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FACILE ISOMERIZATION OF OXIRANES TO ALLYL ALCOHOLS BY MIXED METAL BASES

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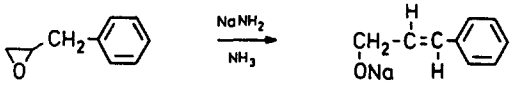
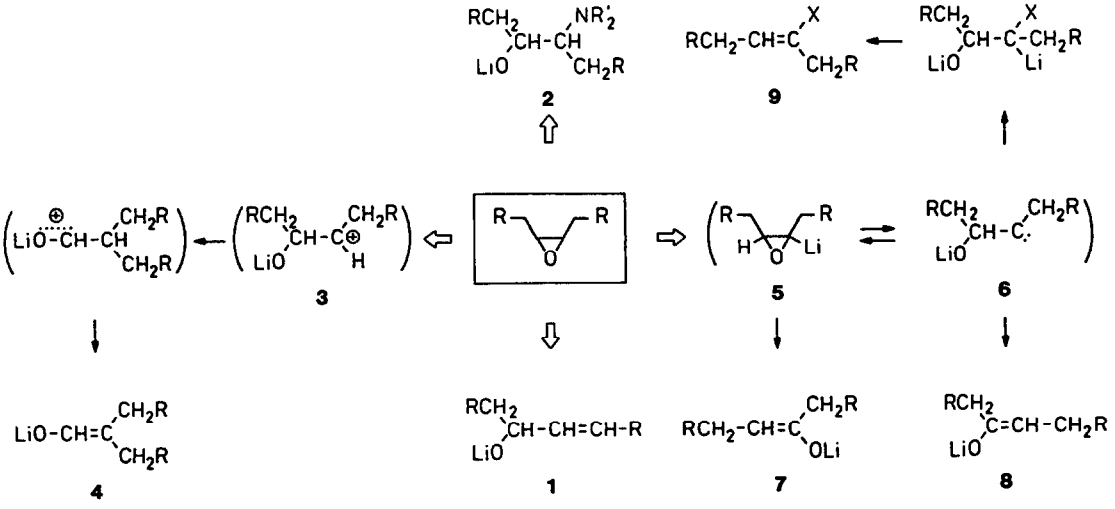
Summary : The mixture of lithium diisopropylamide and potassium *tert*-butoxide ("LIDAKOR reagent") promotes smooth ring opening of oxiranes to afford allyl alcohols with good to excellent yields. Internal epoxyalkanes and large size epoxycycloalkanes give preferentially or exclusively *trans*-alkenols. The regio- and stereochemistry of the ring opening reaction are essentially the consequence of *syn*-periplanar elimination mechanisms.

Huisgen and Sauer were the first to emphasize the exceptionally high "kinetic basicity" (velocity of proton abstraction) of lithium dialkylamides. For example, phenyllithium converts instantaneously and quantitatively piperidine to lithium piperidide. Despite its weaker thermodynamic basicity, the latter reagent brings about the dehydrohalogenation of bromobenzene almost 100 times faster than does its organometallic precursor [1]. Previously lithium diethylamide had been extensively employed by Ziegler [2] for the deprotonation of aliphatic nitriles. - Heilbron, Jones *et al.* [3] have accomplished the first base promoted isomerization of an oxirane to an allyl alcohol when they treated 2-benzyloxirane with sodium amide in liquid ammonia and isolated 80% of cinnamyl alcohol. Obviously relief of ring strain provided sufficient driving force to overcome the reluctance of ether oxygen atoms to act as nucleofugal leaving groups in β-elimination reactions.

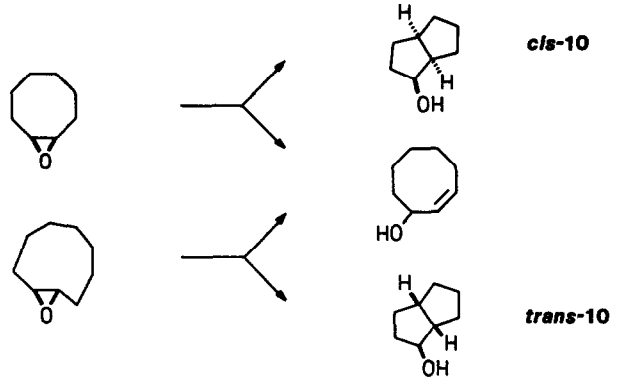


The ring opening was facilitated yet by another factor, *i.e.* the acidity enhancing effect of the phenyl substituent attached to the exocyclic methylene group. Olefinic or acetylenic unsaturation should operate in the same way. Indeed stronger bases than sodium amide are required to achieve the isomerization of totally saturated aliphatic oxiranes. Although potassium *tert*-butoxide in dimethyl sulfoxide suffices in favorable cases [4], the more powerful lithium diethylamide proved to be generally more advantageous [5, 6]. Even this reagent, however, had to be employed in excess, at elevated temperatures and during long reaction times. Thus, only after adding 2.5 equivalents of lithium diethylamide to a solution of cyclohexene oxide [5, 7] in diethyl ether and hexane and heating the mixture 48 h to reflux 67% of 2-cyclohexen-1-ol were obtained. Under the same or similar conditions, cyclopentene oxide [5] and cycloheptene oxide [5, 9] gave only trace amounts of isomerization products.

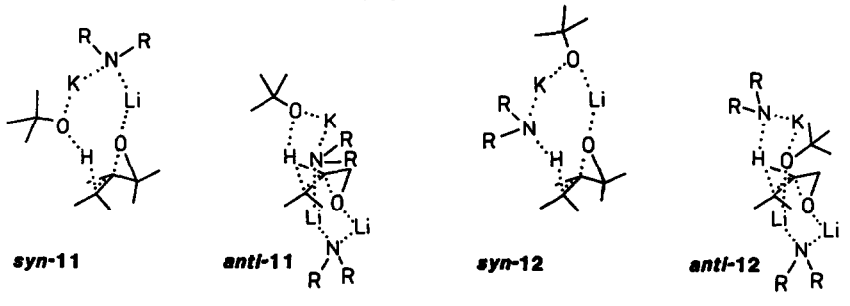
The temperature may be lowered to some extent if the reaction is carried out in the presence of hexamethylphosphoric triamide, employed neat or as a cosolvent [6]. On the other hand, this polar compound inevitably complicates the work-up. Hence it was desirable to establish a more convenient experimental protocol and at the same time to control better the regio- and typoselective outcome of the oxirane reactions. As a matter of fact, several other pathways are competing with the base promoted β-elimination leading to allyl alcohols **1**. First of all the base may act as a nucleophile and react with the oxirane to give an adduct **2**. This is the preferential reaction mode of terminal (*i.e.*, mono- or 2,2-disubstituted) epoxides, but occasionally it occurs even with internal epoxides. Thus, the reaction between cyclopentene oxide and lithium diethylamide affords *trans*-2-diethylamino-1-cyclopentanol as the main product [5]. In the absence of strong donor solvents the lithium reagent may deploy its electrophilic properties and, under ring opening of the oxirane, generate a β-(lithiumoxy)carbenium ion **3** which by 1,2-alkyl migration and deprotonation gets converted to an aldehyde-derived enolate **4**. Only a few examples of this type of transformation are known. Consecutive treatment with lithium diethylamide and neutralization produces 3% of 2-propylheptanal (besides 79% of the allyl alcohol) from *trans*-2,3-dipropyloxirane [10], 32% of cycloheptanecarbaldehyde from *trans*-cyclooctene oxide [11] and 66% of diphenylacetaldehyde from *trans*-2,3-diphenyloxirane [12]. Finally, the base may abstract a proton from a position adjacent to the heterocyclic oxygen atom. The resulting 2-oxiranyllithium intermediate [13] **5** may directly isomerize to form a ketone-derived enolate **7**. The feasibility of this process is demonstrated by the amide promoted conversion of 2,2-diphenyl-3-*p*-tolyloxirane to benzhydryl *p*-tolyl ketone with 31% yield [12]. In general, however, the intermediate **5** prefers to enter into an equilibrium with the valence-tautomeric β-(lithiumoxy)alkylidene **6**. The bivalent carbon species then seeks stabilization through β-hydride shift, producing again an enolate **8** [5, 9, 12, 14] (regioisomeric to the previous one if the oxirane was asymmetrically substituted), through [2+1] cycloaddition with an intramolecularly available double bond [15], or through addition of a nucleophile X followed by lithium oxide elimination , giving rise to an alkene **9** (in general, X being the organic moiety of an organolithium reagent). [16]



The β-lithiumoxy carbene **6** may also undergo insertion into γ-positioned [15, 17] or transannular [11, 18] CH groups if within reach. The reaction between cyclooctene oxide and lithium dialkylamides is particularly revealing. As already mentioned, the *trans*-isomer yielded 32% of cycloheptanecarbaldehyde when treated with excess lithium diethylamide during 72 h in refluxing benzene [11]. In addition, 47% of *trans*-2-bicyclo[3.3.0]octanol (*trans*-**10**) and 10% of 2-cycloocten-1-ol were identified. The *cis*-isomer gave 70% of *cis*-2-bicyclo[3.3.0]octanol (*cis*-**10**) and 16% of 2-cycloocten-1-ol under similar conditions. [11]. This product ratio, however, is only observed if lithium bromide or lithium perchlorate is present [18]. With salt-free lithium diethylamide the opposite ratio is found, in other words the monocyclic allyl alcohol becomes the main product. Conversely, with lithium diisopropylamide the bicyclic compound *cis*-**10** is formed almost eclusively. [19]

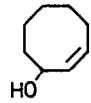
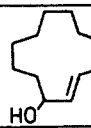


Our approach to the problem was guided by the conviction that the base-promoted conversion of oxiranes to allyl alcoholates implies a conveyer belt mechanism [20] with strong push-pull character. If this is correct, a combination of lithium and potassium bases should be more efficacious than any individual metal amide alone : due to its electrophilic properties, the lighter alkali metal could help to tear the oxirane ring apart while the heavier alkali metal would confer maximum basicity to its anionic counterpart and thus facilitate deprotonation. Potassium *tert*-butoxide activates organolithium compounds immensely [21]. Furthermore the mixed bases sodium amide/sodium *tert*-butoxide [22] and sodium hydride/sodium *tert*-butoxide [23] have been recognized as useful reagents which have been employed with particular success in elimination reactions. This gave us the idea to use the mixture of a lithium dialkylamide and potassium *tert*-butoxide. [24, 25] In this way, we expected to favor push-pull transition states *syn*- and *anti*-**11** or, more likely, *syn*- and *anti*-**12**. [26]



The result was quite rewarding. In tetrahydrofuran solution the mixed bases were found to bring about the oxirane ring-opening β-elimination slowly already at -50 °C and rapidly at 0 °C. All 1,2-epoxycycloalkanes studied gave good to excellent yields of 2-cycloalken-1-ols **13** - **17** (see table). Probably due to diminished self-aggregation [27], lithium diisopropylamide was slightly more reactive than lithium diethylamide, if in the presence of potassium *tert*-butoxide.

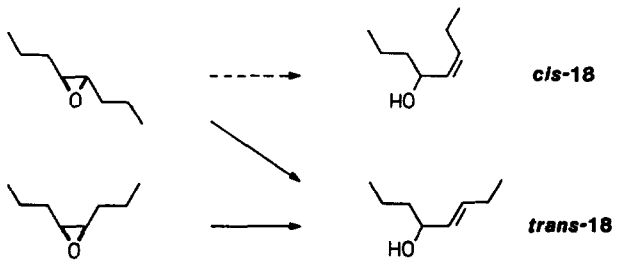
Table. 2-Cycloalken-1-ol by LIDAKOR [a] treatment of 1,2-epoxycycloalkanes. [b]

starting material	product	yield after 20 h at -50°C [c]	yield after 1h at 0°C [d]
	 **13**	58%	88%
	 **14**	78%	76%
	 **15**	70% [e]	40% [f]
	 **16**	34% [e]	68% [f]
	 **17**	68% [e]	84%

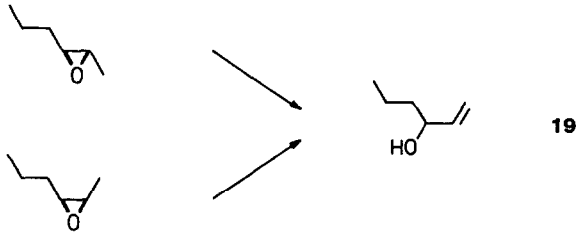
a) LIDA = lithium diisopropylamide (or another lithium dialkylamide), KOR = potassium *tert*-butoxide (or another potassium alcoholate).
b) Epoxycyclododecane was a *cis/trans*-mixture, all others were pure *cis*-isomers.
c) Yield of isolated product, purified by distillation (~ 10% below GC numbers).
d) Yield of product as determined by gas chromatographic analysis.
e) After 40 (**15** and **16**) or 80 (**17**) rather than 20 h at -50 °C.
f) A considerable amount of starting material (45 and, respectively, 30%) remained unconsumed.

The 1,2-epoxycyclododecane case is the most remarkable one. Exclusively *trans*-2-cyclododecen-1-ol was formed, as already reported by Nozaki *et al.* [28] who had accomplished the oxirane ring opening with diethylaluminum 2,2,6,6-tetramethylpiperidide ("DATMP") in benzene at 0 °C. Under the conditions of the Japanese workers, however, only the *trans*-epoxide reacted while the *cis* isomer was almost completely recovered. In contrast, both stereocomponents were converted by the LIDAKOR mixture (LIDA = lithium diisopropylamide, KOR = potassium *tert*-butoxide) at roughly the same rate. Competition kinetics revealed the *cis* isomer to be even 1.7 times more reactive than the *trans* analog.

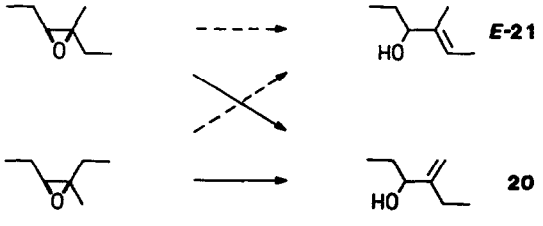
The remarkable stereoselectivity of both *cis*- and *trans*-1,2-epoxycyclododecanes will be rationalized at the end of this article (see next page). It is only partially shown by open-chain analogs. While *cis*-2,3-dipropyloxirane affords exclusively the *trans*-isomer (52%) of 5-octen-4-ol (**18**), the *trans*-substituted oxirane produces a 1 : 2 to 1 : 10 *cis/trans* mixture (48%) of the same alcohol, depending on the base concentration.



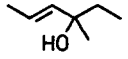
The regio- and stereoselective behavior of the oxirane ring-opening reaction can be readily understood if one assumes a *syn*-periplanar, concerted though E1cb like elimination mechanism. When strong and bulky bases are involved in β-elimination processes they tend to follow the Hofmann rule by abstracting protons from methyl rather than methylene groups, whenever possible. This rule of thumb was confirmed by the clean conversion (78% and 84%, respectively) of both *cis*- and *trans*-2-methyl-3-propyloxirane to 1-hexen-3-ol (**19**).



The Nozaki group has reported a quite intriguing regio- and stereochemical selectivity associated with the ring opening of a trialkyl substituted oxirane : upon treatment with DATMP, (*Z*)-3-butyl-2-methyl-2-pentyloxirane produced exclusively 6-pentyl-6-hepten-5-ol while the (*E*)-isomer afforded pure (*E*)-6-methyl-6-undecen-5-ol [28]. In contrast with these findings the LIDAKOR promoted isomerization of both stereoisomeric 2,3-diethyl-2-methyloxiranes leads to practically an identical mixture (93 - 95%) of the regioisomeric alcohols 2-ethyl-1-penten-3-ol (**20**) and (*E*)-4-methyl-4-hexen-3-ol (*E*-**21**) in the ratio of 28 : 72.



The construction of the double bond in the interior of a hydrocarbon chain, as in *E*-**21**, implies proton abstraction from a methylene rather than a methyl position. The lack of selectivity as well as the absence of the other regioisomer, 3-methyl-4-hexen-3-ol (**22**), is amazing at first sight. It may, however, simply mean that the mechanism of the LIDAKOR attack is shifting from the E1cb to the E1($C^{\oplus}$) end of the variable E2 transition state spectrum [29] if unbranched oxiranes are replaced by *gem*-dialkyl substituted substrates.



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In general, LIDAKOR promoted β-elimination reactions appear to follow a *syn*-periplanar stereochemical course. Strong evidence for this assumption will be presented in one of the accompanying articles [30]. The perfect and imperfect stereoselectivity in the ring opening of *cis*- and, respectively, *trans*-4,5-epoxyoctane (the latter leading to a mixture of *cis*- and *trans*-**18** with ratios ranging from 1 : 2 to 1 : 10, see above) can be rationalized in this way. For reasons of steric repulsion, the conformation *Z*-**23**, the precursor to alcohol *cis*-**18**, is much more disfavored with respect to *Z*-**24** than is conformation *E*-**23**, again precursor to alcohol *cis*-**18**, with respect to *E*-**24** [31]. As molecular models suggest, conformer *E*-**23** appears to suffer from transannular repulsions in the case of *trans*-1,2-epoxycyclododecane (**17**). As a consequence, this substrate leads to little if any *cis*-2-alkenol.

Z-**23** *Z*-**24** *E*-**23** *E*-**24**

R = C_2H_5

In protic solvents, *anti*-periplanar processes are much more probable [32]. Indeed, two cases of *anti*-oriented oxirane fission under the impact of sodium methoxide in methanol have been reported [33]. Initially, the same mode was assumed to be employed by lithium dialkylamide bases too [5]. Later, however, a deuterium label permitted to demonstrate that the reaction between lithium diethylamide and *cis*- or *trans*-4-*tert*-butyl-1,2-epoxycyclohexane follows a *syn*-periplanar mechanism [34].

EXPERIMENTAL PART

1. General remarks

Starting materials have been purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Darmstadt), unless literature sources or details for the preparation are given. *Butyllithium* and sublimed quality *potassium tert-butoxide* were supplied by CheMetall, Frankfurt, and Hüls-Troisdorf (Troisdorf). *Diisopropylamine* was distilled from finely powdered calcium hydride and was stored under nitrogen. All other commercial reagents were used without further purification.

Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen.

Diethyl ether and *tetrahydrofuran* were obtained anhydrous by distillation from sodium wire after the characteristic blue color of *in situ* generated sodium diphenylketyl [35] was found to persist. In case of poor quality, the latter solvent was, in addition, pretreated with cuprous chloride [36] and potassium hydroxide pellets.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice-methanol baths is consistently indicated as -75 °C, "room temperature" (22 - 26 °C) as 25 °C. If no reduced pressure is specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 35 mmHg). *Melting ranges* (mp) are reproducible after resolidification, unless otherwise stated ("dec."), and are corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75 °C.

Whenever reaction products were not isolated, their yields were determined by *gas chromatography* comparing their peak areas with that of an internal standard and correcting the ratios by calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of different polarity. Chromosorb G-AW of 80 - 100 and, respectively, 60 - 80 mesh particle size were chosen as the support for packed analytical or preparative columns (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). All packed columns were made of glass, while quartz was chosen as the material for coated, GROB-type capillary columns (≥ 10 m long). The type of the stationary phase used is abbreviated as SE-30 (silicone rubber), C-20M (polyethylene glycol of average molecular weight 20'000) and FFAP (free fatty acid phase).

Infrared spectra were recorded of films if the sample was liquid at room temperature, while solid substances were embedded in potassium bromide pellets. The intensities of absorption bands are abbreviated : s (strong), m (moderate), w (weak) and b (broad).

Unless otherwise stated, *nuclear magnetic resonance spectra* of hydrogen nuclei were recorded in the 360 MHz field and of carbon-13 nuclei in the 90.6 MHz field (either under broad band or gated decoupling) and deuterochloroform was used as the solvent. Chemical shifts refer to the signal of tetramethylsilane (δ = 0 ppm), which served as an internal standard in all cases. Coupling constants (J) are measured in Hz. Coupling patterns are described by abbreviations : s (singulet), d (doublet), t (triplet), q (quadruplet), pent (pentuplet), hex (hexuplet), hept (heptuplet), non (nonuplet), td (triplet of a doublet) and *m* (multiplet).

In general, *mass spectra* were obtained at a 70 eV ionisation potential. Whenever no molecular peak was observed under standard conditions, chemical ionization ("c.i.") in an ammonia atmosphere was applied.

2. Isomerization of Oxiranes Derived from Cycloalkenes

At -75 °C, precooled tetrahydrofuran (50 mL), diisopropylamine (7.1 mL, 5.1 g, 50 mmol) and potassium *tert*-butoxide (5.6 g, 50 mmol) were consecutively added to butyllithium from which the hexane solvent had been stripped off under reduced pressure. After some 15 min of vigorous stirring a homogeneous solution was obtained. The temperature was allowed to raise to -50 °C and the oxirane (50 mmol) was added.

With 1,2-epoxycyclopentane and 1,2-epoxycyclohexane as substrates, the mixture was kept 20 h at -50 °C. In the case of 1,2-epoxycycloheptane [37] and 1,2-epoxycyclooctane, however, the reaction time was extended to 40 h, in the case of 1,2-epoxycyclododecane even to 80 h. Afterwards the solvent and the amine were evaporated under reduced pressure. The residue was treated with water (0.15 L) and extracted with hexane (3 x 50 mL). The combined organic layers were concentrated and the product was isolated by distillation.

(*Z*)-2-Cyclopenten-1-ol (13) [38] : 58%; bp 57 - 59 °C/25 mmHg; n_D^{20} 1.4708; n_D^{25} 1.4684; ^{1}H-NMR : 5.99 (1 H, dt, *J* 5.4, ~ 2.3), 5.84 (1 H, symm. m), 4.90 (1 H,symm. m, s-like), 2.6 (1 H, m), 2.3 (2 H, m), 1.72 (2 H,symm. m). - MS : 84 (71%, M^+), 66 (100%).

(*Z*)-2-Cyclohexen-1-ol (14) [39] : 78%; bp 68 - 70 °C/20 mmHg; n_D^{20} 1.4853; n_D^{25} 1.4831; ^{1}H-NMR : 5.83 (1 H, ddt, *J* 10.1, 3.5, 1.3), 5.77 (1 H, ddt, *J* 10.1, 3.0, 2.1), 4.24 (1 H, symm. m, s-like), 2.0 (2 H, m), 1.9 (1 H, m), 1.7 (1 H, m), 1.65 (3 H, symm. m); MS : 98 (27%, M^+), 97 (30%), 83 (50%), 79 (30%), 77 (78%), 70 (100%).

(*Z*)-2-Cycloheptен-1-ol (15) [40] : 70%; bp 72 - 75 °C/14 mmHg; n_D^{20} 1.4878; n_D^{25} 1.4864; ^{1}H-NMR : 5.7 (2 H, m), 4.41 (1 H, dm, *J* ~ 10), 2.2 (1 H, m), 2.1 (1 H, m), 1.9 (1 H, m), 1.82 (1 H, s), 1.7 (4 H, m), 1.4 (1 H, m); MS : 112 (21%, M^+), 111 (8%), 97 (55%), 84 (42%), 83 (89%), 79 (65%), 55 (100%).

(*Z*)-2-Cycloocten-1-ol (16) [41] : 34%; bp 91 - 93 °C/10 mmHg; n_D^{20} 1.4967; n_D^{25} 1.4953; ^{1}H-NMR : 5.63 (1 H, dddd, *J* 10.4, 8.5, 7.1, 1.4), 5.55 (1 H, ddd, *J* 10.4, 6.0, 0.8), 4.68 (1 H,symm. m), 2.1 (2 H, m), 1.9 (1 H, m), 1.78 (1 H, s), 1.5 (7 H, m); MS : 126 (8%, M^+), 111 (9%), 83 (100%).

(*E*)-2-Cyclododecen-1-ol (17) [28, 42] : 68%; mp 19 - 22 °C; bp 110 - 112 °C/1 mmHg; n_D^{20} 1.5008; ^{1}H-NMR :5.63 (1 H, ddd, *J* 14.5, 9.4, 4.9), 5.47 (1 H, ddd, *J* 14.5, 8.3, 1.1), 4.15 (1 H, td, *J* 8.8, 3.9), 2.2 (1 H, m), 2.07 (1 H, qd, 9.7, 3.3), 1.8 (1 H, m), 1.71 (1 H, s), 1.4 (15 H, m); MS : 182 (3%, M^+), 164 (7%), 111 (35%), 98 (32%), 97 (25%), 83 (81%), 82 (31%), 81 (30%), 70 (100%). - A 89% yield (by gas chromatography) was obtained already after 16 h at -50 °C if lithium diisopropylamide, potassium *tert*-butoxide and oxirane **17** (50 mmol each) were dissolved in a reduced volume (20 mL) of tetrahydrofuran.

3. Isomerization of Oxiranes Derived from Acyclic Olefins

The experiments were run on a 20 mmol scale. Otherwise the reaction and work-up conditions were the same as described in Section 2. The reaction time was 20 h at -50 °C throughout.

5-Octen-4-ol (18) : *cis*-2,3-Dipropyloxirane [43] afforded pure *E*-**18** (52%) while *trans*-2,3-dipropyloxirane [10, 43] gave a mixture of *Z*- and *E*-**18** (48%), b.p. 68 - 71 °C/6 mmHg. The stereoisomeric components were separated by preparative gas chromatography (6 m, 5% C-20M, 120 °C). - ^{1}H-NMR of *Z*-**18** [10] : 5.50 (1 H, ddt, *J* 10.5, 7.3, 0.8), 5.35 (1 H, ddt, *J* 10.5, 8.7, 1.5), 4.46 (1 H, dt, *J* 8.7, 4.3), 2.1 (2 H, m), 1.5 (5 H, m), 1.02 (3 H, t, *J* 7.5), 0.93 (3 H, t, *J* 7.1). - *E*-**18** [10, 44] n_D^{20} 1.4397; ^{1}H-NMR : 5.69 (1 H, ddt, *J* 15.3, 6.2, 0.8), 5.46 (1 H, ddt, *J* 15.3, 7.0, 1.3), 4.07 (1 H, dt, *J* 6.9, 6.6), 2.07 (2 H, dq, *J* 7.0, 1.5), 1.5 (5 H, m), 1.03 (3 H, t, *J* 7.3), 0.94 (3 H, t, *J* 7.1).

1-Hexen-3-ol (19) [45] : Both *cis*- and *trans*-2-methyl-3-propyloxirane [46] produced **19** with 78% and, respectively, 84% yield, b.p. 69 - 70 °C/40 mmHg, n_D^{20} 1.4280, ^{1}H-NMR (250 MHz) : 5.87 (1 H, ddd, *J* 17.1, 10.2, 7.3), 5.22 (1 H, dt, *J* 17.2, 1.5), 5.10 (1 H, dt, *J* 10.2, 1.5), 4.12 (1 H, q, *J* 6.5), 1.99 (1 H, s), 1.5 (4 H, m), 0.97 (3 H, t, *J* 6.8).

2-Ethyl-1-penten-3-ol (20) and **(*E*)-4-methyl-4-hexen-3-ol (*E*-21)** : *(Z)*-2,3-diethyl-2-methyloxirane [47] gave 93% of a 75 : 25 mixture of **20** and *E*-**21** while the (*E*)-isomer [48] yielded the same products with 95% yield and with a 70 : 30 ratio. The two compounds were separated by preparative gas chromatography (6 m, 5% C-20M, 120 °C). - ^{1}H-NMR of **20** [49] : 5.0 (1 H, m), 4.9 (1 H, m), 4.06 (1 H, t, *J* 6.5), 2.1 (2 H, m), 1.6 (3 H, m), 1.16 (3 H, t, *J* 7.5), 1.00 (3 H, t, *J* 7.4). - *E*-**21** [50] : n_D^{20} 1.4442, ^{1}H-NMR : 5.51 (1 H, q, *J* 6.5), 3.94 (1 H, t, *J* 6.9), 1.91 (1 H, s), 1.6 (8 H, m), 0.83 (3 H, t, *J* 7.5).

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