Enantioselectivity in Odor Perception
Synthesis and Olfactory Properties of the New Tricyclic Sandalwood Odorant *Fleursandol®*

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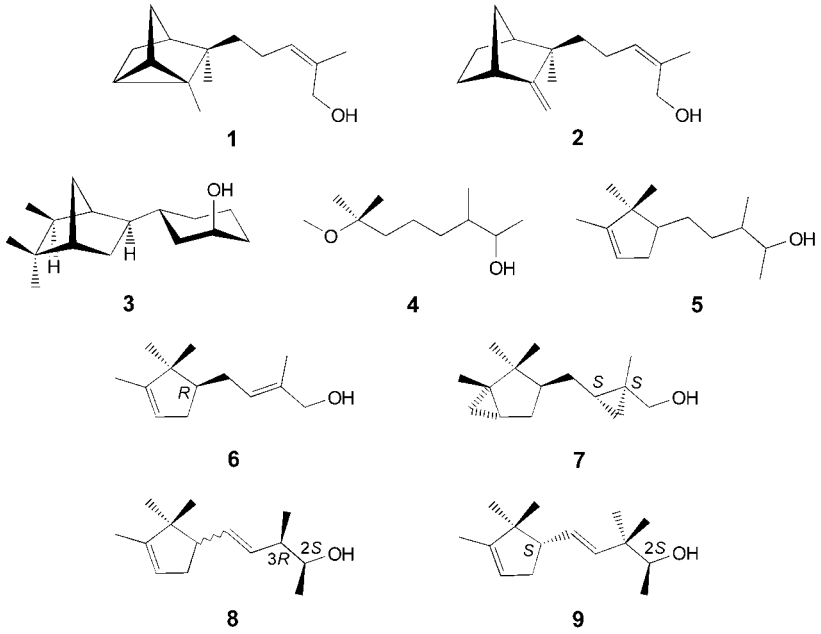
Dedicated to Dr. *Günther Ohloff*, an esteemed friend and teacher and mastermind in flavor and fragrance chemistry, on the occasion of his 80th birthday

The 3-methyl-4-(tricyclo[5.2.1.$0^{2,6}$]dec-4-en-8-ylidene)butan-2-ols (= *Fleursandol®*; *rac*-**10**), a new class of sandalwood odorants, were synthesized in their enantiomerically pure forms by use of tricyclo[5.2.1.$0^{2,6}$]dec-4-en-8-ones **17** and *ent*-**17** and (tetrahydro-2*H*-pyran-2-yl)-protected 4-bromo-3-methylbutan-2-ols **22** and *ent*-**22** as starting materials (*Schemes 2–4*). Only four of 16 possible stereoisomers of *rac*-**10** possess the typical, very pleasant, long-lasting sandalwood odor (*Table 1*). The (2*S*,3*R*,4*E*,1′*R*,2′*R*,6′*R*,7′*R*)-isomer *ent*-**10a** is by far the most important representative, with an odor threshold of 5 μg/l in H_2O.

Introduction. – East-Indian sandalwood oil (*Santalum album* L.) belongs to the oldest known perfumery ingredients [1] and is still today a highly appreciated raw material for fragrances. The qualitative sensory contribution to modern alcoholic fragrances depends on its use level [2]. The first information on the chemical nature of the main compounds in sandalwood oil dates back to 1908 [3], and the first chemical structure of a sesquiterpene alcohol, α-santalol (**1**), was published by *Semmler* four years later [4]. In 1935, *Ruzicka* and *Thomann* elucidated the structure of β-santalol (**2**), the olfactorily most important sandalwood-oil constituent [5]. Forty-five years later, the absolute configuration of the odor-active principle was determined as (−)-(*Z*)-β-santalol (**2**) [6]. But it was not until 1990 that the first total synthesis of enantiomerically pure alcohol **2** was carried out in eleven steps [7]. Despite many synthetic attempts aimed at (−)-**2** or *rac*-**2**, no industrially feasible process has yet been found [8], and the perfumers have, therefore, to rely on either very expensive natural sandalwood oils [9] or cheaper synthetic substitutes [10].

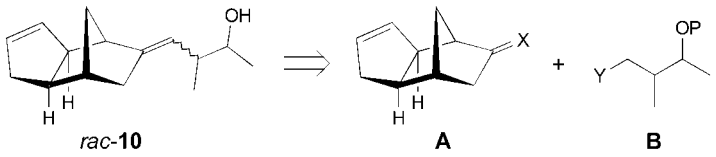
So far, three classes of synthetic sandalwood odorants are of commercial significance, with the last one being by far the most important group [8][10]: *a*) terpenyl-cyclohexanols like *Sandel H&R®* (**3**) [11], *b*) *Osyrol®* (**4**), the only acyclic compound [12], and *c*) α-campholen aldehyde derivatives [13], *e.g.*, *Sandalore®* (**5**). It is commonly known [14] and has been shown for several sandalwood odorants [11a,b] [15], that different diastereoisomers and enantiomers of the same molecular structure, *e.g.*, in *Madrol®* (**6**) [16], *Javanol®* (**7**) [17], *Ebanol®* (**8**) [18], or *Polysantol®* (**9**) [19], can elicit different odor impressions, both qualitatively and quantitatively.



Despite the large variety of commercially available synthetic sandalwood odorants, the search for new aroma chemicals possessing an even more natural, sandalwood-like odor character and/or a different C-skeleton is still ongoing [8].

Here, we report the enantioselective total synthesis of a new class of sandalwood odorants (*Fleursandol*® (*rac*-**10**)) from the tricyclo[5.2.1.$0^{2,6}$]decene building block **A** and butanol derivatives **B** as starting materials (*Scheme 1*). In addition, we present the odor evaluation of the different diastereoisomeric and enantiomeric forms.

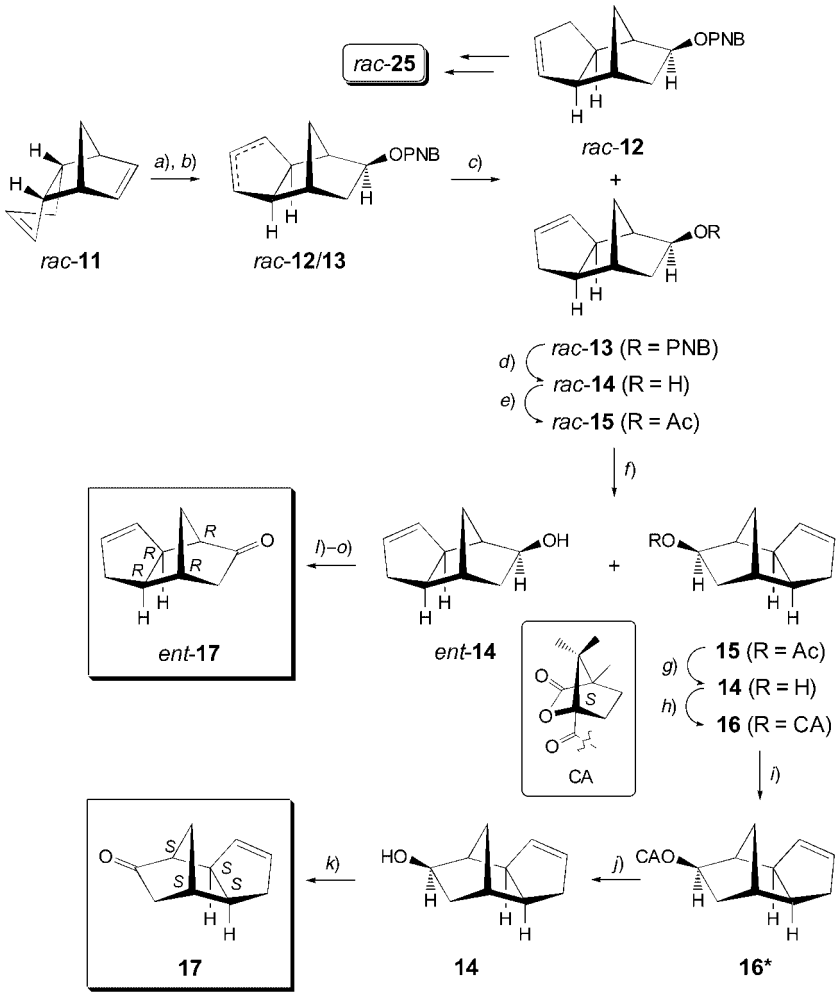
Scheme 1. *Retrosynthetic Analysis of* Fleursandol® (*rac*-**10**)



Results and Discussion. – Ketones **17** and *ent*-**17** are excellent synthons of type **A** that can be coupled *via* a *Grignard*- or *Wittig*-type reaction with halides like **22** and *ent*-**22** (see *Scheme 1*).

Synthesis of the tricyclic ketones **17** and *ent*-**17** started with *endo*-dicyclopentadiene (DCP) *rac*-**11** (*Scheme 2*). Simultaneous acid-catalyzed hydration and rearrangement of the *endo*-skeleton of *rac*-**11** [20] followed by protection of the alcohol function with 4-nitrobenzoyl chloride led to *exo*-isomers *rac*-**12**/**13** in a ratio of 41 : 59. The C=C bond isomers *rac*-**12**/**13** were separated by repeated fractionated crystallization from *tert*-

Scheme 2. *Enantioselective Synthesis of* exo-*Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ones* **17** *and* ent-**17**. PNB = 4-$NO_2C_6H_4CO$.



a) 25% H_2SO_4 soln. *b*) 4-$NO_2C_6H_4COCl$, pyridine; 80% (over two steps). *c*) Repeated crystallization, ^{t}BuOMe; *rac*-**13**, 23%; *rac*-**12**, 15%. *d*) NaOH, MeOH; 96%. *e*) Ac_2O, pyridine; 97%. *f*) Porcine pancreas type-II lipase, phosphate buffer; *ent*-**14**, 55% (ee ≥ 48%); **15**, 45% (ee ≥ 60%). *g*) NaOH, MeOH; 99%. *h*) (−)-(1*S*)-camphanoyl chloride, *N*,*N*-dimethylpyridin-4-amine (DMAP), pyridine; 98%. *i*) Repeated crystallization, Et_2O; 63% (ee > 99%). *j*) NaOH, MeOH. *k*) PDC, CH_2Cl_2, 86% (over two steps). *l*) (+)-(1*R*)-camphanoyl chloride, DMAP, pyridine; 98%. *m*) Repeated crystallization, Et_2O; 36% (ee > 99%). *n*) NaOH, MeOH. *o*) PDC, CH_2Cl_2; 79% (over two steps).

butyl methyl ether (^{t}BuOMe): precipitation of *rac*-**13** was favored, while *rac*-**12** was concentrated in the mother liquor.

Nitrobenzoate *rac*-**13** was then transformed into acetate *rac*-**15**, which was used for the enzymatic resolution of the racemic mixture because alcohol *rac*-**14** proved not to

be a suitable starting material for the separation. Acetate *rac*-**15** was treated with porcine pancreas type-II lipase in a phosphate buffer at pH 7 over 11 days. The transformation was monitored by GC and interrupted upon reaching an alcohol *ent*-**14**/acetate **15** ratio of 55 : 45 [21]. After saponification of acetate **15**, the enantiomer excess (ee) of alcohols **14** (ee $\geq$ 60%) and *ent*-**14** (ee $\geq$ 48%) was determined by chiral GC on a β-cyclodextrin column. Enantiomerically enriched alcohol **14** was treated with (−)-(1*S*)-camphanoyl chloride [22] in pyridine, and the diastereoisomer mixture **16** was repeatedly crystallized from Et_2O to obtain enantiomerically pure **16***. The diastereoisomer excess (de) was monitored *via* ^{13}C-NMR (**16***: C(8′) and C=O at δ 79.0 and 167.1, and at δ 78.9 and 167.0 for corresponding minor diastereoisomer) and the absolute configuration of camphanoyl derivative **16*** was determined relative to (−)-(1*S*)-camphanic acid by X-ray diffractometry of a single crystal (*Fig. 1*)[1]).

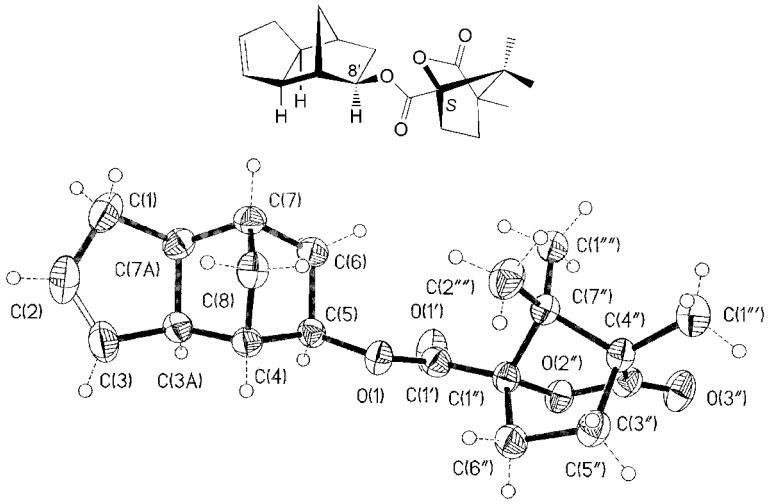


Fig. 1. *X-Ray analysis of camphanic acid ester* **16*** (arbitrary atom numbering)

Ester **16*** was cleaved, and alcohol **14** (ee $\geq$ 99% by chiral GC) was finally oxidized with pyridinium dichromate (PDC) [23] to give ketone **17** in 4.1% overall yield (11 steps). Similarly, alcohol *ent*-**14** was converted into ketone *ent*-**17** (2.6%, 10 steps). For the crystallization, the (1*R*)-camphanate *ent*-**16** was used instead of the corresponding (1*S*)-ester **16**.

(Tetrahydro-2*H*-pyran-2-yl)-protected alcohols **22** and *ent*-**22** were selected as target molecules for synthon **B** [24]. The synthesis started from ester *rac*-**18**, which was prepared *via Baylis–Hillman* reaction from acetaldehyde and butyl propenoate with DABCO (1,4-diazabicyclo[2.2.2]octane) in 95% yield [25] (*Scheme 3*). Alcohol *rac*-**18** was enzymatically cleaved with *Pseudomonas* AK lipase and vinyl acetate in hexane [26], and finally separated to yield 41% of (−)-(*S*)-ester *ent*-**18** and 43% of (+)-(*R*)-acetate **19**. For the determination of the e.e., a small sample of *ent*-**18** was acetylated to

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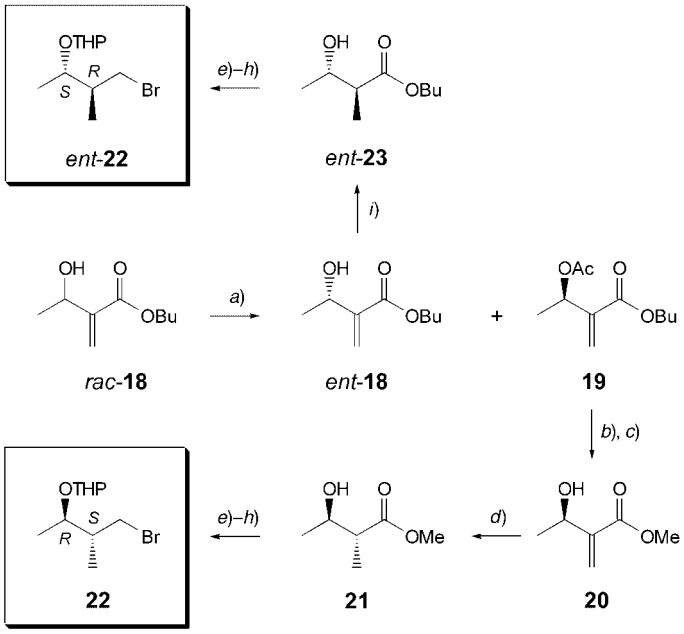
[1]) X-Ray analysis was accomplished by Dr. *Mathias Noltemeyer*, Georg-August-Universität Göttingen, Institut für Anorganische Chemie, Tammannstraße 4, D-37077 Göttingen.

ent-**19** (ee $\geq$ 99%) and analyzed analogously to **19** (ee $\geq$ 98%) on a β-cyclodextrin GC column. Saponification of acetate **19** gave the corresponding β-hydroxy acid, which was transformed into the methyl ester **20** with diazomethane [27]. Alkenes **20** and *ent*-**18** were quantitatively hydrogenated with a rhodium(I) catalyst to give exclusively *anti*-isomers **21** and *ent*-**23**, respectively [28]. Alcohols **21** and *ent*-**23** were transformed into (tetrahydro-2*H*-pyran-2-yl) (THP)-protected bromo compounds **22** and *ent*-**22**, respectively, in four steps, *i.e.*, protection of the OH group with 3,4-dihydro-2*H*-pyran [29], ester reduction with $LiAlH_4$, conversion of the corresponding alcohol into the tosylate, and *Finkelstein* reaction.

Scheme 3. *Synthesis of Enantiomerically Pure 4-Bromo-3-methylbutan-2-ol Derivatives* **22** *and* ent-**22**

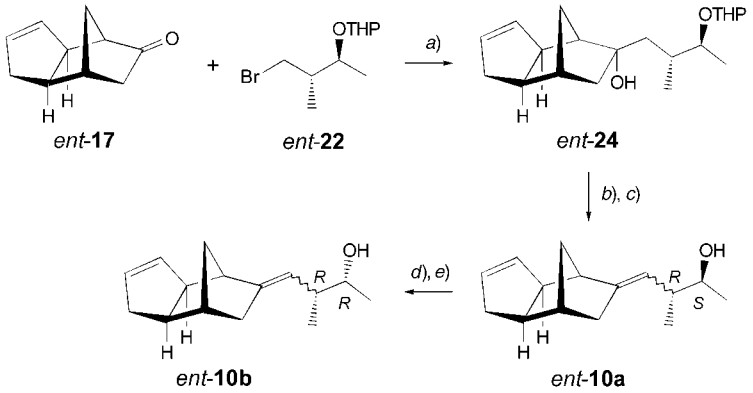


a) *Pseudomonas* AK lipase, vinyl acetate, hexane; *ent*-**18**, 41% (ee $\geq$ 99%); **19**, 43% (ee > 98%). *b*) NaOH, MeOH. *c*) CH_2N_2, Et_2O; 83% (over two steps). *d*) [1,4-bis(diphenylphosphino)butane](norborna-2,5-diene)rhodium(I) tetrafluoroborate, H_2, CH_2Cl_2; 98% (de > 99%). *e*) 3,4-Dihydro-2*H*-pyran, TsOH, Et_2O. *f*) $LiAlH_4$, THF. *g*) TsCl, *N*,*N*,*N*′,*N*′-tetramethylhexane-1,6-diamine, pyridine. *h*) LiBr, acetone, 80% (over four steps). *i*) Rh^I catalyst (see *d*), H_2, CH_2Cl_2; 98% (de > 99%).

With both enantiomerically pure substrates **17** and *ent*-**17** and **22** and *ent*-**22** in hand, the synthesis of the tricyclic target molecules **10** and *ent*-**10** was straightforward, as exemplified in *Scheme 4* (*Entry 1*).

Lithium *Grignard* reaction [30] of ketone *ent*-**17** with bromide *ent*-**22** gave alcohol *ent*-**24**, which was dehydrated with phosphoryl chloride ($POCl_3$) in pyridine [31], and finally deprotected to give *anti*-alcohol *ent*-**10a** as a 80:20 mixture of (*E*/*Z*)-isomers. Similar results were observed for **10a** (*Entry 3*); however, for *ent*-**10c** and **10c** (*Entries 2* and *4* resp.), the (*E*/*Z*) ratio changed to 20:80 pointing to a huge influence of the side-chain configuration on the elimination reaction [32]. However, we were not able until

Scheme 4. *Synthesis of 3-Methyl-4-(*exo*-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene)butan-2-ol Stereoisomers* **10** *and* ent-**10**



Entry	Ketone	Bromide	Tricycle	(*E*/*Z*)
1	*ent*-**17**	*ent*-**22**	*ent*-**10a**, *ent*-**10b**	80:20
2	*ent*-**17**	**22**	*ent*-**10c**, *ent*-**10d**	20:80
3	**17**	**22**	**10a**, **10b**	80:20
4	**17**	*ent*-**22**	**10c**, **10d**	20:80

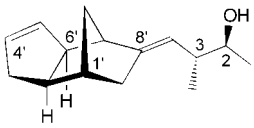
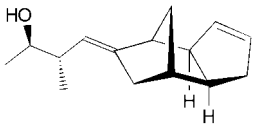
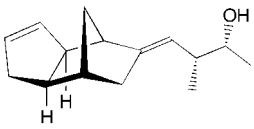
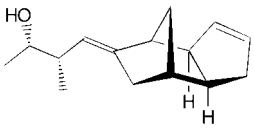
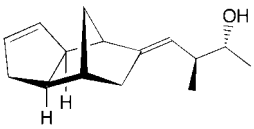
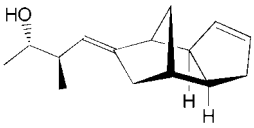
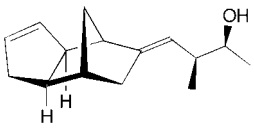
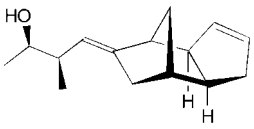
a) Li, THF. *b*) $POCl_3$, pyridine. *c*) TsOH, THF, MeOH; 58% (over three steps). *d*) PhCOOH, diethyl azodicarboxylate (DEAD), Ph_3P, THF. *e*) NaOH, MeOH, 52% (over two steps).

now to establish whether this is due to steric hindrance of the Me group or to an interaction of the THP-protected OH function.

The *anti*-alcohols **10a** and *ent*-**10a**, and **10c** and *ent*-**10c** were finally converted into the corresponding *syn*-products **10b** and *ent*-**10b**, and **10d** and *ent*-**10d**, respectively, *via Mitsunobu* reaction [33] and subsequent saponification of the corresponding benzoates (*Scheme 4*).

All 16 diastereoisomers (*E*/*Z*)-**10a**–**d** and (*E*/*Z*)-*ent*-**10a**–**d** were evaluated by GC olfactometry [34]. Only the (*E*)-isomers contribute significantly to the odor, while the corresponding (*Z*)-isomers are nearly odorless. Moreover, it is obvious that the configuration of the tricyclic skeleton has a huge impact on the odor impression and the odor-detection threshold (*Table 1*). Compounds *ent*-**10a**–**d** with a (1′*R*,2′*R*,6′*R*,7′*R*) configuration of the ring system possess the characteristic long-lasting sandalwood odor, while compounds **10a**–**d** are significantly weaker and smell woody to floral. It is worth mentioning the similar enantiospecificity of odor observed for the bicyclic sandalwood constituent β-santalol (**2**), which has a strong sandalwood smell, whereas the enantiomer *ent*-**2** is odorless [7b]. Similar discoveries were made for sandalwood

Table 1. *Single Stereoisomers of (*exo-*Tricyclodecenylidene)butanols:* **10** *Structure–Odor Relationship* (SOR)

	Configuration	Structure	Odor	Threshold[a])
ent-**10a**	(2*S*,3*R*,1′*R*,2′*R*,6′*R*,7′*R*)		Very strong, sandalwood, animalic	5
10a	(2*R*,3*S*,1′*S*,2′*S*,6′*S*,7′*S*)		Week woody	168
ent-**10b**	(2*R*,3*R*,1′*R*,2′*R*,6′*R*,7′*R*)		Sandalwood, floral	137
10b	(2*S*,3*S*,1′*S*,2′*S*,6′*S*,7′*S*)		Very week, floral	159
ent-**10c**	(2*R*,3*S*,1′*R*,2′*R*,6′*R*,7′*R*)		Sandalwood, animalic	70
10c	(2*S*,3*R*,1′*S*,2′*S*,6′*S*,7′*S*)		Woody	72
ent-**10d**	(2*S*,3*S*,1′*R*,2′*R*,6′*R*,7′*R*)		Strong, sandalwood, floral	46
10d	(2*R*,3*R*,1′*S*,2′*S*,6′*S*,7′*S*)		Weak floral	204

[a]) Odor-detection threshold in H_2O in μg/l.

odorant **3** where also enantiomer *ent*-**3** is much weaker and does not have the typical sandalwood smell [11a,b] [15c]. The similarity between β-santalol (**2**), *Sandel H&R*® (**3**), and *Fleursandol*® (*rac*-**10**) can probably be explained by regarding the tricyclic

skeleton of **10** and *ent*-**10** as a substituted bicyclo[2.2.1]heptane, the ring system of both alcohol **2** as well as **3**.

Moreover, the configuration of the side-chain – especially at position C(2) – is important for the odor intensity. The (2*S*)-configured molecules *ent*-**10a** (5 μg/l) and *ent*-**10d** (46 μg/l) possess by far the lowest odor-detection threshold in H_2O of all *Fleursandol*® isomers. These results are in excellent agreement with previous findings both for *Ebanol*® (**8**) [18a] and *Polysantol*® (**9**) [19a], where also the most intense isomer has (*S*)-configuration at side-chain position C(2). The optimum configuration of the side chain in terms of threshold seems to be (2*S*,3*R*). This is supported not only by the fact that *ent*-**10a** has the lowest threshold of all isomers, but also by alcohol **10c**, which has the lowest threshold (72 μg/l) of the non-sandalwood-smelling isomers. Similar results were obtained for *Ebanol*® (**8**) having the same side-chain as *Fleursandol*® (*rac*-**10**) [18a], and also the (2*S*,3*R*)-configured molecules as odor-predominant isomers.

In addition to the above-described 16 stereoisomers, we also evaluated the odor of the C=C bond isomers *rac*-**25** and the *endo*-isomers *rac*-**26** and *rac*-**27** [35] (*Fig. 2*). None of the 48 possible stereoisomers has a sandalwood odor, they are either odorless or smell weakly woody to herbaceous.

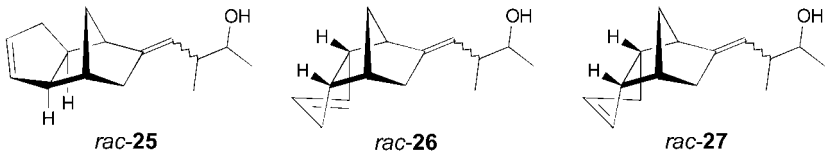


Fig. 2. *Double-bond and* endo-*isomers of* exo-*tricyclo[5.2.1.0^{2,6}]dec-4-ene* rac-**10**

Conclusions. – The synthesis of all isomers of the new tricyclic sandalwood odorant *Fleursandol*® (*rac*-**10**) was realized starting from the enantiomerically pure ketones **17** and *ent*-**17** and bromides **22** and *ent*-**22**. We could show that only four of 16 possible stereoisomers possess a long-lasting sandalwood odor, (*E*)-isomer *ent*-**10a** possessing by far the lowest detection threshold (5 μg/l). The multifaceted odor of *Fleursandol*® (*rac*-**10**) is very reminiscent to East-Indian sandalwood oil [9b,c], the benchmark for sandalwood aroma chemicals.

Sandalwood odorants, including alcohol *rac*-**10**, are excellent examples to illustrate the influence of diastereo- as well as enantioselectivity in odor perception [15]. In addition, alcohol *rac*-**10** nicely confirms the hypothesis put forward by *Kraft* and *Fráter* about the enantioselectivity of odor perception [36] and endorses very well various sandalwood olfactophore models [15c][37].

We are especially grateful to Dr. *Mathias Noltemeyer*, Institut für Anorganische Chemie, Georg-August-Universität Göttingen, for the crystal structure analysis and helpful discussions. We thank our colleagues *Stephan Seilwind*, *Angelika Lückhoff*, *Birgit Kohlenberg*, and *Ferdinand Schröder* for NMR, GC/MS, and HR-MS measurements, and *Benjamin Rost* for the determination of odor thresholds.

Experimental Part

1. General. All reagents and solvents were commercial products (*Fluka*, *Aldrich*, or *Lancaster*) and used as received. All reactions were monitored by TLC. Reaction mixtures were washed with 5% Na_2CO_3, NaOH, and brine solns. or 10% H_2SO_4 soln. and dried (Na_2SO_4), unless otherwise noted. Column chromatography (CC): *Merck* silica gel *60* (63–200 μm). Diastereoisomer ratios (d.r.) and (*E*/*Z*) ratios were determined by GC unless otherwise stated. GC: *Hewlett-Packard 6890* with FID and GC sniffing port; He; column: *DB-Wax*, 60 m × 0.25 mm × 0.25 μm, 50–240° at 4°/min, or *HP5*, 60 m × 0.25 mm × 0.25 μm, 60–250° at 4°/min. Chiral GC: *Hewlett Packard 6890* with FID; He; column: *Ivadex-7* (=2,3-di-*O*-ethyl-6-*O*-[(*tert*-butyl)dimethylsilyl]-β-cyclodextrin (30%) and *PS 086* (70%)), 25 m × 0.25 mm × 0.25 μm, 80–150° with 1°/min. M.p. *Mettler Toledo FP83*; not corrected. $[\alpha]_D$: *Dr.-Kernchen-Propol* polarimeter; in $CHCl_3$ at 20° with concentrations *c* expressed in g/100 ml. NMR: *Varian VXRS-300*; 300 (^{1}H) and 75.45 MHz (^{13}C); in $CDCl_3$ with $SiMe_4$ as internal standard; chemical shifts δ in ppm and coupling constants *J* in Hz. GC/MS: *Hewlett-Packard 5973N*; He; column: *DB-Wax*, 60 m × 0.25 mm × 0.25 μm, 60–240° at 4°/min); EI mode (70 eV); in *m*/*z* (%). HR-MS: *MAT 8200 Finnigan* in EI mode (70 eV).

2. *Ketones* **17** *and* ent-**17**. *(1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-Tricyclo[5.2.1.0^{2,6}]dec-3-en-8-yl 4-Nitrobenzoate* (*rac*-**12**) *and (1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl 4-Nitrobenzoate* (*rac*-**13**). Dicyclopentadiene *rac*-**11** (264 g, 2 mol) and 25% H_2SO_4 soln. (800 g) were stirred under reflux for 5 h. After cooling to r.t., toluene (500 ml) was added and the org. layer neutralized with Na_2CO_3 and evaporated. The residue was purified by fractional distillation to yield 243 g (81%) of alcohol mixture.

To the alcohol mixture (150 g, 1 mol) in anh. pyridine (500 ml), 4-nitrobenzoyl chloride (230 g, 1.24 mol) was added portionwise under stirring at 0–5°, and stirring was continued at r.t. overnight. H_2O (600 ml) was added, and stirring was continued for 1 h. After addition of toluene (600 ml), the org. layer was washed with H_2SO_4 soln., neutralized with Na_2CO_3, and evaporated. The amorphous raw material (298 g, 99%) containing *rac*-**12**/*rac*-**13** 41:59 (by ^{1}H-NMR) was subjected to repeated fractional crystallization from ^{t}BuOMe: *rac*-**13** (70 g, 23%) and *rac*-**12** (46 g, 15%).

Data of rac-**12**: Colorless powder. M.p. 104–104.5°. ^{1}H-NMR: 1.45 (br. *s*, CH_2(10)); 1.64 (*ddd*, *J* = 13.5, 4.0, 2.5, H_a–C(9)); 1.92–2.03 (*m*, H_b–C(9), H_a–C(5)); 2.15–2.26 (*m*, H–C(1), H–C(6), H–C(7)); 2.58–2.66 (*m*, H–C(2)); 2.67 (*ddddd*, *J* = 17.5, 9.7, 2.1, 2.1, 1.3, H_b–C(5)); 4.92 (*dd*, *J* = 7.0, 2.0, H–C(8)); 5.49 (*dddd*, *J* = 5.3, 2.4, 2.4, 2.4, H–C(3)); 5.72 (*dddd*, *J* = 5.7, 1.8, 1.8, 1.8, H–C(4)); 8.18 (*m*, *J* = 9.0, 2 H_o); 8.27 (*m*, *J* = 9.0, 2 H_m). ^{13}C-NMR: 29.2 (*t*, C(10)); 38.8 (*d*, C(6)); 39.2 (*t*, C(5)); 39.2 (*t*, C(9)); 39.5 (*d*, C(1)); 48.5 (*d*, C(7)); 54.9 (*d*, C(2)); 78.6 (*d*, C(8)); 123.5 (2*d*, C_m); 130.6 (2*d*, C_o); 131.8 (*d*, C(3)); 132.4 (*d*, C(4)); 136.1 (*s*, C_{ipso}); 150.4 (*s*, C_p); 164.3 (*s*, C=O).

Data of rac-**13**: Colorless powder. M.p. 134.0–134.5°. ^{1}H-NMR: 1.41 (*d*, *J* = 11.5, H_a–C(10)); 1.45 (*d*, *J* = 11.5, H_b–C(10)); 1.59 (*ddd*, *J* = 13.5, 4.0, 2.5, H_a–C(9)); 1.86–1.99 (*m*, H_a–C(3), H_b–C(9)); 2.08–2.20 (*m*, H–C(1), H–C(2)); 2.30 (br. *s*, H–C(7)); 2.60 (*ddddd*, *J* = 17.0, 9.5, 2.2, 2.2, 1.3, H_b–C(3)); 2.64–2.72 (*m*, H–C(6)); 4.93–5.00 (*m*, H–C(8)); 5.47 (*dddd*, *J* = 5.7, 2.2, 2.2, 2.2, H–C(5)); 5.73 (*dddd*, *J* = 5.7, 1.8, 1.8, 1.8, H–C(4)); 8.18 (*m*, *J* = 9.0, 2 H_o); 8.27 (*m*, *J* = 9.0, 2 H_m). ^{13}C-NMR: 29.1 (*t*, C(10)); 39.2 (*t*, C(9)); 39.3 (*t*, C(3)); 41.9 (*d*, C(1)); 42.9 (*d*, C(2)); 46.0 (*d*, C(7)); 50.8 (*d*, C(6)); 79.2 (*d*, C(8)); 123.4 (2*d*, C_m); 130.6 (2*d*, C_o); 130.7 (*d*, C(5)); 132.9 (*d*, C(4)); 136.1 (*s*, C_{ipso}); 150.4 (*s*, C_p); 164.3 (*s*, C=O).

*(1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ol* (*rac*-**14**). A soln of *rac*-**13** (59.8 g, 0.2 mol) and 50% NaOH soln. (20 g, 0.25 mol) in MeOH (250 ml) was stirred under reflux for 2 h. MeOH was evaporated, the residue taken up in H_2O, and the aq. layer extracted with toluene. The org. layers were washed with H_2O, dried, and evaporated. Bulb-to-bulb distillation of the residue yielded 29 g (96%) of *rac*-**14**. ^{1}H-NMR: 1.21–1.30 (*m*, H_a–C(9), H_a–C(10)); 1.38 (*ddddd*, *J* = 10.3, 1.5, 1.5, 1.5, 1.5, H_b–C(10)); 1.66 (*ddd*, *J* = 13.2, 7.0, 2.6, H_b–C(9)); 1.87 (*m*, *J* = 16.8, H_a–C(3)); 1.96–2.06 (*m*, H–C(1), H–C(2)); 1.97 (*d*, *J* = 1.5, H–C(7)); 2.40–2.48 (*m*, H–C(6)); 2.53 (*ddddd*, *J* = 17.2, 9.5, 2.2, 2.2, 1.3, H_b–C(3)); 3.05 (br. *s*, OH), 3.79 (*d*, *J* = 7.0, H–C(8)); 5.42 (*dddd*, *J* = 5.5, 2.2, 2.2, 2.2, H–C(5)); 5.66 (*dddd*, *J* = 5.5, 2.0, 2.0, 2.0, H–C(4)). ^{13}C-NMR: 28.0 (*t*, C(10)); 39.2 (*t*, C(3)); 41.7 (*t*, C(9)); 42.0 (*d*, C(1)); 42.9 (*d*, C(2)); 48.7 (*d*, C(7)); 51.2 (*d*, C(6)); 74.5 (*d*, C(8)); 131.2 (*d*, C(5)); 132.3 (*d*, C(4)). GC/MS: 150 (45, M^+), 132 (38), 117 (78), 105 (31), 91 (60), 83 (42), 79 (30), 77 (32), 67 (34), 66 (100). HR-MS: 150.1051 ($C_{10}H_{14}O^+$; calc. 150.1045).

*(1*RS,*2*RS,*6*RS,*7*RS,*8*SR*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl Acetate* (*rac*-**15**): Ac_2O (15 g, 0.148 mol) was added dropwise to a suspension of *rac*-**14** (18.5 g, 0.123 mol), toluene (40 ml), and Na_2CO_3 (1.5 g) under reflux. After 1 h, the mixture was cooled to 80°, H_2O (25 ml) was added, and the mixture was further stirred for 15 min. The org. layer was washed with Na_2CO_3 soln. and evaporated: *rac*-**15** (23.1 g, 97%). Light yellow oil. ^{1}H-NMR: 1.32 (br. *s*, CH_2(10)); 1.39 (*ddd*, *J* = 13.5, 4.0, 2.5, H_a–C(9)); 1.76 (*dd*, *J* = 13.5, 7.0, H_b–C(9)); 1.84–1.94

(*m*, H_a–C(3)); 1.97–2.09 (*m*, H–C(1), H–C(2)); 2.01 (*s*, MeCO); 2.12 (*s*, H–C(7)); 2.50–2.62 (*m*, H_b–C(3), H–C(6)); 4.66 (*dd*, *J* = 7.0, 2.5, H–C(8)); 5.43 (*dddd*, *J* = 5.5, 2.0, 2.0, 2.0, H–C(5)); 5.69 (*dddd*, *J* = 5.5, 2.0, 2.0, 2.0, H–C(4)). ^{13}C-NMR: 21.4 (*q*, *Me*CO); 28.8 (*t*, C(10)); 39.1 (*t*, C(9)); 39.3 (*t*, C(3)); 41.9 (*d*, C(1)); 42.9 (*d*, C(2)); 45.9 (*d*, C(7)); 50.9 (*d*, C(6)); 77.5 (*d*, C(8)); 130.9 (*d*, C(5)); 132.7 (*d*, C(4)); 170.7 (*s*, Me*C*O). GC/MS: 192 (40, M^+), 124 (81), 117 (62), 105 (30), 91 (45), 83 (52), 82 (47), 67 (48), 66 (100), 43 (65). HR-MS: 192.1138 ($C_{12}H_{16}O_2^+$ + ; calc. 192.1150).

*(1*R*,2*R*,6*R*,7*R*,8*S*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ol* (*ent*-**14**) *and (1*S*,2*S*,6*S*,7*S*,8*R*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl Acetate* (**15**). Porcine-pancreas type-II lipase (5 g) was suspended in phosphate buffer (430 ml, pH 7) under stirring. After 30 min, the suspension was adjusted with 1M NaOH to pH 7. Then *rac*-**15** (11.50 g, 60 mmol) was added, and the suspension was stirred for 11 days at r.t. During this time, the suspension was adjusted to pH 7 at regular intervals with 1M NaOH, and additional lipase (11 g) was added. The conversion was monitored by GC and interrupted upon reaching a alcohol acetate ratio of 55 : 45 (GC). After addition of H_2O (500 ml), the aq. layer was extracted with ^{t}BuOMe, the org. layer washed with NaCl soln., dried, and evaporated, and the residue purified by CC (cyclohexane/AcOEt 95 : 5 → 80 : 20): **15** (5.2 g, 60% ee) and *ent*-**14** (4.9 g, 48% ee). Colorless oils.

*(1*S*,2*S*,6*S*,7*S*,8*R*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ol* (**14**). A soln. of **15** (5.2 g, 27 mmol; 60% ee) in MeOH (35 ml) and 50% NaOH soln. (5 ml) were heated under reflux for 2 h. After addition of H_2O (100 ml), the aq. layer was extracted with Et_2O, the org. layer washed with NaCl soln., dried, and evaporated and the residue purified by CC (cyclohexane/AcOEt 9 : 1 → 8 : 2): **14** (4.06 g, 60% ee). Pale yellow oil.

*(1*S*,2*S*,6*S*,7*S*,8*R*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate* (**16***). (–)-(*S*)-Camphanoyl chloride (5.96 g, 28 mmol) and DMAP (40 mg) were added to a soln. of **14** (4 g, 27 mmol, 60% ee) in pyridine (40 ml), and stirring was continued at r.t. overnight. After addition of H_2O (100 ml) and acidification with 20% H_2SO_4 soln. the aq. layer was extracted with Et_2O, the org. layer washed with Na_2CO_3 and NaCl soln., dried, and evaporated, and the obtained diastereoisomer mixture **16** repeatedly crystallized from Et_2O (^{13}C-NMR monitoring): **16*** (4.31 g, 63%). The configuration of **16*** was determined by X-ray-analysis (see below). Colorless needles. M.p. 127.5–128°. ^{1}H-NMR (primed locants for tricyclodecenyl): 0.96, 1.05 (2*s*, 2Me–C(7)); 1.11 (*s*, Me–C(4)); 1.34 (br. *s*, CH_2(10′)); 1.48 (*ddd*, *J* = 13.7, 4.2, 2.4, H_a–C(9′)); 1.67 (*ddd*, *J* = 13.7, 9.2, 4.2, H_a–C(5)); 1.82 (*dd*, *J* = 13.5, 6.6, H_b–C(9′); 1.85–2.15 (*m*, H–C(1′), H–C(2′), H_a–C(3′), H_b–C(5), H_a–C(6)); 2.16 (br. *s*, H–C(7′)); 2.41 (*ddd*, *J* = 13.3, 10.4, 4.4, H_b–C(6)); 2.50–2.68 (*m*, H_b–C(3′), H–C(6′)); 4.83 (dd, *J* = 7.0, 2.2, H–C(8′)); 5.44 (*dddd*, *J* = 5.5, 2.4, 2.4, 2.4, H–C(5′)); 5.71 (*dddd*, *J* = 5.5, 2.0, 2.0, 2.0, H–C(4′)). ^{13}C-NMR: 9.7 (*q*, *Me*–C(4)); 16.7, 16.8 (2*q*, 2*Me*–C(7)); 28.9 (*t*, C(10′)); 28.9 (*t*, C(5)); 30.5 (*t*, C(6)); 39.0 (*t*, C(9′)); 39.2 (*t*, C(3′)); 41.8 (*d*, C(1′)); 42.9 (*d*, C(2′)); 46.0 (*d*, C(7′)); 50.7 (*d*, C(6′)); 54.1 (*s*, C(7)); 54.8 (*s*, C(4)); 79.0 (*d*, C(8′)); 91.0 (*s*, C(1)); 130.6 (*d*, C(5′)); 133.0 (*d*, C–(4′)); 167.1 (*s*, O=C–C(1)); 178.3 (*s*, C(3)).

*(1*R*,2*R*,6*R*,7*R*,8*S*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl (1*R*,4*S*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate* (*ent*-**16***). As described for **16***, with *ent*-**14** (2.32 g, 15 mmol; 48% ee) and (+)-(*R*)-camphanoyl chloride (3.4 g, 16 mmol). Repeated crystallization of the diastereoisomer mixture *ent*-**16** afforded *ent*-**16*** (2.77 g, 36%). Colorless needles. M.p. 127.5–128°. Spectral data: corresponding to those of **16***.

*(1*S*,2*S*,6*S*,7*S*,8*R*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-one* (**17**). A 50% NaOH soln. (5 g, 62.5 mmol) was added to **16*** (4.31 g, 14 mmol) in MeOH (50 ml). After refluxing for 2 h, H_2O (100 ml) was added, the aq. layer extracted with Et_2O, and the org. layer washed with NaCl soln., dried, and evaporated: **14** (1.95 g, > 99% ee).

PDC (6.77 g, 18 mmol) was added to a soln. of **14** (1.95 g) in CH_2Cl_2 (100 ml) followed by stirring at r.t. overnight. The mixture was filtered over SiO_2, the filtrate evaporated, and the residue purified by CC (cyclohexane/AcOEt 9 : 1 → 8 : 2): **17** (1.74 g, 86% over 2 steps). Colorless oil. ^{1}H-NMR: 1.52 (*ddddd*, *J* = 10.5, 1.3, 1.3, 1.3, 1.3, H_a–C(10)); 1.62–1.70 (*m*, H_b–C(10)); 1.87 (*dd*, *J* = 17.5, 4.2, H_a–C(9)); 1.98–2.10 (*m*, H_a–C(3), H_b–C(9)); 2.32–2.42 (*m*, H–C(1), H–C(2), H–C(7)); 2.71 (*ddddd*, *J* = 17.5, 9.5, 2.3, 2.3, 1.3, H_b–C(3)); 2.90–2.98 (*m*, H–C(6)); 5.45 (*dddd*, *J* = 5.5, 2.2, 2.2, 2.2, H–C(5)); 5.79 (*dddd*, *J* = 5.7, 2.2, 2.2, 2.2, H–C(4)). ^{13}C-NMR: 30.9 (*t*, C(10)); 39.6 (*t*, C(3)); 41.7 (*d*, C(1)); 42.3 (*d*, C(2)); 45.2 (*t*, C(9)); 50.0 (*d*, C(7)); 53.9 (*d*, C(6)); 129.4 (*d*, C(5)); 133.3 (*d*, C(4)); 217.5 (*s*, C(8)). GC/MS: 148 (100, M^+), 105 (35), 104 (26), 92 (38), 91 (57), 79 (49), 78 (28), 77 (32), 67 (21), 66 (35). HR-MS: 148.0876 ($C_{10}H_{12}O^+$; calc. 148.0888).

*(1*R*,2*R*,6*R*,7*R*,8*S*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-one* (*ent*-**17**). As described for **17**, with *ent*-**16*** (2.77 g, 8.4 mmol): *ent*-**14** (1.25 g, > 99% ee). Then with *ent*-**14** (1.2 g, 3.6 mmol) and PDC (3.76 g, 10 mmol): *ent*-**17** (1.03 g, 79% over two steps). Colorless oil. Spectral data: corresponding to those of **17**.

3. *X-Ray Analysis*[2]) *of* **16*** (see also *Table 2* and *Fig. 2*). All measurements were performed on a *Stoe* four-circle diffractometer with graphite-monochromated MoK_α radiation (λ 71.069 pm). The structure was solved and refined with the SHELXTL system of programs [38]. The absolute configuration was assigned according to the (−)-(1*S*)-camphanoyl residue contained in **16***. All H-atoms were fixed in geometrically calculated positions (d(C−H) = 95 pm) and given isotropic displacement factors of 1.2 U_{eq} of its parent atom.

Table 2. *Crystal Data and Structure Refinement for* **16***

Crystallized from	Et_2O
Empirical formula	$C_{20}H_{26}O_4$
M_r	330.41
Temperature	200(2) K
Wavelength	71.073 pm
Crystal system	monoclinic
Space group	$P2(1)$
Unit-cell dimensions	$a = 635.33(8)$ pm, $\alpha = 90°$ $b = 972.69(12)$ pm, $\beta = 94.105(11)°$ $c = 1420.3(2)$ pm, $\gamma = 90°$
Volume	0.8754(2) nm^3
Z	2
Density (calc.)	1.253 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
$F(000)$	356
Crystal size	1.00 × 0.30 × 0.20 mm
θ Range for data collection	3.56 to 25.01°
Index ranges	$-7 \le h \le 7$, $-11 \le k \le 11$, $-16 \le l \le 16$
Reflections collected	2252
Independent reflections	2176 ($R_{int} = 0.0454$)
Refinement method	full-matrix least-squares on F^2
Data, restraints, parameters	2175, 1, 220
Goodness-of-fit on F^2	1.067
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0370$, $wR_2 = 0.0882$
R indices (all data)	$R_1 = 0.0418$, $wR_2 = 0.0930$
Absolute structure parameter	−1.22(127)
Largest diff. peak and hole	0.127 and −0.186 e·Å^{-3}

4. *Tetrahydropyranyl-Protected 4-Bromo-3-methylbutan-2-ols* **22** *and* ent-**22**. *Butyl 3-Hydroxy-2-methylenebutanoate* (*rac*-**18**). According to [25], *rac*-**18** was prepared in 96% yield. ^{1}H-NMR: 0.96 (t, J = 7.5, Me(4′)); 1.36 (d, J = 6.5, Me(4)); 1.36–1.48 (m, CH_2(3′)); 1.62–1.72 (m, CH_2(2′)); 3.53 (br. s, OH); 4.18 (t, J = 6.5, CH_2(1′)); 4.62 (q, J = 6.5, H−C(3)); 5.86 (dd, J = 1.3, 1.3, 1 H, CH_2=C(2)); 6.20 (dd, J = 1.3, 0.8, 1 H, CH_2=C(2)). ^{13}C-NMR: 13.7 (q, C(4′)); 19.3 (t, C(3′)); 22.5 (q, C(4)); 30.7 (t, C(2′)); 64.7 (t, C(1′)); 66.6 (d, C(3)); 123.6 (t, CH_2=C(2)); 144.4 (s, C(2)); 166.7 (s, C(1)). GC/MS: 157 (35, $[M - Me]^+$), 101 (100), 99 (51), 98 (46), 83 (53), 73 (44), 55 (54), 43 (56), 41 (69), 29 (96), 27 (79).

*Butyl (−)-(3*S*)-3-Hydroxy-2-methylenebutanoate* (*ent*-**18**) *and Butyl (+)-(3*R*)-3-(Acetyloxy)-2-methylenebutanoate* (**19**). According to [26], *rac*-**18** (86 g, 0.5 mol) was converted to *ent*-**18** (35.3 g, 41%; $[\alpha]_D = -11.85$ (c = 2.5); >99.5% ee) and **19** (46 g, 43%; >98% ee). **19**: $[\alpha]_D = +10.36$ (c = 2.6). ^{1}H-NMR: 0.95 (t, J = 7.4, Me(4′)); 1.40 (d, J = 6.5, Me(4)); 1.36–1.46 (m, J = 7.5, CH_2(3′)); 1.62–1.70 (m, J = 7.5, CH_2(2′)); 2.07 (s, MeCO); 4.18 (t, J = 6.5, CH_2(1′)); 4.62 (ddq, J = 6.5, 1.3, 0.6, H−C(3)); 5.78 (dd, J = 1.3, 1.0, 1 H, CH_2=C(2)); 6.28 (dd, J = 1.0, 0.6, 1 H, CH_2=C(2)). ^{13}C-NMR: 13.7 (q, C(4′)); 19.2 (t, C(3′)); 20.2 (q, C(4));

[2]) CCDC-226443 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

21.2 (*q*, *Me*CO); 30.6 (*t*, C(2′)); 64.8 (*t*, C(1′)); 68.3 (*d*, C(3)); 124.5 (*t*, *C*H_2=C(2)); 141.3 (*s*, C(2)); 165.4 (*s*, C(1)); 169.8 (*s*, Me*C*O).

*Methyl (2*R,*3*R*)-3-Hydroxy-2-methylenebutanoate* (**20**). Ester **19** (21.4 g, 0.1 mol) was refluxed with a soln. of NaOH (8.4 g, 0.21 mol) in EtOH (100 ml) and H_2O (10 ml). EtOH was evaporated, H_2O (200 ml) added, and the aq. layer extracted with Et_2O. The aq. layer was adjusted with H_2SO_4 to pH 2.5, saturated with NaCl, and extracted with AcOEt. The extract was dried and evaporated: (3*R*)-3-hydroxy-2-methylenebutanoic acid (11.1 g). ^{1}H-NMR: 1.40 (*d*, *J* = 6.5, Me(4)); 4.69 (*q*, *J* = 6.5, H–C(3)); 5.96 (*s*, 1 H, CH_2=C(2)); 6.35 (*s*, 1 H, CH_2=C(2)); 8.22 (br. *s*, OH). ^{13}C-NMR: 22.1 (*q*, C(4)); 66.7 (*d*, C(3)); 126.2 (*t*, *C*H_2=C(2)); 143.1 (*s*, C(2)); 170.5 (*s*, C(1)).

Freshly produced CH_2N_2 in 350 ml Et_2O, (*ca.* 0.12 mol) [27] was added to a soln. of the acid (11.1 g) in abs. Et_2O (200 ml) at 0°, followed by stirring for 15 min at r.t. After acidification with AcOH (5 g) and stirring for 5 min at r.t., H_2O (100 ml) was added, the org. layer washed with NaOH soln., dried, and evaporated, and the residue (11.5 g) subjected to bulb-to-bulb distillation: **20** (10.9 g, 83% over two steps). GC/MS: 115 (73, [*M* – Me]$^+$), 98 (27), 87 (43), 83 (100), 55 (73), 45 (29), 43 (85), 29 (38), 27 (55).

*Methyl (2*R,*3*R*)-3-Hydroxy-2-methylbutanoate* (**21**). A soln. of **20** (10.9 g, 84 mmol) in CH_2Cl_2 (50 ml) was degassed with N_2. After addition of [1,4-bis(diphenylphosphino)butane](norborna-2,5-diene)rhodium(I) tetrafluoroborate (50 mg), the soln. was stirred for 3 h under H_2 (0.5–1 MPa) at r.t. After evaporation, the residue was bulb-to-bulb distilled: **21** (10.9 g, 98%; 98% de). Colorless oil. ^{1}H-NMR: 1.15 (*d*, *J* = 7.0, Me–C(2)); 1.20 (*d*, *J* = 6.5, Me(4)); 2.49 (*dq*, *J* = 7.0, 7.0, H–C(2)); 3.55 (br. *s*, OH); 3.70 (*s*, Me(1′)); 3.92 (*dq*, *J* = 6.5, 7.0, H–C(3)). ^{13}C-NMR: 13.5 (*q*, *Me*–C(2)); 20.4 (*q*, C(4)); 47.2 (*d*, C(2)); 51.7 (*q*, Me(1′)); 69.2 (*d*, C(3)); 176.2 (*s*, C(1)). GC/MS: 117 (9, [*M* – Me]$^+$), 101 (19), 88 (100), 87 (15), 85 (21), 59 (12), 57 (52), 56 (25), 55 (16), 45 (24), 43 (12).

THP Ether **22** *of (2*R,*3*R*)-4-Bromo-3-methylbutan-2-ol* (*2-[(1*R,*2*R*)-3-Bromo-1,2-dimethylpropoxy]tetrahydro-2*H*-pyran* (**22**)). To a soln. of **21** (17.4 g, 0.1 mol) in anh. Et_2O (100 ml), 3,4-dihydro-2*H*-pyran (10 g, 0.12 mol) was added, and stirring was continued for 4 h. After washing with Na_2CO_3 soln. and evaporation of the solvent, the THP ether of **21** (25.1 g) was obtained. GC/MS (selected diastereoisomer): 257 (trace, [*M* – H]$^+$), 157 (11), 101 (63), 83 (10), 57 (16), 56 (10), 55 (9), 41 (10).

A soln. of THP ether of **21** (25 g) in anh. THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (2.3 g, 0.06 mol) in anh. THF (200 ml) at 0–10°. After refluxing for 1 h, the mixture was carefully quenched with H_2O at 0°. The suspension was filtered, and the filtrate was evaporated to yield the corresponding alcohol (17.9 g). GC/MS (selected diastereoisomer): 187 (peak, [*M* – H]$^+$), 129 (7), 101 (19), 85 (100), 69 (12), 67 (10), 57 (13), 56 (25), 45 (12), 43 (10), 41 (16).

TsCl (12.5 g, 60 mmol) was added to a soln. of the alcohol (9.4 g), Et_3N (12.5 g, 124 mmol), and *N*,*N*,*N*′,*N*′-tetramethylhexane-1,6-diamine (1.0 g) in anh. toluene (100 ml) at 0°, and stirring was continued at 20° overnight. After addition of H_2O (100 ml), the org. layer was washed with H_2SO_4 and Na_2CO_3 soln., dried, and evaporated: corresponding tosylate (17.0 g).

A suspension of this tosylate (17.0 g), freshly dried LiBr (17.4 g, 0.2 mol), Na_2CO_3 (2.5 g), and 4-Å molecular sieves (5 g) in anh. acetone (200 ml) was heated under reflux and N_2 for 3 h. The suspension was filtered over *Celite*, the latter rinsed with CH_2Cl_2, the soln. evaporated, and the residue bulb-to-bulb distilled (1 hPa): **22** (10.5 g, 80% over four steps; d.r. 50:50 by ^{1}H-NMR). ^{1}H-NMR (two diastereoisomers): 1.00, 1.05 (2*d*, *J* = 7.0, 7.0, Me–C(3)); 1.11, 1.24 (2*d*, *J* = 6.0, 6.0, Me(1)); 1.40–2.20 (*m*, H–C(3), CH_2(3′), CH_2(4′), CH_2(5′)); 3.40–4.00 (*m*, H–C(2), CH_2(4), CH_2(6′)); 4.67, 4.71 (2*dd*, *J* = 4.5, 4.0, and 3.0, 3.5, H–C(2′)). ^{13}C-NMR: 14.9, 15.3 (2*q*, *Me*–C(3)); 15.9, 18.6 (2*q*, C(1)); 18.8, 19.7 (2*t*, C(4′)); 25.5, 25.5 (2*t*, C(5′)); 31.1, 31.1 (2*t*, C(3′)); 38.2, 38.6 (2*t*, C(4)); 40.8, 41.4 (2*d*, C(3)); 62.6, 63.0 (2*t*, C(6′)); 72.5, 77.0 (2*d*, C(2)); 95.2, 100.5 (2*d*, C(2′)). GC/MS (selected diastereoisomer): 251, 249 (1, 1, [*M* – H]$^+$), 151, 149 (5, 5), 129 (13), 101 (19), 85 (100), 69 (38), 67 (10), 56 (18), 55 (11), 43 (11), 41 (23).

*Butyl (2*S,*3*S*)-3-Hydroxy-2-methylbutanoate* (*ent*-**23**). As described for **21**, with *ent*-**18** (25 g, 0.145 mol): *ent*-**23** (24.7 g, 98%; 98% de). Colorless oil. ^{1}H-NMR: 0.94 (*t*, *J* = 7.5, Me(4′)); 1.17 (*d*, *J* = 7.0, Me–C(2)); 1.21 (*d*, *J* = 6.5, H–C(4)); 1.32–1.46 (*m*, CH_2(3′)); 1.58–1.68 (*m*, CH_2(2′)); 2.47 (*dq*, *J* = 7.0, 7.0, H–C(2)); 3.26 (br. *s*, OH); 3.91 (*dq*, *J* = 6.5, 7.0, H–C(3)); 4.11 (*t*, *J* = 6.5, CH_2(1′)). ^{13}C-NMR: 13.7 (*q*, *Me*–C(2)); 13.8 (*q*, C(4′)); 19.2 (*t*, C(3′)); 20.5 (*q*, C(4)); 30.7 (*t*, C(2′)); 47.2 (*d*, C(2)); 64.4 (*t*, C(1′)); 69.3 (*d*, C(3)); 175.9 (*s*, C(1)). GC/MS: 159 (4, [*M* – Me]$^+$), 130 (13), 103 (13), 101 (61), 74 (100), 73 (13), 57 (30), 56 (34), 45 (16), 41 (13).

THP Ether ent-**22** *of (2*S,*3*S*)-4-Bromo-3-methylbutan-2-ol* (*2-[(1*S,*2*S*)-3-Bromo-1,2-dimethylpropoxy]-tetrahydro-2*H*-pyran* (*ent*-**22**)). As described for **22** (four-step sequence), from *ent*-**18**: *ent*-**22** (10.5 g, 80%). Spectral data: corresponding to those of **22**.

5. *3-Methyl-4-(*exo-*tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene)butan-2-ols* **10** *and* ent-**10**. *(2*S*,3*R*,4*E/Z*)-3-Methyl-4-[(1*R*,2*R*,6*R*,7*R*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-*ent*-**10a**). A soln. of *ent*-**17** (0.74 g, 5.0 mmol) and *ent*-**22** (1.38 g, 5.5 mmol) in anh. THF (2.5 ml) was added dropwise to a suspension of granulated Li (87 mg, 12.5 mmol) in anh. THF (5 ml) under N_2 at r.t. After stirring overnight, the remaining Li was filtered off. The filtrate was hydrolyzed with ice-water, and Et_2O was added. The aq. layer was separated and the Et_2O soln. evaporated: crude mixture *ent*-**24** (1.6 g). GC/MS (selected isomer): 302 (2, $[M-H_2O]^+$), 219 (14), 218 (13), 191 (22), 149 (12), 105 (11), 91 (10), 85 (100), 84 (10), 79 (11), 67 (24).

$POCl_3$ (7.67 g, 50 mmol) was added to a soln. of crude mixture *ent*-**24** (1.6 g) in anh. pyridine (25 ml) at 0°, and the mixture was stirred overnight at 20°. The mixture was then poured into ice-water and extracted with Et_2O. The org. layer was washed with H_2SO_4 and Na_2CO_3 soln., and evaporated: 1.50 g of the corresponding dehydrated product. GC/MS (selected isomer): 302 (peak, M^+), 174 (5), 146 (5), 107 (10), 86 (5), 85 (100), 79 (7), 67 (17), 41 (5).

A suspension of the THP-protected *ent*-**10a** (1.5 g), TsOH (50 mg), and 3-Å molecular sieves (1.0 g) in anh. MeOH (15 ml) was stirred for 2 h at r.t. The molecular sieves were filtered off, Na_2CO_3 (0.1 g) was added, and MeOH was distilled off. H_2O (100 ml) was added, the aq. layer extracted with Et_2O, the org. layer dried and evaporated, and the residue (1.1 g) purified by CC (hexane/Et_2O 7:3): (*E*/*Z*)-*ent*-**10a** 80:20 (0.62 g, 57%, over three steps). ^{1}H-NMR: (*E*)-*ent*-**10a**: 0.93 (*d*, *J* = 6.8, Me–C(3)); 0.85–1.16 (*m*, H_a–C(10′)); 1.15 (*d*, *J* = 6.0, Me(1)); 1.38–1.45 (*m*, H_b–C(10′)); 1.78–1.90 (*m*, H_a–C(9′)); 1.86–1.98 (*m*, H_a–C(3′)); 2.00–2.24 (*m*, H–C(1′), H–C(2′), H–C(3), H_b–C(9′)); 2.41 (br. *s*, H–C(7′)); 2.59 (*ddddd*, *J* = 18.7, 9.7, 2.0, 2.0, 1.3, H_b–C(3′)); 2.64–2.72 (*m*, H–C(6′)); 3.46 (*dq*, *J* = 6.2, 6.2, H–C(2)); 5.08 (*dd*, *J* = 10.0, 2.9, H–C(4)); 5.47 (*dddd*, *J* = 5.9, 2.0, 2.0, 2.0, H–C(5′)); 5.68 (*dddd*, *J* = 5.9, 2.0, 2.0, 2.0, H–C(4′)); (*Z*)-*ent*-**10a**: 0.94 (*d*, *J* = 7.0, Me–C(3)); 1.17 (*d*, *J* = 6.2, Me(1)); 3.50 (*dq*, *J* = 6.6, 6.6, H–C(2)); 4.85 (*d*, *J* = 9.9, H–C(4)). ^{13}C-NMR; (*E*)-*ent*-**10a**: 16.8 (*q*, *Me*–C(3)); 20.0 (*q*, C(1)); 32.4 (*t*, C(10′)); 35.7 (*t*, C(9′)); 39.8 (*t*, C(3′)); 41.7 (*d*, C(3)); 43.1 (*d*, C(2′)); 43.2 (*d*, C(1′)); 49.3 (*d*, C(7′)); 55.8 (*d*, C(6′)); 71.7 (*d*, C(2)); 119.6 (*d*, C(4)); 131.4 (*d*, C(5′)); 132.2 (*d*, C(4′)); 148.4 (*s*, C(8′)); (*Z*)-*ent*-**10a**: 17.3 (*q*, *Me*–C(3)); 20.0 (*q*, C(1)); 32.3 (*t*, C(10′)); 38.2 (*t*, C(9′)); 39.7 (*t*, C(3′)); 41.6 (*d*, C(3)); 42.4 (*d*, C(1′)); 43.0 (*d*, C(2′)); 44.4 (*d*, C(7′)); 55.2 (*d*, C(6′)); 71.5 (*d*, C(2)); 120.4 (*d*, C(4)); 131.4 (*d*, C(5′)); 132.3 (*d*, C(4′)); 147.4 (*s*, C(8′)). GC/MS: (*E*)-*ent*-**10a**: 218 (8, M^+), 174 (17), 173 (53), 151 (18), 108 (14), 107 (100), 91 (22), 79 (24), 67 (55); (*Z*)-*ent*-**10a**: 218 (8, M^+), 174 (15), 173 (49), 151 (16), 108 (13), 107 (100), 91 (22), 79 (23), 67 (57). HR-MS: 218.1664 ($C_{15}H_{22}O^+$; calc. 218.1671).

*(2*R*,3*S*,4*E/Z*)-3-Methyl-4-[(1*S*,2*S*,6*S*,7*S*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-**10a**). As described for (*E*/*Z*)-*ent*-**10a**, from **17** and **22**: (*E*/*Z*)-**10a** 80:20 (0.61 g, 56%, over three steps). Spectral data: corresponding to those of (*E*/*Z*)-*ent*-**10a**.

*(2*R*,3*S*,4*E/Z*)-3-Methyl-4-[(1*R*,2*R*,6*R*,7*R*)-Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-*ent*-**10c**). As described for (*E*/*Z*)-*ent*-**10a**, from *ent*-**17** and **22**: (*E*/*Z*)-*ent*-**10c** 20:80 (0.63 g, 58%, over three steps). ^{1}H-NMR: (*Z*)-*ent*-**10c**: 0.97 (*d*, *J* = 6.8, Me–C(3)); 0.85–1.04 (*m*, H_a–C(10′)); 1.17 (*d*, *J* = 6.1, Me(1)); 1.40–1.48 (*m*, H_b–C(10′)); 1.84–1.94 (*m*, H_a–C(9′)); 1.86–2.00 (*m*, H_a–C(3′)); 2.00–2.26 (*m*, H_b–C(9′), H–C(1′), H–C(2′)); 2.34 (*ddq*, *J* = 9.7, 7.0, 7.0, H–C(3)); 2.60 (*ddddd*, *J* = 17.2, 9.7, 2.3, 2.3, 1.5, H_b–C(3′)); 2.60–2.70 (*m*, H–C(6′)); 2.73 (br. *s*, H–C(7′)); 3.43 (*dq*, *J* = 7.1, 6.2, H–C(2)); 4.85 (*d*, *J* = 9.9, H–C(4)); 5.43–5.50 (*m*, H–C(5′)); 5.69 (*dddd*, 5.5, 2.0, 2.0, 2.0, H–C(4′)); (*E*)-*ent*-**10c**: 0.93 (*d*, *J* = 6.8, Me–C(3)); 1.16 (*d*, *J* = 6.2, Me(1)); 2.42 (br. *s*, H–C(7′)); 3.48 (*dq*, *J* = 6.4, 6.4, H–C(2)); 5.08 (*dt*, *J* = 9.9, 2.0, H–C(4)). ^{13}C-NMR: (*Z*)-*ent*-**10c**: 17.4 (*q*, *Me*–C(3)); 19.9 (*q*, C(1)); 32.3 (*t*, C(10′)); 38.3 (*t*, C(9′)); 39.7 (*t*, C(3′)); 42.3 (*d*, C(3)); 42.9 (*d*, C(1′)); 43.0 (*d*, C(2′)); 44.5 (*d*, C(7′)); 55.3 (*d*, C(6′)); 71.5 (*d*, C(2)); 120.2 (*d*, C(4)); 131.3 (*d*, C(5′)); 132.4 (*d*, C(4′)); 147.9 (*s*, C(8′)); (*E*)-*ent*-**10c**: 16.7 (*q*, *Me*–C(3)); 20.0 (*q*, C(1)); 32.0 (*t*, C(10′)); 35.5 (*t*, C(9′)); 39.7 (*t*, C(3′)); 41.5 (*d*, C(3)); 43.1 (*d*, C(2′)); 43.1 (*d*, C(1′)); 49.5 (*d*, C(7′)); 56.4 (*d*, C(6′)); 71.7 (*d*, C(2)); 119.4 (*d*, C(4)); 131.3 (*d*, C(5′)); 132.3 (*d*, C(4′)); 148.7 (*s*, C(8′)). GC/MS: (*Z*)-*ent*-**10c**: 218 (8, M^+), 174 (19), 173 (58), 151 (12), 108 (14), 107 (100), 91 (25), 79 (28), 67 (61); (*E*)-*ent*-**10c**: 218 (7, M^+), 174 (12), 173 (40), 151 (18), 108 (13), 107 (100), 91 (21), 79 (24), 67 (51).

*(2*S*,3*R*,4*E/Z*)-3-Methyl-4-[(1*S*,2*S*,6*S*,7*S*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-**10c**). As described for (*E*/*Z*)-*ent*-**10a**, from **17** and *ent*-**22**: (*E*/*Z*)-**10c** 20:80 (0.62 g, 57%, over three steps). Spectral data: corresponding to those of (*E*/*Z*)-*ent*-**10c**.

*(2*R*,3*R*,4*E/Z*)-3-Methyl-4-[(1*R*,2*R*,6*R*,7*R*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-*ent*-**10b**). A soln. of mixture (*E*/*Z*)-*ent*-**10a** (0.1 g, 0.46 mmol), Ph_3P (2.0 g, 7.63 mmol), benzoic acid (0.06 g, 0.5 mmol), and DEAD (0.1 g, 0.57 mmol) in anh. THF (4 ml) was stirred for 3 days at r.t. H_2O and Et_2O were added, and the org. layer was washed with H_2SO_4 and Na_2CO_3 soln. and evaporated. The residue (0.45 g) was purified by CC (hexane/Et_2O 7:3): benzoate mixture (82 mg) of the corresponding alcohols (*E*/*Z*)-*ent*-**10b**. GC/

MS (selected isomer): 322 (peak, M^+), 200 (38), 173 (22), 134 (27), 133 (100), 107 (26), 106 (16), 105 (85), 91 (17), 79 (12), 77 (31), 67 (32).

A soln. of the benzoate mixture (82 mg) and 50% NaOH (25 mg, 0.625 mmol) in MeOH (3 ml) was refluxed for 2 h. MeOH was evaporated, H_2O (200 ml) added, and the aq. layer extracted with CH_2Cl_2. The org. layer was washed with H_2O and evaporated: (*E*/*Z*)-*ent*-**10b** 80:20 (52 mg, 52%, over two steps). ^{1}H-NMR: (*E*)-*ent*-**10b**: 0.97 (*d*, *J* = 6.8, Me–C(3)); 1.03–1.14 (*m*, H_a–C(10′)); 1.12 (*d*, *J* = 6.4, MeC(1)); 1.40 (*dddd*, *J* = 8.4, 2.8, 1.5, 1.5, H_b–C(10′)); 1.80–1.90 (*m*, H_a–C(9′)); 1.86–1.98 (*m*, H_a–C(3′)); 2.00–2.13 (*m*, H–C(1′), H_b–C(9′)); 2.03–2.22 (H–C(2′)); 2.23 (*ddq*, *J* = 9.7, 6.6, 6.6, H–C(3)); 2.39 (br. *s*, H–C(7′)); 2.60 (*ddddd*, *J* = 17.2, 9.7, 2.2, 2.2, 1.5, H_b–C(3′)); 2.64–2.72 (*m*, H–C(6′)); 3.58 (*dq*, *J* = 6.2, 6.2, H–C(2)); 5.09 (*dt*, *J* = 9.9, 2.2, H–C(4)); 5.47 (*dddd*, *J* = 5.6, 2.4, 2.4, 2.4, H–C(5′)); 5.68 (*dddd*, 5.7, 2.0, 2.0, 2.0, H–C(4′)); (*Z*)-*ent*-**10b**: 0.99 (*d*, *J* = 6.8, H_3C–C(3)); 1.16 (*d*, *J* = 6.2, Me(1)); 3.59 (*dq*, *J* = 6.2, 6.2, H–C(2)); 4.86 (*d*, *J* = 9.5, H–C(4)). ^{13}C-NMR: (*E*)-*ent*-**10b**: 16.6 (*q*, *Me*–C(3)); 20.2 (*q*, C(1)); 32.3 (*t*, C(10′)); 35.7 (*t*, C(9′)); 39.7 (*t*, C(3′)); 40.8 (*d*, C(3)); 43.1 (*d*, C(2′)); 43.2 (*d*, C(1′)); 49.3 (*d*, C(7′)); 55.9 (*d*, C(6′)); 72.1 (*d*, C(2)); 119.1 (*d*, C(4)); 131.5 (*d*, C(5′)); 132.2 (*d*, C(4′)); 147.1 (*s*, C(8′)); (*Z*)-*ent*-**10b**: 17.3 (*q*, *Me*–C(3)); 20.6 (*q*, C(1)); 32.3 (*t*, C(10′)); 38.2 (*t*, C(9′)); 39.7 (*t*, C(3′)); 41.6 (*d*, C(3)); 43.0 (*d*, C(1′)); 43.1 (*d*, C(2′)); 44.3 (*d*, C(7′)); 55.0 (*d*, C(6′)); 72.0 (*d*, C(2)); 119.9 (*d*, C(4)); 131.4 (*d*, C(5′)); 132.4 (*d*, C(4′)); 146.2 (*s*, C(8′)). GC/MS: (*E*)-*ent*-**10b**: 218 (8, M^+), 174 (17), 173 (52), 151 (14), 108 (14), 107 (100), 91 (26), 79 (30), 67 (67); (*Z*)-*ent*-**10b**: 218 (5, M^+), 174 (15), 173 (47), 151 (12), 108 (12), 107 (100), 91 (25), 79 (30), 67 (72).

*(2*S*,3*S*,4*E/Z*)-3-Methyl-4-[(1*S*,2*S*,6*S*,7*S*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-**10b**). As described for (*E*/*Z*)-*ent*-**10b**: (*E*/*Z*)-**10b** 80:20 (53 mg, 53%, over two steps). Spectral data: corresponding to those of (*E*/*Z*)-*ent*-**10b**.

*(2*S*,3*S*,4*E/Z*)-3-Methyl-4-[(1*R*,2*R*,6*R*,7*R*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-*ent*-**10d**). As described for (*E*/*Z*)-*ent*-**10b**: (*E*/*Z*)-*ent*-**10d** 20:80 (53 mg, 53%, over two steps). ^{1}H-NMR: (*Z*)-*ent*-**10d**: 1.01 (*d*, *J* = 6.8, Me–C(3)); 1.03–1.14 (*m*, H_a–C(10′)); 1.12 (*d*, *J* = 6.4, Me(1)); 1.36–1.48 (*m*, H_b–C(10′)); 1.80–1.90 (*m*, H_a–C(9′)); 1.86–1.98 (*m*, H_a–C(3′)); 2.00–2.26 (*m*, H–C(1′), H_b–C(9′), H–C(2′)); 2.50 (*ddq*, *J* = 9.9, 6.6, 6.6, H–C(3)); 2.60 (*ddddd*, *J* = 17.2, 9.7, 2.2, 2.2, 1.5, H_b–C(3′)); 2.62–2.74 (*m*, H–C(6′)); 2.73 (br. *s*, H–C(7′)); 3.60 (*dq*, *J* = 6.2, 6.2, H–C(2)); 4.86 (*d*, *J* = 9.9, H–C(4)); 5.47 (*dddd*, *J* = 5.6, 2.4, 2.4, 2.4, H–C(5′)); 5.67 (*dddd*, 5.6, 2.0, 2.0, 2.0, H–C(4′)); (*E*)-*ent*-**10d**: 0.97 (*d*, *J* = 6.8, Me–C(3)); 1.14 (*d*, *J* = 6.4, Me(1)); 2.40 (br. *s*, H–C(7′)); 3.57 (*dq*, *J* = 6.2, 6.2, H–C(2)); 5.07 (*dt*, *J* = 9.9, 2.3, H–C(4)). ^{13}C-NMR: (*Z*)-*ent*-**10d**: 17.4 (*q*, *Me*–C(3)); 19.7 (*q*, C(1)); 32.2 (*t*, C(10′)); 38.3 (*t*, C(9′)); 39.7 (*t*, C(3′)); 41.2 (*d*, C(3)); 42.9 (*d*, C(1′)); 43.0 (*d*, C(2′)); 44.5 (*d*, C(7′)); 55.3 (*d*, C(6′)); 72.0 (*d*, C(2)); 119.5 (*d*, C(4)); 131.5 (*d*, C(5′)); 132.2 (*d*, C(4′)); 146.7 (*s*, C(8′)); (*E*)-*ent*-**10d**: 16.7 (*q*, *Me*–C(3)); 20.3 (*q*, C(1)); 32.0 (*t*, C(10′)); 35.5 (*t*, C(9′)); 39.7 (*t*, C(3′)); 40.8 (*d*, C(3)); 43.2 (*d*, C(2′)); 43.2 (*d*, C(1′)); 49.4 (*d*, C(7′)); 55.3 (*d*, C(6′)); 72.3 (*d*, C(2)); 119.2 (*d*, C(4)); 131.4 (*d*, C(5′)); 132.3 (*d*, C(4′)); 147.3 (*s*, C(8′)). GC/MS: (*Z*)-*ent*-**10d**: 218 (7, M^+), 174 (18), 173 (56), 151 (11), 108 (14), 107 (100), 91 (24), 79 (31), 67 (75); (*E*)-*ent*-**10d**: 218 (6, M^+), 174 (12), 173 (43), 151 (14), 108 (13), 107 (100), 91 (24), 79 (28), 67 (68).

*(2*R*,3*R*,4*E/Z*)-3-Methyl-4-[(1*S*,2*S*,6*S*,7*S*)-tricyclo[5.2.1.0^{2,6}]dec-4-en-8-ylidene]butan-2-ol* ((*E*/*Z*)-**10d**). As described for (*E*/*Z*)-*ent*-**10b**: (*E*/*Z*)-**10d** 20:80 (51 mg, 51%, over two steps). Spectral data: corresponding to those of (*E*/*Z*)-*ent*-**10d**.

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