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Addition of a tiglyltitanocene to chiral aldehydes: factors influencing simple and diastereofacial stereoselectivities

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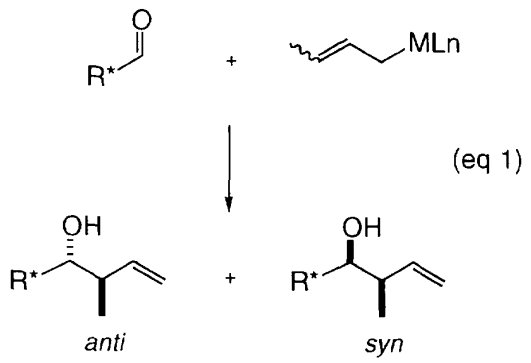
Summary — The η^3-tiglyltitanium(III) complex formed in situ from isoprene was reacted with a series of chiral aldehydes, some of which bear α- and/or β-benzyloxy groups, or a remote double bond. *anti* Diastereomeric homoallylic alcohols were formed stereospecifically starting from the alkoxy-free saturated aldehydes. In contrast, mixtures of *anti* and *syn* stereomers were obtained by using alkoxy- or ε-unsaturated aldehydes. The simple diastereoselectivities and diastereofacial selectivities observed are rationalized in terms of the chelation versus non-chelation-controlled process.

η^3-tiglyltitanocene complex / chiral aldehyde / stereoselectivity / chelation control

Résumé — Addition du tiglyltitanocene sur des aldéhydes chiraux : facteurs influençant les phénomènes de stéréosélectivité. Un complexe π-allylique de titane (III) formé à partir d'isoprène, a été opposé à une série d'aldéhydes chiraux, porteurs soit d'un groupe benzyloxy en α et/ou en β, soit d'une double liaison en bout de chaîne. Les alcools homoallyliques de configuration *anti* ont été formés de façon stéréospécifique à partir d'aldéhydes saturés non alcoxylés. Par contre, les réactions mettant en jeu des aldéhydes alcoxylés ou insaturés, ont conduit à un mélange de stéréoisomères *anti* et *syn*. Le contrôle par chélation permet d'interpréter la diastéréosélectivité simple et l'induction asymétrique observées.

complexe η^3-tiglyltitanocène / aldéhyde chiral / stéréosélectivité / contrôle par chélation

The addition of allyl organometallic reagents to carbonyl compounds to produce homoallylic alcohols (equation [1]) is a powerful carbon-carbon bond-forming reaction, useful in the context of acyclic stereocontrol [1]. This reaction can show two kinds of stereoselection. A simple diastereoselectivity is related to the *anti/syn* configuration of the two newly created stereogenic carbon centers. On the other hand, diastereofacial selectivity is encountered if the aldehyde (or the metal reagent) is chiral.



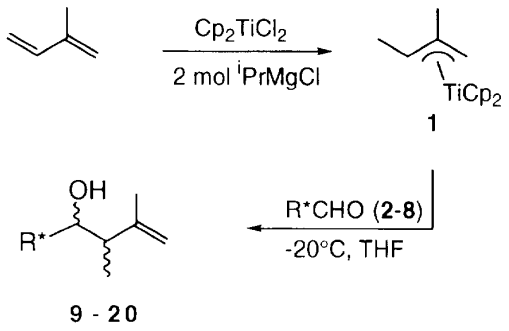
Several allylmetallation reactions proceed in a stereoconvergent manner, exhibiting high simple as well as diastereofacial selectivities. Notably, silicon-, tin-, and boron-based reagents were successfully employed to develop stereoselective routes to versatile synthons, such as polypropionate building blocks [2]. However, despite the excellent results obtained with simple allyl metals as above, an easy preparation and selective use of the functionalized reagents is more difficult to achieve.

In this matter, titanium-based complexes open interesting possibilities. Particularly, η^3-allyltitanocene complexes may be used as allylmetallation reagents. These compounds can be easily obtained by hydrotitanation of the corresponding (functionalized) dienes [3]. Their addition to aldehydes occurs regiospecifically on the more substituted carbon, with a good to excellent simple diastereoselectivity. Thus, the *anti* isomers are obtained preferentially starting from the simple [4] as well as functionalized [3b-c, 5] titanium reagents. The reaction can be applied to construct the carbon framework in a stereocontrolled way. For example, we have recently shown that a combination of allyltitanation and Mukaiyama aldol reactions provides a short stereoselective entry to the acyclic propionate building blocks (as racemates) [6]. The analogous enantioselective sequence leading to the propionate chirons could be envisaged.

* Correspondence and reprints

Nevertheless, little is known about the enantioselective allyltitanation of aldehydes. The only approach developed employ allyltitanium reagents based on the chiral cyclopentadienyl ligands [7, 8]. Since the allyltitanation reaction is a stoichiometric and not a catalytic process, chiral precursor dienes or chiral aldehydes should also be considered to induce the diastereofacial selectivity. The double asymmetric synthesis is a relevant anticipated aim, which can be achieved in this way.

Consequently, stereochemical studies, particularly of the asymmetric process, are needed to make full use of the potential of allyltitanation reaction. In keeping with this aim, here a simple 1,2-dimethylallyl (tiglyl) titanocene complex (compound **1**, scheme 1) has been reacted with a series of chiral aldehydes. We describe herein the structural effects controlling both the simple diastereoselectivity and the diastereofacial selectivity in these reactions.



Scheme 1

Results and discussion

Little information is available regarding the effect of the aldehyde R group on the stereochemical outcome of the allyltitanation reaction [3b, 4]. To the best of our knowledge, neither the simple chiral aldehydes nor the chelating alkoxy aldehydes [9] have been employed in the reaction with η^3-allyltitanium reagents. Thus, four of the aldehydes considered in this study (table I, compounds **5**–**8**) possess an α and/or a β-alkoxy substituent. These are (benzyloxy)acetaldehyde **5**, (*S*)-(−)-2-(benzyloxy)propanal **6**, (*S*)-(+)-3-(benzyloxy)-2-methylpropanal **7** and (*R*)-2,3-*O*-isopropylideneglyceraldehyde **8**. The remaining alkoxy-free aldehydes (*S*)-(+)-2-methylbutanal **2** and (*S*)-(−)-3,7-dimethyloctanal **3** bear the chiral center in the α- or β-position. Moreover, an unsaturated analogue of **3**, namely *S*-(−)-citronellal **4**, has also been considered.

The isoprene-derived tiglyltitanium reagent **1** (scheme 1) was prepared in each case according to a previously described protocol [4]. Thereafter, the in situ addition of aldehydes **2**–**8** to complex **1** was carried out in THF at −20 °C. After additional stirring for 1.5 h at rt, basic workup ($NaHCO_3$ aq, followed by extraction with ether) afforded homoallylic alcohols (**9**–**20**, table I) as mixtures of diastereomers. The crude products were systematically analyzed by ^{13}C NMR (Invgate, J-MOD) and ^1H NMR spectroscopy, and gas chromatography to evaluate the isomer ratio. The products were then flash-chromatographed to give stereopure compounds in some cases. In the others, mixtures of two or three stereomers were isolated, making the attribution of stereochemistry possible. The stereochemical assignments for **9**–**20** were established based on the observed differences in the ^{13}C NMR chemical shifts in accordance with the data provided in the literature [10]. In several cases they could also be deduced using ^{13}C NMR Heathcock rule [11], and/or from ^1H vicinal coupling constants.

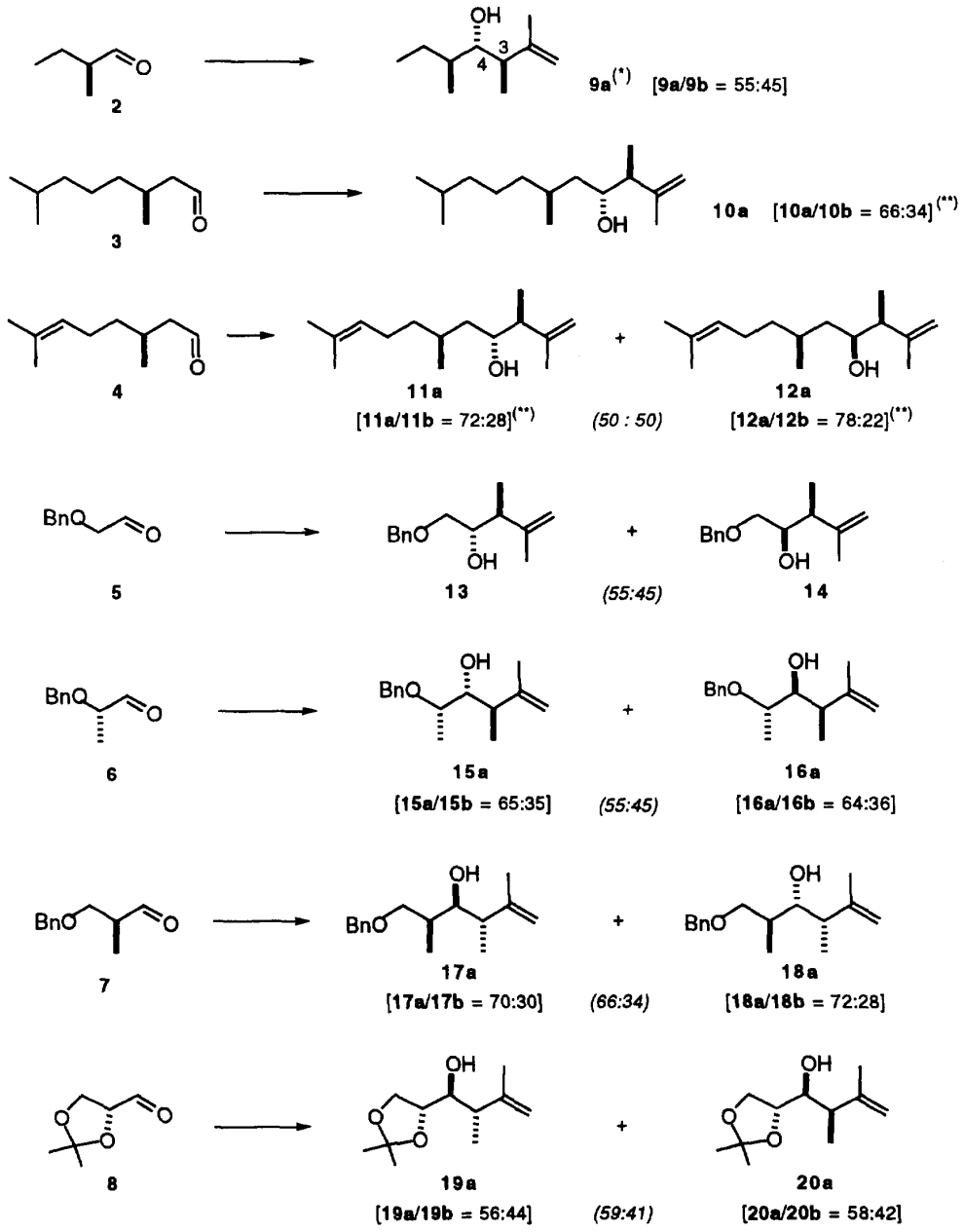
As can be seen in table I, the addition of aldehydes **2**–**8** occurred in the usual way, regiospecifically at the more substituted carbon atom of the allyl reagent. Furthermore, the two reactions involving saturated, alkoxy-free, α- and β-chiral aldehydes **2** and **3** occurred with a total simple diastereoselectivity. The *anti* homoallylic alcohols **9** and **10** were formed exclusively, in accordance with the similar reactions employing simple aliphatic aldehydes [4]. In contrast, the 1,2-asymmetric induction appears to be low with aldehyde **2** (**9a**/**9b** = 55:45), and the 1,3-asymmetric induction is only moderate with aldehyde **3**, possessing a longer carbon chain (**10a**/**10b** = 66:34). These modest diastereofacial selectivities are similar to those often exhibited in the addition of organometallic reagents to chiral aldehydes, bearing small α- or β-substituents.

We observed an unexpected, marked decrease in the simple diastereoselectivity by introducing an unsaturation in the remote position (C-6 atom) of the aldehyde chain. Indeed, while the unique *anti* stereochemistry was noticed for the saturated aldehyde **3**, an almost equal mixture of *anti* (compound **11**) and *syn* (compound **12**) diastereomers was detected starting from its unsaturated analogue **4**. In contrast, the diastereofacial selectivity increases from 66:34 for **3** to 72:28 and 78:22, respectively for the *anti* and *syn* diastereomers obtained from **4**. Thus, both the simple diastereoselectivity and diastereofacial bias seem to be exerted with the assistance of the aldehyde double bond. The large decrease in the *anti* diastereoselectivity prompted by the remote double bond in **4** contrasts significantly with a strikingly lower decrease observed for the similar addition of the tiglyltitanocene **1** to the α,β-unsaturated acrolein (*anti*/*syn* = 90:10) [4a].

The particularly high increase of the *syn* selectivity for the unsaturated aldehyde **4** (*anti*/*syn* $\approx$ 1) can possibly be explained by a mechanism involving competing early chair transition states **A** and **S** (fig 1) [12]. In the absence of the remote double bond, the favored pseudo-equatorial position of the aldehyde R group appears to be responsible for the generally high *anti* diastereoselection observed. On the other hand, the remote double bond in **4** would coordinate reversibly on the electronically unsaturated titanium easier in **S** than in **A** for steric reasons, stabilizing the former and thus ensuring a competing *syn* stereochemistry. The enhancement of the diastereofacial selectivity for aldehyde **4** in comparison with **3** may also be rationalized by assuming an equilibrium between the transition structures **A** and **S**.

We next examined the stereochemical outcome of the reactions involving alkoxy aldehydes **5**–**8**. As depicted in table I, a mixture of *anti* and *syn* diastereomers was

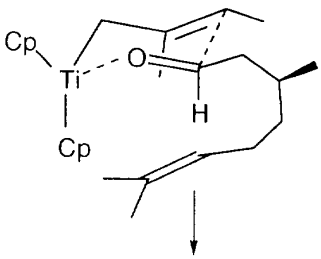
Table I. Reaction of aldehydes **2**–**8**.



* The diastereomer possessing the antipodal 3C, 4C configuration (**9b**) and **13b**–**20b** are not presented. Diastereofacial selectivities are given in brackets. ** Arbitrary assignment.

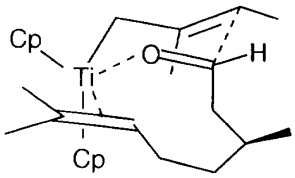
detected, with a significant level of the *syn* compound in each case. The *anti*/*syn* diastereomeric ratio of 55:45 was noticed for achiral α-alkoxy aldehyde **5**, for which only a simple diastereoselectivity is concerned. The same value was observed in the reaction employing the analogous chiral α-alkoxy aldehyde **6**. The *anti*/*syn* ratio appears to be slightly greater for the β-alkoxy aldehyde **7**. Finally, an intermediate value was obtained for glyceraldehyde acetonide **8**, possessing both α- and β-alkoxy fragments. Such results contrast with the high *anti* stereochemistry always observed for the alkoxy-free, simple aldehydes.

Moreover, the reaction of chiral aldehydes **6**–**8** provides the *anti* as well as *syn* products in a rather low diastereofacial selectivity. Thus, a stereomer ratio of about 1.8 was observed for both *anti* (**15**) and *syn* (**16**)



chair **A**

11a (*anti*)



chair **S**

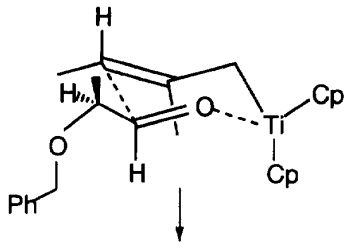
12a (*syn*)

Fig 1

homoallylic alcohols derived from α-alkoxy aldehyde **6**. The diastereofacial selectivity is only a little higher for the β-alkoxy aldehyde **7** (**17a**/**17b** and **18a**/**18b** ratios are both about 2.4–2.5), and a little lower for the α,β-alkoxy aldehyde **8**. Indeed, our results clearly show that the presence of the alkoxy group drastically influences the simple diastereoselectivity of the reaction compared with that involving alkoxy-free saturated aldehydes, without significantly affecting the diastereofacial bias.

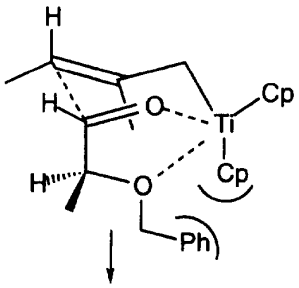
The stereochemical outcome of the addition of organometallic reagents to chiral aldehydes is usually explained by the Felkin–Anh model. However, the introduction of an alkoxy (or hydroxy) group into the carbonyl compound can make the opposite carbonyl Π-face sterically more accessible. This phenomenon is related to the chelation of metal species between the carbonyl oxygen and the α- or β-oxygen atom and may then be described by the Cram's cyclic model. Particularly, the chelation control prevails using a 'tied-up' approach, which involves the precomplexation of alkoxy carbonyl compounds with Lewis acid capable of bisligation (often $TiCl_4$, $SnCl_4$, MgX_2, $ZnBr_2$,...) followed by the addition of soft C-nucleophiles. The chelation versus non-chelation control in addition reactions to chiral α- or β-alkoxy carbonyl compounds has been extensively studied [9, 13]. The external Lewis-acid-mediated addition reactions of η^1-allyl metals to the alkoxy carbonyl compounds have also been carried out [1, 14]. However, to the best of our knowledge, the chelation control in the reactions involving η^3-allyl metal reagents has never been reported. We presume that an 'internal' chelation control can explain the exceptionally high level of *syn* diastereoselection observed in the addition of the reagent **1** to alkoxy aldehydes **5**–**8**.

Figure 2 shows two selected transition structures **a** and **s**, for the reaction of **1** with α-alkoxy aldehyde **6**. The conventional Zimmerman–Traxler transition state (**a**) should be associated with the *anti* stereochemistry observed (non-chelation control). Furthermore, a competing transition state **s** operates, in which the pseudo-axial position of the aldehyde group is induced by chelation of alkoxy oxygen on electronically unsaturated titanium (chelation control). The above transition structure results in a significant amount of the *syn* stereomers (similarly for the achiral α-alkoxy aldehyde **5**). Moreover the low asymmetric induction may be rationalized by inspecting the transition structures **a** and **s**, both related to the favored Π-facial selectivities. Indeed, the attack on the opposite face of the carbonyl group appears to be only slightly disfavored with regard to the α-methyl nonbonding interactions for both chelation and nonchelation geometries.



chair **a**

15a (*anti*)



chair **s**

16a (*syn*)

Fig 2

The above model can be extended to the β-alkoxy aldehyde **7**. However, we do not speculate about the slight increase of both the *anti*/*syn* ratio and the level of asymmetric induction observed for **7** relative to **6**. Finally, the equilibrated mixture of four diastereomeric products obtained starting from glyceraldehyde acetonide **8** reveals quite a complicated synergistic effect in this case. In fact, whereas the acetonide protected α,β-dihydroxy aldehydes exhibit non-chelation selectivities with several nucleophiles (for example, Grignard reagents), the addition of η^1-allylmetals generally occurs with a significant participation of the α- and especially β-chelation control [15]. Both non-chelation

and chelation control can clearly also coexist in the addition of complex **1** to aldehyde **8**.

Although the chelation might explain the stereochemical outcome of the reactions employing aldehydes **4–8**, another mechanism cannot a priori be ruled out. The *syn* isomers would then arise from the reversal of facial selectivity at the rapidly equilibrating (*E*)- and (*Z*)-tiglyl reagent. However, such an explanation is rather unlikely. In fact, type III η^3-crotyl (tiglyl) dicyclopentadienyl reagents appear to be configurationally stable [3a, 4a, 16]. The (*E*)-isomer is either highly favored or the more reactive of the two. As a result, *anti*-homoallylic alcohols were formed predominantly (*anti/syn* $\geqslant$ 95:5) starting from the simple saturated or α,β-unsaturated (acrolein) aldehydes [3–5]. Neither the transfer of the double bond to the remote position nor the introduction of the alkoxy group into the aldehyde should modify significantly the configurational behavior of the tiglyltitanium reagent.

In order to provide further insight into the stereochemistry we then examined the BF_3-mediated allyltitanation reactions involving complex **1**, and alternatively propanal or alkoxy aldehyde **5**. Indeed, as previously demonstrated, BF_3 is incapable of chelation but may inverse the diastereoselectivity by favoring a noncyclic mechanism over the cyclic one (non-chelation control). The reversal of diastereoselectivity (*anti* to *syn*) was observed in the reaction similar to ours, involving η^1-crotyltitanium(IV) complex $C_4H_7TiCp_2X$ (X = Cl, Br, I), and a series of simple aliphatic or aromatic aldehydes [14c, 17]. Moreover the BF_3-mediated allylmetallations of the chelating alkoxy aldehydes usually proceed with the reversal of stereochemistry [18].

The addition of the precomplexed propanal (1 mol $BF_3{\cdot}OEt_2$) or aldehyde **5** (2 mol $BF_3{\cdot}OEt_2$) to **1** at −78 °C (and warming to rt over 2 h) afforded the expected homoallylic alcohols. However, while the marked effect on diastereoselectivity was noticed in the case of propanal (95% *anti* without BF_3, *anti/syn* = 40:60 with BF_3), no variation was observed for alkoxy aldehyde **5** (*anti/syn* = 55:45 in both cases). The stereochemistry of the reaction involving an alkoxy aldehyde was unaffected by a mono-coordinating Lewis acid. This result suggests a quite particular character of the chelation in the reactions between (α or β)-alkoxy aldehydes and η^3-tiglyltitanocene **1**.

In conclusion, although the use of ε-unsaturated and alkoxy-substituted aldehydes leads to rather modest selectivities, the results reported should contribute to a better understanding of the structural effects on stereochemical outcome of the allyltitanation reaction. For this purpose, mechanistic studies (kinetics, solvent effects, detection of intermediate chelates, etc) and theoretical calculations may be useful. Work is in progress to control the selectivity, and increase the enantioselectivity by means of a double asymmetric synthesis.

Experimental section

Materials and methods

All manipulations were carried out under argon using vacuum-line techniques. The solvents used were distilled under argon from sodium benzophenone ketyl. Titanocene dichloride was prepared by a literature method [19]. Other reagents and chiral starting materials were purchased from Aldrich or Fluka. Aldehydes **2–8** were prepared (> 95% ee) according to the described procedures, [20] and used directly. NMR spectra were recorded at 200 and 500 MHz (^{1}H) and 50 MHz (^{13}C), respectively. Mass spectra were obtained on the GC-coupled instrument by the EI (70 eV) technique. Gas chromatography (GC) was carried out on 30 m × 0.25 mm copper column packed with methyl silicone with a flow rate of 1.6 mL/min, and temperature 60 to 250 °C (2 or 5 °C/min). Column flash chromatography was performed on silica gel 60 (Merk).

*Representative procedure for the preparation of homoallylic alcohols **9–20***

A solution of isopropylmagnesium chloride (4 mmol, 1 equiv) in THF (2 mL) was added via syringe at rt to a stirred suspension of titanocene dichloride (1.00 g, 4 mmol, 1 equiv) in THF (20 mL). After 0.5 h the solution of *i*-PrMgCl (4 mmol, 1 equiv) in THF (2 mL) and isoprene (0.4 g, 6 mmol, 1.5 equiv) were added simultaneously, and stirring was continued for 1 h. The violet solution of complex **1** was then cooled to −20 °C and the aldehyde (4.2 mmol, 1.2 equiv) was added neat via syringe. The mixture was allowed to warm gradually to rt over a period of 1 h, and further stirred at this temperature for 0.5 h. The reaction mixture was poured into a separation funnel containing 100 mL of ether, and treated with saturated aqueous $NaHCO_3$ (20 mL). The ether layer was separated and the aqueous layer was extracted with a second portion of ether. The combined organics were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was treated with ether/hexane 1:1 (80 mL) and the titanium derivatives eliminated by filtration through a frit. After concentration of the organic filtrate in vacuo, the crude reaction mixture was analyzed by ^{1}H and ^{13}C NMR (Invgate) spectroscopy, and gas chromatography to determine the isomer ratio. Flash chromatography separation on silica gel (230–400 mesh, hexane/ether 3:1 to 10:1 v/v) afforded stereopure products and/or mixtures of two or three stereomers, all as colorless oils (total yields are given).

- *Compound **9** (82%)*

Mixture of **9a** and **9b** was analyzed by capillary GC; the retention times were **9a** 22.67 min and **9b** 23.54 min.

^{1}H NMR (C_6D_6) major isomer (**9a**) δ 4.72 (m, 2H), 3.32 (ddd, J = 9.5, 9.5, 2.2 Hz, 1H), 2.35–2.15 (m, 3H), 1.55 (br s, 3H), 1.48–1.40 (m, 2H), 0.92 (t, J = 6.3 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H), minor isomer (**9b**) δ 4.72 (m, 2H), 3.18 (ddd, J = 8.6, 3.0, 3.0 Hz, 1H), 2.35–2.15 (m, 3H), 1.51 (br s, 3H), 1.48–1.40 (m, 2H), 1.08 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**9a**) δ 148.0, 112.8, 76.8, 44.8, 36.0, 21.4, 18.2, 16.9, 15.4, 11.3, minor isomer (**9b**) δ 148.0, 112.9, 73.9, 45.3, 35.6, 27.5, 18.7, 15.8, 12.1, 11.3.

MS major isomer (**9a**) m/e 156 (M^+), 99, 87, 70, minor isomer (**9b**) m/e 156 (M^+), 99, 87, 70.

- *Compound **10** (87%)*

Stereomers **10a** and **10b** were isolated.

10a: ^{1}H NMR (C_6D_6) δ 4.75 (m, 2H), 3.50 (dt, J = 7.2, 7.8 Hz, 1H), 2.05 (dq, J = 7.2, 7.2 Hz, 1H), 1.95 (br s, 1H, D_2O exchangeable), 1.56 (br s, 3H), 1.55–1.10 (m, 10H), 0.98 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.3 Hz, 6H), 0.87 (d, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 147.7, 112.8, 70.7, 48.7, 41.6, 39.3, 38.6, 29.3, 28.0, 24.8, 22.7, 22.6, 19.3, 19.0, 15.5.

MS m/e 226 (M^+), 157, 137, 70.

10b: ^{1}H NMR (C_6D_6) δ 4.76 (m, 2H), 3.52 (m, 1H), 2.06 (dq, J = 7.0, 7.0 Hz, 1H), 1.90 (br s, 1H, D_2O exchangeable), 1.58 (br s, 3H), 1.53–1.05 (m, 10H), 1.00 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 147.6, 112.8, 70.2, 48.5, 42.0, 39.4, 36.0, 29.5, 28.0, 24.5, 22.8, 22.5, 20.8, 19.2, 15.5.

MS m/e 226 (M^+), 157, 137, 70.

• *Compounds **11** + **12** (85%)*

Stereomer mixtures **11(a + b)** and **12(a + b)** were separated.

GC retention times for **11a** 19.62 min, **11b** 19.88 min, **12a** 19.82 min, and **12b** 20.01 min.

11(a + b): ^{1}H NMR (C_6D_6) major isomer (**11a**) δ 5.24 (m, 1H), 4.75 (m, 2H), 3.48 (m, 1H), 2.03 (dq, J = 7.1, 7.1 Hz, 1H), 1.68 (br s, 3H), 1.58 (br s, 3H), 1.55 (br s, 3H), 1.50–1.10 (m, 8H), 0.97 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H), minor isomer (**11b**) δ 5.24 (m, 1H) 4.75 (m, 2H), 3.48 (m, 1H), 2.12 (dq, J = 7.8, 7.8 Hz, 1H), 1.68 (br s, 3H), 1.58 (br s, 3H), 1.55 (br s, 3H), 1.50–1.10 (m, 8H), 1.01 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 7.8 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**11a**) δ 147.5, 131.0, 124.9, 112.8, 70.6, 48.6, 41.9, 38.4, 29.3, 25.7, 20.7, 19.4, 18.8, 15.5, minor isomer (**11b**) δ 147.5, 131.0, 124.8, 112.8, 70.1, 48.5, 41.5, 35.8, 28.9, 25.5, 25.3, 20.7, 19.3, 17.6, 15.5.

12 (a + b): ^{1}H NMR (C_6D_6) major isomer (**12a**) δ 5.23 (m, 1H), 4.75 (m, 2H), 3.56 (dt, J = 7.1, 3.8 Hz, 1H), 2.15–1.90 (m, 1H), 1.68 (br s, 3H), 1.56 (m, 6H), 1.50–1.20 (m, 8H), 1.03 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), minor isomer (**12b**) δ 5.23 (m, 1H), 4.75 (m, 2H), 3.50 (dt, J = 7.0, 3.6 Hz, 1H), 2.15–1.90 (m, 1H), 1.68 (br s, 3H), 1.56 (m, 6H), 1.50–1.20 (m, 8H), 1.06 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**12a**) δ 148.2, 131.2, 124.8, 111.3, 69.9, 46.0, 41.9, 36.5, 29.1, 25.7, 25.3, 21.5, 20.3, 17.6, 12.7, minor isomer (**11b**) δ 148.2, 131.2, 124.8, 111.3, 70.0, 47.0, 42.2, 38.0, 29.4, 25.7, 25.5, 21.5, 21.1, 19.0, 13.6.

• *Compounds **13** + **14** (77%)*

GC retention times for the mixture of two stereomers: **13** 22.46 min and **14** 22.12 min.

^{1}H NMR (C_6D_6) major isomer (**13**) δ 7.13–7.07 (m, 5H), 4.82–4.74 (m, 2H), 4.29 (m, 2H), 3.78–3.56 (m, 1H), 2.48 (br s, 1H, D_2O exchangeable), 2.35 (dq, J = 7.1, 7.1 Hz, 1H), 1.68 (br s, 3H), 0.93 (d, J = 7.1 Hz, 3H), minor isomer (**14**) δ 7.13–7.07 (m, 5H), 4.74–4.66 (m, 2H), 4.24 (m, 2H), 3.78–3.56 (m, 1H), 2.59 (br s, 1H, D_2O exchangeable), 2.26 (dq, J = 7.0, 5.9 Hz, 1H), 1.53 (br s, 3H), 1.17 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**13**) δ 146.9, 137.7, 128.0, 127.3, 111.8, 73.0, 72.9, 71.8, 43.7, 19.0, 15.2, minor isomer (**14**) δ 146.8, 137.7, 128.0, 127.3, 111.2, 72.9, 72.0, 71.7, 43.7, 19.6, 15.0.

MS major isomer (**13**) m/e 220 (M^+), 189, 176, 129, minor isomer (**14**) m/e 220 (M^+), 189, 176, 129.

• *Compounds **15** + **16** (82%)*

Stereomer mixtures **15(a + b)** and **16(a + b)** were separated.

GC retention times for **15a** 45.02 min, **15b** 43.64 min, **16a** 43.21 min, and **16b** 43.92 min.

15(a + b): ^{1}H NMR (C_6D_6) major isomer (**15a**) δ 7.25–7.00 (m, 5H), 4.76 (m, 2H), 4.38 (d, J = 11.7 Hz, 1H), 4.10 (d, J = 11.7 Hz, 1H), 3.33–3.18 (m, 2H), 2.43 (dq, J = 7.1, 7.1 Hz, 1H), 2.15 (br s, 1H, D_2O exchangeable), 1.73 (br s, 3H), 1.12 (d, J = 7.1 Hz, 3H), 1.03 (d, J = 7.1 Hz, 3H), minor isomer (**15b**) δ 7.25–7.00 (m, 5H), 4.76 (m, 2H), 4.36 (d, J = 11.9 Hz, 1H), 4.14 (d, J = 11.9 Hz, 1H), 3.46–3.34 (m, 2H), 2.36 (dq, J = 7.1, 7.1 Hz, 1H), 2.11 (br s, 1H, D_2O exchangeable), 1.56 (br s, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**15a**) δ 148.0, 138.3, 128.2, 127.8, 127.5, 112.4, 75.1, 74.2, 70.6, 43.6, 19.0, 16.0, 14.6, minor isomer (**15b**) 147.6, 138.3, 128.2, 127.8, 127.5, 111.4, 76.8, 75.2, 71.0, 43.6, 20.1, 15.8, 14.6.

16(a + b): ^{1}H NMR (C_6D_6) major isomer (**16a**) δ 7.30–7.00 (m, 5H), 4.86 (m, 2H), 4.37 (d, J = 11.7 Hz, 1H), 4.24 (d, J = 11.7 Hz, 1H), 3.71–3.57 (m, 1H), 3.38 (dq, J = 6.8, 6.8 Hz, 1H), 2.45–2.26 (m, 1H), 2.01 (d, J = 2.9 Hz, 1H, D_2O exchangeable), 1.72 (br s, 3H), 1.15 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), minor isomer (**16b**) δ 7.30–7.00 (m, 5H), 4.66 (m, 2H), 4.33 (d, J = 11.7 Hz, 1H), 4.19 (d, J = 11.7 Hz, 1H), 3.71–3.57 (m, 1H), 3.42 (dq, J = 3.5, 6.5 Hz, 1H), 2.45–2.26 (m, 1H), 2.09 (d, J = 2.9 Hz, 1H, D_2O exchangeable), 1.49 (br s, 3H), 1.21 (d, J = 7.4 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$) major isomer (**16a**) δ 147.7, 138.4, 128.3, 128.0, 127.5, 112.0, 75.4, 73.6, 70.4, 43.5, 18.8, 15.8, 12.3, minor isomer (**16b**) δ 147.1, 138.4, 128.3, 128.0, 127.5, 111.7, 75.4, 74.0, 70.4, 43.0, 19.5, 15.6, 13.0.

• *Compounds **17** + **18** (72%)*

Stereomers **17a**, **17b** and the mixture **18(a + b)** were isolated.

17a: ^{1}H NMR (C_6D_6) δ 7.30–7.00 (m, 5H), 4.76 (m, 1H), 4.70 (m, 1H), 4.22 (m, 2H), 3.71 (dd, J = 9.2, 3.1 Hz, 1H), 3.38–3.19 (m, 2H), 2.36 (dq, J = 9.2, 7.0 Hz, 1H), 2.20 (br s, 1H, D_2O exchangeable), 1.93–1.72 (m, 1H), 1.55 (br s, 3H), 1.21 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 149.9, 138.0, 128.4, 127.5, 112.5, 75.1, 73.9, 73.2, 44.9, 34.4, 18.2, 15.6, 9.7.

MS m/e 248 (M^+), 179, 91.

17b: ^{1}H NMR (C_6D_6) δ 7.35–7.00 (m, 5H), 4.79 (m, 2H), 4.24 (m, 2H), 3.49–3.28 (m, 3H), 2.65 (d, J = 3.4 Hz, 1H, D_2O exchangeable), 2.38 (dq, J = 6.9, 6.9 Hz, 1H), 2.06–1.87 (m, 1H), 1.71 (br s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 147.7, 137.8, 128.6, 127.6, 112.2, 77.5, 74.8, 72.7, 44.7, 35.1, 19.3, 16.3, 14.7.

MS m/e 248 (M^+), 179, 91.

18(a + b): ^{13}C NMR ($CDCl_3$) major isomer (**18a**) δ 148, 138.0, 128.1, 127.6, 111.5, 77.2, 75.3, 73.1, 43.7, 34.9, 19.0, 15.5, 13.0, minor isomer (**18b**) δ 148.2, 138.3, 128.2, 127.5, 111.2, 76.7, 76.0, 72.9, 44.9, 35.5, 20.7, 16.2, 8.9.

• *Compounds **19** + **20** (79%)*

Stereomers **19a**, and the mixture **19b** + **20a** + **20b** were isolated.

19a: ^{1}H NMR (C_6D_6) δ 4.74 (m, 1H), 4.68 (m, 1H), 4.01–3.92 (m, 1H), 3.78–3.74 (m, 2H), 3.19 (ddd, J = 7.0, 7.0, 5.3 Hz, 1H), 2.33 (dq, J = 7.0, 7.0 Hz, 1H), 2.09 (d, J = 5.3 Hz, 1H, D_2O exchangeable), 1.67 (br s, 3H), 1.36 (br s, 3H), 1.29 (br s, 3H), 0.98 (d, J = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$) δ 146.8, 112.0, 108.6, 77.0, 72.8, 64.6, 43.8, 26.4, 25.1, 19.1, 15.5.

MS m/e 200 (M^+), 185, 131, 101.

19b + 20a + 20b: ^{13}C NMR ($CDCl_3$) (**19b**) δ 146.9, 111.5, 108.3, 76.3, 72.9, 65.8, 44.2, 26.4, 25.4, 19.5, 15.8, (**20a**) δ 144.2, 111.6, 108.6, 76.6, 72.4, 64.5, 42.9, 26.6, 25.2, 19.8, 14.9, (**20b**) δ 144.5, 112.4, 109.0, 76.1, 71.6, 66.0, 44.4, 26.5, 25.3, 20.1, 14.1.

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