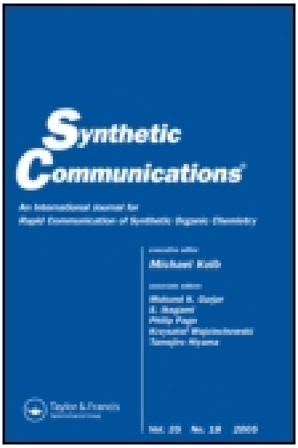

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SYNTHESIS OF BETULIN DERIVATIVES WITH SOLID SUPPORTED REAGENTS

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ABSTRACT

Betulin–allobetulin transformation is effected with ferric nitrate or ferric chloride adsorbed onto silica gel or alumina, in excellent yields. In addition, allobetulin can be converted to allobetulone with silica adsorbed ferric nitrate or to 19β,28-epoxy-A-neo-18α-olean-3(5)-ene and 19β,28-epoxy-A-neo-5β-methyl-25-nor-18α-olean-9-ene with silica or alumina adsorbed ferric chloride.

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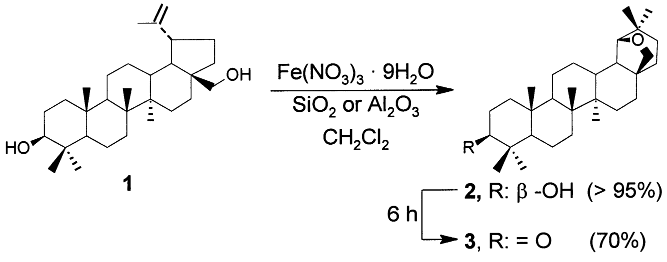
Betulin (**1**), a triterpene of the lupane family, is found in large amounts in white birch bark (*Betula paperyfera* March).[1] Since it is abundant and easy to extract and purify, betulin is an interesting substrate for synthesizing several triterpene derivatives presenting various biological activities.[2–4] Allobetulin, one of these derivatives, is often prepared from betulin in low yields, using various acids.[5–10] This transformation was recently achieved in good yields, with acid reagents previously adsorbed onto solid supports or even with certain solid supports used alone.[11]

Our laboratory is interested in developing simple methods for synthesizing derivatives of betulin. Various oxidizing agents adsorbed onto solid supports have been tested, since, in some cases, selective oxidations can be performed with these reagents under mild reaction conditions.[12] It has been reported that alcohol functions can be efficiently oxidized with iron nitrate ($Fe(NO_3)_3$) adsorbed onto clays or silica gel.[13] However, in the course of our studies on the oxidation of betulin, we discovered that allobetulin (**2**) could be quantitatively prepared with this reagent, and in very short reaction times (Scheme 1). In addition, we noted that allobetulone could be synthesized in good yields when longer reaction times were used.

The reagent was prepared by grinding iron nitrate with silica gel or alumina. The obtained yellowish powder was combined with betulin (**1**) dissolved in CH_2Cl_2 and then refluxed. Under these conditions, allobetulin (**2**) was obtained in yields exceeding 95% in 15 min (Table 1). If the reaction is maintained for 6 h, allobetulin (**2**) is transformed into allobetulone (**3**) in 70% yield. To our knowledge, the synthesis of allobetulone (**3**) from betulin (**1**) in a single step has never been reported. Other allobetulone (**3**) synthetic approaches reported in the literature always involve two synthetic steps.[14,15]



Scheme 1.

The transformation shown in Scheme 1 occurs via a rearrangement of betulin's E ring (**1**). This rearrangement is due to the Lewis acid

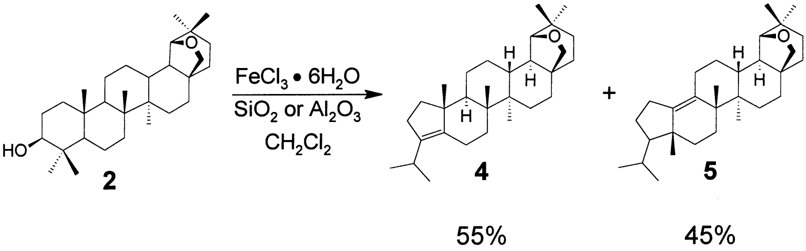
Table 1. Transformation of Betulin with Solid-Supported Reagents[a]

Reaction	Reagent	Solid support	Reaction time	Yield[b] (%)			
				2	**3**	**4**	**5**
1	$FeCl_3$	SiO_2	5 m	>95	—	—	—
2	$FeCl_3$	SiO_2	2 h	—	—	55	45
3	$FeCl_3$	Al_2O_3	5 m	>95	—	—	—
4	$FeCl_3$	Al_2O_3	2 h	—	—	55	45
5	$FeCl_3$	—	5 m	>95	—	—	—
6	$FeCl_3$	—	2 h	—	—	55	45
7	$Fe(NO_3)_3$	SiO_2	15 m	>95	—	—	—
8	$Fe(NO_3)_3$	SiO_2	6 h	—	70	trace	trace
9	$Fe(NO_3)_3$	Al_2O_3	30 m	>95	—	—	—
10	$Fe(NO_3)_3$	—	90 m	>95	—	—	—

[a]FeX_3/adsorbent ratio 1:4 (wt/wt), solvent: CH_2Cl_2, room temperature, magnetic stirring; [b]GC-determined. Isolated yields are available in Experimental.

nature of the iron of $Fe(NO_3)_3$, and is not due to the adsorbent. Indeed, when betulin is combined with the adsorbent alone, no reaction is observed. However, the reaction between the unadsorbed $Fe(NO_3)_3$ and betulin is much slower, indicating that the adsorbent greatly accelerates the reaction's progression. The transformation to allobetulin (**2**) with a well-known Lewis acid such as $FeCl_3$ adsorbed onto either of the two adsorbents is even faster than with the adsorbed $Fe(NO_3)_3$ (Table 1). These observations seem to indicate that $Fe(NO_3)_3$ initially acts as a Lewis acid rather than an oxidant.

Allobetulone (**3**) can be obtained in excellent yields if the reaction between $Fe(NO_3)_3$ adsorbed on silica gel and betulin is maintained for a 6-h period. In this case, $Fe(NO_3)_3$ adsorbed onto silica gel first transforms betulin into allobetulin and subsequently acts as an oxidant by transforming the secondary alcohol function into a ketone. It is important to specify that oxidation of the secondary alcohol is solely observed when silica gel is used as the adsorbent. Increasing the reaction time between betulin and $FeCl_3$ or adsorbed $FeCl_3$ results in the formation of two allobetulin-derived products: 19β,28-epoxy-A-*neo*-18α-olean-3(5)-ene (**4**) and 19β,28-epoxy-A-*neo*-5β-methyl-25-nor-18α-olean-9-ene (**5**) (Scheme 2). The formation of such ring-A contracted products has been previously studied in lupane-type triterpenes[16] and rationalized on the basis of Wagner-Meerwein rearrangements. As such, the products resulted from 1,2-hydride and alkyl shifts following the initial generation of a carbocation by the acid-catalyzed loss of the 3β-OH in ring A.



Scheme 2.

EXPERIMENTAL

General

Reagents and solid supports were bought and used without purification. GC-MS analyses were performed with a HP 5890/HP 5972 instrument. Seperation was achieved on a 25 m x 0.25 mm i.d. HP-5MS capillary column. The operating conditions were as follows: injector temperature 280°C, column temperature 100°C (1 m), 100°–280°C (25°C/m), 280°–325°C (5°C/m) and 325°C (30 m), carrier gas (helium) flow-rate 1 mL/m. NMR spectra were done with Bruker (300 and 400 MHz) instruments. Thin-layer chromatographies were performed on silica gel-covered glass plates $60F_{254}$ (Merck).

Isolation of betulin (**1**)

Finely ground birch bark (100 g) was macerated under reflux in 1 L of chloroform. The mixture was filtered and then vacuum-evaporated to obtain 28 g of crude betulin (**1**). This extract was purified by silica gel chromatography using a petroleum ether and ethyl acetate solution as eluent (90:10 to 85:15). Betulin (17 g) was obtained as a white solid, which was >95% pure by GC and showed only one spot on TLC. Only signals due to this compound were observed and were essentially identical to the NMR spectrum of the literature.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (1 H, d, H-29), 4.58 (1 H, d, H-29), 3.77 (1 H, d. J = 7.8 Hz, H-28), 3.31 (1 H, d, J = 7.8 Hz, H-28), 3.18 (1 H, m, H-3), 2.38 (1 H, m, H-19), 1.02–1.95 (complex, CH_2, CH), 1.68, 1.02, 0.98, 0.96, 0.82, 0.76 (18 H, all s, 6 x CH_3); EIMS, *m*/*z*, 442 (M^+, 5%), 43 (100), 95 (96), 55 (96), 81 (95), 69 (84), 41 (81), 67 (79), 93 (79), 189 (76).

Example of Reagent Preparation

$Fe(NO_3)_3 \cdot 9H_2O$ (0.2 g, 0.50 mmol) and silica gel (0.8 g) were ground in a mortar until a fine homogeneous powder was obtained. Other reagents were prepared using the same mass ratio (1:4).

Preparation of allobetulin (**2**)

Betulin (1, 50 mg, 0.11 mmol) was dissolved into 10 mL of freshly distilled dichloromethane. The solution was heated at reflux, then 456 mg of $Fe(NO_3)_3/SiO_2$ (0.22 mmol $Fe(NO_3)_3$) was added and the resulting mixture was stirred for 30 m. When the reaction was over (followed by TLC, approximately 30 m), the solution was filtered through a sintered glass funnel covered with silica gel. The solution was then thoroughly rinsed with a solution of 2% methanol in dichloromethane. The solvent was removed by vacuum distillation and 45.5 mg of allobetulin (**2**) was obtained as an amorphous solid in 91% yield. The isolated product was >95% pure by GC and showed only one spot by TLC. Only signals due to this compound were observed and essentially identical to the NMR spectrum of the literature.[15] ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (1 H, d, J = 7.8 Hz, H-28), 3.53 (1 H, s, H-19), 3.44 (1 H, d, J = 7.8 Hz, H-28), 3.20 (1 H, m, H-3), 1.01–1.78 (complex, CH_2, CH), 0.98, 0.93, 0.92, 0.85, 0.80, 0.77 (21 H, all s, 7 × CH_3); EIMS, *m*/*z*, 442 (M^+, 9%), 81 (100), 95 (92), 69 (90), 43 (86), 189 (80), 55 (78), 207 (70), 41 (69), 135 (59).

The reagent can also be prepared with $FeCl_3{\cdot}6H_2O$ and alumina as solid support.

Preparation of allobetulone (**3**)

To obtain allobetulone (**3**), the previous reaction was maintained another 6 h. Afterward, the mixture was filtered with a sintered glass funnel covered with silica gel (1 cm). Thorough rinsing with a dichloromethane solution containing 2% methanol was required for maximum product recovery. The solvent was vacuum evaporated and allobetulone (**3**) was recovered as an amorphous solid (35 mg, 70%) by silica gel chromatography with a petroleum ether/ethyl acetate 95:5 mixture. The isolated product was >95% pure by GC and showed only one spot on TLC. Only signals due to this compound were observed and were essentially identical to the NMR spectrum of the literature.[15] ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (1 H, d, J = 6 Hz, H-28), 3.53 (1 H, s, H-19), 3.45 (1 H, d, J = 6 Hz, H-28), 2.46 (2 H, m, H-2), 1.94 (1 H, m, H-5), 1.20–1.75 (complex, CH_2, CH), 1.08, 1.03, 1.01, 0.94, 0.93, 0.92, 0.80 (21 H, all s, 7 × CH_3); EIMS, *m/z*, 440 (M^+, 22%), 81 (100), 55 (91), 69 (85), 95 (79), 41 (75), 43 (66), 67 (63), 93 (54), 107 (54).

Preparation of 19β,28-epoxy-A-*neo*-18α-olean-3(5)-ene (**4**) and of 19β,28-epoxy-A-*neo*-5β-methyl-25-nor-18α-olean-9-ene (**5**)

These products were obtained by maintaining the reaction with ferric chloride an additional hour. The reaction medium was then filtered with a sintered glass funnel covered with a layer of silica gel (1 cm). Both products were isolated by chromatography with 10% $AgNO_3$-SiO_2 using a petroleum ether solution containing dichloromethane as eluent (90:10 to 50:50 v/v). 19β,28-Epoxy-A-*neo*-18α-olean-3(5)-ene (**4**, 10 mg) and 19β,28-epoxy-A-*neo*-5β-methyl-25-nor-18α-olean-9-ene (**5**, 15 mg) were obtained as amorphous solids, which where > 90% pure GC and showed only one spot by TLC. Only signals due to these compounds were observed and were essentially identical to the NMR spectra of the literature.[11] **4** ^{1}H NMR ($CDCl_3$) δ 3.81 (d, J = 8 Hz, 1 H, H-28), 3.57 (s, 1 H, H-19), 3.47 (d, J = 8 Hz, 1 H, H-28), 2.66 (m, 1 H, H-4), 1.10–2.31 (complex, CH_2, CH), 1.00, 0.94 (all d, J = 6.9 Hz, 6 H, H-23 and H-24), 1.06, 0.96, 0.89, 0.88, 0.82 (all s, 21 H, 5×CH_3); EIMS, *m/z*, 424 (M^+, 5%), 121 (100), 381 (82), 135 (79), 93 (72), 136 (67), 107 (65), 161 (59), 81 (59), 95 (54). **5** ^{1}H NMR ($CDCl_3$) δ 3.82 (d, J = 8 Hz, 1 H, H-28), 3.57 (s, 1 H, H-19), 3.47 (d, J = 8 Hz, 1 H, H-28), 1.10–2.31 (complex, CH_2, CH), 0.95, 0.91 (all d, J = 6.6 Hz, 6 H, H-23 et H-24), 1.08, 0.95, 0.82, 0.80, 0.79 (all s, 21 H, 5 × CH_3); EIMS, *m/z*, 424 (M^+, 28%), 55 (100), 69 (89), 119 (79), 105 (78), 41 (72), 95 (70), 189 (69), 81 (67), 91 (64).

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