Preparation of a 24-Nor-1,4-dien-3-one Triterpene Derivative from Betulin: A New Route to 24-Nortriterpene Analogues[1]

Yonghong Deng and John K. Snyder*

Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

jsnyder@chem.bu.edu

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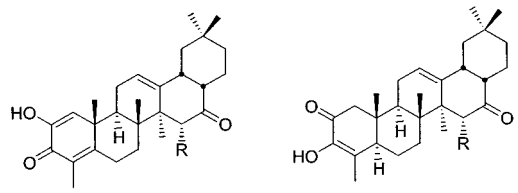
A new route to 24-nortriterpene derivatives with 2-hydroxy-$\Delta^{1,4}$-cyclohexadien-3-one A-rings from triterpene precursors has been demonstrated beginning with betulin to prepare derivatives of betulinic acid. The key steps in the transformation are a Suárez cleavage of the A-ring with a subsequent SmI_2-mediated pinacol-type coupling to reclose the A-ring following removal of the C-24 carbon by oxidative cleavage.

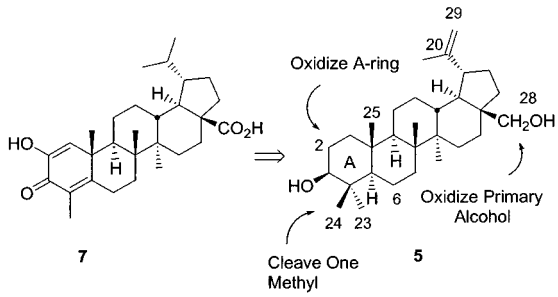
Introduction

We recently reported the isolation and structure of the cytotoxic remangilones A− D (**1**−**4**), from the Madagascar plant *Physena madagascariensis*, which have the 24,28-bisnoroleanane skeleton, with **1** and **2** possessing 2-hydroxy-$\Delta^{1,4}$-cyclohexadien-3-one A-rings.[2] The cytotoxicity of the remangilones led us to consider the possibility of converting readily available polycyclic triterpenes into 24-noranalogues with similar A-rings and examining these derivatives for biological activity. The ready availability of the triterpene betulin (**5**) from local collections (betulin comprises up to 30% of the outer bark of the white-barked birches, *Betula* spp.)[3] suggested an abundant source of material to test this possibility. Furthermore, the recent discovery of the highly selective anticancer activity of betulinic acid (**6**)[4] against human melanoma,[5] as well as its value as an anti-HIV agent,[6] and the ease with which betulin can be converted into betulinic acid[7] suggested **7** as a target (Scheme 1). This conversion would also require the generation of the C-28 carboxylic acid, which



has been suggested to be essential for the anticancer activity of betulinic acid.[8] Indeed, modifications of biologically active triterpenoid carboxylic acids,[9] including betulinic acid,[10] are well-known to enhance both the anti-HIV and anticancer activities.

Scheme 1



Conversions of sterols into derivatives with 1,4-cyclohexadien-3-one A-rings,[11] and of triterpenes into both 24-nor-[12] and 23,24-bisnortriterpenes,[13] have long been es-

* To whom correspondence should be addressed. Phone: 617/353-2621 (353-2575). Fax: 617/353-6466.

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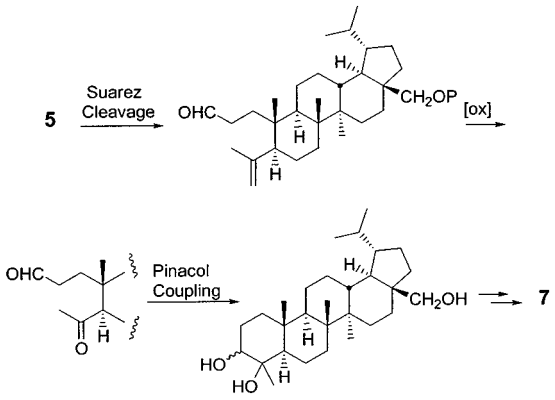
tablished, though strategies that also allow for incorporation of a C-2 hydroxyl group in a $\Delta^{1,4}$-dien-3-one system (Δ^4-2,3-diketones in enol tautomer) are less well-known.[14] The conversions of triterpenes into 24-nor and 23,24-bisnor derivatives typically feature A-ring cleavage under relatively harsh conditions followed by removal of the unwanted carbon(s) and A-ring reclosure. Approaches proceeding through selective oxidation and subsequent removal of a C-4 methyl group via decarboxylation have also been reported,[15] though these are less attractive from a synthetic viewpoint. We felt a more efficient route to oxidized 24-nor A-rings, as targeted in **7**, from 3-hydroxytriterpenes such as **5** could begin with a Suárez cleavage[16] and proceed through formation of a terminal olefin from C-4/C-24 of the original triterpene (Scheme 2). Oxidative olefin cleavage and subsequent pinacol-type coupling to reclose the A-ring would then form the 24-norskeleton, with further transformations ultimately giving the target **7**. To avoid complications arising from the introduction of the methyl ketone at C-20 from the oxidative olefin cleavage, the 20,29-dihydro derivative was the final target. We now report the fruition of this work culminating in the efficient conversion of **5** into **7**.

Scheme 2



Results and Discussion

Monoacetylation of betulin (**5**) resulted in selective acylation of the primary alcohol to give **8** (60−72% depending upon the scale, Scheme 3). Selective protection of the C-28 alcohol in **5** with TBSCl or TBSOTf was unsuccessful presumably due to the relatively hindered nature of this neopentyl-type primary alcohol, invariably resulting in a mixture of mono- and disilylated products. Further transformations were carried out initially on **8** to optimize procedures and then subsequently on 20,29-dihydro derivative **9**, quantitatively prepared from **8** by hydrogenation, though only the dihydro derivative **9** was completely transformed into the desired oxidized A-ring. Suárez cleavage[16,17] of **8** and **9** produced aldehydes **10a** and **10b**, respectively (63% crude yield of **10a** and 55% yield of **10b** after purification). Similar olefin production has been previously noted in the β-fragmentations of alkoxy radicals photolytically generated from hypoiodites, particularly when a tertiary radical is produced, and has been proposed to proceed by oxidation of the radical to the tertiary carbocation with subsequent olefin formation or through an intermediate tertiary iodide followed by in situ HI elimination (Scheme 4).[16,18]

As aldehydes **10a** and **10b** were not robust, slowly decomposing upon standing on the benchtop over the course of a few days, they were immediately protected as the dimethyl acetals **11a** and **11b**, respectively (55% yield over two steps for **11a** from **8** and 91% yield of **11b** from **10b**), with trimethyl orthoformate.[19] Originally, the ethylene glycol acetal was prepared from **10a**; however, subsequent removal of the protecting group to regenerate

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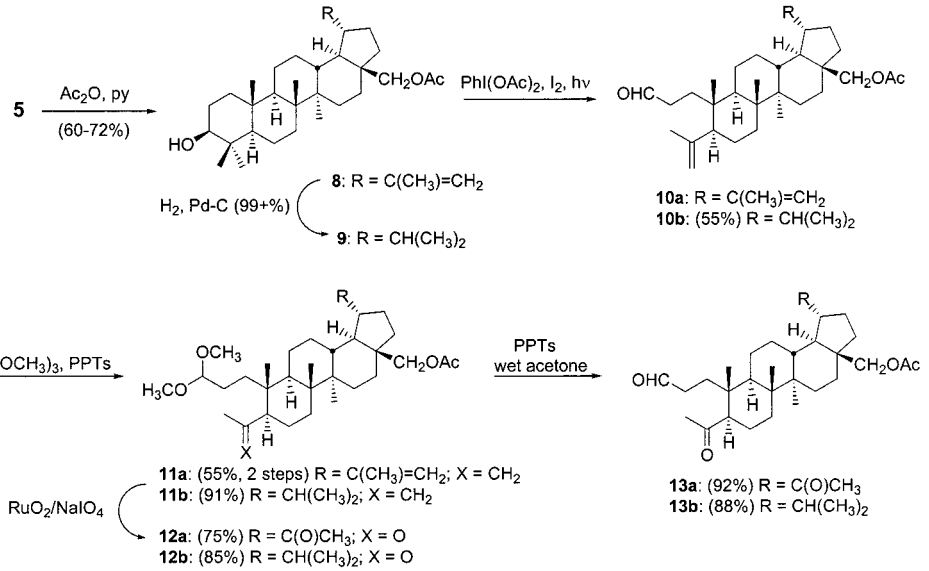
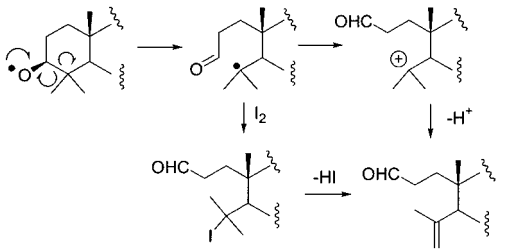
Scheme 3



Scheme 4



the aldehyde proved to be surprisingly troublesome,[20] so the more labile dimethyl acetals were used. Oxidative cleavage of the olefins with stoichiometric $RuO_2/NaIO_4$[21] gave diketone **12a** from **11a** (75%) and monoketone **12b** from **11b** (85%). The use of catalytic $[RuO_4]$[22] resulted in significantly more sluggish reactions and lower yields, while ozonolysis also gave considerably lower yields of **11a** and **11b** contaminated with over-oxidized products. Deprotection of the aldehydes (PPTS/wet acetone) gave keto aldehydes **13a** (92%) and **13b** (88%), respectively, setting the stage for the pinacol coupling to reclose the A-ring with a C-4 methyl group now removed.

Initial efforts attempting to utilize McMurry couplings with **13a** were unsuccessful.[23] Samarium diiodide reductive coupling of **13a** and **13b** in THF in the presence of *tert*-BuOH as a proton source (2 equiv),[24] however, provided the desired diols **14a** (77%) and **14b** (87%), respectively, in good yields, both as mixtures of α- and *β*-oriented cis vicinal diols (α:*β* = 10.7:1 for **14a** and 10:1 for **14b**; Scheme 5, Eq 1). While these diols proved to be extremely difficult to separate by chromatography, the diols of **14a** were ultimately purified, whereas only the major diol of **14b** could be obtained in pure form.

The stereochemistry of the major diol α**14a** was assigned on the basis of extensive NMR experiments. The proton at *δ* 3.52 (br s, $W_{1/2}$ = 6.3 Hz with the corresponding carbon identified in the HMQC spectrum at *δ* 73.8) showed long-range heteronuclear coupling in the HMBC spectrum with C-1 (*δ* 32.3), C-2 (*δ* 21.8), C-4 (*δ* 73.2), and C-5 (*δ* 49.8) and was assigned as H-3. The relatively narrow line width indicated the proton was *β*-oriented since a $W_{1/2}$ of 6.3 Hz indicates an equatorial proton with vicinal couplings ≤ 3 Hz (H-3 has two vicinal partners). The methyl resonance ($^1H/^{13}C$, *δ* 1.09/21.1), which showed long-range heteronuclear coupling with C-3, C-4, and C-5, was assigned to the C-24 methyl group. Another methyl resonance ($^1H/^{13}C$, *δ* 0.77/14.9), which showed long-range heteronuclear coupling with C-1, C-5, and C-10 (*δ* 37.5), must therefore be the C-25 methyl group. Irradiation of this methyl group (C-25) resulted in enhancements of the C-24 methyl signal as well as another methyl singlet (*δ* 0.993), which therefore must be the C-26 methyl group, indicating that the C-24 methyl group lies on the *β*-face and both hydroxyl groups must be in a cis relationship and α-oriented.

The stereochemistry of the minor diol *β***14a** was similarly defined. Thus, the proton resonance at *δ* 3.20 (dd, *J* = 7.9, 7.9 Hz, corresponding carbon at *δ* 75.3 from the HMQC spectrum), which showed long-range heteronuclear couplings in the HMBC spectrum with C-1 (*δ* 37.7), C-2 (*δ* 27.5), and C-4 (*δ* 74.1), was assigned as H-3. The methyl singlet ($^1H/^{13}C$, *δ* 1.21/25.1), which showed long-range heteronuclear couplings with C-3, C-4, and C-5 (*δ* 53.4), was assigned as the C-23 methyl group, while the proton resonance at *δ* 0.73 (dd, *J* = 2.1, 11.9 Hz, 1H), correlating to C-5 in the HMQC spectrum, was assigned as H-5. Nuclear Overhauser enhancements

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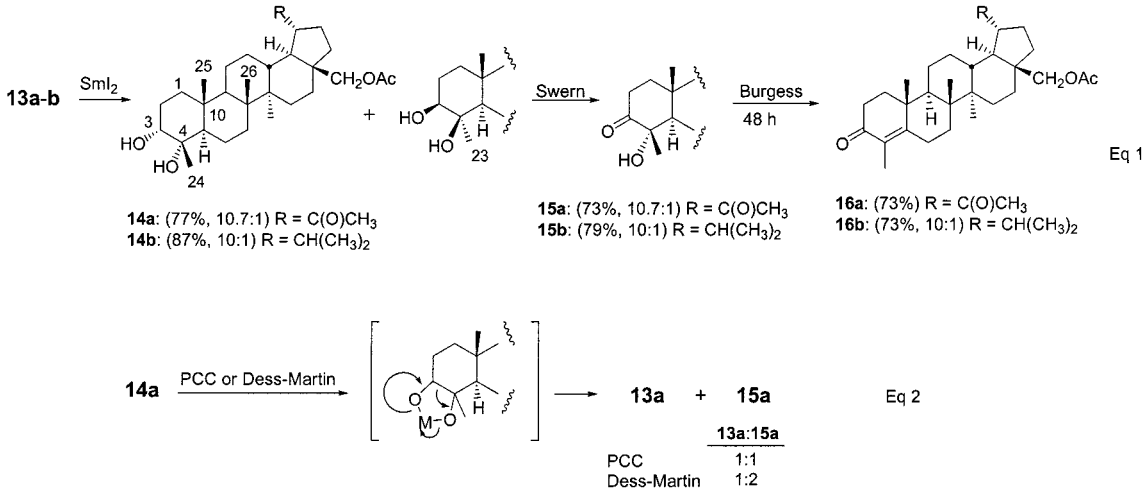
Scheme 5



(NOEs) of H-5 with H-3 and H-23 indicated that these protons were on the α-face of the molecule; thus, the hydroxyl groups are cis and *β*-oriented. Similar experiments established the stereochemistry of the major diastereomer of **14b** as α**14b**.

The exclusive production of cis vicinal diols in the intramolecular pinacol coupling promoted by SmI_2 observed in these reactions parallels results noted by Molander,[24c,d] Hanessian,[25] and others[24f,26] in intramolecular SmI_2-mediated pinacolic cyclizations. Presumably, the stereoselectivity favoring the α-diols **14** results from the greater steric interactions between the samarium ligands of the chelated ketyl[24c,d,27] and the C-25 angular methyl group in the transition state leading to the *β*-diols in comparison to the analogous interactions between the C-24 and C-25 methyl groups in the transition state leading to the α-diols (Figure 1). Since the dienone A-ring of the target lacks stereochemical identity at C-3 and C-4, further transformations of the diols could be accomplished on the mixtures of the diastereomers.

Oxidation of the secondary alcohol to the C-3 ketone was accomplished with the Swern protocol[28] yielding ketones **15a** (73%) and **15b** (79%) from **14a** and **14b**, respectively (Scheme 5, Eq 1). Oxidations employing PCC[29] or the Dess−Martin reagent,[30] both potential chelating oxidants, were also examined with **14a**, but in these cases, significant amounts of diol cleavage accompanied the formation of **15a**, regenerating the diketo aldehyde **13a** (Scheme 5, Eq 2). Subsequent dehydration of **15a** and **15b** with the Burgess reagent,[31] though sluggish, gave the α,*β*-unsaturated ketones **16a** (73%, 48 h) and **16b** (73%, 48 h), respectively. While these dehydrations were performed on the mixtures of α- and *β*-ketols, presumably only the major α-ketols undergo dehydration since the Burgess reagent functions by syn elimination. Thus, the dominant α-diol stereoselectivity in the SmI_2-coupling was critical to the success of this later Burgess elimination.

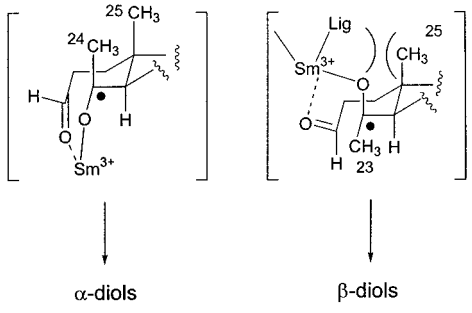


Figure 1. SmI_2-promoted pinacol coupling of ketoaldehydes **13a** and **13b** favoring α-diols due to diaxial interactions between samarium ligands and the C-25 methyl group in the closure leading to *β*-diols.

With the 3-keto-Δ^4-nor-24 A-ring construction complete, all that remained was oxidation of C-2 in the A-ring as well as oxidation of C-28 to the carboxylic acid. Since oxidation of the kinetic enolate was envisioned as a straightforward means to establish the 2-hydroxy-$\Delta^{1,4}$-dien-3-one A-ring from **16b**, and complications were anticipated from the second enolizable ketone at C-20 of **16a** following this strategy, a second model **17c**, easily prepared from betulin (**5**) by hydrogenation (>99%) and a Jones oxidation (62%),[7a] served to optimize the procedures for manipulation of the carboxylic acid during the A-ring oxidation (Scheme 6). Since considerable material was lost during the isolation of **17c** by chromatography, the crude product mixture from the Jones oxidation was converted to the methyl ester **18c** to enable optimal purification. Classic esterification procedures ($MeOH/H^+$, $SOCl_2$/MeOH) failed, presumably due to the hindered tertiary nature of the carboxylic α-position,[7c,32] but simple nucleophilic substitution by the carboxylate anion (MeI/CsF)[33] was successful, providing **18c** in 87% yield.

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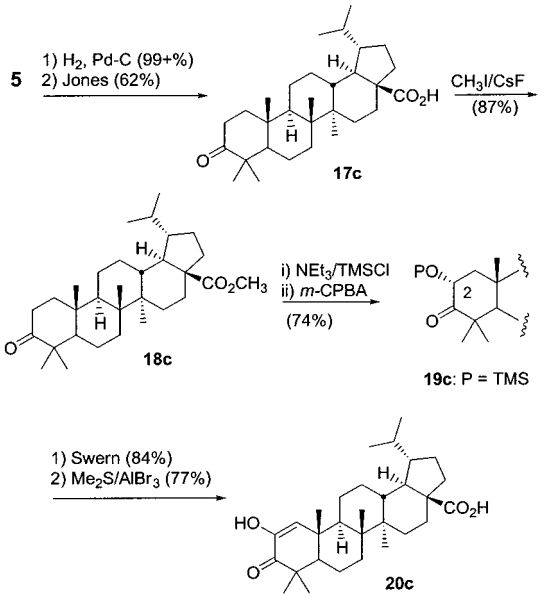
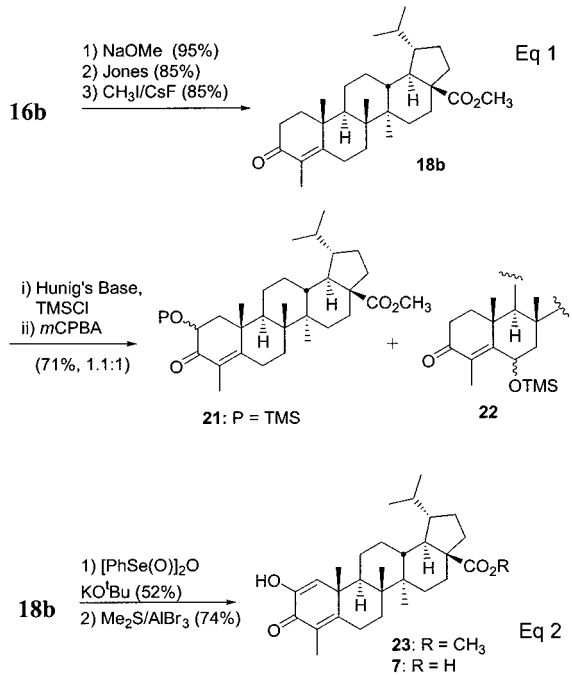
Scheme 6



α-Oxidation of the ketone enolate of **18c** at C-2 was then achieved under modified Rubottom conditons[34] (Et_3N/TMSCl and then *m*-CPBA)[35] to give the silylated α-hydroxyketone **19c** (74%). The large, transdiaxial coupling observed for H-2 (δ 4.55, dd, J = 6.4, 12.4 Hz) indicated that the silyl ether is α-oriented. Other α-oxidation procedures (LDA/TMSCl/*m*-CPBA[34] and KHMDS/3-phenyl-2-(phenylsulfonyl)oxaziridine[36]) were less successful. Swern oxidation of **19c** (84%) and demethylation (Me_2S/$AlBr_3$, 77%)[37] yielded the model **20c**.[38] Other attempts to demethylate the methyl ester by basic hydrolysis (NaOH, LiOH, LiOH/H_2O_2, *tert*-BuOK) all failed, again illustrating the hindered nature of this neopentyl-type carbonyl.[39]

With the model studies completed, methyl ester **18b** was prepared from **16b** following the same protocols employed in the model study with **18c** (Scheme 7): methanolysis gave the primary alcohol (95%) followed by Jones oxidation (85%) and esterification (85%) yielding **18b**. Thus, only the A-ring oxidation of **18b** remained to be undertaken. Originally, it was anticipated that C-2 enolate formation would be favored under kinetic conditions, which would minimize or avoid formation of the thermodynamically favored enolate at C-6.[14c,40] However, treatment of **18b** with a variety of hindered bases at low

Scheme 7



temperatures (HMDS, KHMDS, LDA, Hünig's base, LTMP, and proton sponge) to form the kinetic enolate, followed by oxidation with 2-(phenylsulfonyl)-3-phenyloxaziridine[36,41] or by a TMSCl quench and then *m*-CPBA, invariably produced a mixture of C-2 and C-6 oxidized products. For example, Hünig's base ($^iPr_2NEt$) followed by TMSCl/*m*CPBA gave a 1.1:1 mixture of C-2 and C-6 keto alcohols **21** and **22** in 71% combined yield, each as single diastereomers (Scheme 7, Eq 1). Selective C-2 oxidation was finally achieved with benzeneseleninic anhydride/KO^tBu[42] to produce the desired **23** in 52% yield (with 30% recovered starting material, Scheme 6, Eq 2). The target **7** was completed by the $Me_2S/AlBr_3$ demethylation of the ester (74%) as described in the model studies.

Bioactivity. Both the target compound **7** and model **20c** were submitted to NCI for anticancer screening. Overall, both compounds were slightly less active than betulinic acid as evidenced by the GI_{50}, TGI, and LC_{50} values averaged over all 60 cell lines (see Supporting Information). Notable in the activity of **7**, however, was a GI_{50} of <10 nM against SK-OV-3 ovarian cancer cells (TGI = 363 nM), far exceeding the activity observed with any other cell line. Betulinic acid derivative **20c** with the C-4 *gem*-dimethyl group intact also showed significant activity against all six leukemia cell lines screened (GI_{50} = 2−7 μM).

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Conclusions

A new route to 24-nortriterpene derivatives with oxidized A-rings from triterpene precursors has been demonstrated beginning with betulin to prepare derivatives of betulinic acid. The key steps in the transformation are a Suárez cleavage of the A-ring with a subsequent SmI_2-mediated pinacol-type coupling to reclose the A-ring following removal of the C-24 carbon by oxidative cleavage. Further applications of this chemistry are underway to prepare other derivatives of betulin for anticancer screening.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 93.94 kG (^1H NMR 400 MHz, ^{13}C NMR 100 MHz), 70.50 kG (^1H NMR 300 MHz, ^{13}C NMR 75 MHz), or 63.41 kG (^1H NMR 270 MHz, ^{13}C NMR 67.5 MHz) at ambient temperature in the solvents as indicated. Chemical shifts (in parts per million) are relative to an internal reference using the residual protio solvent for the proton reference and the center line of the solvent multiplet for the carbon reference ($^1H/^{13}C$ ($CDCl_3$) 7.24/77.0, (C_6D_6) 7.16/128.0). Unless otherwise noted, each carbon resonance represents a single carbon (relative intensity); intensities of more than a single carbon were established from integration of spectra acquired under inverse-gated decoupled conditions (delay between transients of 10 s). All O*H* proton assignments were confirmed by D_2O exchange. Only distinctive resonances from the proton spectra of the triterpenoid derivatives are given; in all spectra, considerable overlap of the nonmethyl resonances exists between δ 1.0−2.0. Mass spectra (HRMS) were recorded in either CI (140 eV) or EI (70 eV) mode as noted. Infrared spectra were recorded on NaCl plates; solid samples were prepared by depositing a solution of the sample (typically in $CDCl_3$) on the plate and allowing the solvent to evaporate prior to recording the spectra.

All reaction solvents were dried and distilled immediately prior to use (THF and Et_2O over sodium/benzophenone, CH_2Cl_2 over CaH_2);[43] chromatography solvents were distilled prior to use. Commercially available reagents were used without further purification; all reactions were carried out in oven-dried (105 °C) glassware. Dry ice−acetone baths were used to maintain reactions at −78 °C and dry ice−50% aqueous acetone baths to maintain reactions at −30 °C. Flash chromatography was performed using silica gel 60 (43−60 μm); TLC was performed on silica gel plates, with visualization accomplished by either UV illumination or staining with acidic vanillin solution (2 g of vanillin in 2 mL of concd H_2SO_4 per 100 mL of 95% EtOH).

Betulin (5). The bark of the white birch (*Betula papyrifera*, ~1 kg), collected in Harvard, MA, was cut into small pieces and soaked in acetone with 0.5% MeOH for 2 days. The extraction was filtered and the solvent removed in vacuo to produce a dark yellow solid residue (239 g). A portion of this crude extract (80 g) was dissolved in MeOH/$CHCl_3$ (1:1, 300 mL), and the solution was briefly refluxed and then allowed to stand overnight at room temperature. The crystals that formed were collected to give betulin (**5**, 9 g) that was 95% pure by ^1H NMR[44] and used without further purification.

28-*O*-Acetyl-20(29)-lupen-3-ol (8).[45] The yield of this reaction varied with the scale (60−72%), with highest yields obtained at smaller scales (200 mg of **5**). In a larger-scale reaction, to a solution of betulin (**5**, 4 g, 9.04 mmol), 4-(dimethylamino)pyridine (DMAP, 0.4 g, 1% w/w), and pyridine (6 mL, 25.2 mmol) in CH_2Cl_2 (36 mL) was added acetic anhydride (0.90 mL, 9.53 mmol), and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was washed with 10% aqueous HCl, water, saturated aqueous $NaHCO_3$ solution, and then saturated brine and then dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography of the crude product on silica gel (85:15 hexanes:EtOAc) afforded **8** (2.59 g, 60%) as a white solid, accompanied by 3,28-diacetate[10f] (290 mg, 6%) and recovered betulin (651.9 mg, 16%): mp 217−219 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (s, 3H), 0.79 (s, 3H), 0.93 (s, 3H), 0.94 (s, 3H), 0.99 (s, 3H), 1.64 (s, 3H), 2.04 (s, 3H), 2.41 (ddd, J = 6.0, 11.2, 11.2 Hz, 1H), 3.15 (dd, J = 5.2, 11.6 Hz, 1H), 3.82 (d, J = 11.2 Hz, 1H), 4.21 (dd, J = 1.2, 11.2 Hz, 1H), 4.55 (br s, 1H), 4.65 (d, J = 1.6 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.7, 15.3, 15.95, 16.04, 18.2, 19.0, 20.7, 21.0, 25.1, 27.0, 27.3, 27.9, 29.5, 29.7, 34.1, 34.5, 37.1, 37.5, 38.6, 38.8, 40.8, 42.6, 46.2, 47.6, 48.7, 50.3, 55.2, 62.7, 78.9, 109.8, 150.1, 171.6.

28-*O*-Acetyl-3-lupanol (9). A solution of **8** (2.56 g, 5.48 mmol) in a mixture of THF:MeOH (1:2, v/v, 55 mL) was hydrogenated under H_2 (40 psi) over 10% Pd/C (0.768 g, 30 wt %) with shaking for 22 h and then filtered. Removal of the solvent in vacuo afforded **9**[46] (2.57 g, 99+%) as a white solid. No further purification was necessary: mp 243−245 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.739 (d, J = 6.4 Hz, 3H), 0.741 (s, 3H), 0.81 (s, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.93 (s, 3H), 0.95 (s, 3H), 1.01 (s, 3H), 2.04 (s, 3H), 3.17 (dd, J = 5.2, 11.6 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 4.21 (dd, J = 1.6, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 14.8, 15.4, 16.0 (2C), 18.2, 20.7, 21.0, 21.5, 22.9, 26.9, 26.9, 27.3, 27.9, 29.4, 29.8, 34.2, 34.6, 37.05, 37.08, 38.6, 38.8, 40.8, 42.8, 44.4, 46.4, 48.0, 50.0, 55.2, 62.8, 78.9, 171.6; HRMS (EI, 70 eV) m/z calcd for $C_{32}H_{54}O_3$ 486.4073, found 486.4099 ($[M]^+$, 1.8%).

Suárez Cleavage of 8: *seco*-Dimethylacetal 11a. A solution of **8** (2 g, 4.13 mmol) in dry hexanes (142 mL), containing diacetoxyiodobenzene (DIB, 1.996 g, 6.20 mmol) and I_2 (1.050 g, 4.13 mmol), was irradiated with a 425 W sunlamp for 4 h at 25 °C. The reaction mixture was then poured into saturated aqueous sodium thiosulfate solution (70 mL) and then extracted with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo to give crude **11a**, which was used in the next step without further purification. A small sample of the crude product could be purified by flash chromatography on silica gel (95:5 hexanes:EtOAc) to give a sample of pure **10a** as a colorless oil (R_f = 0.4, 9:1 hexanes:EtOAc) for characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.97 (s, 3H), 1.06 (s, 3H), 1.67 (s, 3H), 1.69 (s, 3H), 2.05 (s, 3H), 2.18−2.28 (m, 1H), 2.36−2.47 (m, 2H), 3.84 (d, J = 11.0 Hz, 1H), 4.23 (dd, J = 1.8, 11.0 Hz, 1H), 4.58 (br s, 1H), 4.59 (d, J = 1.8 Hz, 1H), 4.67 (d, J = 1.8 Hz, 1H), 4.81 (br s, 1H), 9.69 (dd, J = 2.1, 2.1 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 16.0, 19.1, 20.2, 21.1, 21.3, 22.9, 24.4, 25.0, 27.6, 29.5, 29.6, 31.0, 32.6, 34.5, 37.6, 38.2, 39.0, 40.6, 40.8, 43.1, 46.3, 47.6, 48.7, 50.5, 62.7, 110.0, 113.4, 147.6, 150.0, 171.6, 202.9; HRMS (EI, 70 eV) m/z calcd for $C_{32}H_{50}O_3$ 482.3760, found 482.3758 ($[M]^+$, 16%).

Crude **10a** was dissolved in dry MeOH (40 mL), then treated with *p*-TsOH monohydrate (35.6 mg, 0.187 mmol, 4.5 mol %), and trimethyl orthoformate (3.6 mL, 33.0 mmol). The reaction mixture was refluxed for 1 h and then the solvent removed in vacuo. The residue was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (98:2 hexanes:EtOAc) afforded **11a** (1.20 g, 55% for two steps, R_f = 0.42, 9:1 hexanes:EtOAc) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.94 (s, 3H), 1.02 (s, 3H), 1.64 (s, 3H), 1.68 (s, 3H), 2.03 (s, 3H), 2.41 (ddd, J = 5.8, 11.0, 11.0 Hz, 1H), 3.28 (s, 3H), 3.30

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(s, 3H), 3.82 (d, J = 11.0 Hz, 1H), 4.16−4.22 (m, 2H), 4.55 (br s, 1H), 4.61 (d, J = 2.0 Hz, 1H), 4.64 (d, J = 2.0 Hz, 1H), 4.78 (br s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 15.9, 19.0, 20.4, 21.0, 21.3, 23.0, 24.6, 25.0, 26.3, 27.0, 29.5, 29.6, 32.6, 33.9, 34.4, 37.5, 39.0, 40.4, 40.5, 43.0, 46.2, 47.6, 48.6, 50.4, 52.9, 53.6, 62.7, 105.8, 109.8, 112.9, 148.0, 150.0, 171.5; IR (NaCl) 1740 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{34}H_{56}O_4$ 528.4178, found 528.4132 ([M]$^+$, 0.05%).

Suárez Cleavage of 9: *seco*-Aldehyde 10b. Prepared as described above for **10a** from **9** (2 g, 4.11 mmol). Flash chromatography of the crude product on silica gel (98:2 hexanes:EtOAc) gave **10b** (1.10 g, 55%, R_f = 0.48, 9:1 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.83 (s, 3H), 0.93 (s, 3H), 1.05 (s, 3H), 1.67 (s, 3H), 1.91 (dd, 1.8, 12.6 Hz, 1H), 2.02 (s, 3H), 2.18−2.27 (m, 1H), 2.36−2.44 (m, 1H), 3.78 (d, J = 11.0 Hz, 1H), 4.20 (d, J = 11.0 Hz, 1H), 4.58 (s, 1H), 4.79 (s, 1H), 9.68 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.4, 14.8, 16.0, 20.1, 21.0, 21.3, 21.5, 22.8, 22.9, 24.3, 26.6, 26.9, 29.4, 29.7, 30.9, 32.7, 34.6, 37.1, 38.2, 38.9, 40.4, 40.6, 43.2, 44.4, 46.4, 48.0, 50.4, 62.7, 113.4, 147.5, 171.5, 202.6; IR (NaCl) 1738 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{32}H_{52}O_3$ 484.3916, found 484.3933 ([M]$^+$, 10.1%).

***seco*-Dimethylacetal 11b.** A solution of **10b** (1.05 g, 2.17 mmol) in dry MeOH (21.7 mL, 0.1 mM), containing pyridinium *p*-toluenesulfonate (PPTS, 1.26 g, 5.02 mmol) and trimethyl orthoformate (2.37 mL, 21.7 mmol), was stirred for 48 h at room temperature. The solvent was removed in vacuo, and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution (25 mL each). The organic solution was washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (99:1:0.5 hexanes:EtOAc:Et_3N) afforded **11b** (1.05 g, 91%, R_f = 0.52, 9:1 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.4 Hz, 3H), 0.79 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.93 (s, 3H), 1.04 (s, 3H), 1.70 (s, 3H), 1.96 (dd, J = 2.1, 12.9 Hz, 1H), 2.03 (s, 3H), 3.29 (s, 3H), 3.31 (s, 3H), 3.80 (d, J = 10.7 Hz, 1H), 4.18−4.23 (m, 2H), 4.62 (d, J = 1.6 Hz, 1H), 4.79 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 14.8, 16.0, 20.4, 21.0, 21.3, 21.5, 22.8, 23.1, 24.6, 26.2, 26.7, 26.9, 29.3, 29.7, 32.7, 33.9, 34.6, 37.1, 39.0, 40.2, 40.5, 43.2, 44.4, 46.4, 48.0, 50.4, 52.6, 53.6, 62.8, 105.7, 113.0, 148.1, 171.6; IR (NaCl) 1740 cm^{-1}; HRMS (CI, CH_4, 140 eV) m/z calcd for $C_{34}H_{58}O_4$ 530.4335, found 530.4339 ([M]$^+$, 1.1%).

Oxidative Cleavage of 11a: Diketoacetal 12a. To a stirred suspension of ruthenium dioxide hydrate (1.308 g, 7.72 mmol) in CCl_4 (196 mL) was added a solution of sodium metaperiodate (16.83 g, 78.6 mmol) in water (155 mL) at 0 °C. After the mixture was stirred for 1 h at this temperature, the lower yellow layer (RuO_4) was separated and added to a solution of **11a** (1.238 g, 2.34 mmol) in a mixture of CCl_4 (52 mL) and water (32 mL). The mixture was stirred at room temperature for 4 h; then, the water layer was removed, and 2-propanol (5 mL) was added to the reaction mixture. The solution was filtered twice, the second time through Celite. The filtrate was dried (Na_2SO_4) and the solvent removed in vacuo; the crude product was purified by flash chromatography on silica gel (8:2 hexanes:EtOAc) to give **12a** (932 mg, 75%, R_f = 0.10, 8:2 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.98 (s, 3H), 1.05 (s, 3H), 2.05 (s, 3H), 2.13 (s, 3H), 2.15 (s, 3H), 2.42 (dd, J = 2.9, 12.9 Hz, 1H), 2.64 (ddd, J = 5.9, 11.1, 11.1 Hz, 1H), 3.30 (s, 3H), 3.32 (s, 3H), 3.76 (d, J = 12.2 Hz, 1H), 4.17 (d, J = 12.2 Hz, 1H), 4.23 (dd, J = 5.3, 5.3 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.5, 15.8, 19.8, 20.6, 20.9, 21.7, 26.4, 26.9, 27.0, 27.4, 29.1, 29.8, 31.6, 31.7, 34.2, 34.6, 36.3, 38.5, 40.2 (2C), 42.8, 46.2, 49.0, 51.4, 53.0, 53.5, 56.0, 62.3, 105.2, 171.4, 211.5, 212.6; IR (NaCl) 1736, 1708 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{32}H_{52}O_6$ 532.3764, found 532.3776 ([M]$^+$, 0.17%).

Oxidative Cleavage of 11b: Ketoacetal 12b. Prepared as described above for **12a** from **11b** (991.5 mg, 1.87 mmol). The crude product was purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to give **12b** (846 mg, 85%, R_f = 0.19, 9:1 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 0.87 (s, 3H), 0.90 (s, 3H), 1.05 (s, 3H), 2.01 (s, 3H), 2.10 (s, 3H), 2.39 (dd, J = 2.7, 12.9 Hz, 1H), 3.29 (s, 3H), 3.31 (s, 3H), 3.77 (d, J = 11.4 Hz, 1H), 4.19 (d, J = 11.4 Hz, 1H), 4.22 (dd, J = 5.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 14.8, 15.9, 19.9, 20.6, 21.0, 21.5, 21.8, 22.8, 26.5 (2C), 26.9, 29.3, 29.6, 31.5, 31.8, 34.5, 34.6, 37.1, 38.5, 40.0, 40.3, 43.2, 44.3, 46.3, 47.9, 53.0, 53.8, 56.2, 62.6 105.5, 171.5, 212.8; IR (NaCl) 1738, 1707 cm^{-1}; HRMS (CI, CH_4, 140 eV) m/z calcd for $C_{33}H_{56}O_5$ 532.4128, found 532.4082 ([M]$^+$, 0.08%).

Deprotection of 12a: Diketo Aldehyde 13a. A solution of **12a** (260 mg, 0.488 mmol) in wet acetone (50 mL, 10:1 distilled acetone:distilled H_2O), containing pyridinium *p*-toluenesulfonate (PPTS, 365 mg, 1.46 mmol), was refluxed for 1 h. After removing the solvents in vacuo, the residue was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution (25 mL each); then, the organic layer was washed with saturated brine and dried (Na_2SO_4) and the solvent removed in vacuo. Flash chromatography of the crude product on silica gel (8:2 hexanes:EtOAc) gave **13a** (218 mg, 92%, R_f = 0.21, 7:3 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 0.97 (s, 3H), 1.04 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.24 (m, 1H), 2.27 (dd, J = 2.6, 13.2 Hz, 1H), 2.52 (ddd, J = 4.1, 11.7, 16.3 Hz, 1H), 2.62 (ddd, J = 5.9, 11.7, 11.7 Hz, 1H), 3.73 (d, J = 11.1 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.5, 15.8, 19.7, 20.6, 20.9, 21.6, 26.87, 26.93, 27.4, 29.1, 29.9, 31.0, 31.4, 31.6, 34.2, 36.2, 38.0, 38.4, 40.2, 40.4, 42.9, 46.1, 48.8, 51.2, 56.4, 62.2, 171.4, 201.8, 211.5, 212.0; IR (NaCl) 1734, 1710 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{46}O_5$ 486.3345, found 486.3383 ([M]$^+$, 1.8%).

Deprotection of 12b: Keto Aldehyde 13b. Prepared as described above for **13a** from **12b** (820 mg, 1.54 mmol). Flash column chromatography of the crude product on silica gel (85:15 hexanes:EtOAc) gave **13b** (660 mg, 88%, R_f = 0.3, 8:2 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 1.09 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.28 (m, 2H), 2.56 (dddd, J = 1.2, 4.5, 11.8, 15.0 Hz, 1H), 3.79 (d, J = 11.1 Hz, 1H), 4.22 (dd, J = 1.5, 11.1 Hz, 1H), 9.74 (dd, J = 1.5, 2.1 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.4, 14.8, 16.0, 19.8, 20.6, 21.0, 21.5, 21.7, 22.8, 26.5, 26.9, 29.4, 29.7, 30.9, 31.5, 31.8, 34.6, 37.0, 38.2, 38.5, 40.3, 40.4, 43.3, 44.4, 46.4, 47.9, 56.7, 62.6, 171.6, 202.3, 212.3; IR (NaCl) 1737 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{31}H_{56}O_4$ 486.3709, found 486.3717 ([M]$^+$, 6.8%).

28-*O*-Acetyl-3α,4α-dihydroxy-24-norlupan-20-one (α14a) and 28-*O*-Acetyl-3β,4β-dihydroxy-24-norlupan-20-one (β14a). A solution of 1,2-diiodoethane (668 mg, 2.37 mmol) in anhydrous THF (24 mL) was added to samarium (427 mg, 2.84 mmol) under argon. The reaction mixture was stirred at room temperature for 1 h, and to the resulting deep blue solution was added a mixture of **13a** (288 mg, 0.59 mmol) and *t*-BuOH (113 μL, 1.18 mmol) in anhydrous THF (16 mL) over a period of 1 h. The mixture was stirred overnight at room temperature, and then saturated aqueous $NaHCO_3$ solution (15 mL) was added. The organic layer was separated; the aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic extracts were washed with saturated aqueous sodium thiosulfate solution and saturated brine and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the crude product on silica gel (7:3 hexanes:EtOAc) afforded pure **α14a** (203 mg, 70.4%, R_f = 0.25, 6:4 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (s, 3H), 0.987 (s, 3H), 0.993 (s, 3H), 1.08 (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 2.40 (br s, OH), 2.63 (ddd, J = 5.9, 11.7, 11.7 Hz, 1H), 3.52 (br s, 1H), 3.76 (d, J = 11.1 Hz, 1H), 4.17 (d, J = 11.1 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.7, 14.9, 15.9, 17.2, 20.8, 21.0, 21.9, 25.3, 26.8, 27.2, 27.5, 29.3, 29.7, 32.3, 33.4, 34.4, 36.4, 37.5, 40.9, 42.6, 46.3, 49.3, 49.7, 49.9, 51.6, 62.5, 73.2, 73.8, 171.6, 211.8; IR (NaCl) 3454, 1736, 1712 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{48}O_{45}$488.3502, found 488.3535 ([M]$^+$, 13.3%); and **β14a** (19 mg, 6.6%, R_f = 0.28, 6:4 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (dd, J = 2.1, 11.9 Hz, 1H), 0.84 (m, 1H), 0.91 (s, 3H), 0.95 (s, 3H), 1.02

(s, 3H), 1.20 (s, 3H), 2.04 (s, 3H), 2.13 (s, 3H), 2.63 (ddd, J = 5.8, 11.3, 11.3 Hz, 1H), 3.20 (br dd, J = 7.9, 7.9 Hz, 1H), 3.74 (d, J = 11.2 Hz, 1H), 4.17 (dd, J = 1.2, 11.2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 15.3, 16.2, 17.7, 20.6, 21.0, 25.1, 26.9 (2C), 27.2, 27.5, 29.3, 29.9, 33.8, 34.4, 36.3, 36.8, 37.7, 40.6, 42.6, 46.3, 49.2, 49.3, 51.5, 53.4, 62.5, 74.1, 75.3, 171.5, 211.8; IR (NaCl) 3481, 1734, 1716 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{48}O_{45}$ 488.3502, found 488.3511 ([M]$^+$, 19.1%).

28-*O*-Acetyl-24-norlupane-3α,4α-diol (α14b) and 28-*O*-Acetyl-24-norlupane-3β,4β-diol (β14b). Prepared as described above for α**14a** and β**14a** from **13b** (0.643 g, 1.32 mmol). Flash chromatography of the crude product on silica gel (8:2 hexanes:EtOAc) afforded pure α**14b** (143 mg) and a mixture of α**14b** and β**14b** (417 mg, combined yield 87%, 10.7:1, R_f = 0.15, 8:2 hexanes:EtOAc) as a colorless oil. **28-*O*-Acetyl-24-norlupane-3α,4α-diol (α14b)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 7.0 Hz, 3H), 0.78 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.94 (s, 3H), 1.02 (s, 3H), 1.10 (s, 3H), 1.97 (s, OH), 2.04 (s, 3H), 2.43 (s, OH), 3.53 (br d, J = 2.7 Hz, 1H), 3.80 (d, J = 10.5 Hz, 1H), 4.21 (d, J = 10.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 14.86, 14.90, 16.0, 17.3, 20.9, 21.1, 21.6, 22.0, 22.9, 25.3, 26.77, 26.83, 29.4, 29.8, 32.4, 33.5, 34.6, 37.1, 37.5, 41.1, 43.0, 44.5, 46.4, 48.0, 49.6, 49.8, 62.8, 73.3, 73.9, 171.1; IR (NaCl) 3435, 1741 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{31}H_{52}O_4$ 488.3865, found 488.3884 ([M]$^+$, 22.9%).

28-*O*-Acetyl-4α-hydroxy-24-norlupane-3,20-dione (15a). To a stirred solution of oxalyl chloride (49.1 μL, 0.56 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of DMSO (80.6 μL, 1.13 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, and then a solution of α**14a** (106 mg, 0.217 mmol) in CH_2Cl_2 (2.5 mL) was added and stirring continued for an additional 45 min. Triethylamine (300 μL, 2.15 mmol) was added with subsequent stirring for 15 min, and then the reaction mixture was allowed to warm to room temperature. Water (3 mL) was added; the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the crude product on silica gel (7:3 hexanes:EtOAc) gave **15a** (77 mg, 73%, R_f = 0.30, 7:3 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.04 (s, 6H), 1.23 (s, 3H), 2.06 (s, 3H), 2.14 (s, 3H), 2.34 (ddd, J = 2.4, 4.0, 14.6 Hz, 1H), 2.64 (ddd, J = 5.8, 11.6, 11.6 Hz, 1H), 2.67 (ddd, J = 6.1, 14.3, 14.6 Hz, 1H), 3.76 (d, J = 11.3 Hz, 1H), 3.90 (s, OH), 4.17 (d, J = 11.3 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 14.8, 15.9, 18.1, 21.0, 21.2, 22.0, 26.9, 27.1, 27.4, 29.3, 29.7, 33.2, 33.6, 34.4, 36.4, 37.1, 40.9, 41.0, 42.6, 46.2, 49.2, 49.7, 51.6, 58.8, 62.4, 76.8, 171.6, 211.6, 215.4; IR (NaCl) 3427, 1738, 1712 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{46}O_5$ 486.3345, found 486.3343 ([M]$^+$, 8.2%).

28-*O*-Acetyl-4α-hydroxy-24-norlupan-3-one (15b). Prepared as described above for **15a** from α**14b** (172 mg, 0.352 mmol). Flash chromatography of the crude product on silica gel (9:1 hexanes:EtOAc) gave **15b** (135 mg, 79%, R_f = 0.67, 8:2 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.24 (s, 3H), 2.04 (s, 3H), 2.34 (ddd, J = 2.7, 4.3, 14.5 Hz, 1H), 2.69 (ddd, J = 6.4, 14.5, 14.5 Hz, 1H), 3.80 (d, J = 11.3 Hz, 1H), 3.90 (s, OH), 4.21 (d, J = 11.3 Hz, 1H). Due to ^{13}C NMR signal overlap in $CDCl_3$, spectra were also run in C_6D_6: ^{1}H NMR (400 MHz, C_6D_6) δ 0.70 (s, 3H), 0.76 (s, 3H), 0.77 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H), 0.89 (s, 3H), 1.08 (s, 3H), 1.73 (s, 3H), 1.94 (m, 3H), 2.12 (ddd, J = 2.7, 4.3, 14.5 Hz, 1H), 2.22 (ddd, J = 5.9, 14.5, 14.5 Hz, 1H), 3.92 (d, J = 11.3 Hz, 1H), 4.19 (s, OH), 4.44 (dd, J = 1.6, 11.3 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 15.0, 15.1, 15.4, 16.3, 18.6, 20.9, 21.6, 22.3, 22.6, 23.4, 27.3, 27.6, 30.2, 30.6, 34.0, 34.1, 35.5, 37.4, 37.6, 41.4, 41.5, 43.4, 45.1, 47.2, 48.8, 50.0, 59.4, 63.0, 77.5, 171.0, 214.8; IR (NaCl) 3492, 1733, 1714 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{31}H_{50}O_4$ 486.3709, found 486.3663 ([M]$^+$, 1.1%).

28-*O*-Acetyl-24-norlup-4-en-3,20-dione (16a). To a solution of the mixture of epimers of **15a** (10.7:1, α:β-OH, 41 mg, 0.084 mmol) in benzene (5 mL) was added freshly recrystallized methyl (carboxysulfamoyl)triethylammonium hydroxide inner salt[47] (Burgess' reagent, 100 mg, 0.42 mmol). The reaction mixture was refluxed for 46 h, and then the reaction was quenched by adding water (3 mL). The aqueous layer was extracted with EtOAc (3 × 3 mL); the combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (75:25 hexanes:EtOAc) gave **16a** (37 mg, 73%, R_f = 0.35, 7:3 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.08 (s, 3H), 1.19 (s, 3H), 1.75 (s, 3H), 2.06 (s, 3H), 2.14 (s, 3H), 2.30 (ddd, J = 2.9, 5.0, 17.1 Hz, 1H), 2.40 (ddd, J = 5.3, 15.2, 17.1 Hz, 1H), 2.62 (ddd, J = 3.5, 3.5, 14.6 Hz, 1H), 2.66 (ddd, J = 5.9, 11.7, 11.7 Hz, 1H), 3.76 (d, J = 11.1 Hz, 1H), 4.21 (dd, J = 1.2, 11.1 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.0, 14.4, 15.4, 18.1, 21.0, 21.5, 24.5, 26.9, 27.3, 27.4, 29.1, 29.8, 32.5, 33.2, 34.3, 36.4, 36.5, 39.3, 40.3, 42.8, 46.3, 48.8, 49.1, 51.4, 62.4, 128.1, 164.1, 171.5, 198.8, 211.5; IR (NaCl) 1736, 1715, 1664 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{44}O_4$ 468.3239, found 468.3215 ([M]$^+$, 3.6%).

28-*O*-Acetyl-24-norlup-4-en-3-one (16b). Prepared as described above for **15a** from a mixture of **15b** C-4 epimers (147 mg, 0.302 mmol). Flash chromatography of the crude product on silica gel (93:7 hexanes:EtOAc) gave **16b** (102 mg, 73%, R_f = 0.59, 8:2 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.89 (s, 3H), 1.10 (s, 3H), 1.22 (s, 3H), 1.76 (s, 3H), 2.04 (s, 3H), 2.24 (ddd, J = 6.4, 15.0, 15.0 Hz, 1H), 2.30 (ddd, J = 2.7, 4.8, 17.0 Hz, 1H), 2.42 (ddd, J = 5.4, 14.9, 17.0 Hz, 1H), 2.60 (ddd, J = 3.2, 3.2, 15.0 Hz, 1H), 3.80 (d, J = 11.3 Hz, 1H), 4.24 (dd, J = 1.6, 11.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 14.3, 14.8, 15.6, 18.1, 21.0, 21.51, 21.54, 22.9, 24.6, 26.84, 26.86, 29.4, 29.6, 32.8, 33.3, 34.6, 36.5, 37.3, 39.3, 40.5, 43.1, 44.4, 46.5, 47.8, 49.0, 62.7, 128.0, 164.4, 171.7, 198.9; IR (NaCl) 1739, 1668 cm^{-1}; HRMS (EI, 70 eV) m/z calcd for $C_{31}H_{48}O_3$ 468.3603, found 468.3581 ([M]$^+$, 100%).

3-Oxo-28-lupanoic Acid (17c). A solution of betulin (**5**, 3.46 g, 7.82 mmol) in a mixture of THF and methanol (1:2, v/v, 156 mL) was hydrogenated under 40 psi of H_2 over 10% Pd/C (1.04 g, 30 wt %) overnight and then filtered. Removal of the solvent in vacuo afforded lupane-3β,28-diol[10f] as a white solid (3.48 g, 100%). No further purification was necessary: mp 276−278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.4 Hz, 3H), 0.74 (s, 3H), 0.81 (s, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 1.00 (s, 3H), 3.18 (dd, J = 5.4, 11.3 Hz, 1H), 3.28 (d, J = 10.7 Hz, 1H), 3.75 (dd, J = 1.1, 10.7 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.6, 14.9, 15.4, 15.9, 16.0, 18.3, 20.8, 21.7, 22.9, 26.8 (2C), 27.3, 28.0, 29.3, 29.5, 34.0, 34.2, 36.8, 37.1, 38.6, 38.8, 40.9, 42.8, 44.5, 47.9, 48.0, 50.0, 55.2, 60.6, 79.0; HRMS (EI, 70 eV) m/z calcd for $C_{30}H_{52}O_2$ 444.3967, found 444.3953 ([M]$^+$, 8.1%).

To a solution of lupane-3β,28-diol (1.0 g, 2.25 mmol) in acetone (100 mL) was added freshly prepared Jones' reagent[48] dropwise at 0 °C until the color remained orange (2.2 mL). The solution was stirred for 1.5 h at 0 °C, and the reaction was quenched with 2-propanol (5 mL); the mixture was stirred for 5 min, and then H_2O (30 mL) was added. The organic solvent was removed in vacuo, and the aqueous residue was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water and saturated brine and then dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography on silica gel (85:15 hexanes:EtOAc) afforded **17**[49] (635 mg, 62%, R_f = 0.55, 8:2 hexanes:EtOAc) as a white solid: mp 244 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.90 (s, 3H), 0.93 (s,

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(48) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39−45.

(49) Previous preparations of **17c** did not report spectroscopic data: (a) Ruzicka, L.; Frame, G. F.; Leicester, H. M.; Liguori, M.; Brüngger, H. *Helv. Chim. Acta* **1934**, *17*, 426−442. (b) Ruzicka, L.; Brüngger, H.; Gustus, E. L. *Helv. Chim. Acta* **1932**, *15*, 634−648. Also, see ref 38. For partial data, see refs 9d and 11d.

3H), 0.94 (s, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 2.118−2.23 (m, 3H), 2.34−2.52 (m, 2H), 11.4 (br s, OH); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.5, 14.6, 15.8, 15.9, 19.6, 21.0, 21.4, 22.7, 23.0, 26.6, 26.8, 29.65, 29.71, 32.0, 33.6, 34.1, 36.8, 37.4, 38.3, 39.5, 40.6, 42.6, 44.1, 47.3, 48.6, 49.6, 54.8, 56.8, 182.9, 218.2.

Methyl 3-Oxo-28-lupanoate (18c). To a solution of **17c** (179 mg, 0.406 mmol) in DMF (4 mL), containing cesium fluoride (92.6 mg, 0.610 mmol), was added methyl iodide (40 μL, 0.610 mmol). The reaction mixture was stirred at room temperature for 24 h; the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (93:7 hexanes:EtOAc) gave **18**[50] (156 mg, 87%, R_f = 0.28, 9:1 hexanes:EtOAc) as a white solid: mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 1.05 (s, 1H), 1.67 (m, 1H), 1.74−1.81 (m, 2H), 1.90 (ddd, J = 4.3, 7.5, 12.4 Hz, 1H), 2.18−2.26 (m, 3H), 2.38 (ddd, J = 4.3, 7.5, 15.6 Hz, 1H), 2.48 (ddd, J = 7.5, 10.2, 15.6 Hz, 1H), 3.63 (s, 3H).

Methyl 2-*O*-Trimethylsilyl-3-oxo-28-lupanoate (19c). To a solution of **18c** (183 mg, 0.389 mmol) in CH_2Cl_2 (8 mL) at −78 °C under argon was added with stirring triethylamine (0.54 mL, 3.87 mmol) followed by trimethylsilyl trifluoromethanesulfonate (0.352 mL, 1.95 mmol). After 1 h at −78 °C, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with hexanes (3 × 3 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude silyl enol ether (assumed to be 0.389 mmol) was dissolved in CH_2Cl_2 (8 mL) at 0 °C, and a precooled solution of *m*-chloroperoxybenzoic acid (*m*-CPBA, 107 mg, 0.434 mmol) in CH_2Cl_2 (10 mL) was added. The solution was stirred for 2 h; the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (97:3 hexanes:EtOAc) gave **19c** (156 mg, 74%, R_f = 0.52, 9:1 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.1 (s, 9H), 0.71 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.88 (s, 3H), 0.92 (s, 3H), 1.02 (s, 3H), 1.07 (s, 3H), 1.12 (s, 3H), 1.66 (m, 1H), 1.72−1.79 (m, 2H), 2.15−2.24 (m, 4H), 3.62 (s, 3H), 4.55 (dd, J = 6.4, 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.26 (3C), 14.5, 14.7, 16.1, 16.8, 19.1, 21.2, 21.6, 22.7, 23.0, 25.1, 26.7, 29.6, 29.7, 32.0, 34.1, 37.2, 38.0 (2C), 40.7, 42.6, 44.2, 48.3, 48.9, 50.0, 50.5, 51.2, 56.86, 56.93, 70.9, 176.8, 214.1; IR (NaCl) 1723 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{34}H_{58}SiO_4$ 558.4104, found 558.4076 ([M]$^+$, 5.4%).

2-Hydroxy-3-oxo-1-lupen-28-oic Acid (20c). To a stirred solution of oxalyl chloride (40.6 μL, 0.466 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of dry DMSO (66 μL, 0.93 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, and a solution of **19c** (100 mg, 0.179 mmol) in CH_2Cl_2 (3 mL) was added; stirring was continued for an additional 45 min. Triethylamine (249 μL, 1.79 mmol) was added, and the reaction mixture was stirred for 15 min and then allowed to warm to room temperature. Water (3 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were washed with saturated brine and dried (Na_2SO_4). Evaporation of the solvent in vacuo and flash chromatography of the crude product on silica gel (9:1 hexanes:EtOAc) gave methyl 2-hydroxy-3-oxo-1-lupen-28-oate[51] (73 mg, 84%, R_f = 0.38, 9:1 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 0.95 (s, 3H), 1.08 (s, 3H), 1.10 (s, 3H), 1.18 (s, 3H), 2.4−2.6 (m, 3H), 3.63 (s, 3H), 5.88 (s, 1H), 6.43 (s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 14.7, 16.5, 18.8, 20.2, 21.2, 21.6, 22.8, 23.0, 26.8, 27.2, 29.6, 29.8, 32.1, 34.1, 37.4, 38.3, 38.7, 41.6, 42.9, 44.0, 44.2, 45.6, 48.9, 51.2, 54.1, 57.0, 128.8, 144.0, 176.8, 201.3; IR (NaCl) 3450, 1728, 1669 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{31}H_{48}O_4$ 484.3552, found 484.3563 ([M]$^+$, 15%).

To a stirred solution of aluminum bromide (63.3 mg, 0.237 mmol) in dimethyl sulfide (1 mL) was added a solution of methyl 2-hydroxy-3-oxo-1-lupen-28-oate (23 mg, 0.0474 mmol) in dimethyl sulfide (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h, and the reaction was quenched with water (2 mL); then, the mixture was extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:EtOAc), affording **20c** (17.2 mg, 77%, R_f = 0.40, 8:2 hexanes:EtOAC) as a white solid: mp 242 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.93 (s, 3H), 0.98 (s, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.18 (s, 3H), 1.88 (dd, J = 7.7, 12.3 Hz, 1H), 2.19−2.29 (m, 3H), 5.90 (s, 1H), 6.44 (s, OH), 10.47 (bs, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.6, 16.5, 18.7, 20.1, 21.2, 21.6, 22.7, 22.9, 26.7, 27.1, 29.6, 29.7, 32.0, 34.1, 37.4, 38.4, 38.6, 41.6, 42.9, 44.0, 44.1, 45.5, 48.7, 54.0, 56.8, 128.7, 143.9, 181.2, 201.1; IR (NaCl) 3450, 1694, 1669 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{30}H_{46}O_4$ 470.3396, found 470.3368 ([M]$^+$, 6.1%).

Methyl 3-Oxo-24-norlup-4-en-28-oate (18b). A solution of **16b** (253 mg, 0.542 mmol) in a mixture of MeOH and THF (1:1, v/v, 11 mL), containing NaOMe (87.8 mg, 1.63 mmol), was refluxed for 3 h. After the solvents were removed in vacuo, the residue was partitioned between Et_2O and water (20 mL each); the organic layer was washed with saturated brine and dried (Na_2SO_4) and the solvent removed in vacuo. Flash chromatography of the crude product on silica gel (85:15 hexanes:EtOAc) gave 28-hydroxy-24-norlup-4-en-3-one (220 mg, 95%, R_f = 0.2, 8:2 hexanes:EtOAc) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.90 (s, 3H), 1.11 (s, 3H), 1.21 (s, 3H), 1.76 (d, J = 1.1 Hz, 3H), 1.89 (ddd, J = 2.2, 4.8, 13.4 Hz, 1H), 1.97 (ddd, J = 2.7, 4.8, 12.9 Hz, 1H), 2.22 (ddd, J = 5.9, 12.4, 14.5 Hz, 1H), 2.31 (ddd, J = 2.7, 4.8, 17.1 Hz, 1H), 2.43 (ddd, J = 4.8, 14.9, 17.1 Hz, 1H), 2.61 (ddd, J = 3.8, 3.8, 14.5 Hz, 1H), 3.32 (d, J = 10.7 Hz, 1H), 3.77 (d, J = 10.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 14.3, 14.8, 15.5, 18.1, 21.6, 21.7, 22.9, 24.6, 26.8, 26.9, 29.1, 29.4, 32.8, 33.3, 34.0, 36.5, 36.9, 39.3, 40.5, 43.1, 44.4, 47.8, 47.9, 49.1, 60.5, 128.0, 164.5, 199.0; IR (NaCl) 3444, 1666 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{29}H_{46}O_2$ 426.3498, found 426.3493 ([M]$^+$, 14.3%).

To a solution of 28-hydroxy-24-norlup-4-en-3-one (220 mg, 0.516 mmol) in acetone (15 mL) was added freshly prepared Jones' reagent[48] dropwise until the color remained orange (0.5 mL) at 0 °C. The solution was stirred for 1.5 h at 0 °C. The reaction was quenched with 2-propanol (1 mL), and the mixture was stirred for an additional 5 min; H_2O (5 mL) was added. The organic solvent was removed in vacuo, and the aqueous residue was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water and then saturated brine and dried (Na_2SO_4). Removal of the solvent in vacuo and flash chromatography of the crude product on silica gel (85:15 hexanes:EtOAc) afforded 3-oxo-24-norlup-4-en-28-oic acid (194 mg, 85%, R_f = 0.24, 8:2 hexanes:EtOAc) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.91 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.76 (s, 3H), 1.89 (dd, J = 7.2, 12.3 Hz, 1H), 1.99 (ddd, J = 2.6, 5.1, 13.2 Hz, 1H), 2.16−2.38 (m, 5H), 2.43 (ddd, J = 5.1, 14.6, 14.6 Hz, 1H), 2.61 (ddd, J = 3.7, 3.7, 14.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 14.3, 14.6, 15.5, 18.2, 21.7, 22.7, 22.9, 24.6, 27.0, 29.7 (2C), 31.9, 33.0, 33.3, 36.6, 37.4, 38.4, 39.4, 40.4, 42.9, 44.1, 48.5, 49.4, 56.9, 128.1,

(50) Previous preparations of **18c** did not report spectroscopic data: (a) Ruzicka, L.; Brenner, M.; Rey, E. *Helv. Chim. Acta* **1941**, *24*, 515−529. (b) Mahato, S. B.; Banerjee, S. K.; Chakravarti, R. N. *Tetrahedon* **1971**, *27*, 177−186.

(51) Previous preparations of methyl 3-hydroxy-4-oxo-1-lupen-28-oate did not report any characterizing data: (a) Pradhan, B. P.; Ghosh, P. *Indian J. Chem., Sect. B* **1993**, *32B*, 590−591. (b) Pradhan, B. P.; Ghosh, P. *Indian J. Chem., Sect. B* **1993**, *32B*, 920−923.

164.3, 181.3, 198.9; IR (NaCl) 1694, 1667 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{29}H_{44}O_3$ 440.3290, found 440.3283 ($[M]^+$, 61.4%).

To a solution of 3-oxo-24-norlup-4-en-28-oic acid (179 mg, 0.406 mmol) in DMF (4 mL), containing cesium fluoride (92.6 mg, 0.610 mmol), was added methyl iodide (40 μL, 0.610 mmol). The reaction mixture was stirred at room temperature for 24 h; the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (93:7 hexanes:EtOAc) gave **18b** (156 mg, 85%, R_f = 0.28, 9:1 hexanes:EtOAc) as a white solid: mp 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.87 (s, 3H), 1.07 (s, 3H), 1.08 (s, 3H), 1.74 (s, 3H), 1.96 (ddd, J = 2.9, 5.4, 13.2 Hz, 1H), 2.14−2.24 (m, 5H), 2.41 (ddd, J = 4.9, 15.1, 17.0 Hz, 1H), 2.58 (ddd, J = 3.4, 3.4, 14.6 Hz, 1H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 14.3, 14.6, 15.5, 18.1, 21.7, 22.7, 22.9, 24.6, 27.0, 29.66, 29.70, 31.9, 32.9, 33.3, 36.6, 37.2, 38.2, 39.3, 40.3, 42.8, 44.1, 48.7, 49.4, 51.1, 57.0, 128.0, 164.4, 176.7, 198.8; IR (NaCl) 1727, 1667 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{30}H_{46}O_3$ 454.3447, found 454.3433 ($[M]^+$, 94.2%).

Methyl 2-Hydroxy-3-oxo-24-norlup-1,4-dien-28-oate (23). A solution of **18b** (15 mg, 0.033 mmol) in THF (2.2 mL) at −78 °C was treated with *tert*-BuOK (0.24 M solution in THF, 0.55 mL, 0.132 mmol), and the mixture was then placed in a −20 °C bath. After 45 min, the mixture was allowed to briefly warm to 0 °C, and then transferred via cannula to a solution of $(PhSeO)_2O$ (95.8 mg, 0.265 mmol) in THF (2.2 mL) also at 0 °C. After 45 min, the mixture was diluted with EtOAc (20 mL) and poured into saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was washed with saturated aqueous sodium thiosulfate solution and then saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (85:15 hexanes:Et_2O), affording **23** (8 mg, 52%, 74% based on 70% conversion, R_f = 0.34, 8:2 hexanes:Et_2O) as a white solid, along with recovered **18b** (4.5 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J = 6.4 Hz, 3H), 0.78 (s, 3H), 0.84 (d, J = 7.0 Hz, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.97 (s, 3H), 2.2−2.4 (m, 4H), 2.70 (ddd, J = 3.2, 3.2, 13.4 Hz, 1H), 3.65 (s, 3H), 6.34 (s, 1H,), 6.36 (s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 14.2, 14.6, 16.1, 21.4, 22.8, 22.9, 23.5, 25.3, 26.8, 29.7, 29.9, 32.0, 36.0, 37.2, 38.3, 41.1, 43.4, 44.0, 44.2, 48.0, 48.7, 51.2, 57.0, 125.3, 125.9, 144.4, 167.2, 176.8, 181.4; IR (NaCl) 3400, 1726, 1625 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{30}H_{44}O_4$ 468.3239, found 468.3239 ($[M]^+$, 3.9%).

2-Hydroxy-3-oxo-24-norlupa-1,4-dien-28-oic Acid (7). To a stirred solution of aluminum bromide (23.9 mg, 0.0897 mmol) in dimethyl sulfide (1 mL) was added a solution of **23** (8.4 mg, 0.0179 mmol) also in dimethyl sulfide (1 mL). The reaction mixture was stirred at room temperature for 24 h; the reaction was quenched with water (2 mL), and then the mixture was extracted with EtOAc (3 × 3 mL). The organic layer was washed with saturated brine and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (8:2 hexanes:EtOAc) to afford **7** (6 mg, 74%, R_f = 0.19, 8:2 hexanes:EtOAC) as a white solid: mp 286 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 6.7 Hz, 3H), 0.80 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H), 1.17 (s, 3H), 1.19 (s, 3H), 1.90 (dd, J = 7.5, 12.4 Hz, 1H), 1.97 (s, 3H), 2.2−2.4 (m, 4H), 2.71 (ddd, J = 3.4, 3.4, 13.4 Hz, 1H), 6.34 (s, 1H), 6.40 (br s, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 14.1, 14.6, 16.1, 21.4, 22.7, 22.9, 23.4, 25.2, 26.7, 29.6, 29.9, 31.9, 35.9, 37.3, 38.4, 41.1, 43.4, 44.0 (2C), 47.8, 48.4, 56.7, 125.4, 126.0, 144.4, 167.0, 180.8, 181.3; IR (NaCl) 3360, 1696, 1625 cm^{-1}; HRMS (EI, 70 eV) *m*/*z* calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3106 ($[M]^+$, 8.4%).

Supporting Information Available: ^{1}H NMR of all compounds and ^{13}C NMR spectra of all compounds except the known **18c**; NOE spectra for α**14a**, β**14a**, and α**14b**; and bioactivity data from NCI for **7** and **20c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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