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(+)-(*R*,*Z*)-5-Muscenone and (−)-(*R*)-Muscone by Enantioselective Aldol Reaction and Grob Fragmentation

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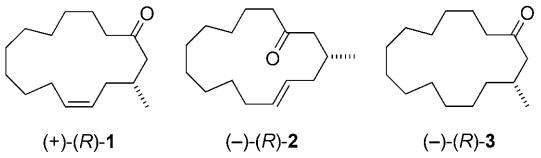
Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday

Abstract: (+)-(*R*,*Z*)-5-Muscenone ((*R*)-**1**) was synthesized by an enantioselective aldol reaction, catalyzed by new ephedrine-type Ti reagents (up to 70% enantiomeric excess). Substrate-directed diastereoselective reduction of the aldol product and Grob fragmentation of the tosylate of the resultant 1,3-diol afforded (+)-**1**. This approach also gave access to (−)-(*R*,*E*)-5-muscenone and (−)-(*R*)-muscone.

Keywords: aldol reaction · amino alcohols · asymmetric synthesis · fragmentation · fragrances

Introduction

Muscenone, a highly appreciated Firmenich musk odorant, is a racemic mixture of (*Z*)-5-muscenone (**1**), (*E*)-5-muscenone (**2**) (ca. 80%), and (*E*)- and (*Z*)-4-muscenone (ca. 20%).[1] The 5-muscenones are more strongly scented than the 4-muscenones, and **1** (ca. 45%) is particularly appreciated for its better top note and nitro-musk character.



As the natural (*R*)-muscone **3** exhibits a much more pronounced musk character than its enantiomer, some years ago we prepared the then unknown enantiomers of **1** and **2**.[2] (*R*,*Z*)-5-Muscenone ((*R*)-**1**) turned out to be much more strongly scented than its enantiomer, and its threshold value is more than 100 times lower than that of (*S*)-**1**.[2]

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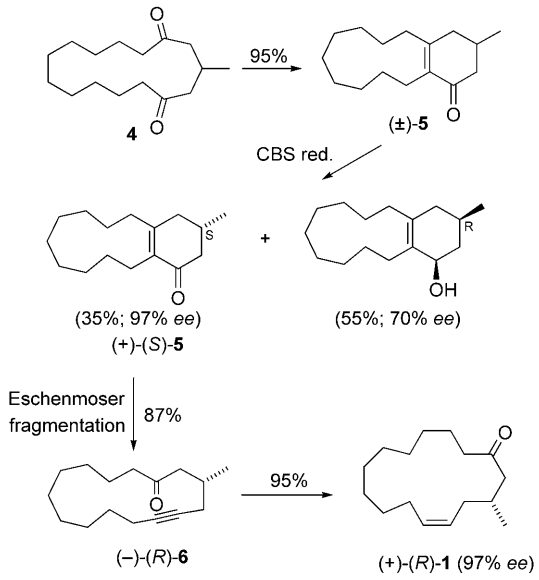
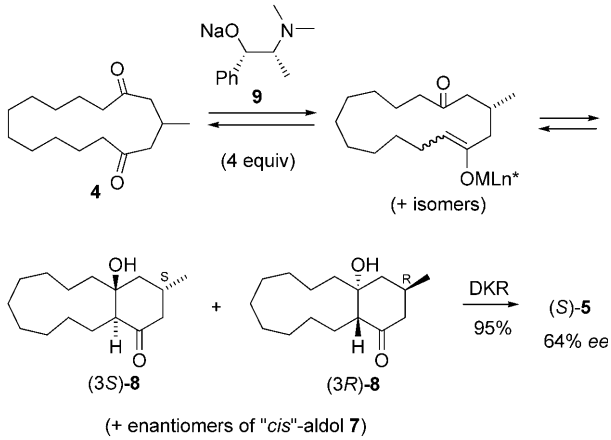
Our synthesis was based on a catalytic kinetic resolution by enantioselective Corey–Bakshi–Shibata (CBS) reduction of racemic bicyclic enone (±)-**5**, readily accessible by intramolecular aldolization of muscodione (**4**) under basic conditions (Scheme 1). An Eschenmoser fragmentation (H_2NNHTs, cat. AcOH, toluene, then AcOOH), followed by Lindlar hydrogenation then afforded (*R*)-**1**.

Having identified (*R*)-**1** as the ultimate target, we then had the challenge to envisage an enantioselective intramo-



Scheme 1. (*R*)-**1** by kinetic resolution (CBS reduction) according to reference [2].

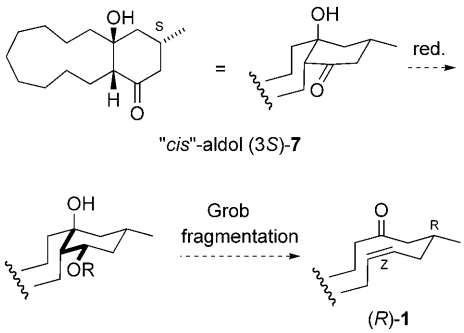
lecular aldol reaction of **4**. It should be noted that, in principle, deprotonation already leads to a chiral product, since it is the result of an enantiotopic group differentiation; if the deprotonation is reversible, it would then, in principle, be possible to effect the intramolecular aldol reaction in a kinetically controlled, enantioselective manner. If all preceding steps are reversible, the irreversible dehydration can take place enantioselectively. This pathway, a dynamic kinetic resolution (DKR), has been successfully realized at Firmenich by using four (or eight) equivalents of the sodium alkoxide of (+)-*N*-methylephedrine (**9**). Compound (*S*)-**5** was isolated in almost quantitative yield with 64% enantiomeric excess (*ee*) (Scheme 2).[3]



Scheme 2. Reversible aldolization/enantioselective dehydration according to reference [3].

In parallel, we explored the possibility of an enantioselective aldolization through the formation of the *cis*-fused aldol product **7** (less stable than **8**), out of four possible diastereomers. Subsequent diastereoselective reduction and Grob fragmentation of the corresponding tosylate should guarantee the direct formation of the desired *Z* olefin (Scheme 3), as an alternative to Eschenmoser fragmentation of (*S*)-**5** followed by Lindlar hydrogenation.

In recent years, considerable progress has been achieved in the area of enantioselective aldol reactions,[4] based on metal enolate chemistry[5–7] or organocatalysis.[8,9] However, these reactions mostly involve aldehydes, or sometimes α-ketoesters, as the electrophilic partners. The rare examples of ketone–ketone aldolizations are restricted to intramolecular cases, such as the desymmetrizations of triketones **10**[6,9a] or



Scheme 3. New strategy: (*R*)-**1** by enantioselective aldol reaction, diastereoselective reduction, and Grob fragmentation.

diketones **11**,[9b] and the transannular aldolizations of **16**[7] and **18**[9c] (Scheme 4).

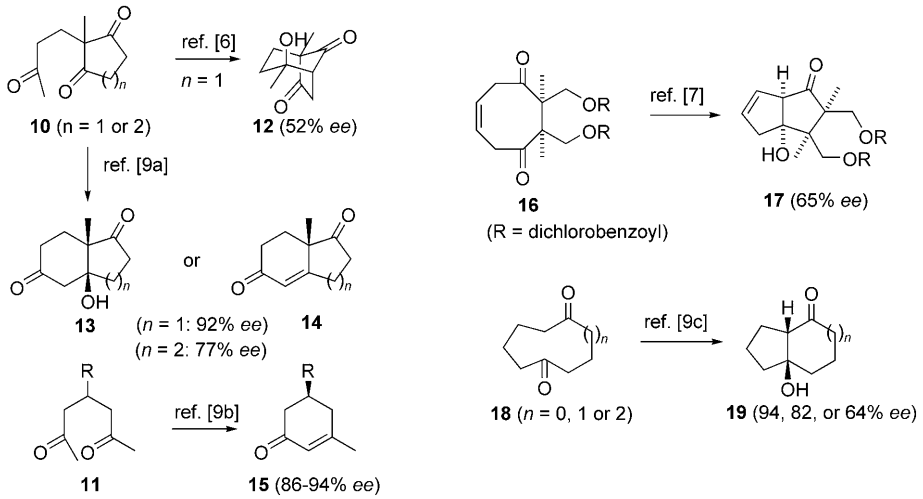
It is important to note that ketone–ketone aldolizations are difficult to achieve because of the inherent propensity of the aldol product to undergo a retro-aldol reaction. The lanthanide-catalyzed aldol addition of triketone **10** ($n=1$) to **12** is a typical example of this problem of reversibility.[6]

Another possible issue in the aldol reaction of **4** is the diastereocontrol (**7** versus **8**). In contrast to the literature examples (**17**[7] and **19**[9c]), which involve the formation of stable *cis*-fused five-membered rings, we wanted to favor the less stable *cis*-aldol product **7**.

Herein, we describe the enantioselective aldolization of muscodione **4**, promoted by new chiral Ti reagents (70% *ee*) and the stereocontrolled reduction/fragmentation of crystallized aldol (−)-**7** (≥98% *ee*) to afford (*R*)-**1** with an unaltered *ee* value.

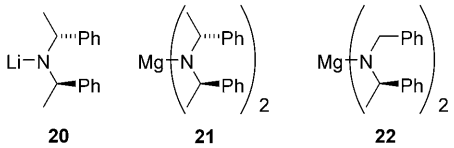
Results and Discussion

The enantioselective aldol reaction: The preliminary aldol reactions of muscodione (**4**) with (*S*)-proline gave no reaction; consequently we tested chiral Li and Mg amides in



Scheme 4. Published enantioselective ketone–ketone aldolizations.

place of (*S*)-proline. Li amide **20** deprotonated **4**, but no aldol reaction ensued, and the Mg amides **21** and **22**[10] also showed a low reactivity (ca. 10% conversion). The 1,1′-bi(2-naphthol) (BINOL)-derived mixed La–Li–BINOL alkoxide, LLB-II,[6a] was also ineffective, even when doped with potassium hexamethyl disilazide (KHMDS) or NaO*t*Bu.



20 **21** **22**

Finally, it was found that Ti or Zr enolates underwent the desired aldol addition.[11] $TiCl_4$ (1.2 equiv)/NBu_3 (1.4 equiv) in CH_2Cl_2 at −5 °C smoothly afforded aldol products **7** and **8** in a ratio of approximately 1:5. Recrystallization from heptane afforded pure **8** (46%) and the minor isomer **7** (10%) was isolated after chromatography of the mother liquors (Scheme 5). Treatment of **4** with $ZrCl_3OPr/NBu_3$ in CH_2Cl_2 at −10 °C (or $ZrCl_4$/*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethane (TMEDA) in CH_2Cl_2 at 25 °C) also afforded **8** in 88% yield. In both **7** and **8** the OH group is axial and the Me group is equatorial (*trans* with respect to the OH group), as shown by NMR spectroscopy. New calculations indicate that *cis*-aldol **7** is less stable than *trans*-aldol **8** by approximately 1.8 kcal mol^{-1}. The two other possible diastereomers with a *cis* relationship between the OH and Me groups were not observed.

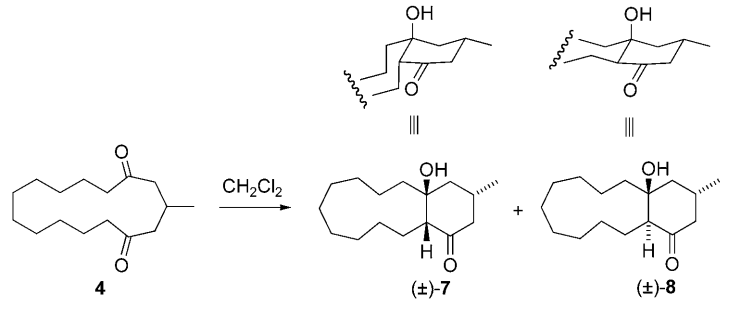
We next tested the aldol reaction with $TiCl_4$/(−)-sparteine ((−)-**23**) in CH_2Cl_2 at −70 °C. After 90 min, the reaction was quenched (ca. 65% conversion) and **8** was isolated in 42% yield (7% *ee*). The combination Cl_3TiO*i*Pr/(−)-**23**/CH_2Cl_2/−60 °C also afforded **8** with a low *ee* value (10%). Variation of the reaction conditions (temperature, solvent (CH_3CN)) did not change the outcome of the reaction. Replacement of (−)-**23** by diamine **24**[12] or aminoether **25**,[13] or the use of methyl mandelate or mandelic acid and $TiCl_4$[5c] gave **8** with a maximum *ee* value of 12%.

A significant improvement in both diastereoselectivity (allowing the formation of the desired diastereomer **7**) and enantioselectivity (up to 70% *ee*) was attained with the Ti reagents formed from $TiCl_4$ and ephedrine-type amino alcohols (+)-**26** to (−)-**32**. We found that the Ti reagents obtained from $TiCl_4$ and an amino alcohol possessing a tertiary amino group (**26** to **32**) in *N*-methylpyrrolidone (NMP) and TMEDA effectively promoted the aldol reaction of **4**. In most cases variable amounts of the less stable *cis*-diastereomer **7** were formed together with **8**. After having identified a better selectivity with (+)-*N*-methylephedrine ((+)-**26**) (**7**/**8** = 45:55; **7**: 36% *ee*, **8**: 20% *ee*) than with (−)-*N*-methylpseudoephedrine ((−)-**33**) (**7**/**8** = 10:90; **7**: <7% *ee*, **8**: 7% *ee*) (Table 1; entries 1 and 2), we focused on the ephedrine series. The more highly substituted (+)-*N*-isopropylephedrine ((+)-**27**)[14] gave **7** with 44–46% *ee* (**7**/**8** ≈ 1:1) and was used for several optimization experiments (Table 1; entries 3 and 4).[15] Lastly, we varied the steric bulk of the N-substituents to find the most efficient amino alcohol in terms of enantioselectivity, by analogy with a study of Alexakis and co-workers on diamines.[16]

Table 1. Enantioselective aldol reaction of **4**.

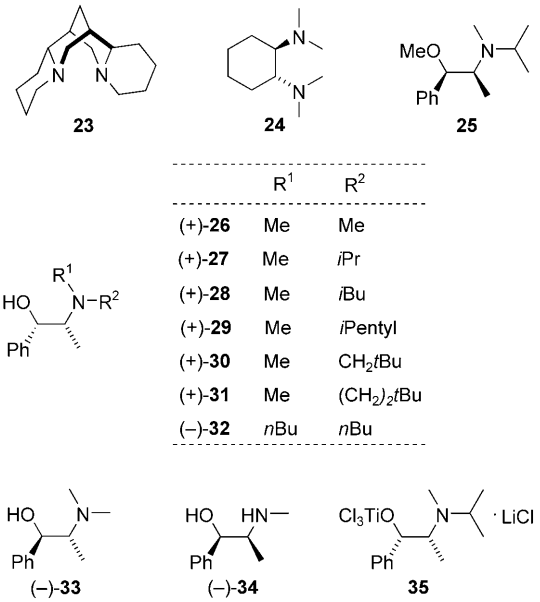
Entry	Amino alcohol	*T* [°C]	Time [h]	Conversion [%]	Yield of **7** [%] (*ee* [%])	Yield of **8** [%] (*ee* [%])
1[a]	(+)-**26**	8	2	≈20	≈9 (36)	≈11 (20)
2[a]	(−)-**33**	25	1.5	≈50	≈5 (<7)	≈45 (7)
3[b]	(+)-**27**	0	3	≈65	29 (44)	32 (18)
4[b]	(+)-**27**	−20	72	≈75	33 (46)	34 (19)
5[b]	(+)-**28**	0	3	≈35	8 (67)	23 (18)
6[b]	(+)-**28**	0	9	≈50	7 (68)	36 (24)
7[b]	(+)-**29**	0	5	≈50	21 (40)	24 (18)
8[b]	(+)-**30**	0	9	≈40	≈1 (–)	30 (0)
9[b]	(+)-**31**	0	5	≈70	23 (45)	39 (25)
10[b]	(−)-**32**	0	4	≈45	10 (64)	27 (17)
11[b]	(−)-**32**	−20	96	≈85	21 (70)	52 (17)
12[c]	(−)-**32**	0	7.5	≈40	9 (62)	12 (20)
13[c]	(−)-**32**	−20	72	≈30	11 (68)	12 (38)

Reaction conditions: [a] Amino alcohol/$TiCl_4$ (2.40 equiv), TMEDA (2.80 equiv), NMP. [b] Amino alcohol/$TiCl_4$ (0.80 equiv), TMEDA (0.93 equiv), NMP, H_2O (0.1 equiv). [c] [(−)-**32**·$TiCl_4$ (0.40 equiv), TMEDA (0.46 equiv), NMP, H_2O (0.05 equiv).



Scheme 5. Synthesis of (±)-**7** and (±)-**8** by Ti- and Zr-mediated aldol reactions.

We found that use of (+)-**28**·$TiCl_4$, possessing an *N*-isobutyl substituent, gave **7** with a much higher *ee* value (68% *ee*; Table 1; entry 6) compared with (+)-**27**·$TiCl_4$ (bearing an *N*-isopropyl group) (44% *ee*; Table 1; entry 3). Going from *N*-isobutyl to *N*-isopentyl ((+)-**29**·$TiCl_4$), the *ee* value dropped again (40% *ee*; Table 1; entry 7). The analogous *N*-*tert*-butyl-substituted reagents (+)-**30**·$TiCl_4$ and (+)-**31**·$TiCl_4$ were no more selective (Table 1; en-



	R^1	R^2
(+)-**26**	Me	Me
(+)-**27**	Me	*i*Pr
(+)-**28**	Me	*i*Bu
(+)-**29**	Me	*i*Pentyl
(+)-**30**	Me	CH_2tBu
(+)-**31**	Me	$(CH_2)_2t$Bu
(−)-**32**	*n*Bu	*n*Bu

tries 8 and 9). However, the commercial (−)-*N*,*N*-dibutylnorephedrine ((−)-**32**) showed good reactivity, even at −20 °C, and a high enantioselectivity (21 %; 70 % *ee*; Table 1; entry 11); one recrystallization from acetone/heptanes afforded enantiopure (−)-**7** (10 %; ≥98 % *ee*). In spite of the unfavorable diastereoselectivity, this result is outstanding and bears comparison with published transannular reactions that, probably due to the ring sizes, only afforded the *cis*-diastereomers (see above). Moreover, the readily separated, undesired diastereomer **8** undergoes rapid and quantitative retro-aldol reaction in the presence of NaOMe, and **4** can be recycled without any loss.

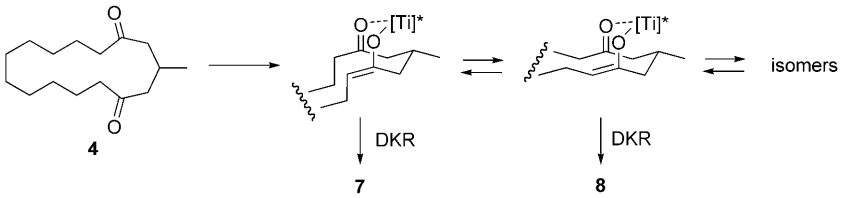
This new enantioselective aldol reaction is probably stoichiometric, but using 0.8 molar equivalents of Ti reagent (Table 1; entries 3–11) proved to be much more effective than 2.4 equiv (Table 1; entries 1 and 2), because unreacted **4** is readily recovered. The amount of Ti complex can be reduced to 0.4 equiv, but the conversion is somewhat lower (Table 1; entries 12 and 13).[17] Traces of water (added or present in aged TMEDA) increased the rate of the reaction.

The complex formed from (−)-ephedrine ((−)-**34**) and $TiCl_4$ does not catalyze the aldol reaction: presumably the resulting complex lacks electrophilic character due to the Ti–N bond. On the other hand, the complex formed from (−)-**34**·HCl and $TiCl_4$ allowed a rapid aldol addition, affording **8** and minor amounts of **7**, both with low *ee* values.

When the Li alkoxide derived from (+)-**27** ((+)-**27**+BuLi) was treated with $TiCl_4$, complex **35** was formed, which did not promote the desired aldol addition. Here the diminished electrophilicity of the complex is due to the replacement of one chlorine atom at Ti by an oxygen atom (Ti–O bond). Therefore, we assume that the active complex is an adduct between the amino alcohol and $TiCl_4$, in which the OH bond (as part of a chelate) is still intact (e.g., (−)-**32**·$TiCl_4$) and can be considered as a combined Lewis acid–Brønsted acid catalyst.[18] A broad signal between 3500 and 2400 cm^{-1} and a signal at 1602 cm^{-1} in the IR spectrum supports this assertion.

When the experiment of entry 10 (Table 1) was repeated with (−)-**32**·$TiCl_4$ of 50 % *ee*, the aldol product **7** had an *ee* value of 32 %, thus indicating a linear relationship between reagent *ee* and product *ee* values. Probably **7** and **8** are formed by DKR from the (*E*)- and (*Z*)-Ti enolates (of low *ee* value), which interconvert readily (Scheme 6).

Comparison of entries 5 and 6 in Table 1 (35 and 50 % conversion, respectively) shows that the formation of *cis*-fused aldol **7** is more pronounced at low conversion. The proportional increase of aldol product **8** in the course of the reaction is certainly due to an equilibration through enolization[19] and not (or only in part) to a retro-aldol pathway, as the enantiomeric excess of **8** increases from 18 to 24 %.



Scheme 6. Postulated reaction course for the formation of enantio-enriched **7** and **8**: reversible Ti enolate formation followed by DKR.

In another series of experiments we replaced TMEDA by (−)-**23** (Table 2). Several differences were noticed, most remarkably, the diastereoselectivity in favor of the *cis*-fused aldol **7** was improved.[20] Additionally, the *ee* value of **7** was always lower and the *ee* value of **8** was equal or higher. The two experiments performed with (−)-**27** and (+)-**27** (Table 2; entries 1 and 2) show that there is no marked matched or mismatched combination. When using (−)-**23** as the base, traces of water inhibited the aldol reaction.

Table 2. Enantioselective aldol reaction of **4** in the presence of (−)-**23**.

Entry	Amino alcohol	Conversion [%]	Yield of **7** [%] (*ee* [%])	Yield of **8** [%] (*ee* [%])
1[a]	(−)-**27**	≈40	≈25 (34)	≈9 (n.d.)[e]
2[a]	(+)-**27**	≈40	≈26 (36)	≈10 (23)
3[b]	(+)-**28**	≈25	10 (56)	11 (23)
4[c]	(+)-**28**	≈40	11 (52)	23 (31)
5[d]	(−)-**32**	≈30	14 (45)	8 (32)

Reaction conditions: [a] Amino alcohol/$TiCl_4$ (0.80 equiv), (−)-**23** (1.20 equiv), NMP, 0 °C, 3 h. [b] Amino alcohol/$TiCl_4$ (0.80 equiv), (−)-**23** (0.93 equiv), NMP, 0 to 20 °C over 4.5 h. [c] Amino alcohol/$TiCl_4$ (0.80 equiv), (−)-**23** (1.20 equiv), NMP, 0 °C (4 h), then 20 °C (3 h). [d] Amino alcohol/$TiCl_4$ (0.80 equiv), (−)-**23** (0.93 equiv), NMP, 0 °C, 4 h. [e] n.d. = none detected.

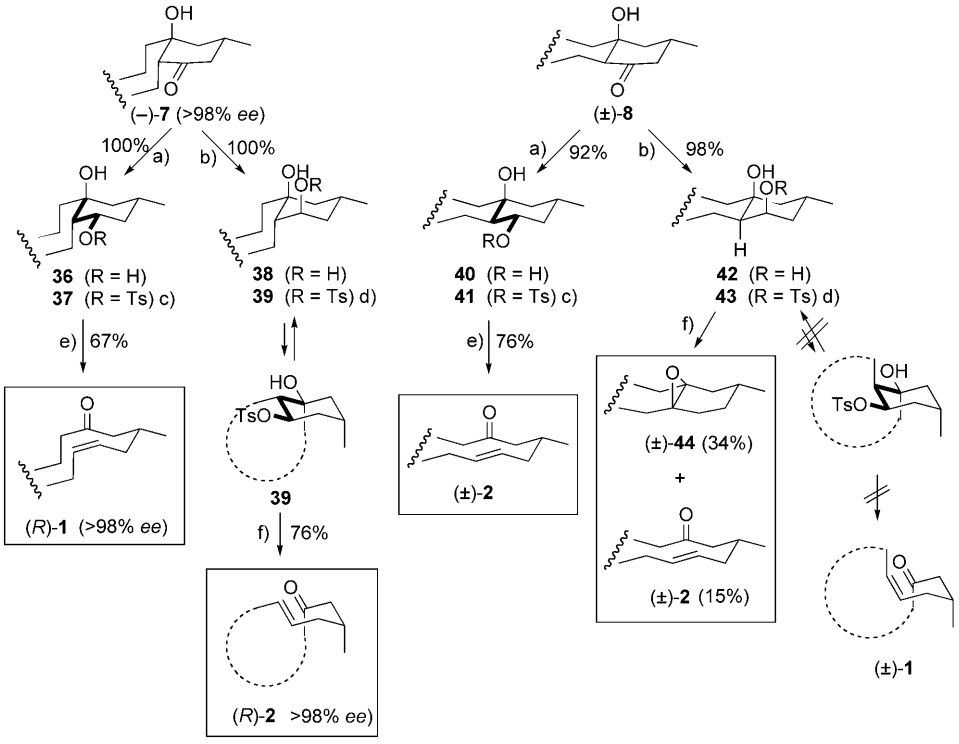
Stereocontrolled access to (+)-(*R*,*Z*)-5-muscenone ((*R*)-1) and (−)-(*R*,*E*)-5-muscenone((*R*)-2) by Grob fragmentation: We presumed that hydroxy ketone (−)-**7** (≥98% *ee*) would be ideally suited for the synthesis of enantiopure (*R*)-**1** by OH-directed reduction to diol **36**, followed by a Grob fragmentation[21] of tosylate **37** (Scheme 7). Indeed, compound **37** possesses the required configuration for the formation of (*R*)-**1**, since the bonds to be broken are in an antiperiplanar arrangement and the vicinal C–C bonds of the future olefin are synclinal to each other. Likewise, equatorial reduction of (−)-**7**, followed by tosylation and Grob fragmentation would give access to enantiopure (*R*)-**2**.[22] Here, the corresponding tosylate **39** has to undergo a conformational change to adopt the antiperiplanar arrangement needed for the fragmentation to (*R*)-**2**.

In principle, hydroxy ketone **8** could also be transformed into two diasteromeric 1,3-diols, **40** and **42**, respectively, and hence into the target fragmentation products **1** and **2** (Scheme 7). Here, *trans*-diol **40** should lead to **2**, and *cis*-diol **42** to **1**. Whereas *trans*-hydroxy tosylate **41** is ideally suited for fragmentation, *cis*-hydroxy tosylate **43** has to undergo a conformational flip, which would force the *trans*-11-ring to adopt a 1,2-diaxial orientation. Models and calculations seem to indicate that such a conformational change is unfavorable, though not impossible.

In the event, hydroxy ketone (−)-**7** (≥98% *ee*) was reduced with $NMe_4BH(OAc)_3$ in AcOH[23] to afford the desired *trans*-diol **36** in high yield (99% crude) and with excellent diastereoselectivity (≥98:2). Tosylate **37** (pyridine, *p*-toluenesulfonyl chloride (TsCl)) was then submitted to fragmentation (KO*t*Bu, *t*BuOH, 30 min), affording (+)-**1** (≥98% *Z*) (67% from (−)-**7**, ≥98% *ee*).

Alternatively, (−)-**7** (≥98% *ee*) was reduced with lithium tri-*sec*-butylborohydride (L-Selectride) in THF at −65 °C.[24] Exclusive equatorial hydride addition afforded *cis*-diol **38** (100% crude). Tosylation (BuLi, TsCl; 100% crude) and fragmentation of tosylate **39** (KO*t*Bu, *t*BuOH, 15 h) afforded (*R*)-**2** (≥98% *E*) (76% from (−)-**7**; ≥98% *ee*).

We next applied the same reduction/fragmentation reactions on (±)-**8**. The reductions of (±)-**8** using either $NMe_4BH(OAc)_3$ or L-Selectride afforded diols **40** and **42**, respectively, with excellent yields and selectivities. Whereas tosylate **41** underwent smooth fragmentation to afford **2** (≥98% *E*) as expected (76% from **40**), tosylate **43** underwent an unprecedented OH-assisted 1,2-hydride migration/elimination to afford epoxide **44** (34%; tentative assignment of configuration)[25] and through a minor pathway, a *syn*-fragmentation, produced (*E*)-macrocyclic ketone **2** (15%). Indeed, calculations demonstrate that the *trans*-diaxial conformer is highly disfavored with respect to the *trans*-diequatorial conformer due to the three axial C–C bonds (versus three equatorial C–C-bonds). However, the ring strain in the 11-membered ring is approximately the same in both conformations. On the other hand, the analogous conformational change of **39** (*cis*-fused bicycle) is energetically less disfavored (1 versus 2 axial C–C bonds).[26]



Scheme 7. Synthesis of (*R*)-**1** and (*R*)-**2** from (−)-**7** and synthesis of (±)-**2** from (±)-**8**. Formation of epoxide (±)-**44** by 1,2-hydride shift. Reagents and conditions: a) $NMe_4BH(OAc)_3$ (1.3 equiv), AcOH, 24 h; b) L-Selectride (2.0 equiv), −60 °C, 20–30 min, then H_2O_2, 5% aqueous NaOH; c) TsCl (2.0–2.1 equiv), pyridine, 5 °C, 15 h; d) BuLi (1.0–1.5 equiv), 40 °C, 15 min; then TsCl (1.17–1.50 equiv), −20 °C, 15 min; e) KO*t*Bu (3.0 equiv), *t*BuOH, 25–35 °C, 30 min.; f) KO*t*Bu (9.0–10.5 equiv), *t*BuOH, 25–35 °C, 2–15 h.

Conclusion

We have explored the intramolecular, enantioselective aldol reaction of muscodione **4**, in which both carbonyl functionalities are keto groups and have found that the highly electrophilic Ti catalysts, formed from $TiCl_4$ and an amino alcohol, were able to promote these reactions with appreciable enantioselectivity (up to 70% *ee*). Enantiopure hydroxy ketone (−)-**7** (≥98% *ee*) was obtained by one recrystallization. Compound (−)-**7** was efficiently transformed into (*R*)-**1** (≥98% *ee*) by an internally directed diastereoselective reduction, tosylation and base treatment (Grob fragmentation). Moreover, we have compared the reactivity of the four diastereo-

meric monotosylates **37**, **39**, **41**, and **43**. Interestingly, compound **43** cannot adopt the required conformation for *anti* fragmentation (*trans*-antiperiplanar arrangement of the bonds to be broken) and preferentially undergoes an unprecedented epoxidation/1,2-hydride migration, with concomitant departure of the tosylate to afford epoxide **44**. In addition, unexpectedly, *syn* fragmentation of **43** is also observed, leading to **2**.

Experimental Section

General: Bulb-to-bulb distillation was performed with a Büchi GKR-51 glass-oven; b.p. corresponds to the oven temperature. TLC was performed on silica gel F-254 plates (Merck); detection with EtOH/anisaldehyde/H_2SO_4 18:1:1. Column chromatography was performed on silica 32–63, 60 Å (Brunschwig). GC spectra were recorded on a Varian 3500 instrument fitted with one of the following capillary columns: DB1 30 W (15 m × 0.319 mm), DB-WAX 15W (15 m × 0.32 mm) or the chiral capillary column: CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack); carrier gas He at 0.63 bar. Optical rotations were determined by using a 1 mL cell and a Perkin–Elmer 241 polarimeter; *c* in g/100 mL solution. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 instrument (^{1}H decoupling frequency at 2.5 ppm). Mass spectra were recorded on a Hewlett Packard MSD 5972 automated GC–MS instrument, electron energy 70 eV.

Preparation of the amino alcohols

Compounds (+)-27 and (−)-27:[14] These compounds were prepared by following the procedure reported by Saavedra[27] or in an autoclave as follows: (+)-**34** (120 g, 0.727 mol), 5% Pd/C (9.0 g), acetone (379 mL), H_2, 70 bar, 50 °C, 24 h. Yield of (+)-**27** after filtration, concentration and distillation: 135–143 g (90–95%).

Accordingly, (−)-**34** afforded (−)-**27** with the same yield.

Compound (+)-28: This compound was prepared by following the procedure reported by Saavedra:[27] Isobutyraldehyde (5.190 g; 6.57 mL, 72.09 mmol) was added dropwise to a solution of freshly distilled (+)-**34** (7.93 g; 48.06 mmol) in absolute ethanol (50 mL) at RT, under nitrogen, and the resulting mixture was stirred at RT for 3 h. After consumption of (+)-**34**, $NaBH_4$ (3.65 g, 96.1 mmol) was added and the reaction mixture was stirred at RT over the weekend. A solution of 5% HCl was added dropwise to adjust the pH to approximately 1, then most of the ethanol was evaporated under vacuum. The residue was made basic with a 5% aqueous solution of NaOH and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, concentrated, and distilled by bulb-to-bulb distillation at 140 °C and 3 mbar to afford (+)-**28** as a colorless oil (7.40 g, 70%). $[\alpha]_D^{20} = +12.9$ ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.85–0.89 (m, 9H), 1.75 (hept, $J = 6.8$ Hz, 1H), 2.17 (s, 3H), 2.18–2.27 (m, 4H), 3.73 (br s, 1H), 4.78 (d, $J = 4.5$ Hz, 1H), 7.20–7.25 (m, 1H), 7.29–7.33 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.4$ (s), 127.9 (d), 126.8 (d), 126.2 (d), 73.2 (d), 64.4 (d), 63.8 (t), 38.6 (q), 26.5 (d), 20.7 (q), 20.5 (q), 10.1 ppm (q); MS: *m*/*z* (%): 221 (1) $[M]^+$, 114 (100), 105 (10), 77 (10), 70 (10), 58(30), 42 (8).

Compound (+)-29: This compound was prepared by following the procedure reported by Saavedra:[27] $KHCO_3$ (5.00 g, 50.0 mmol) was added to a solution of (+)-ephedrine hydrochloride (10.08 g, 50.0 mmol) in absolute ethanol (50 mL) at RT and the mixture was stirred for 30 min. 3-Methyl butanal (6.45 g, 8.00 mL, 75.0 mmol) was added dropwise under nitrogen and the resulting mixture was stirred at RT for 1 h. After consumption of ephedrine, $NaBH_4$ (3.80 g, 100 mmol) was added and the reaction mixture was stirred at RT over the weekend. A solution of 5% HCl was added dropwise to adjust the pH to 1 and most of the ethanol was evaporated under vacuum. The residue was made basic with a 5% aqueous solution of NaOH and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, concentrated, and purified by bulb-to-bulb distillation at 120 °C and 3 mbar to afford (+)-**29** as a white solid (7.78 g, 66%). M.p. 35–37 °C; $[\alpha]_D^{20} = -5.2$ ($c = 0.96$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$–0.90 (m, 9H), 1.31 (m, 2H), 1.48–1.58 (hept, $J = 6.8$ Hz, 1H), 2.23 (s, 3H), 2.40–2.55 (m, 4H), 3.90 (br s, 1H), 4.80 (d, $J = 4.2$ Hz, 1H), 7.20–7.25 (m, 1H), 7.29–7.33 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.5$ (s), 127.9 (d), 126.8 (d), 126.1 (d), 72.9 (d), 63.5 (d), 53.2 (t), 38.9 (q), 36.4 (t), 26.3 (d), 22.9 (q), 22.7 (q), 10.1 ppm (q); MS: *m*/*z* (%): 235 (1) $[M]^+$, 128 (100), 105 (10), 77 (10), 70 (10), 58 (22), 56 (8), 43 (11).

Compound (+)-30: This compound was prepared by following the procedure reported by Saavedra[27] (first part): $KHCO_3$ (5.00 g, 50.0 mmol) was added to a solution of (+)-ephedrine hydrochloride (10.08 g, 50.0 mmol) in absolute ethanol (50 mL) at RT, and the resulting mixture was stirred for 60 min at RT. Pivalaldehyde (6.45 g, 8.23 mL, 75 mmol) was added dropwise under nitrogen and the resulting mixture was stirred at RT for 2 d. After consumption of (+)-ephedrine, an aqueous solution of 5% HCl was added dropwise to adjust the solution to pH 1 and most of the ethanol was evaporated under vacuum. The residue was made basic with a 5% aqueous solution of NaOH and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water, saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated.

Reduction of the intermediate oxazolidine:[28] The crude oxazolidine (11.05 g, 47.40 mmol) in dry CH_3CN (235 mL) was treated at 0 °C with $NaBH_3CN$ (5.97 g, 94.80 mmol) in one portion, followed by the addition of trimethylsilylchloride (TMSCl; 25.7 g, 30.3 mL, 237 mmol) over 15 min. The resulting mixture was allowed to reach RT, then stirred at RT for 4 h. $NaBH_3CN$ (5.97 g, 94.80 mmol) and TMSCl (12.87 g, 15 mL, 118.5 mmol) were added at RT and the reaction was stirred at RT overnight, before being quenched with a saturated aqueous solution of K_2CO_3 and stirred at RT for 1 h. CH_3CN was evaporated under vacuum, and the residue was partitioned between water and Et_2O. The organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic phases were washed with water, a saturated aqueous solution of NaCl, dried over Na_2SO_4, filtered, and concentrated to give an orange colored oil. Flash column chromatography on silica gel (cyclohexane/AcOEt, 8:2 to 1:1) and bulb-to-bulb distillation (130 °C/3 mbar) afforded (+)-**30** as a pale yellow oil (1.5 g, 13%). $[\alpha]_D^{20} = +5.1$ ($c = 0.98$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$ (s, 9H), 0.94 (d, $J = 6.70$ Hz, 3H), 2.19–2.30 (m, 2H), 2.27 (s, 3H), 2.76 (m, 1H), 3.20 (br s, 1H), 4.78 (d, $J = 4.8$ Hz, 1H), 7.20–7.35 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.2$ (s), 127.9 (d), 126.8 (d), 126.2 (d), 74.5 (d), 69.3 (t), 66.5 (d), 40.9 (q), 33.1 (s), 28.2 (q), 10.1 ppm (q); MS (GC–MS): *m*/*z* (%): 235 (1) $[M]^+$, 178 (10), 128 (100), 105 (5), 77 (10), 71 (10), 58 (40), 56 (8), 44 (11).

Compound (+)-31: This compound was prepared by following the procedure reported by Saavedra:[27] $KHCO_3$ (2.60 g, 26 mmol) was added to a solution of (+)-ephedrine hydrochloride (5.22 g, 26.0 mmol) in absolute ethanol (30 mL) at RT, and the mixture was stirred for 30 min. 3,3-Dimethylbutanal (3.90 g, 4.90 mL, 39.0 mmol) was added dropwise under nitrogen and the resulting mixture was stirred at RT for 3 h. After consumption of (+)-ephedrine, $NaBH_4$ (1.976 g, 52 mmol) was added and the reaction mixture was stirred at RT overnight then for 8 h at 55 °C. A solution of 5% HCl was added dropwise to adjust the solution to pH 1 and most of the ethanol was evaporated under vacuum. The residue was made basic with a 5% aqueous solution of NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solutions of NaCl, dried over Na_2SO_4, filtered, concentrated, and purified by bulb-to-bulb distillation at 110 °C and 3 mbar to afford (+)-**31** as a white solid (6.16 g, 95%). M.p. 66–69 °C; $[\alpha]_D^{20} = +14.9$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H), 1.35–1.42 (m, 1H), 2.26 (s, 3H), 2.41–2.55 (m, 2H), 2.79–2.86 (m, 1H), 3.90 (br s, 1H), 4.80 (d, $J = 4.4$ Hz, 1H), 7.20–7.24 (m, 1H), 7.30–7.32 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 142.4$ (s), 127.9 (d), 126.8 (d), 126.1 (d), 72.7 (t), 63.2 (d), 50.7 (t), 40.6 (t), 39.3 (q), 29.8 (s), 29.5 (q), 10.1 ppm (q); MS: *m*/*z* (%): 178 (10), 142 (100), 77 (8), 70 (10), 58 (15), 55 (10), 43 (10).

Compound (−)-32:[29] This compound was prepared by following the procedure previously reported[29] or purchased from Aldrich. $[\alpha]_D^{20} = -24.7$ ($c = 1.21$ in $CHCl_3$); (lit.:[29] $[\alpha]_D^{22} = -24.4$ ($c = 2.00$ in hexane)).

Compound (+)-32:[29] This compound was prepared by following the procedure previously reported[29] or purchased from Aldrich. $[\alpha]_D^{20} = +26.7$ ($c = 1.82$ in $CHCl_3$); (lit.:[29] $[\alpha]_D^{25} = +24.4$ ($c = 2.05$ in hexane)).

Aldol reactions

Compound (±)-8: A solution of muscodione (**4**) (15.12 g, 60.0 mmol) in CH_2Cl_2 (210 mL) was treated at 22–24 °C with a solution of $ZrCl_3OPr$ (36 % in AcOEt) (65.25 g, 91.6 mmol). After 5 min, the yellowish solution was treated at −10–0 °C with NBu_3 (19.43 g, 25.0 mL, 105 mmol). After 15 min, the reaction mixture was poured into water and extracted with Et_2O. The organic phases were washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. Recrystallization from heptane (345 mL) afforded **8** (11.93 g, 79 %) and 2.80 g of mother liquors, from which **8** (1.39 g, 9 %) was recovered.

Compounds (−)-7 and (−)-8

*Preparation of the (−)-**32**·$TiCl_4$ (Table 1, entry 13 (large-scale experiment)*: A solution of $TiCl_4$ (1 M in CH_2Cl_2; 54.8 mL, 54.8 mmol) was added to a solution of (−)-**32** (14.45 g, 54.8 mmol) in CH_2Cl_2 (55 mL) over 5 min, under nitrogen. The temperature rose to 40 °C. The resulting brown mixture was stirred for 15 min, concentrated at 40 °C under N_2, and dried under vacuum (6 mbar) for 2 h. All other Ti complexes were prepared accordingly.

*Aldol reaction (Table 1, entry 13 (large-scale experiment using 0.4 equiv of (−)-**32**·$TiCl_4$)*: The above brown complex (−)-**32**·$TiCl_4$ (0.4 equiv) was dissolved in NMP (137 mL) under N_2 at RT. The temperature rose to 31 °C. After 30 min **4** (34.6 g, 137.1 mmol) was added under stirring. After 30 min the dark solution was treated at 0–5 °C with a solution of TMEDA (7.39 g, 9.60 mL, 63.8 mmol) and H_2O (123 μL, 6.85 mmol). The turbid reaction mixture was kept in the freezer (−20–−18 °C) for 3 d, before being poured onto a 5 % HCl/ice mixture and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water, saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated (34.6 g). The acidic aqueous phase was basified with a 5 % aqueous solution of NaOH (300 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water, saturated aqueous NaCl, dried over Na_2SO_4, concentrated, and bulb-to-bulb distilled to afford (−)-**32** (12.86 g, 89 %). The remaining heavy oil (34.2 g) was purified by flash chromatography on silica gel (800 g) and cyclohexane/Et_2O 1:1 to afford, successively, unreacted **4** (22.9 g, 66 %), (−)-**8** (4.20 g (12 %, 38 % *ee*), a mixture of **7** and **8** (537 mg, 1.5 %) and (−)-**7** (3.81 g, 11 %; 68 % *ee*). Recrystallization of (−)-**7** from heptane/2 % acetone (99 mL) afforded enantiopure (−)-**7** (1.94 g, 6 %; ≥98 % *ee*). M.p. 162–164 °C; $[\alpha]_D^{20} = -39$ ($c = 0.5$ in $CHCl_3$).

(−)-**8** (38 % *ee*). $[\alpha]_D^{20} = -14.9$ ($c = 1.46$ in $CHCl_3$) (extrapolation for enantiomerically pure (−)-**8**: $[\alpha]_D^{20} = -39$).

For the determination of the *ee* values of **7** and **8**, the crude mixture containing **7** and **8** (250 mg) in THF (5 mL) was treated with TMSOTf (290 μL) and NEt_3 (210 μL) (30 min, 0 °C) and the corresponding silyl ethers were extracted with NH_4Cl/Et_2O and injected on the chiral GC column. Order of elution: (+)-**8**, (−)-**8**, (+)-**7**, and (−)-**7**. The same *ee* values were found after chromatography.

*Aldol reaction (Table 1, entry 11 (using 0.8 equiv of (−)-**32**·$TiCl_4$)*: The complex (−)-**32**·$TiCl_4$, prepared from (−)-**32** (421 mg, 1.60 mmol) and $TiCl_4$ (1 M in CH_2Cl_2; 1.60 mL, 1.60 mmol) was dissolved in NMP (2 mL) and treated as above with **4** (504 mg, 2.00 mmol), TMEDA (216 mg, 0.28 mL, 1.86 mmol), and H_2O (4 μL, 0.2 mmol) and kept in the freezer for 96 h. Chromatographic purification as above afforded **4** (70 mg, 14 %), (−)-**8** (261 mg (52 %; 17 % *ee*), and (−)-**7** (107 mg, 21 %; 70 % *ee*). Recrystallization of (−)-**7** as above afforded enantiopure (−)-**7** (51 mg, 10 %; ≥98 % *ee*).

*NMR spectra of **7***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J = 6.5$ Hz, 3H), 1.20–1.68 (m, 20H), 1.74 (m, 1H), 2.18–2.45 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.2$ (s), 78.3 (s), 58.67 (d), 44.8 (t), 42.5 (t), 37.8 (t), 27.7 (d), 26.8 (t), 26.4 (t), 25.7 (t), 25.5(t), 25.1 (t), 25.0 (t), 24.9 (t), 22.0 (q), 18.6 ppm (t).

*NMR spectra of **8***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.02$ (d, $J = 6.5$ Hz, 3H), 1.08 (m, 1H), 1.20–1.73 (m, 18H), 1.85 (m, 1H), 1.96 (t, $J = 13$ Hz, 1H), 2.14 (m, 1H), 2.36 (m, 1H), 2.41 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.0$ (s), 79.7 (s), 55.7 (d), 49.9 (t), 45.0 (t), 39.7 (t), 28.7 (d), 26.9 (t), 26.4 (t), 26.2 (t), 26.0 (t), 25.2 (t), 25.0 (t), 22.2 (t), 22.1 (q), 19.3 ppm (t).

Compound (+)-36: A solution of (−)-**7** (1.54 g, 6.11 mmol; ≥98 % *ee*) in AcOH (35 mL) was treated with $NMe_4BH(OAc)_3$ (1.61 g, 6.12 mmol) under cold water cooling. After stirring the resulting solution at RT for 90 min (90 % conversion), additional $NMe_4BH(OAc)_3$ (561 mg, 2.13 mmol) was added and stirring was continued for 17 h. The solution was poured into a 30 % aqueous solution of NaOH (130 mL) and extracted with EtOAc. The organic phases were washed with H_2O and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated to afford (+)-**36** as a white solid (1.58 g, 100 %). M.p. 101–104 °C; $[\alpha]_D^{20} = +24.6$ ($c = 0.79$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.5$ Hz, 3H), 0.92 (m, 1H), 1.03 ("t", $J = 13$ Hz, 1H), 1.08 ("q", $J = 12$ Hz, 1H), 1.18–1.82 (m, 21H), 1.82–1.93 (m, 2H), 4.24 ppm (ddd, $J = 12$, 4.5, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.4$ (s), 70.0 (d), 48.7 (d), 43.5 (t), 39.1 (t), 38.2 (t), 28.0 (t), 27.0 (t), 26.4 (t), 25.8 (d), 25.3 (t), 23.9 (t), 23.5 (t), 22.7 (t), 21.9 (q), 18.7 ppm (t); MS: *m*/*z* (%): 236 [$M^+ - 18$] (24), 218 (29), 175 (13), 161 (21), 147 (30), 137 (32), 133 (33), 119 (37), 111 (83), 91 (83), 81 (83), 55 (94), 41 (100).

Tosylate 37: A solution of crude **36** (474 mg, max. 1.87 mmol) in pyridine (1.9 mL) was treated with TsCl (355 mg, 1.84 mmol) under ice cooling. The reaction mixture was stirred at 0 °C for 2 h. Further TsCl was added (355 mg, 1.84 mmol) and the mixture was kept in the refrigerator (5 °C) overnight. The suspension was treated with AcOEt and water and the phases were separated. The organic phases were washed with 5 % HCl, H_2O, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated. Tosylate **37** (923 mg, 100 %) was used without purification. ^{1}H NMR (400 MHz, [D$_8$]THF): characteristic signals: $\delta = 0.86$ (d, $J = 6.5$ Hz, 3H), 2.44 (s, 3H), 4.66 ppm (ddd, $J = 12$, 5, 5 Hz, 1H); ^{13}C NMR (100 MHz, [D$_8$]THF): characteristic signals: $\delta = 144.8$ (s), 136.7 (s), 130.4 (2d), 128.5 (2d), 83.5 (d), 76.4 (s), 47.1 (d), 44.0 (t), 27.0 (2t), 26.5 (d), 23.5 (t), 22.0 (q), 21.5 (q), 19.6 ppm (t).

Compound (+)-(*R*)-1: A suspension of crude **37** (878 mg, max. 1.78 mmol) in *tert*-butanol (18 mL) was treated at 25 °C with KO*t*Bu (598 mg, 5.34 mmol). The reaction mixture was stirred at 25–35 °C for 30 min, poured into a 5 % aqueous solution of HCl and extracted with EtOAc. The organic phases were washed with H_2O, a saturated aqueous solution of $NaHCO_3$, saturated aqueous NaCl, dried over Na_2SO_4, and evaporated. Bulb-to-bulb distillation (100–130 °C/0.02 mbar) afforded (+)-(*R*)-**1** (314 mg; 90 % pure; >98 % isomeric purity; 67 % from (−)-**7**, ≥98 % *ee*), identical to an authentic sample.[1] $[\alpha]_D^{20} = +11.6$ ($c = 1.12$ in MeOH); (lit.:[2] $[\alpha]_D^{20} = +11.7$ ($c = 2.45$ in MeOH). The *ee* value was determined by chiral GC of the reduced $LiAlH_4$ product.

Compound (+)-38: A cooled (−70 °C) solution of (−)-**7** (500 mg, 1.98 mmol; ≥98 % *ee*) in THF (15 mL) was treated with L-Selectride (1 M in THF; 3.95 mL, 3.95 mmol). After stirring the resulting solution at −60 °C for 20 min, the mixture was poured into a 5 % aqueous solution of NaOH (50 mL). The reaction flask was rinsed with AcOEt. The two-phase system was treated with 35 % H_2O_2 (2.8 mL), stirred for 90 min, and extracted with EtOAc. The organic phases were washed with a saturated aqueous solution of NaCl, a 10 % aqueous solution of Na_2SO_3, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated to afford a pale oil (547 mg, 100 %). $[\alpha]_D^{20} = +23.7$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.5$ Hz, 3H), 1.00–1.65 (m, 23H), 1.73 (br d, $J = 14$ Hz, 1H), 1.92 (br d, $J = 8$ Hz, 1H), 2.15 (m, 1H), 3.93 ppm (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.5$ (s), 72.1 (d), 46.1 (d), 44.6 (t), 39.4 (t), 37.0 (t), 29.7 (t), 26.9 (t), 26.2 (t), 25.7 (t), 25.3 (t), 24.9 (t), 24.0 (t), 22.1 (q), 21.6 (d), 18.6 ppm (t); MS: *m*/*z* (%): 236 (33) [$M - 18$]$^+$, 221 (13), 218 (20), 178 (14), 161 (15), 147 (22), 137 (28), 111 (100), 95 (61), 81 (75), 67 (61), 55 (75), 41 (66).

Tosylate 39: A solution of crude **38** (540 mg, max. 1.96 mmol) in THF (20 mL) was treated at 25–41 °C (exothermic reaction) with BuLi (1.48 M in hexane; 2.0 mL, 2.96 mmol). The solution was stirred at 40 °C for 15 min, cooled at −20 °C, and treated at once with TsCl (438 mg,

2.30 mmol). The reaction mixture (−15 °C) was stirred for 15 min and poured into a 5% aqueous solution of HCl. The product was extracted with AcOEt and the organic phases were washed with a 5% aqueous solution of HCl, H_2O, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated (893 mg, 100%). ^{1}H NMR characteristic signals (400 MHz, $CDCl_3$): 0.86 (d, J=6.5 Hz, 3H), 4.69 ppm (d, J=2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.9 (s), 134.1 (s), 129.9 (2d), 128.1 (2d), 83.9 (d), 75.5 (s), 44.8 (d), 43.8 (t), 38.6 (t), 34.3 (t), 26.6 (t), 25.7–24.8 (5t), 23.6 (t), 21.7 (2q), 21.6 (d), 18.3 ppm (t).

Compound (−)-(*R*)-2 from (+)-38: A suspension of crude **39** (438 mg, max. 0.86 mmol) in *tert*-butanol (10 mL) was treated with KO*t*Bu (336 mg, 3.00 mmol) at 25 °C. The reaction mixture was stirred at 25–30 °C for 30 min. As the reaction was very slow, a second and (after another 30 min) a third portion of KO*t*Bu (336 mg, 3.00 mmol) was added. After 15 h, the mixture was poured into a 5% aqueous solution of NaOH and extracted with diethyl ether. The organic phases were washed with H_2O and saturated aqueous NaCl, dried over Na_2SO_4, and evaporated (307 mg). Bulb-to-bulb distillation (100–120 °C/0.02 mbar) afforded 209 mg of (*R*)-**2** (74% pure; >98% isomeric purity; 76%, ≥98% *ee*). Flash column chromatography on SiO_2 (6 g, cyclohexane/AcOEt=98:2) afforded (*R*)-**2** (152 mg, 75%), identical to an authentic sample.[1] The *ee* value was determined by chiral GC of the reduced $LiAlH_4$ product. $[\alpha]_D^{20}=-3.6$ (c=0.10 in MeOH); (lit.:[2] $[\alpha]_D^{20}=-3.3$ (c=0.06 in MeOH).

Compound (−)-(*R*)-3 from (−)-(*R*)-2: Hydrogenation of (−)-(*R*)-**2** (150 mg, 0.636 mmol) over washed Raney Ni in EtOH according to reference [2] afforded (−)-(*R*)-**3** (146 mg (≥98% *ee*). $[\alpha]_D^{20}=-12.6$ (c=0.48 in MeOH); (lit.:[2] $[\alpha]_D^{20}=-12.7$ (c=0.09 in MeOH).

Compound 40: A solution of (±)-**8** (2.00 g, 7.94 mmol) in AcOH (45 mL) was treated with $NMe_4BH(OAc)_3$ under cold water cooling (95% pure; 2.39 g, 8.64 mmol). After stirring the resulting solution at RT for 15 h (90% conversion), additional $NMe_4BH(OAc)_3$ (1.20 g, 4.32 mmol) was added and stirring continued for 72 h. The solution was poured into 30% NaOH (150 mL) and extracted with EtOAc. The organic phases were washed with H_2O and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated (1.95 g, 95% pure; 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (d, J=6.5 Hz, 3H), 0.93 (q, J=11.5 Hz, 1H), 1.16 (dd, J=14, 13 Hz, 1H), 1.20–1.76 (m, 21H), 1.82–1.98 (m, 3H), 3.68 ppm (td, J=11, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=76.5 (s), 74.7 (d), 49.2 (d), 45.6 (t), 44.5 (t), 40.0 (t), 27.9 (t), 27.2 (t), 26.5 (t), 26.1 (t), 26.0 (t), 25.7 (d), 25.1 (t), 24.5 (t), 22.0 (q), 21.8 ppm (t); MS: m/z (%): 236 (11) $[M]^+$-18, 221 (7), 166 (8), 137 (12), 128 (100), 109 (37), 98 (35), 69 (45), 55 (57), 41 (58).

Tosylate 41: A solution of crude **40** (95% pure; 533 mg, max. 2.00 mmol) in pyridine (2.1 mL) was treated with TsCl (800 mg, 4.20 mmol) under ice cooling. The reaction mixture was stirred at 0 °C for 90 min and kept in the refrigerator (5 °C) overnight. The suspension was treated with AcOEt and water and the phases were separated. The organic phases were washed with a 5% aqueous solution of HCl, H_2O, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated (1.02 g). ^{1}H NMR characteristic signals (400 MHz, $CDCl_3$): δ=0.86 (d, J=6.5 Hz, 3H), 2.44 (s, 3H), 4.66 ppm (ddd, J=11, 11, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.4 (s), 134.7 (s), 129.6 (2d), 127.7 (2d), 87.7 (d), 76.6 (s), 46.7 (d), 45.0 (t), 41.6 (t), 40.1 (t), 27.0 (2t), 26.1 (t), 25.7 (t), 25.6 (d), 25.3 (2t), 24.7 (t), 22.0 (t), 21.6 (2q), 21.7 (q), 21.6 ppm (q).

Compound 2 from 41: A suspension of crude **41** (967 mg, max. 1.89 mmol) in *tert*-butanol (20 mL) was treated with KO*t*Bu (668 mg, 5.97 mmol) at 25 °C. The reaction mixture was stirred at 25–35 °C for 20 min, poured into a 5% aqueous solution of HCl and extracted with EtOAc. The organic phases were washed with H_2O, a saturated aqueous solution of $NaHCO_3$, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated. Bulb-to-bulb distillation (100–130 °C/0.02 mbar) afforded **2** (351 mg; 96% pure; >98% isomeric purity; 76% from (±)-**8**).

Compound 42: A cooled (−70 °C) solution of **8** (1.00 g, 3.96 mmol) in THF (30 mL) was treated with L-Selectride (1 M in THF; 7.90 mL, 7.90 mmol). After stirring the resulting solution at −65 °C for 30 min, the mixture was poured into a 5% aqueous solution of NaOH (50 mL). The reaction flask was rinsed with AcOEt. The two-phase system was treated with 35% H_2O_2 (5.6 mL), stirred for 90 min, and extracted with EtOAc. The organic phases were washed with a 10% aqueous solution of Na_2SO_3, H_2O, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated (986 mg, 98%). Bulb-to-bulb distillation (180–210 °C/0.05 mbar) over $CaCO_3$ (45 mg) afforded **42** (986 mg; 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.93 (d, J=6.5 Hz, 3H), 1.07 (td, J=13, 2.5 Hz, 1H), 1.12–1.68 (m, 19H), 1.75 (m, 1H), 1.86 (m, 1H), 1.95 (m, 1H), 2.17 (m, 1H), 3.07 (br, 1H), 3.43 (br, 1H), 3.98 ppm (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=77.4 (s), 70.4 (d), 46.1 (t), 43.5 (d), 42.5 (t), 39.0 (t), 27.1 (t), 26.2 (2t), 25.5 (t), 25.2 (t), 25.0 (t), 22.5 (t), 22.0 (q), 21.6 (d), 21.5 ppm (t); MS: m/z (%): 236 (40) $[M-18]^+$, 221 (12), 193 (10), 178 (13), 137 (19), 127 (41), 109 (48), 98 (61), 81 (67), 55 (100), 41 (99).

Tosylate 43: A solution of **42** (986 mg, 3.88 mmol) in THF (40 mL) was treated with BuLi (1.48 M in hexane; 3.90.0 mL, 3.90 mmol) at 25–41 °C (exothermic reaction). The solution was stirred at 40 °C for 15 min, diluted with THF (10 mL) (milky aspect unchanged), cooled at −20 °C, and treated at once with TsCl (1.11 g, 5.83 mmol). The reaction mixture (−15 °C) was stirred for 15 min (clear solution) and poured into a 5% aqueous solution of HCl. The product was extracted with diethyl ether and the organic phases were washed with H_2O, a saturated aqueous solution of $NaHCO_3$, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated. Excess TsCl was removed at 100 °C/0.01 mbar. The residual viscous oil (1.57 g, 99%) was used without purification. ^{1}H NMR characteristic signals (400 MHz, $CDCl_3$): δ=0.85 (d, J=6.5 Hz, 3H), 4.93 (br d, J=2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=144.8 (s), 134.1 (s), 129.8 (2d), 127.7 (2d), 83.5 (d), 75.5 (s), 45.5 (t), 43.9 (d), 39.3 (t), 37.6 (t), 27.0 (t), 26.2 (t), 26.0 (t), 25.1 (t), 25.0 (t), 24.7 (t), 22.1 (t), 21.6 (2q), 21.6 (d), 21.4 ppm (t).

Compound 44: A suspension of crude **43** (398 mg, 0.975 mmol) in *tert*-butanol (10 mL) was treated with KO*t*Bu (336 mg, 3.00 mmol) at 25 °C. The reaction mixture was stirred at 25–30 °C for 30 min. As the reaction was very slow, a second and (after another hour) a third portion of KO*t*Bu (328 mg, 2.93 mmol) was added. After 2 h, the mixture was poured into a 5% aqueous solution of HCl and extracted with diethyl ether. The organic phases were washed with H_2O, a saturated aqueous solution of $NaHCO_3$, and a saturated aqueous solution of NaCl, dried over Na_2SO_4, and evaporated (226 mg). The crude material was purified by flash column chromatography on SiO_2 (5 g, cyclohexane/AcOEt=70:30) to afford a mixture of **44** and **2** (112 mg; 70:30; yield **44**/**2**=34:15%). Treatment of this mixture with excess $NaBH_4$ in MeOH/H_2O (5:1) converted **2** into the corresponding alcohol, thus allowing ready purification of **44** by flash column chromatography on SiO_2 (cyclohexane/AcOEt=9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.85 (d, J=6.5 Hz, 3H), 0.90 (m, 1H), 1.25 (s, 1H), 1.22–1.88 (m, 22H), 1.94 ppm (ddd, J=15, 7, 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=67.3 (s), 66.5 (s), 38.1 (t), 33.3 (t), 32.3 (t), 30.5 (t), 27.7 (t), 26.4 (2t), 25.4 (d), 23.5 (t), 22.8 (t), 21.9 (t), 21.6 (t), 21.6 (q), 21.4 ppm (t). MS: m/z (%): 236 (17) $[M]^+$, 221 (15), 193 (7), 181 (8), 165 (9), 151 (14), 135 (15), 109 (36), 95 (63), 81 (88), 55 (100), 41 (85).

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