Bismuth triflate-catalyzed Wagner-Meerwein rearrangement in terpenes. Application to the synthesis of the 18α-oleanane core and A-*neo*-18α-oleanene compounds from lupanes†

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The use of bismuth(III) salts as catalysts for the Wagner-Meerwein rearrangement of lupane derivatives with expansion of ring E and formation of an additional O-containing ring is reported. This process has also been extended to other terpenes, such as the sesquiterpene (–)-caryophyllene oxide. When the reaction was performed with oleanonic acid, 28,13β-lactonization occurred, without Wagner-Meerwein rearrangement. Under more vigorous reaction conditions, dehydration of the 3β-hydroxyl group and subsequent additional Wagner-Meerwein rearrangement led to the selective synthesis of A-*neo*-18α-oleanene compounds, in very high yields.

Introduction

Terpenes[1] were among those natural products wherein rearrangements were earliest detected and studied.[2] Rearrangements involving the formation of a carbocation and 1,2-migrations of hydrogen or alkyl groups from one carbon to a neighboring carbon are designated as Wagner-Meerwein rearrangements.[3] This group of transformations constitutes a particularly important field of research in organic chemistry and has been widely reported in terpenoid chemistry.[2,3]

One such well-known transformation involves the acid catalyzed ring E rearrangement of betulin **1** and important related triterpene derivatives,[4] to 18α-oleanane compounds bearing a 19β,28-epoxide or 28,19β-lactone ring, and is commonly referred to "betulin-allobetulin rearrangement" (Fig. 1).[2]

The "betulin-allobetulin rearrangement" was first reported by Schulze and Pieroh by the use of formic acid.[5] The reaction involves the formation and hydrolysis of allobetulin formate, and was later applied by other authors.[6,7] A variety of acidic reagents has been employed to promote the one-step conversion of betulin and betulinic acid to the corresponding ring E expanded products.[7–11] In addition, Linkowska used dimethyl sulfate as a catalyst, for the same conversion.[12] Later, the use of solid acids, such as sulfuric acid on silica, montmorillonite clays (both K10 and KSF), kaolinite, bleaching clay and *p*-toluenesulfonic acid on silica,[13] as well as ferric nitrate or ferric chloride adsorbed on silica gel or alumina[14] have been reported in the high yield synthesis of allobetulin and other 18α-oleanane derivatives.

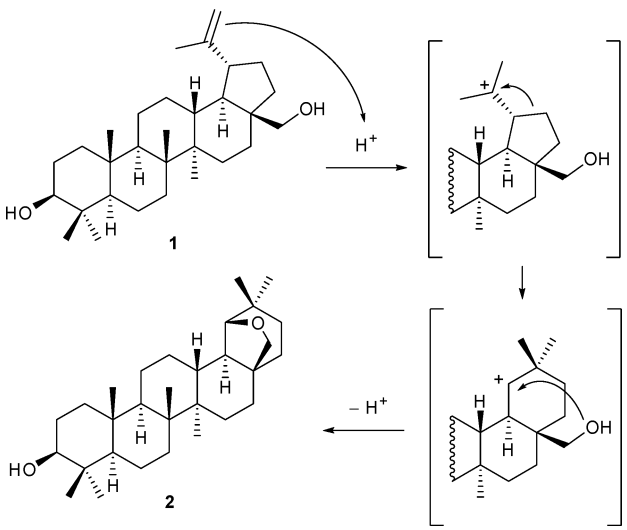

Fig. 1 Acid-catalyzed Wagner-Meerwein rearrangement of ring E of betulin **1** to allobetulin **2**.

More recently, a new process for the isomerisation of betulin to allobetulin using orthophosphoric acid in either homogeneous or heterogeneous reaction conditions, has been patented,[15] whereas the use of trifluoroacetic acid has been reported by Medvedeva and co-workers.[16] The bromination of betulin with molecular bromine afforded 29,30-dibromoallobetulin in high yields, with rearrangement of the starting material leading to ring E expansion.[17]

Allobetulin and related ring E rearranged compounds have been prepared and tested for biological activity. Antifeedant properties have been found for some of these compounds[6] whereas others have been used as biomarkers.[13,18] Allobetulin and its 3-oxo derivatives have been used as starting materials in the synthesis of compounds that have been tested for anti-inflammatory,[19] cytotoxic[20] and immunotropic activities.[21] Quite

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recently, moderate cytotoxicity has been found in A-549, DLD-1 and WSI cell lines for some derivatives of allobetulin and 28-oxoallobetulin, which have been prepared and evaluated by Thibeault and co-workers.[22] The same group described a useful synthetic route to obtain germanicanes (*e.g.* machaeroceric acid and 19β-machaerocerol) from betulinic acid, which involved Wagner-Meerwein rearrangement with formation of the typical ring E of both 18α-oleanane- and germanicane-type compounds, and subsequent lactone ring-opening.[23]

The generality of the methods reported in the literature for the synthesis of the referred compounds present drawbacks, such as the use of toxic, corrosive and/or expensive reagents, as well as the fact that most of them are non-catalytic. Thus, the development of new catalytic processes using environmentally friendly, cheap and easily available reactants would be of considerable interest in this area.

Bismuth(III) salts emerged in the past few years as "eco-friendly" reagents suitable for green chemistry.[24,25] As part of our current interest on the development of new bismuth-based processes[26] applied to natural product chemistry,[27–29] we herein report the use of bismuth(III) salts as catalysts for the Wagner-Meerwein rearrangement of both betulin and betulinic acid as well as their derivatives, which occurs with expansion of ring E and formation of an additional O-containing ring. We found that under more vigorous reaction conditions, A-*neo*-18α-oleanene compounds can be selectively obtained in very high yields, from the above mentioned lupanes, in a one-pot procedure. The scope of this procedure has been extended by the use of other terpenic compounds, such as the sesquiterpene (–)-caryophyllene oxide and the 3-oxo derivative of oleanolic acid.

Results and discussion

Catalyst and solvent screening

We have recently reported the use of bismuth(III) salts as catalysts for the Westphalen and "backbone" rearrangements of 5β,6β-epoxysteroids. These reactions involve the migration of one or two of the angular C18 and C19 methyl groups with the formation of a double bond on ring B or D of the steroid nucleus.[29]

The interesting results achieved with those reactions in particular, have turned our attention to the study of the Wagner-Meerwein rearrangement in terpenes. Screening assays for catalyst choice using betulin **1** in refluxing CH_2Cl_2 are depicted on Table 1 (Scheme 1, Table 1). These results were promising, as the expected product **2** was obtained in very high yield using 5 mol% of $Bi(OTf)_3{\cdot}xH_2O$ (Table 1, entry 1). Almost no reaction occured with $Bi(OAc)_3$ and $BiCl_3$ (Table 1, entries 2 and 3), as opposed to the reaction with $BiBr_3$ and $Bi(NO_3)_3{\cdot}5H_2O$ (Table 1, entries 4–7). However, a loading amount of 20 mol% of these catalysts was needed to obtain full conversion (Table 1, entries 5 and 7). Among the other metal triflates screened for this reaction (Table 1, entries 8–10), only $Sc(OTf)_3$ (10 mol%) afforded allobetulin **2** in very high yield, after a relatively short reaction time. Thus, we chose $Bi(OTf)_3{\cdot}xH_2O$ as the optimal catalyst for the study of Wagner-Meerwein rearrangements.

Table 1 Catalyst screening for the Wagner-Meerwein rearrangement of betulin **1** to allobetulin **2**[a]

Entry	Catalyst (mol%)	Time (h)	Yield (%)[b]
1	$Bi(OTf)_3{\cdot}xH_2O$ (5)	3	95
2	$Bi(OAc)_3$ (10)	24	–
3	$BiCl_3$ (10)	24	traces
4	$BiBr_3$ (10)	24	45[c]
5	$BiBr_3$ (20)	3	97
6	$Bi(NO_3)_3{\cdot}5H_2O$ (10)	24	32[c]
7	$Bi(NO_3)_3{\cdot}5H_2O$ (20)	48	97
8	$Sc(OTf)_3$ (10)	4	94
9	$Yb(OTf)_3$ (10)	7	20[c]
10	$La(OTf)_3$ (10)	4	–

[a] Reaction conditions: 0.10 mmol of **1**, 5 mL of CH_2Cl_2, reflux; [b] Isolated yield; [c] The yield was determined by integration of the 19α-H signals of **1** and **2** on the ^{1}H NMR spectrum of the crude mixture.

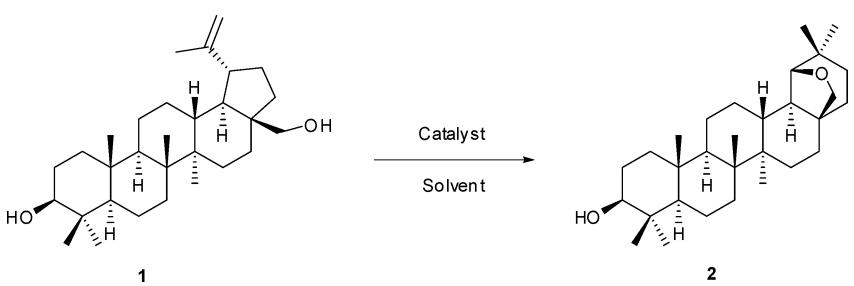
Table 2 Wagner-Meerwein rearrangement of betulin **1** to allobetulin **2** in different solvents[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	CH_2Cl_2	*rt*	24	90[b]
2	$MeNO_2$	50	24	50[c]
3	Toluene	50	24	40[c]
4	*t*-BuOMe	50	24	traces
5	MeOH	50	24	–
6	EtOH	50	24	–

[a] Reaction conditions: 0.10 mmol of **1**, 5 mol% of $Bi(OTf)_3{\cdot}xH_2O$, 5 mL of solvent; [b] Isolated yield; [c] The yield was determined by integration of the 19α-H signals of **1** and **2** on the ^{1}H NMR spectrum of the crude mixture.

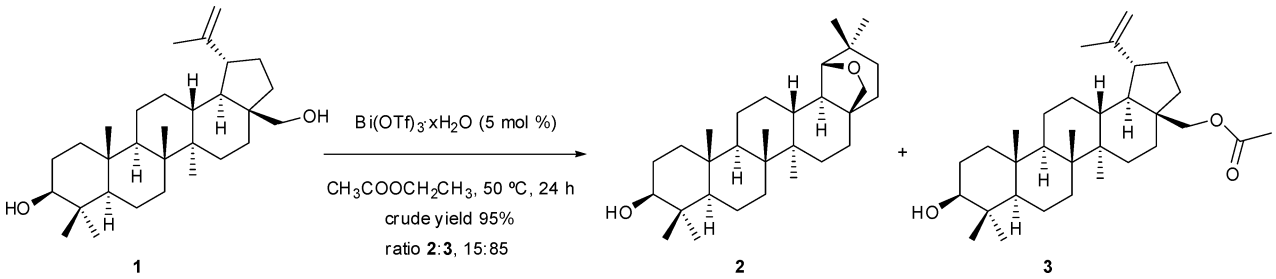
Further optimization of the reaction conditions using various solvents was undertaken (Scheme 1, Table 2). The $Bi(OTf)_3{\cdot}xH_2O$-catalyzed reaction of betulin **1** in CH_2Cl_2 was performed at room temperature, and allobetulin **2** was afforded in 90% yield, after 24 h (Table 2, entry 1). The use of other solvents led to poorer results (Table 2, entries 2–6).

Low yields were achieved in the reactions carried out in $MeNO_2$ and toluene (Table 2, entries 2 and 3), and no reaction was observed



1 2

Scheme 1 Wagner-Meerwein rearrangement of betulin **1** to allobetulin **2**.



Scheme 2 $Bi(OTf)_3 \cdot xH_2O$-catalyzed reaction of betulin **1** in ethyl acetate. The allobetulin **2**:betulin-28-yl acetate **3** ratio was determined by integration of the 19β-H signals of **1** and **2** on the ^1H NMR of the crude mixture.

in MeOH or EtOH (Table 2, entries 5 and 6) while only trace amounts of product were seen on the TLC plate using methyl *tert*-butyl ether as the solvent (Table 2, entry 4).

Interestingly, when the reaction was performed in ethyl acetate at 50 °C, 3β-hydroxylup-20(29)-en-28-yl acetate **3**[30] was found to be the major reaction product and allobetulin **2** was obtained as by-product (Scheme 2). This result, shows that $Bi(OTf)_3 \cdot xH_2O$ is an effective and selective catalyst for the transesterification reaction of the primary hydroxyl group of betulin **1**, in the presence of ethyl acetate.

The acid protons derived from the hydrolysis of bismuth(III) salts have been identified as the true catalytic species in some reactions.[31,32] In the light of this fact, a set of experiments has been carried out to determine whether the observed reactivity in the "betulin-allobetulin rearrangement" is due to Lewis or Brønsted acid catalysis. Thus, when the reaction was performed in the presence of 2,6-di-*tert*-butylpyridine, a known proton scavenger which binds to protons only and is unable to coordinate to metal ions due to the bulky *tert*-butyl groups,[32] no reaction was observed (0.1 mmol of betulin **1**, 5 mol% of $Bi(OTf)_3 \cdot xH_2O$ and 15 mol% of 2,6-di-*tert*-butylpyridine in CH_2Cl_2 at reflux, 4 h, no reaction). $BiPh_3$ was also used as a proton scavenger for the first time, due to the high lability of the Bi-Ph bond under acidic conditions.[24] As expected, only traces of product **2** were observed on the TLC plate (0.1 mmol of betulin **1**, 5 mol% of $Bi(OTf)_3 \cdot xH_2O$ and 15 mol% of $BiPh_3$ in CH_2Cl_2 at reflux, 4 h, traces of allobetulin **2**). The confirmation that the true catalytic species is a Brønsted acid generated *in situ*, was unequivocally demonstrated by the isomerisation of betulin **1** to allobetulin **2**, which was efficiently achieved in the presence of TfOH (0.1 mmol of betulin **1**, 15 mol% of TfOH in CH_2Cl_2 at reflux, 1 h, 95% yield of allobetulin **2**).

These results indicate that $Bi(OTf)_3 \cdot xH_2O$ is hydrolyzed under the reaction conditions, affording a Brønsted acid species *in situ*, which is the real catalyst.[33]

Wagner-Meerwein rearrangement in terpenes

This new bismuth triflate-based process was then applied to other terpenic substrates, showing good versatility, as both lupane-, 18α-oleanane- and caryophyllene-type compounds rearranged, under the optimized reaction conditions (Table 3). Thus, in the presence of 5 mol% of $Bi(OTf)_3 \cdot xH_2O$ in refluxing CH_2Cl_2, betulin-3β-yl acetate **4** afforded the corresponding 19β,28-epoxy-18α-oleanane product **5**, in 96% yield, after 1 h of reaction (Table 3, entry 1). In addition to spectroscopic evidence, the structure of compound **5** was confirmed by single crystal X-ray analysis (Fig. 2).‡ Starting from betulonic acid **6**, the Wagner-Meerwein rearrangement of ring E resulted in the high yielding preparation of the 18α-oleanane compound **7**,† bearing an 28,19β-lactone function (Table 3, entry 2).

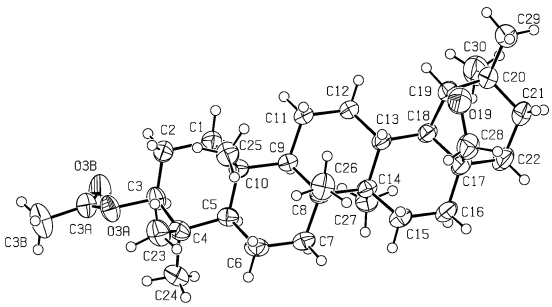


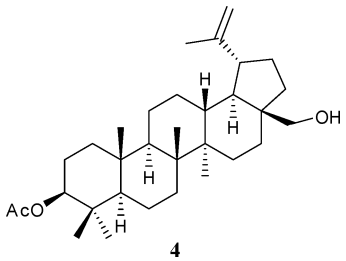
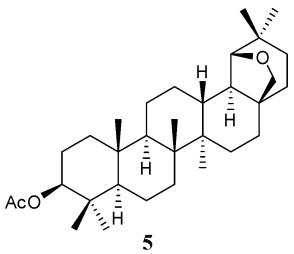
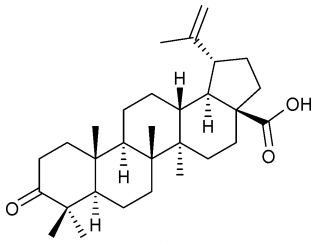
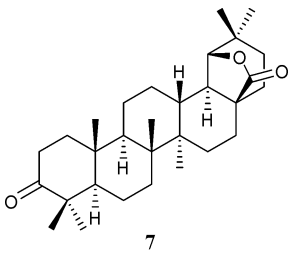
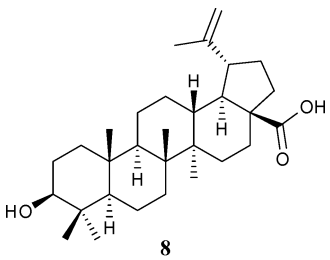
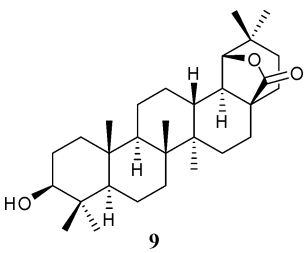
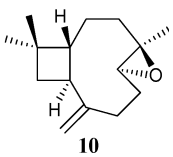
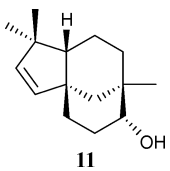
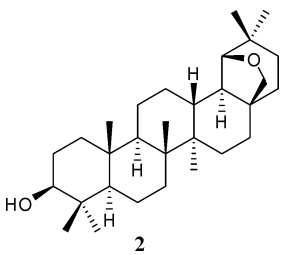
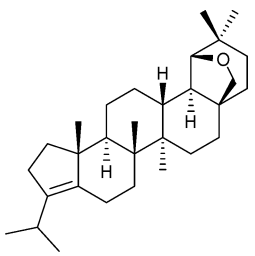
Fig. 2 ORTEP diagram of compound **5** (50% probability level, H atoms of arbitrary sizes).

When the reaction was performed with betulinic acid **8**, a slower conversion rate was observed along with formation of a trace amount of an apolar side product, as observed on TLC plates. NMR analysis of the crude mixture, after 30 h of reaction, showed a 79% conversion of **8**. Thus, the 18α-oleanan-28,19β-olide compound **9** was isolated by flash column chromatography in 66% yield. A lower reactivity and selectivity for the acid-catalyzed Wagner-Meerwein rearrangement of betulinic acid had already been reported by other authors.[11,13]

The $Bi(OTf)_3 \cdot xH_2O$-catalyzed Wagner-Meerwein rearrangement was further studied using the sesquiterpene (−)-caryophyllene oxide **10**. The reaction was completed in 10 minutes, and after purification by flash column chromatography, the clovane-type compound **11** was isolated in 60% yield (Table 3, entry 4). Analytical data of clov-2-en-9α-ol **11**† was in accordance with literature.[34] However, 2D NMR spectroscopy was performed in order to unequivocally assign the orientation of the 9α-hydroxyl group. The "caryophyllene-clovane rearrangement" has previously been reported under acid conditions,[35] and it has been found that 2-substituted clovane-type compounds may be formed when a nucleophilic species is present.[28,36]

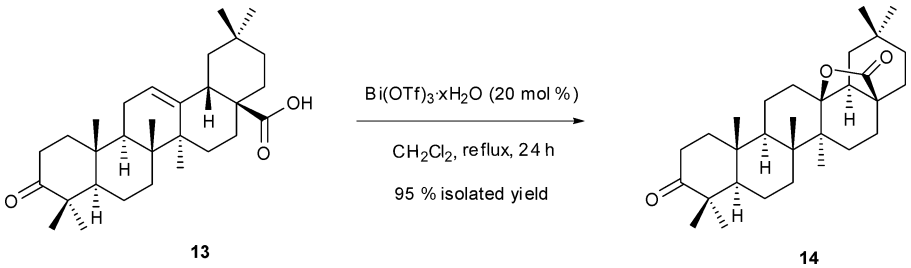
‡ **Crystal data for compound 5**. $C_{32}H_{52}O_3$, $M = 484.76$, monoclinic, $a = 13.3520(2)$, $b = 6.54000(10)$, $c = 32.4439(5)$ Å, $V = 2798.13(7)$ Å^3, $T = 293(2)$ K, space group $C2$, $Z = 4$, 26879 reflections measured, 3074 unique ($R_{int} = 0.027$) which were used in all calculations. Final R indices: $R1 = 0.036$ for 2759 reflections with $I > 2\sigma(I)$, $wR(F^2)$ was 0.099 (all data).

Table 3 Wagner-Meerwein rearrangement in triterpenes **2**, **4**, **6** and **8** and (–)-caryophyllene oxide **10** catalyzed by $Bi(OTf)_3 \cdot xH_2O$[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **4**	1	 **5**	96
2	 **6**	3	 **7**	97
3	 **8**	30	 **9**	66[c,d]
4	 **10**	10 min	 **11**	60[e]
5[f]	 **2**	21	 **12**	94

[a] Reactions conditions: 5 mol% of $Bi(OTf)_3 \cdot xH_2O$, CH_2Cl_2 (5 mL/0.10 mmol of substrate), reflux; [b] Isolated yield; [c] There was 79% conversion of betulinic acid **8**, as calculated by integration of the 29-Ha and 19α-H signals of **8** and **9**, respectively, on the ^{1}H NMR spectrum of the crude mixture; [d] Purification by flash column chromatography on SiO_2 using $CHCl_3$/petroleum ether 40–60 °C 80:20 (v:v) as eluent; [e] After flash column chromatography on SiO_2 using toluene/diethyl ether 95:5 (v:v) as eluent; [f] The reaction was performed with 20 mol% of $Bi(OTf)_3 \cdot xH_2O$.

When oleanonic acid **13** was used as substrate in the presence of 5 mol% of $Bi(OTf)_3 \cdot xH_2O$, a single product was detected on the TLC plate, however low conversion was observed after 24 h. By increasing the amount of bismuth(III) salt to 20 mol%, quantitative formation of the 3-oxo-18α-olean-28,13β-olide **14**† occurred (Scheme 3). This lactonization reaction of triterpenoids with a C12=C13 double bond has already been reported under acid conditions.[37] Thus, whereas in lupanes the formation of the additional O-containing ring occurs along with a Wagner-Meerwein rearrangement that causes ring E expansion, in the oleanolic acid derivative **13** only 28,13β-lactonization with 18-H inversion of orientation is observed.



Scheme 3 $Bi(OTf)_3 \cdot xH_2O$-promoted lactonization of oleanonic acid **13**.

The Wagner-Meerwein rearrangement has also been applied to the construction of cyclopentyl units by ring contraction of six-membered carbocyclic compounds during the total synthesis of natural products.[38] The presence of the 3β-hydroxyl group is a typical feature of triterpenic compounds. The loss of this function is often associated with a Wagner-Meerwein rearrangement of ring A, with contraction and formation of a double bond, that may be located at C3=C4, C3=C5 or C9=C10 (Fig. 3).[2]

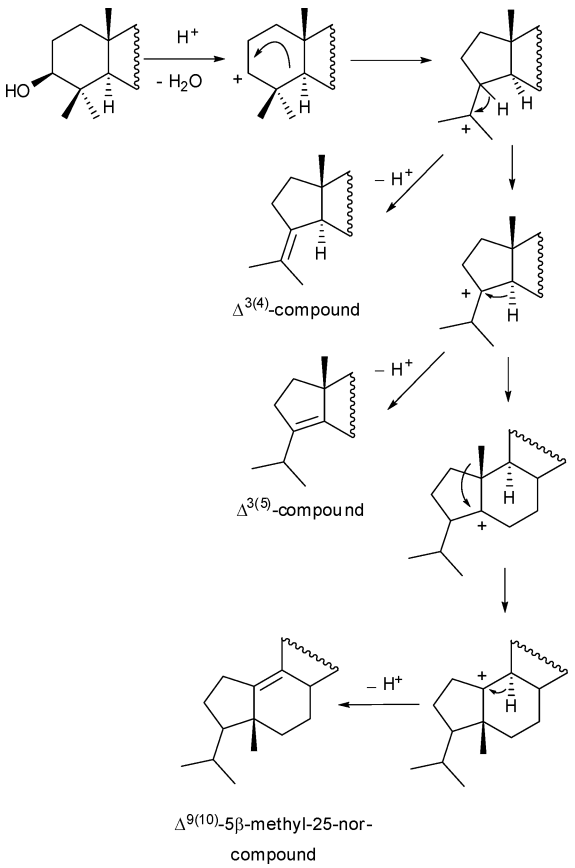


Fig. 3 Dehydration of the 3β-hydroxyl group on triterpenes followed by Wagner-Meerwein rearrangement on ring A.

Under more vigorous reaction conditions than the ones needed for the "betulin-allobetulin rearrangement", further Wagner-Meerwein rearrangement may take place on ring A of lupane compounds.[13] Thus, the loss of the 3β-hydroxyl group induces an additional Wagner-Meerwein rearrangement, with migration of the C4-C5 bond electrons that generate olefinic ring A contracted products, with a five-membered A-ring bearing a 3-isopropyl group, which is designated as the A-*neo* ring.[39] The formation of these A-*neo*-18α-oleanene compounds as by-products of the "betulin-allobetulin rearrangement" has been reported, and the location of the double bond has been found to be dependent on the reaction conditions employed.[11,13,14] This transformation has also been described through the use of typical dehydration agents, such as PCl_5, P_2O_5 and Fuller's earth,[9,40] and by solvolysis of the corresponding 3β-tosyl derivatives.[40] A-*neo*-18α-oleanene compounds bearing a double bond on rings A or B have been used both as biomarkers in geochemical studies[13,18] and as synthetic intermediates, due to the presence of the highly versatile alkene group.[41]

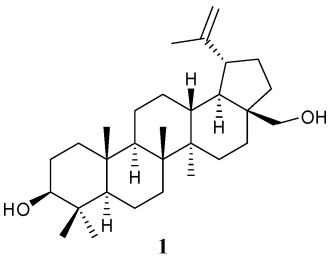
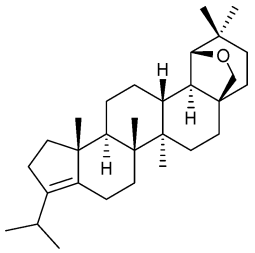
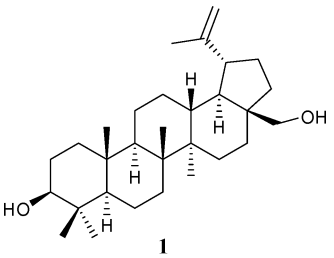
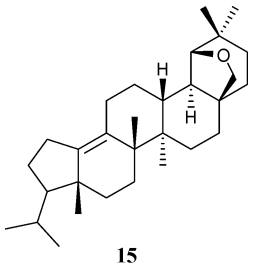
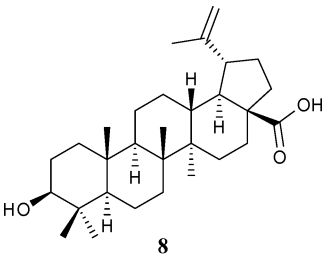
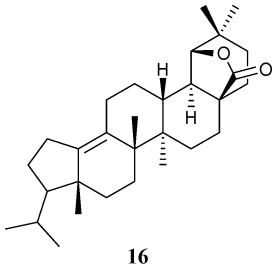
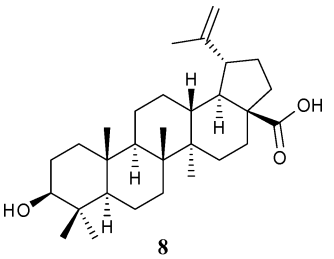
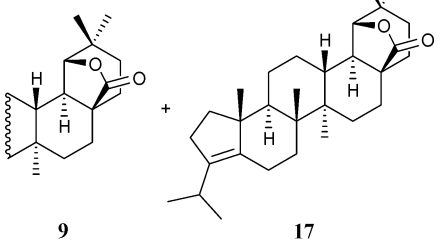
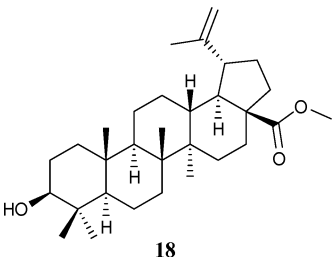
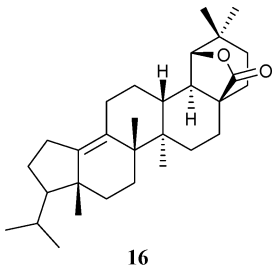
The fact that these compounds are interesting and the lack of selective high yielding methods for their synthesis, have prompted us to investigate whether $Bi(OTf)_3 \cdot xH_2O$ was a suitable reagent to promote these transformations. Thus, reaction of allobetulin **2** in the presence of 5 and 10 mol% of $Bi(OTf)_3 \cdot xH_2O$ afforded a highly apolar product after 24 h, however low conversion was achieved. Nonetheless, when 20 mol% of this Bi(III) salt was used, 19β,28-epoxy-A-*neo*-18α-olean-3(5)-ene **12** was selectively obtained after 21 h, in refluxing CH_2Cl_2 (Table 3, entry 5). Spectroscopic data were in agreement with the pointed structure for compound **12**. The presence of a well-defined septet at 2.65 ppm on the ^1H NMR spectrum confirmed the presence of the double bond at C3=C5.[13]

Double Wagner-Meerwein rearrangement in lupane compounds

This last result, together with the observation that traces of a very apolar by-product were seen on the TLC plates of the $Bi(OTf)_3 \cdot xH_2O$-catalyzed reaction of betulinic acid **8**, which we rationalized as the result of dehydration of the 18α-oleanan-28,19β-olide derivative **9**, prompted us to study the direct and selective double Wagner-Meerwein rearrangement on lupane compounds (Table 4).

Betulin **1** could be selectively converted into the corresponding rings A and E rearranged 18α-olean-3(5)-ene compound **12**, by using 20 mol% of $Bi(OTf)_3 \cdot xH_2O$ in refluxing CH_2Cl_2. The reaction was completed after 40 h and the product was isolated in 98% yield (Table 4, entry 1). As observed on the TLC plates, betulin **1** was initially converted into allobetulin **2**, which was then converted into compound **12**. The same reaction, performed in the presence of a higher amount of $Bi(OTf)_3 \cdot xH_2O$ (50 mol%), showed a higher conversion rate, and a highly apolar product was obtained after 8 h of reaction. Analytical data of this compound indicated that a more complex rearrangement had occurred, with selective formation of 19β,28-epoxy-A-*neo*-5β-methyl-25-nor-18α-olean-9(10)-ene **15**[13] (Table 4, entry 2).

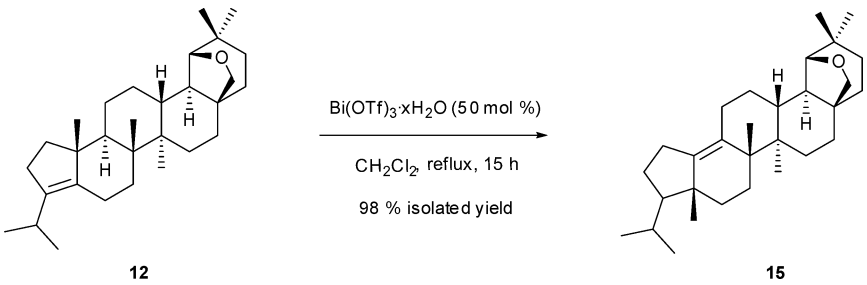
Table 4 $Bi(OTf)_3 \cdot xH_2O$ promoted dehydration and double Wagner-Meerwein rearrangement of lupane derivatives **1**, **8**, and **18**[a]

Entry	Substrate	$Bi(OTf)_3 \cdot xH_2O$ (mol%)	Time (h)	Product	Yield (%)[b]
1	 **1**	20	40	 **12**	98
2	 **1**	50	8	 **15**	96
3	 **8**	20	16	 **16**	92
4	 **8**	20	9	 **9** + **17**	95[c] (77:23)[d]
5	 **18**	20	22	 **16**	82[e]

[a] Reactions performed in refluxing CH_2Cl_2 (5 mL/0.10 mmol of substrate); [b] Isolated yield; [c] Yield of the reaction crude based on the major product; [d] The ratio was determined by integration of the 3α-H and 4-H signals of **9** and **17**, respectively, on the ^1H NMR spectrum of the crude mixture; [e] After flash column chromatography on SiO_2 using toluene/diethyl ether 95:5 (v/v) as eluent.

Under the same reaction conditions (50 mol% of $Bi(OTf)_3 \cdot xH_2O$, in refluxing CH_2Cl_2), compound **15** can also be selectively obtained from allobetulin **2** in 97% yield, after 20 h of reaction.

Rearrangement of betulin **1** in the presence of $Bi(OTf)_3 \cdot xH_2O$ either proceeds to rings A and B or occurs exclusively on ring E depending on the amount of catalyst. Conversion of the



Scheme 4 $Bi(OTf)_3 \cdot xH_2O$-promoted isomerisation of the 18α-olean-3(5)-ene compound **12** into the 5β-methyl-25-nor-18α-olean-9(10)-ene compound **15**.

18α-olean-3(5)-ene compound **12** into the 5β-methyl-25-nor-18α-olean-9(10)-ene compound **15**, under strongly acidic conditions, has been previously reported.[42]

In order to understand whether the $Bi(OTf)_3 \cdot xH_2O$-promoted transformation of betulin **1** to product **15** occurs by the intermediacy of a discrete cationic species only, or directly from the intermediate compound **12**,[2] reaction with **12** in the presence of $Bi(OTf)_3 \cdot xH_2O$ (50 mol%) in CH_2Cl_2, at reflux, was performed. After 15 h, the A-*neo*-5β-methyl-25-nor-18α-olean-9(10)-ene compound **15** has been isolated in 98% yield (Scheme 4).

The reaction of both betulin-3β-yl acetate **4** and betulonic acid **6** in the presence of 20 mol% of $Bi(OTf)_3 \cdot xH_2O$ afforded the corresponding ring E rearranged products **5** and **7**, after 22 and 20 h, in 87 and 92% yield, respectively, as the result of a single Wagner-Meerwein rearrangement. These results showed that both 3β-acetoxy and 3-oxo groups are stable under the reaction conditions used, and do not undergo further rearrangements.

When the reaction was carried out with betulinic acid **8**, in the presence of 20 mol% of $Bi(OTf)_3 \cdot xH_2O$, the reaction proceeded similarly to the one observed with betulin **1** under the same reaction conditions (Table 4, entry 3). Betulinic acid **8** was initially converted into its corresponding ring E rearranged product **9** along with a highly apolar compound, as observed by TLC. After 16 h, a white solid was isolated and analysis of its spectroscopic data showed formation of the new triterpenic compound, A-*neo*-5β-methyl-25-nor-18α-olean-9(10)-ene-28,19β-olide **16**, in 92% yield (Table 4, entry 3). EI-mass spectrometry showed a 438 molecular ion peak indicative of the loss of a H_2O molecule. No signal at 2.65 ppm or at the olefinic region was observed on the ^1H NMR spectrum, however the characteristic 19α-H signal at 3.96 ppm was present. ^{13}C NMR spectroscopy confirmed the presence of two olefinic carbons at 130.5 and 142.5 ppm and a carbonyl group at 179.9 ppm. The olefinic carbons were not found on the DEPT 135 experiment, which confirmed the existence of olefinic quaternary carbons. This data, combined with the available analytical information for related compounds[13,14] allowed us to assign the structure of compound **16**.† Using 50 mol% of $Bi(OTf)_3 \cdot xH_2O$, under the same reactions conditions, the A-*neo*-5β-methyl-25-nor-18α-oleanene product **16** was quantitatively obtained, after 8 h.

The reaction of betulinic acid **8** in the presence of 20 mol% of $Bi(OTf)_3 \cdot xH_2O$ was then repeated and stopped after full conversion of the substrate **8** (Table 4, entry 4). Analysis of the ^1H NMR spectrum of the crude mixture allowed the determination of a 77:23 ratio of the 18α-oleanan-28,19β-olide compound **9** and the A-*neo*-18α-$\Delta^{3(5)}$ product **17** (Table 4, entry 4). Compound **17** was isolated by flash column chromatography in 17% yield. Spectroscopy data of product **17** was in accordance with literature,[13] however its structure was unequivocally elucidated by single-crystal X-ray diffractometry analysis (Fig. 4).§

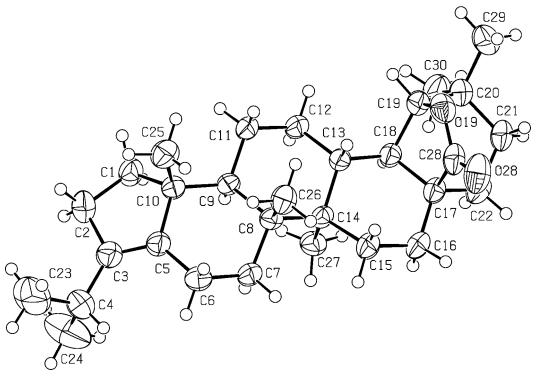


Fig. 4 ORTEP diagram of compound **17** (50% probability level, H atoms of arbitrary sizes).

In order to establish whether $Bi(OTf)_3 \cdot xH_2O$ is a suitable reagent to promote the dehydration with subsequent Wagner-Meerwein rearrangement of ring A only, we used methyl 3β-hydroxylup-20(29)-en-28-oate **18**[43] as the substrate. However, contrary to our expectations, cleavage of the methyl ester function occurred, and subsequent double Wagner-Meerwein rearrangement afforded compound **16** (Table 4, entry 5).

Conclusions

In conclusion we have developed a novel procedure for the Wagner-Meerwein rearrangement of lupane compounds involving the expansion of ring E with formation of an additional O-containing ring, using the "eco-friendly" bismuth(III) salts as catalysts. This new process allowed the preparation of several 18α-oleanane compounds in high yields. The optimized reaction conditions were extended to the sesquiterpene (−)-caryophyllene oxide and oleanonic acid with success. Under more vigorous conditions, using 20–50 mol% of $Bi(OTf)_3 \cdot xH_2O$, an additional Wagner-Meerwein rearrangement occurred on ring A of lupane and

§ **Crystal data for compound 17**. $C_{30}H_{46}O_2$, $M = 438.67$, monoclinic, $a = 13.2214(4)$, $b = 6.4962(2)$, $c = 29.8420(9)$ Å, $V = 2558.00(13)$ Å^3, $T = 293(2)$ K, space group $C2$, $Z = 4$, 22819 reflections measured, 2655 unique ($R_{int} = 0.061$) which were used in all calculations. Final R indices: $R1 = 0.046$ for 1677 reflections with $I > 2\sigma(I)$, $wR(F^2)$ was 0.116 (all data).

18α-oleanane derivatives with the selective formation of A-*neo*-18α-oleanene compounds. Full structural elucidation of the obtained products was made using IR, MS, NMR spectroscopy and X-ray crystallography. Some mechanistic considerations were provided, namely the confirmation that the true catalytic species involved is a Brønsted acid generated *in situ*.

Experimental section

General methods

Betulin [lup-20(29)-en-3β,28-diol] **1**, betulinic acid [3β-hydroxy-lup-20(29)-en-28-oic acid] **8**, (–)-caryophyllene oxide **10** and commercial bismuth salts were purchased from Sigma-Aldrich Co. Solvents were obtained from VWR Portugal and used without further purification. Betulin-3β-yl acetate [28-hydroxylup-20(29)-en-3β-yl acetate] **4**,[30] betulonic acid [3-oxolup-20(29)-en-28-oic acid] **6**,[44] oleanonic acid (3-oxo-olean-12-en-28-oic acid) **13**[45] and methyl 3β-hydroxylup-20(29)-en-28-oate **18**[43] were synthesized as previously described. Bismuth triflate, $Bi(OTf)_3 \cdot xH_2O$ (with $1<x<5$) was prepared according to the literature.[46] Kieselgel 60 F_{254}/Kieselgel 60G was used for TLC plates. Silica gel 60 (230–400 mesh ASTM) was used for flash column chromatography. Melting points were determined on a Buchi Melting point B-540 apparatus and are uncorrected. IR spectroscopy was performed on a Jasco FT/IR 420 spectrophotometer. ^1H and ^{13}C NMR were recorded on a Bruker AMX 300 MHz or on a Bruker Avance III 400 MHz. 2D NMR spectroscopy, which included 2D Homonuclear Correlation (COSY), Nuclear Overhauser Enhancement Spectroscopy (NOESY), 2D Heteronuclear Single Quantum Correlation (HSQC) or 2D Heteronuclear Multiple Quantum Correlation (HMQC), and 2D Heteronuclear Multiple Bond Correlation (HMBC), were recorded on a Bruker Avance 300 MHz or 500 MHz equipped with a BBO-ATMA 5 mm probe or on a Bruker Avance III 400 MHz. The NMR samples were prepared in a $CDCl_3$ or $CDCl_3$/THF-*d*8 solution with Me_4Si as internal standard. Chemical shifts (δ) are given in ppm and coupling constants are presented in Hz. Mass spectral analysis was performed by direct injection on a Thermo Finnigan PolarisQ GC/MS Benchtop Ion Trap equipped with a direct insertion probe. Single-crystal X-ray diffractometry analysis was made on a Bruker-Nonius Kappa Apex II CCD diffractometer using graphite monochromated Mo *K*α radiation (λ= 0.71073 Å). The structures were solved by direct methods and conventional Fourier synthesis (SHELXS-97). The refinement of the structures was made by full matrix least-squares on F^2 (SHELXL-97). All non-H-atoms were refined anisotropically. The H atoms positions were initially placed at idealized calculated positions and refined with isotropic thermal factors while allowed to ride on the attached parent atoms using SHELXL-97 defaults.

General experimental procedure for the $Bi(OTf)_3 \cdot xH_2O$-catalyzed Wagner-Meerwein rearrangement on terpenes

To a solution of betulin **1** (44.2 mg, 0.10 mmol) in CH_2Cl_2 (5 mL), $Bi(OTf)_3 \cdot xH_2O$ (3.6 mg, 0.005 mmol) was added. After 3 h under magnetic stirring at reflux temperature, the reaction was completed as verified by TLC control. The reaction mixture was concentrated under reduced pressure and the resulting residue dissolved in diethyl ether (50 mL). The organic phase was washed with $NaHCO_3$ (10% aq), water, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give allobetulin (19β,28-epoxy-18α-olean-3β-ol) **2** as a white solid (42.0 mg, 95% yield). Mp 264–266 °C (from ethanol) (lit.,[13] 266–268 °C); ν_{max}(film)/cm^{-1} 3394, 2927, 1450, 1025; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.77 (3 H, s), 0.80 (3 H, s), 0.85 (3 H, s), 0.91 (3 H, s), 0.93 (3 H, s), 0.97 (6 H, s), 3.20 (1 H, dd, *J* 10.9 and 5.4, 3α-H), 3.44 (1 H, d, *J* 7.8, 28-H_a), 3.53 (1 H, s, 19α-H), 3.78 (1 H, dd, *J* 7.8 and 0.9, 28-H_b); δ_C (75 MHz; $CDCl_3$; Me_4Si) 13.5, 15.4, 15.7, 16.5, 18.2, 20.9, 24.5, 26.4, 26.2, 26.4, 27.4, 27.9, 28.8, 32.7, 33.9, 34.1, 36.2, 36.7, 37.2, 38.8, 38.9, 40.6, 40.7, 41.4, 46.8, 51.0, 55.4, 71.2, 78.9, 87.9; *m*/*z* (EI) 442 (M^+, 12%), 424 (27), 371 (14), 220 (19), 207 (28), 189 (100), 149, (38), 119 (39).

19β,28-Epoxy-18α-olean-3β-yl acetate 5. Obtained from 28-hydroxylup-20(29)-en-3β-yl acetate **4** in 96% yield, after 1 h under the above described reaction conditions. Recrystallization from ethanol/*n*-hexane at room temperature gave colourless single crystals suitable for X-ray crystallography. Mp 285–287 °C (from ethanol/*n*-hexane) (lit.,[13] 285–287 °C); ν_{max}(film)/cm^{-1} 2925, 1727, 1250, 1219; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.80 (3 H, s), 0.84 (3 H, s), 0.85 (3 H, s), 0.87 (3 H, s), 0.91 (3 H, s), 0.93 (3 H, s), 0.97 (3 H, s), 2.05 (3 H, s, 3β-$COCH_3$), 3.44 (1 H, d, *J* 7.8, 28-H_a), 3.53 (1 H, s, 19α-H), 3.77 (1 H, d, *J* 7.8, 28-H_b), 4.48 (1 H, m, 3α-H); δ_C (75 MHz; $CDCl_3$; Me_4Si) 13.5, 15.7, 16.5, 16.5, 18.1, 21.0, 21.3, 23.7, 24.5, 26.2, 26.4 (2 C), 27.9, 28.8, 32.7, 33.8, 34.1, 36.2, 36.7, 37.1, 37.8, 38.6, 40.6, 40.7, 41.4, 46.8, 51.0, 55.5, 71.2, 81.0, 87.9, 171.0; *m*/*z* (EI) 484 (M^+, 20%), 424 (100), 409 (34), 381 (63), 355 (41), 204 (49), 189 (78), 119, (75).

3-Oxo-18α-olean-28,19β-olide 7. Obtained from betulonic acid **6** in 97% yield, after 3 h under the above described reaction conditions. Mp 310–312 °C (from *n*-hexane/CH_2Cl_2) (lit.,[10] 315 °C); ν_{max}(film)/cm^{-1} 2942, 1760, 1710, 1448, 1119, 966, 925; δ_H (500 MHz; $CDCl_3$/THF-*d*8; Me_4Si) 0.83 (3 H, s), 0.87 (3 H, s), 0.88 (3 H, s), 0.89 (3 H, s), 0.94 (3 H, s), 0.94 (3 H, s) 0.99 (3 H, s), 2.31–2.45 (2 H, m, 2-H_2), 3.86 (1 H, s, 19α-H); δ_C (125 MHz; $CDCl_3$/THF-*d*8; Me_4Si) 12.6, 14.3, 15.4, 18.6, 19.9, 20.6, 22.8, 24.7, 25.6, 25.7, 27.0, 27.7, 31.0, 31.5, 32.1, 32.7, 33.0, 35.3, 36.1, 38.9, 39.1, 39.6, 45.1, 45.7, 46.2, 49.7, 54.0, 84.8, 178.4, 216.0; *m*/*z* (EI) 454 (M^+, 39%), 436 (14), 327 (15), 203 (24), 190 (100), 134 (32), 119, (38), 91 (37).

3β-Hydroxy-18α-olean-28,19β-olide 9. Obtained from betulinic acid **8**, under the above described reaction conditions. TLC analysis after 30 h of reaction showed spots corresponding to the starting compound, the product **9** and traces of a highly apolar by-product. There was a 79% conversion of betulinic acid **8**, as calculated by integration of the 29-Ha and 19α-H signals of **8** and **9**, respectively, in the ^1H NMR spectrum of the crude mixture. The main product **9** was isolated by flash column chromatography on SiO_2 using $CHCl_3$/petroleum ether 40–60 °C 80:20 (v:v) as eluent, and isolated as a white solid in 66% yield. Mp 335–337 °C (from *n*-hexane/CH_2Cl_2) (lit.,[13] 338–340 °C); ν_{max}(film)/cm^{-1} 3424, 2938, 1764, 1446, 1387, 1025, 969; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.76 (3 H, s), 0.84 (3 H, s), 0.87 (3 H, s), 0.91 (3 H, s), 0.95 (3 H, s), 0.97 (3 H, s), 1.03 (3 H, s), 3.20 (1 H, dd, *J* 11.2 and 4.9, 3α-H), 3.93 (1 H, s, 19α-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 13.7, 15.4, 15.6, 16.5, 18.2, 20.9, 24.0, 25.6, 26.6, 27.4, 27.9, 28.0, 28.8, 32.0, 32.4, 33.6,

33.8, 36.1, 37.3, 38.9, 39.0, 40.0, 40.6, 46.1, 46.8, 51.3, 55.6, 79.0, 86.0, 179.8; *m/z* (EI) 457 [(M + 1)$^+$, 4%], 438 (10), 423 (4), 395 (7), 204 (13), 189 (25), 119, (56), 91 (100).

Clov-2-en-9α-ol 11. Obtained from (−)-caryophyllene oxide **10** after 10 minutes, under the above described reaction conditions. The product was purified by flash column chromatography on SiO_2 using toluene/diethyl ether 95:5 (v/v) as eluent and isolated as a white solid in 60% yield. Mp 77–80 °C (from acetone) (lit.,[34] 79–80 °C); ν_{max}(film)/cm^{-1} 3373, 3030, 2947, 1468, 1359, 983; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.94 (3 H, s), 0.95 (3 H, s), 1.06 (3 H, s), 3.35 (1 H, m, 9β-H), 5.26 (1 H, d, *J* 5.6), 5.34 (1 H, d, *J* 5.6); δ_C (75 MHz; $CDCl_3$; Me_4Si) 21.2, 24.9, 27.3, 28.3, 32.8, 33.4, 33.6, 34.2, 35.4, 47.9, 49.6, 49.9, 74.4, 136.4, 138.9; *m/z* (EI) 220 (M$^+$, 5%), 205 (41), 203 (100), 187 (56), 161 (98), 131 (17), 119, (19), 93 (10).

General experimental procedure for the $Bi(OTf)_3 \cdot xH_2O$ promoted dehydratation and double Wagner-Meerwein rearrangement on terpenes

To a solution of betulin **1** (44.2 mg, 0.10 mmol) in CH_2Cl_2 (5 mL), $Bi(OTf)_3 \cdot xH_2O$ (14.4 mg, 0.02 mmol) was added. After 40 h under magnetic stirring at reflux temperature, the reaction was completed as verified by TLC control. The reaction mixture was concentrated under reduced pressure and the resulting residue dissolved in diethyl ether (50 mL). The organic phase was washed with $NaHCO_3$ (10% aq), water, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give 19β,28-epoxy-A-*neo*-18α-olean-3(5)-ene **12** as a white solid (41.5 mg, 98% yield). Mp 205–208 °C (from acetonitrile/acetone) (lit.,[13] 208–211 °C); ν_{max}(film)/cm^{-1} 2928, 1455, 1380, 1363, 1040; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.80 (3 H, s), 0.86 (3 H, d, *J* 0.7), 0.87 (3 H, s), 0.92 and 0.98 (each 3 H, 2d, *J* 6.8, 23-CH_3 and 24-CH_3), 0.94 (3 H, s), 1.04 (3 H, s), 2.65 (1 H, sept, *J* 6.8, 4-H), 3.45 (1 H, d, *J* 7.8, 28-H_a), 3.56 (1 H, s, 19α-H), 3.80 (1 H, dd, *J* 7.8 and 1.1, 28-H_b); δ_C (100 MHz; $CDCl_3$; Me_4Si) 13.4, 14.3, 19.2, 19.8, 21.3, 21.9, 23.7, 24.6, 26.3, 26.4, 26.5, 26.8, 27.4, 28.8, 32.6, 32.8, 34.7, 36.3, 36.8, 40.6, 40.8, 41.5, 42.2, 46.9, 49.9, 50.1, 71.3, 88.0, 136.2, 139.9; *m/z* (EI) 425 [(M + 1)$^+$, 31%], 409 (12), 381 (100), 259 (15), 175 (10), 161 (22), 121, (28), 95 (12).

Compound **12** could also be obtained from allobetulin **2** in 94% yield, after 21 h under the above described reaction conditions.

19β,28-Epoxy-A-*neo*-5β-methyl-25-nor-18α-olean-9(10)-ene 15. Obtained from betulin **1** in 96% yield, after 8 h under the above described reaction conditions, with 50 mol% of $Bi(OTf)_3 \cdot xH_2O$. Mp 147–149 °C (from *n*-hexane/CH_2Cl_2) (lit.,[13] 148–150 °C); ν_{max}(film)/cm^{-1} 2950, 2867, 1468, 1453, 1381, 1363, 1037; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.78 (3 H, s), 0.79 (3 H, s), 0.81 (3 H, s), 0.90 and 0.94 (each 3 H, 2d, *J* 6.6, 23-CH_3 and 24-CH_3), 0.94 (3 H, s), 1.08 (3 H, s), 3.46 (1 H, d, *J* 7.8, 28-H_a), 3.56 (1 H, s, 19α-H), 3.81 (1 H, dd, *J* 7.8 and 0.8, 28-H_b); δ_C (75 MHz; $CDCl_3$; Me_4Si) 15.5, 17.9, 22.9, 23.1, 24.5, 25.7, 26.0, 26.1, 26.4, 26.5, 27.1, 27.5, 28.8, 29.3, 29.8, 32.7, 35.6, 36.3, 36.6, 37.3, 40.2, 41.0, 41.7, 42.7, 46.8, 59.1, 71.3, 87.9, 131.2, 141.8; *m/z* (EI) 424 (M$^+$, 96%), 409 (24), 381 (97), 363 (26), 204 (54), 190 (100), 147, (39), 121 (31).

Compound **15** could also be obtained from allobetulin **2** in 97% yield, after 20 h under the above described reaction conditions.

A-*neo*-5β-methyl-25-nor-18α-olean-9(10)-ene-28,19β-olide 16. Obtained from betulinic acid **8** in 92% yield, after 16 h under the above described reaction conditions. Mp 185–187 °C (from *n*-hexane/acetone); ν_{max}(film)/cm^{-1} 2951, 1763, 1451, 1372, 1156, 1115, 1048; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.74 (3 H, s), 0.79 (3 H, s), 0.89 and 0.94 (each 3 H, 2d, *J* 6.6, 23-CH_3 and 24-CH_3), 0.94 (3 H, s), 1.00 (3 H, s), 1.03 (3 H, s), 3.96 (1 H, s, 19α-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 15.3, 17.9, 22.8, 23.0, 23.9, 25.5, 25.6, 25.7, 26.0, 26.5, 27.5, 28.5, 28.7, 29.3, 29.8, 31.8, 32.3, 33.6, 37.1, 37.4, 40.0, 40.2, 42.8, 46.4, 46.6, 59.1, 86.0, 130.5, 142.6, 179.8; *m/z* (EI) 438 (M$^+$, 70%), 423 (40), 395 (100), 204 (60), 189 (46), 159 (51), 119, (41), 105 (36).

Compound **16** could also be obtained directly from methyl 3β-hydroxylup-20(29)-en-28-oate **18**, after 22 h, under the above described reaction conditions. The product was purified by flash column chromatography on SiO_2 using toluene/diethyl ether 95:5 (v/v) as eluent and isolated as a white solid in 82% yield.

A-*neo*-18α-olean-3(5)-en-28,19β-olide 17. Obtained from betulinic acid **8**, under the above described reaction conditions. TLC analysis after 9 h of reaction showed complete conversion of the starting compound, and two spots corresponding to more apolar products. ^{1}H NMR analysis of crude mixture after work-up showed a 77:23 ratio of compounds **9** and **17**. Product **17** was isolated by flash column chromatography on SiO_2 using $CHCl_3$/petroleum ether 40–60 °C 80:20 (v:v) as eluent, as a white solid in 17% yield. Recrystallization from *n*-hexane/CH_2Cl_2 at room temperature gave colourless single crystals suitable for X-ray crystallography. Mp 292–294 °C (from *n*-hexane/CH_2Cl_2) (lit.,[13] 291–293 °C); ν_{max}(film)/cm^{-1} 2939, 1758, 1451, 1380, 1123, 969; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.83 (3 H, s), 0.86 (3 H, d, *J* 0.6), 0.92 and 0.98 (each 3 H, 2d, *J* 6.8, 23-CH_3 and 24-CH_3), 0.96 (3 H, s), 0.97 (3 H, s), 1.03 (3 H, s), 2.64 (1 H, sept, *J* 6.8, 4-H), 3.96 (1 H, s, 19α-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 13.6, 14.1, 19.1, 19.7, 21.3, 21.8, 23.6, 24.0, 25.6, 26.3, 26.6, 27.4, 28.2, 28.8, 32.0, 32.4, 32.4, 33.6, 36.5, 39.7, 40.8, 42.3, 46.2, 46.7, 49.8, 50.3, 86.0, 136.5, 139.7, 179.9; *m/z* (EI) 439 [(M + 1)$^+$, 8%], 423 (12), 395 (97), 349 (5), 285 (8), 259 (21), 135, (38), 121 (100).

Procedure for the lactonization of oleanonic acid 13. To a solution of oleanonic acid **13** (91.4 mg, 0.20 mmol) in CH_2Cl_2 (10 mL), $Bi(OTf)_3 \cdot xH_2O$ (29.1 mg, 0.04 mmol) was added. After 24 h under magnetic stirring at reflux temperature, the reaction was completed as verified by TLC control. The reaction mixture was concentrated under reduced pressure and the resulting residue dissolved in diethyl ether (100 mL). The organic phase was washed with $NaHCO_3$ (10% aq), water, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give 3-oxo-18α-olean-28,13β-olide **14** as a white solid (86.8 mg, 95% yield). Mp thermal decomposition observed at about 310 °C (from acetonitrile/acetone); ν_{max}(film)/cm^{-1} 2958, 1757, 1703, 1447, 1393, 1260; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.84 (3 H, s), 0.89 (3 H, s), 1.00 (3 H, s), 1.04 (3 H, s), 1.09 (3 H, s), 1.15 (3 H, d, *J* 0.5), 1.22 (3 H, s), 2.41 (1 H, ddd, *J* 15.8, 7.3 and 4.2, 2-H_a), 2.54 (1 H, ddd, *J* 15.8, 10.3 and 7.5, 2-H_b); δ_C (100 MHz; $CDCl_3$; Me_4Si) 16.0, 17.8, 18.7, 19.1, 19.4, 21.1, 23.1, 26.0, 26.5, 26.6, 27.8, 29.9, 31.5, 33.0, 34.1, 34.2, 35.2, 36.2, 36.7, 39.8, 41.3, 43.9, 45.0, 47.3, 47.4, 49.4, 54.9, 89.5, 179.1, 217.6; *m/z* (EI) 455 [(M + 1)$^+$, 18%], 437 (5), 409 (4), 235 (15), 218 (38), 203 (64), 189, (100), 119 (93).

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