95 (63), 81 (66), 67 (33), 55 (37).

A solution of epoxide **33** (1 g, 5 mmol) and tributylphosphine (0.2 g, 1 mmol) in acetic anhydride (30 mL) was heated at reflux under nitrogen for 1 h, then concentrated at reduced pressure and diluted with ether (100 mL) and water (50 mL). The organic phase was washed in turn with water, saturated $NaHCO_3$ aq, and brine, then was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford pure (1R,3S,4S)-3-(1′,2′-diacetoxyethyl)-*p*-menthan-3-ol (+)-**36** (1.3 g, 87% yield, 9:1 mixture of diastereoisomers by GC analysis) as a colorless oil. The latter oil was crystallized from hexane to give (+)-**36** as a single diastereoisomer (stereochemistry at 1′ not determined): mp 103–105 °C; $[\alpha]_D^{20} = +31.7$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max} 3443, 1752, 1712, 1699, 1295, 1258, 1224, 1049, 1019; ^1H NMR (250 MHz) δ 0.80–0.95 (m, 1H), 0.83 (d, 3H, *J* = 6.9 Hz), 0.88 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.5 Hz), 1.15–1.28 (m, 2H), 1.32–1.63 (m, 3H), 1.61 (s, 1H), 1.66–1.85 (m, 2H), 2.05 (s, 3H), 2.06–2.20 (m, 1H), 2.08 (s, 3H), 4.18 (dd, 1H, *J* = 11.7, 8.2 Hz), 4.51 (dd, 1H, *J* = 11.7, 2.6 Hz), 5.30 (dd, 1H, *J* = 8.2, 2.6 Hz); ^{13}C NMR (62.8 MHz) δ 17.9, 20.1, 20.8, 20.9, 22.2, 23.4, 25.2, 27.6, 34.5, 42.2, 45.5, 63.7, 73.9, 75.7, 170.0, 171.0; MS, *m/z* (%) 258 (2), 240 (1), 225 (1), 215 (2), 197 (9), 180 (2), 155 (100), 137 (27), 113 (8), 95 (16), 81 (28), 69 (12), 55 (8).

A sample of vinyl menthol **32** (35 g, 192 mmol) was acetylated as described in the preparation of (+)-**29**. The crude acetate was dissolved in a mixture of methanol and CH_2Cl_2 (1:1 v/v, 250 mL), then cooled to −70 °C and treated with ozone until the appearance of a deep blue color. The excess of ozone was removed by flushing with nitrogen, and the solution was treated with $NaBH_4$ (7.3 g, 193 mmol). The reaction mixture was warmed to rt for 2 h, then diluted with water and extracted with CH_2Cl_2 (2 × 100 mL). The organic phase was washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (9:1 v/v) to afford (1*R*,3*S*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol acetate (−)-**37** (30.8 g, 70% yield) that was further purified by crystallization from hexane: colorless crystals; mp 53–55 °C; $[\alpha]_D^{20} = -4.8$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3507, 1724, 1263, 1235, 1035, 1017, 933; ^1H NMR (250 MHz) δ 0.78–1.10 (m, 2H), 0.89 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz), 1.15–1.31 (m, 1H), 1.36–1.86 (m, 6H), 1.92–2.22 (m, 1H), 2.11 (s, 3H), 4.02 (d, 1H, *J* = 11.2 Hz), 4.15 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (62.8 MHz) δ 17.8, 20.1, 20.8, 22.2, 23.4, 26.1, 27.4, 34.8, 45.0, 47.0, 70.6, 73.7, 171.0; MS, *m/z* (%) 228 (M^+, $C_{13}H_{24}O_3$, 1), 186 (7), 155 (100), 143 (17), 137 (30), 111 (8), 101 (27), 95 (37), 81 (57), 69 (20), 55 (15).

The same ozonolysis procedure described above was applied for the transformation of vinyl menthol **32** into diol **38**. Accordingly, a sample of (−)-**32** (20 g, 110 mmol) afforded (1*R*,3*S*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol (−)-**38** (12.7 g, 62% yield) that was further purified by crystallization from hexane: colorless crystals; mp 80–82 °C; $[\alpha]_D^{20} = -6.7$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3526, 3219, 1265, 1165, 1042, 906, 819; ^1H NMR (250 MHz) δ 0.77–1.05 (m, 2H), 0.90 (d, 3H, *J* = 6.2 Hz), 0.91 (d, 6H, *J* = 7.0 Hz), 1.18 (ddd, 1H, *J* = 6.6, 4.3, 2.3 Hz), 1.35–1.60 (m, 2H), 1.61–1.84 (m, 3H), 1.66 (br s, 2H), 2.08 (m, 1H), 3.43 (d, 1H, *J* = 10.8 Hz), 3.73 (d, 1H, *J* = 10.8 Hz); ^{13}C NMR (62.8 MHz) δ 18.1, 20.4, 22.3, 23.5, 26.0, 27.7, 35.0, 44.8, 47.3, 69.3, 74.9; MS, *m/z* (%) 186 (M^+, $C_{11}H_{22}O_2$, 1), 155 (100), 137 (42), 125 (1), 111 (10), 101 (15), 95 (48), 81 (75), 69 (24), 55 (22), 43 (16).

A sample of (−)-**32** (9.5 g, 52 mmol) in dry DMF (40 mL) was added dropwise to a stirred suspension of NaH (3.8 g of a 50% dispersion in mineral oil, 79 mmol) in dry THF (50 mL). The reaction mixture was warmed to reflux and after 1 h, allyl bromide (7 g, 58 mmol) in dry DMF (10 mL) was added dropwise. After further 2 h at reflux, the mixture was cooled (0 °C), quenched with a saturated solution of NH_4Cl aq (100 mL), and extracted with ether (2 × 100 mL). The combined organic phases were concentrated under reduced pressure, and the residue was purified by chromatography eluting with hexane/ethyl acetate (95:5 v/v) to afford **39** as colorless oil (8.9 g, 77% yield, 94% of purity by GC analysis). The latter compound was submitted to the same oxonolysis procedure that was described in the preparation of (−)-**37**. Chromatographic purification afforded (1*R*,3*S*,4*S*)-3-(hydroxymethyl)-3-(2′-hydroxyethoxyl)-*p*-menthane (−)-**40** (7.4 g, 80% yield) as a colorless oil; $[\alpha]_D^{20} = -3.3$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3368, 1381, 1148, 1074, 1042, 1010; ^1H NMR (250 MHz) δ 0.75–0.96 (m, 2H), 0.88 (d, 3H, *J* = 7.0 Hz), 0.90 (d, 3 H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 1.10–1.28 (m, 1H), 1.40–1.70 (m, 3H), 1.71–1.90 (m, 2H), 2.18 (s, 2H), 2.31 (m, 1H), 3.5 (t, 2H, *J* = 4.0 Hz), 3.61 (d, 1H, *J* = 11.5 Hz), 3.66–3.78 (m, 3H); ^{13}C NMR (62.8 MHz) δ 18.3, 20.3, 22.3, 23.6, 26.3, 27.8, 35.0, 39.6, 50.4, 62.2, 62.4, 67.0, 78.3; MS, *m/z* (%) 230 (M^+, $C_{13}H_{26}O_3$, 1), 199 (100), 183 (1), 169 (1), 155 (6), 145 (4), 137 (47), 111 (7), 95 (46), 81 (71), 69 (21), 55 (18).

DIBAH (30 mL of 1.2 M solution in toluene) was added dropwise under nitrogen to a stirred solution of cyanohydrin (−)-**41** (3 g, 16.5 mmol) in dry toluene (60 mL) at −45 °C. The reaction mixture was stirred at 0 °C for 1 h, then diluted with ether (50 mL) and quenched with a saturated solution of NH_4Cl aq (40 mL). A solution of H_2SO_4 aq (1 M, 60 mL) was added, and the mixture was stirred vigorously for 8 h at rt. The reaction mixture was extracted with ether (2 × 100 mL), and the combined organic phases were concentrated under reduced pressure. The residue was dissolved in methanol (50 mL) and treated with $NaBH_4$ (0.8 g, 21.2 mmol). After 1 h, the work-up procedure afforded the crude diol that was purified by chromatography eluting with hexane/ethyl acetate (2:1 v/v) to give pure (1*R*,3*R*,4*S*)-3-(hydroxymethyl)-*p*-menthan-3-ol (−)-**42** (1.9 g, 62% yield) as a oil that crystallized on standing; colorless crystals; mp 48–50 °C; $[\alpha]_D^{20} = -19.6$ (*c* 1, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3333, 1389, 1369, 1299, 1165, 1055, 910; ^1H NMR (250 MHz) δ 0.73–1.02 (m, 2H), 0.79 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.97 (d, 3H, *J* = 7.0 Hz), 1.1 (dq, 1H, *J* = 13.1, 3.1 Hz), 1.23–1.36 (m, 1H), 1.38–1.58 (m, 1H), 1.64 (ddd, 1H, *J* = 10.1, 6.6, 3.1 Hz), 1.70–1.81 (m, 1H), 2.04–2.24 (m, 2H), 3.15 (br s, 2H), 3.63 (d, 1H, *J* = 11.2 Hz), 3.69 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR (62.8 MHz) δ 19.4, 22.3, 23.5, 24.5, 24.6, 30.0, 34.9, 44.8, 51.9, 62.8, 76.3; MS, *m/z* (%) 186 (M^+, $C_{11}H_{22}O_2$, 5), 155 (98), 137 (41), 125 (1), 111 (13), 101 (54), 95 (76), 81 (100), 69 (56), 55 (90), 43 (42).

Allylmagnesium bromide (380 mL of 1 M solution in THF) was added under nitrogen to a cooled (−20 °C) and stirred solution of (−)-menthone **15** (50 g, 0.324 mol) in dry THF (250 mL). The reaction mixture was stirred for 2 h at rt, then cooled to 0 °C and quenched by careful addition of saturated NH_4Cl aq (400 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (2 × 150 mL). The combined organic phases were washed with brine (200 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue (60.5 g, 95% yield) consisted of alcohol **43** (93% of the mixture by GC analysis), and was used in the next steps without further purification.

Borane-dimethyl sulfide complex (5.8 mL, 61 mmol) in dry THF (10 mL) was added dropwise to a cooled (0 °C) solution of **43** (12 g, 61 mmol) in dry THF (100 mL) under nitrogen. The resulting clear solution was stirred at rt for 2 h. Then, KOH aq (50 mL of 4 M solution) was added slowly, and the resulting mixture was warmed to 50 °C for 2 h. After this time, 30% aq H_2O_2 solution (50 mL, 0.44 mol) was added dropwise, keeping the temperature below 30 °C by external cooling (ice bath). After the addition, the mixture

was stirred at rt overnight. The main part of THF was evaporated, and the mixture was extracted with ether (3 × 100 mL). The organic phase was successively washed with 5% aq $Na_2S_2O_5$ solution (50 mL) and brine, dried, and evaporated. The residue was purified by chromatography eluting with hexane/ethyl acetate (7:3 v/v) to afford (1*R*,3*S*,4*S*)-3-(3′-hydroxypropyl)-*p*-menthan-3-ol (+)-**44** (10.8 g, 83% yield) as a colorless oil. The latter compound was crystallized from hexane at −20 °C to give (+)-**44** as a single diastereoisomer: mp 90–92 °C; $[\alpha]_D^{20} = +4.2$ (*c* 1, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3346, 1367, 1326, 1296, 1203, 1069, 1002, 945; ^{1}H NMR (250 MHz) δ 0.74–1.03 (m, 2H), 0.88 (d, 3H, *J* = 6.4 Hz), 0.89 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz), 1.04–1.15 (m, 1H), 1.38 (ddd, 1H, *J* = 13.2, 12.4, 3.4 Hz), 1.48–1.83 (m, 8H), 2.00 (br s, 2H), 2.13 (m, 1H), 3.56–3.76 (m, 2H); ^{13}C NMR (62.8 MHz) δ 18.0, 20.5, 22.4, 23.6, 25.4, 27.0, 28.0, 35.0, 37.4, 46.4, 48.5, 63.3, 74.8; MS, *m/z* (%) 214 (M^+, $C_{13}H_{26}O_2$, 1), 199 (4), 181 (2), 155 (40), 137 (15), 129 (100), 111 (97), 102 (14), 95 (20), 81 (30), 69 (42), 55 (21).

(−)-Menthone **15** (15 g, 97.2 mmol) and ethyl 2-bromopropionate (23 g, 127 mmol) were condensed by a Reformatsky reaction according to the procedure described for the preparation of (−)-**16**/(−)-**17**. Chromatographic purification afforded (1*R*,3*S*,4*S*)-3-(1′-ethoxycarbonylethyl)-*p*-menthan-3-ol (+)-**45** as an oil consisting of a single diastereoisomer (20.6 g, 83% yield, up to 96% de by GC analysis, stereochemistry at C1′ not determined): $[\alpha]_D^{20} = +8.8$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3493, 1702, 1367, 1255, 1189, 1159, 1049, 1024, 945; ^{1}H NMR (400 MHz) δ 0.74–0.96 (m, 2H), 0.85 (d, 3H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.8 Hz), 0.95 (d, 3H, *J* = 6.8 Hz), 0.98–1.10 (m, 1H), 1.08 (d, 3H, *J* = 7.1 Hz), 1.12–1.20 (m, 1H), 1.29 (t, 3H, *J* = 7.0 Hz), 1.31–1.38 (m, 1H), 1.42–1.50 (m, 1H), 1.58 (ddd, 1H, *J* = 13, 12.9, 3.5 Hz), 1.70–1.79 (m, 1H), 1.79–1.89 (m, 1H), 1.95 (m, 1H), 2.92 (q, 1H, *J* = 7.1 Hz), 3.24 (br s, 1H), 4.19 (q, 2H, *J* = 7.0 Hz); ^{13}C NMR (100.6 MHz) δ 11.8, 14.2, 18.0, 20.4, 22.4, 23.3, 25.6, 27.6, 35.2, 42.3, 46.4, 47.1, 60.7, 76.4, 176.0; MS, *m/z* (%) 256 (M^+, $C_{15}H_{28}O_3$, 2), 241 (2), 211 (2), 193 (3), 171 (100), 155 (34), 144 (25), 137 (26), 125 (34), 112 (28), 102 (28), 95 (22), 81 (32), 69 (52), 55 (25). The latter compound (15 g, 58.6 mmol) was reduced with $LiAlH_4$ according to the procedure described for the preparation of (−)-**18**. Chromatographic purification afforded *(1R,3S,4S)-3-(2′-hydroxy-1′-methylethyl)-p-menthan-3-ol* (+)-**46** (10.9 g, 87% yield) as a colorless oil that was further purified by crystallization from hexane: mp 72–74 °C; $[\alpha]_D^{20} = +10.2$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3301, 1159, 1037; ^{1}H NMR (250 MHz) δ 0.73 (d, 3H, *J* = 7.1 Hz), 0.80–1.10 (m, 2H), 0.91 (d, 6H, *J* = 6.8 Hz), 0.92 (d, 3H *J* = 6.5 Hz), 1.11–1.25 (m, 1H), 1.27–1.46 (m, 1H), 1.47–1.60 (m, 1H), 1.62–1.90 (m, 3H), 1.95 (br s, 2H), 2.05–2.21 (m, 1H), 2.23–2.44 (m, 1H), 3.54 (dd, 1H, *J* = 10.6, 4.5 Hz), 3.85 (t, 1H, *J* = 10.6 Hz); ^{13}C NMR (62.8 MHz) δ 12.2, 17.9, 19.8, 22.5, 23.3, 24.7, 27.5, 34.8, 39.7, 39.8, 46.9, 65.5, 78.6; MS, *m/z* (%) 214 (M^+, $C_{13}H_{26}O_2$, 3), 199 (2), 173 (4), 155 (30), 137 (18), 129 (100), 123 (14), 112 (32), 95 (30), 81 (36), 69 (43), 55 (20).

4-Benzyloxybutyl magnesium bromide (100 mL of 0.5 M solution in diethyl ether) was added under nitrogen to a cooled (0 °C) and stirred solution of (−)-menthone **15** (5 g, 32.4 mmol) in dry ether (60 mL). The reaction mixture was stirred for 1 h at rt, then cooled to 0 °C and quenched with saturated NH_4Cl aq (100 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (2 × 60 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (80 mL), and then hydrogenated at atmospheric pressure using Pd/C (10% w/w) as catalyst. After filtration, the solution was concentrated, and the residue was purified by chromatography eluting with hexane/ethyl acetate (7:3 v/v). The obtained diol was crystallized from hexane to give pure (1*R*,3*S*,4*S*)-3-(4′-hydroxybutyl)-p-menthan-3-ol (+)-**47** (4.6 g, 62% yield): mp 60–62 °C; $[\alpha]_D^{20} = +5.9$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3373, 3331, 1325, 1195, 1084, 921; ^{1}H NMR (250 MHz) δ 0.70–0.98 (m, 1H), 0.87 (d, 3H, *J* = 6.6 Hz), 0.89 (d, 3H, *J* = 7.0 Hz), 0.90 (d, 3H, *J* = 7.0 Hz), 1.00–1.17 (m, 2H), 1.27–1.82 (m, 11H), 1.42 (s, 2H), 2.08 (m, 1H), 3.68 (t, 2H, *J* = 6.6 Hz); ^{13}C NMR (62.8 MHz) δ 18.0, 20.0, 20.3, 22.3, 23.5, 25.3, 27.8, 33.1, 34.9, 40.7, 46.5, 47.7, 62.1, 75.0; MS, *m/z* (%) 228 (M^+, $C_{14}H_{28}O_2$, 1), 213 (3), 210 (2), 195 (2), 155 (70), 143 (96), 137 (26), 125 (100), 116 (22), 95 (30), 81 (48), 69 (63), 55 (33).

Methylmagnesium iodide (100 mL of 1 M solution in diethyl ether) was added under nitrogen to a cooled (0 °C) and stirred solution of hydroxy ester (−)-**16** (5 g, 20.7 mmol) in dry ether (80 mL). The reaction mixture was stirred for 2 h at rt, then cooled to 0 °C and quenched by careful addition of saturated NH_4Cl aq (100 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/ethyl acetate (7:3 v/v) to afford (1*R*,3*R*,4*S*)-3-(2′-hydroxy-2′-methylpropyl)-*p*-menthan-3-ol (−)-**48** (3.8 g, 80% yield) as a colorless oil that crystallized on standing: mp 83–85 °C; $[\alpha]_D^{20} = -45.0$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3173, 1191, 1172, 1028, 869; ^{1}H NMR (250 MHz) δ 0.80–1.20 (m, 4H), 0.85 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.5 Hz), 0.98 (d, 3H, *J* = 6.8 Hz), 1.29 (s, 3H), 1.39 (s, 3H), 1.42–1.58 (m, 1H), 1.58–1.88 (m, 4H), 2.06–2.20 (m, 1H), 2.26–2.48 (m, 3H); ^{13}C NMR (62.8 MHz) 19.7, 22.1, 24.3, 25.1, 25.2, 30.4, 30.4, 34.4, 35.1, 40.8, 49.1, 55.7, 72.0, 77.6; MS, *m/z* (%) 228 (M^+, $C_{14}H_{28}O_2$, 2), 210 (2), 195 (10), 177 (23), 155 (44), 143 (35), 137 (41), 125 (42), 112 (86), 95 (59), 85 (100), 69 (95), 59 (62).

A sample of allyl alcohol **43** (30 g, 153 mmol) was submitted to the same epoxidation procedure that was described for the preparation of **33**. Chromatographic purification afforded epoxide **49** (27.6 g, 85% yield, 3:2 mixture of diastereoisomer by GC analysis) as a colorless oil.

A solution of epoxide **49** (5 g, 23.6 mmol) in methanol (40 mL) was treated with LiOH (4 g, 167 mmol), stirred at rt until complete conversion of the starting material (24 h, TLC monitoring) was achieved. The solvent was removed under reduced pressure, and the residue was purified by chromatography eluting with hexane/ethyl acetate (2:1 v/v). The first eluted fractions afforded (1*R*,3*R*,4*S*,2′*S*)-3-(2′-hydroxy-3′-methoxypropyl)-*p*-menthan-3-ol (−)-**50** (2.3 g, 40% yield) as a colorless oil that crystallized on standing: mp 51–53 °C; $[\alpha]_D^{20} = -15.8$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3264, 1193, 1127, 1071, 965, 856; ^{1}H NMR (250 MHz) δ 0.79–1.04 (m, 3H), 0.89 (d, 6H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 1.26 (dd, 1H, *J* = 14.3, 2.0 Hz), 1.33–1.58 (m, 2H), 1.63–1.86 (m, 2H), 1.96 (m, 1H), 2.06 (dd, 1H, *J* = 14.3, 11.2 Hz), 2.18 (m, 1H), 2.81 (br s, 2H), 3.27–3.37 (m, 2H), 3.40 (s, 3H), 4.15–4.29 (m, 1H); ^{13}C NMR (62.8 MHz) δ 17.9, 20.3, 22.4, 23.6, 25.5, 27.8, 35.0, 41.1, 46.2, 50.8, 59.0, 67.2, 74.7, 77.5; MS, *m/z* (%) 244 (M^+, $C_{14}H_{28}O_3$, 4), 229 (3), 199 (56), 181 (5), 159 (88), 137 (17), 127 (100), 109 (16), 95 (20), 81 (29), 69 (31), 55 (17). The last eluted fractions gave (1*R*,3*R*,4*S*,2′*R*)-3-(2′-hydroxy-3′-methoxy-propyl)-*p*-menthan-3-ol (−)-**51** (1.3 g, 22% yield) as a colorless oil: $[\alpha]_D^{20} = -10.1$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3443, 1365, 1295, 1194, 1120, 952, 863; ^{1}H NMR (250 MHz) δ 0.79–1.04 (m, 2H), 0.88 (d, 3H, *J* = 6.6 Hz), 0.90 (d, 6H, *J* = 7.0 Hz), 1.05–1.20 (m, 2H), 1.29–1.84 (m, 6H), 2.09–2.23 (m, 1H), 2.28 (br s, 2H), 3.24–3.35 (m, 1H), 3.37–3.48 (m, 1H), 3.40 (s, 3H), 4.01–4.18 (m, 1H); ^{13}C NMR (62.8 MHz) δ 18.0, 20.6, 22.4, 23.5, 25.8, 27.9, 34.8, 43.7, 48.4, 50.2, 58.8, 67.3, 74.4, 77.6; MS, *m/z* (%) 244 (M^+, $C_{14}H_{28}O_3$, 2), 229 (2), 199 (53), 181 (4), 159 (91), 137 (19), 127 (100), 109 (20), 95 (25), 81 (34), 69 (33), 55 (18).

A sample of epoxide **49** (5 g, 23.6 mmol) was reduced with $LiAlH_4$ according to the procedure that was described for the

preparation of (+)-**34**. Chromatographic purification afforded the following two diastereoisomeric diols. First eluted diol (2.6 g, 51% yield); (1*R*,3*R*,4*S*,2′*R*)-3-(2′-hydroxypropyl)-*p*-menthan-3-ol (−)-**52**: mp 108–110 °C; $[\alpha]_D^{20} = -29.7$ (*c* 2, $CHCl_3$); IR (Nujol, cm^{-1}), ν_{max}: 3314, 1298, 1126, 1068, 939, 817; ^1H NMR (250 MHz) δ 0.76–1.08 (m, 3H), 0.90 (d, 6H, *J* = 6.7 Hz), 0.91 (d, 3H, *J* = 6.7 Hz), 1.14–1.46 (m, 2H), 1.20 (d, 3H, *J* = 6.2 Hz), 1.48–1.86 (m, 3H), 1.94–2.13 (m, 2H), 2.15–2.32 (m, 1H), 2.47 (br s, 2H), 4.18–4.38 (m, 1H); ^{13}C NMR (62.8 MHz) δ 17.9, 20.3, 22.4, 23.6, 24.4, 25.3, 27.8, 34.9, 46.0, 46.5, 50.6, 64.4, 75.5; MS, *m/z* (%) 214 (M^+, $C_{13}H_{26}O_2$, 3), 199 (3), 155 (10), 139 (9), 129 (100), 121 (2), 111 (16), 102 (5), 95 (15), 85 (15), 69 (65), 55 (16). Last eluted diol (1.5 g, 30% yield); oil; (1*R*,3*R*,4*S*,2′*S*)-3-(2′-hydroxypropyl)-*p*-menthan-3-ol (+)-**53**: $[\alpha]_D^{20} = +9.4$ (*c* 2, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3396, 1365, 1162, 1122, 945, 851; ^1H NMR (250 MHz) δ 0.76–1.26 (m, 3H), 0.88 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.5 Hz), 0.92 (d, 3H, *J* = 6.5 Hz), 1.22 (d, 3H, *J* = 6.4 Hz), 1.26–1.85 (m, 7H), 2.06–2.25 (m, 1H), 2.47 (br s, 2H), 4.05–4.25 (m, 1H); ^{13}C NMR (62.8 MHz) δ 17.9, 20.4, 22.2, 23.5, 24.6, 26.0, 27.8, 34.8, 49.5, 50.1, 50.9, 65.7, 74.9; MS, *m/z* (%) 214 (M^+, $C_{13}H_{26}O_2$, 2), 199 (3), 155 (15), 139 (11), 129 (100), 121 (2), 111 (18), 102 (6), 95 (19), 81 (18), 69 (72), 55 (18).

A sample of epoxide **49** (6 g, 28.3 mmol) was treated with LiOH according to the procedure that was described for the preparation of (−)-**35**. Chromatographic purification afforded the following two diastereoisomeric triols. First eluted triol (2.5 g, 38% yield); (1*R*,3*R*,4*S*,2′*S*)-3-(2′,3′-dihydroxypropyl)-*p*-menthan-3-ol (−)-**54**: $[\alpha]_D^{20} = -17.0$ (*c* 1, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3382, 1365, 1090, 1031, 985, 945, 854; ^1H NMR (250 MHz) δ 0.78–1.08 (m, 3H), 0.90 (d, 6H, *J* = 6.8 Hz), 0.91 (d, 3H, *J* = 6.5 Hz), 1.14–1.46 (m, 2H), 1.48–1.86 (m, 3H), 1.93–2.05 (m, 1H), 2.08–2.28 (m, 2H), 2.78 (br s, 3H), 3.46 (dd, 1H, *J* = 11.0, 6.2 Hz), 3.62 (dd, 1H, *J* = 11.0, 3.4 Hz), 4.05–4.25 (m, 1H); ^{13}C NMR (62.8 MHz) δ 17.9, 20.3, 22.4, 23.6, 25.4, 27.8, 34.9, 40.5, 46.1, 50.7, 67.3, 69.0 75.2; MS, *m/z* (%) 230 (M^+, $C_{13}H_{26}O_3$, 3), 215 (2), 199 (22), 181 (5), 163 (9), 155 (25), 145 (100), 137 (17), 127 (78), 118 (6), 109 (10), 95 (26), 81 (36), 69 (52), 55 (25).

The last eluted triol (1.7 g, 26% yield); (1*R*,3*R*,4*S*,2′*R*)-3-(2′,3′-dihydroxypropyl)-*p*-menthan-3-ol (−)-**55**: $[\alpha]_D^{20} = -4.3$ (*c* 1, $CHCl_3$); IR (film, cm^{-1}), ν_{max}: 3394, 1365, 1151, 1102, 1065, 945, 860; ^1H NMR (250 MHz) δ 0.80–0.98 (m, 1H), 0.89 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 6H, *J* = 6.8 Hz), 0.98–1.18 (m, 2H), 1.20–1.44 (m, 2H), 1.48–1.92 (m, 5H), 2.06–2.26 (m, 1H), 2.56 (br s, 3H), 3.54 (dd, 1H, *J* = 11.2, 6.7 Hz), 3.65 (dd, 1H, *J* = 11.2, 3.5 Hz), 3.95–4.07 (m, 1H); ^{13}C NMR (62.8 MHz) δ 18.0, 20.6, 22.3, 23.6, 25.7, 27.9, 34.8, 43.5, 48.1, 50.5, 67.2, 69.2, 74.6; MS, *m/z* (%) 230 (M^+, $C_{13}H_{26}O_3$, 2), 215 (3), 199 (23), 181 (3), 163 (7), 155 (28), 145 (100), 137 (16), 127 (80), 118 (6), 109 (10), 95 (24), 81 (34), 69 (47), 55 (23).

4.3. X-ray analyses of compounds (−)-18, (−)-22 and (−)-52

Crystal structures were determined by single-crystal X-ray diffraction using data collected on a *Siemens P4* diffractometer (graphite-monochromated Cu-Kα radiation) for (−)-**18** and (−)-**22**, and on a *Nonius CAD4* diffractometer (graphite-monochromated Mo-Kα radiation) for (−)-**52.**

Compound **18**: $C_{12}H_{24}O_2$, *M* = 200.31, orthorhombic, space group *P*212121, *a* = 8.091(1) Å, *b* = 9.441(1) Å, *c* = 16.406(2) Å, *V* = 1253.2(3) $Å^3$, *Z* = 4, *F*(000) = 448, $D_c = 1.062$ g cm^{-1}, 1502 unique reflections, final *R* = 0.0368 (136 parameters), $R_w = 0.0981$.

Compound **22**: $C_{12}H_{24}O_2$, *M* = 200.31, monoclinic, space group *P*21, *a* = 9.990(1) Å, *b* = 9.710(1) Å, *c* = 13.492(2) Å, $\beta = 107.94(1)^\circ$, *V* = 1245.3(2) $Å^3$, *Z* = 2 (two independent molecules in the unit cell), *F*(000) = 448, $D_c = 1.071$ g cm^{-1}, 2461 unique reflections, final *R* = 0.0578 (276 parameters), $R_w = 0.1503$.

Compound **52**: $C_{13}H_{26}O_2$, *M* = 214.34, orthorhombic, space group *P*212121, *a* = 8.346(1) Å, *b* = 9.594(1) Å, *c* = 17.238(2) Å, *V* = 1380.3(2) $Å^3$, *Z* = 4, *F*(000) = 480, $D_c = 1.031$ g cm^{-1}, 4012 unique reflections, final *R* = 0.0531 (169 parameters), $R_w = 0.1303$.

The three structures were solved by direct methods using SIR97 program[39] and refined on F^2 by full-matrix least-squares procedure with SHELXL97,[40] with anisotropic temperature factors for all non-H atoms.

Crystallographic data (excluding structure factors) for the structures reported have been deposited at the *Cambridge Crystallographic Data Centre* under deposition codes (**22**) 689477, (**18**) 689478, and (**52**) 689479.

4.4. Sensory evaluation

The Sensory Panel was recruited and trained within Robertet S.A. in Grasse, France. Since the 3-alkyl-*p*-methan-3-ol derivatives tested were virtually odorless, each compound was evaluated by taste, using 100 ppm solutions in water. Two properties were tested: cooling effect and bitterness. The number of panelists ranged between 4 and 6; each panelist tasted (blindfold) each product at 20 min minimum intervals. The intensity rating was performed by assigning a number between 0 and 5, where 0 corresponds to no sensation, 5 corresponds to the strongest intensity. At the end of each session, the scores for cooling effect and bitterness were obtained by adding the rate.

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