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Total Synthesis of (+)-*seco*-C-Oleanane via Stepwise Controlled Radical Cascade Cyclization

Victoriano Domingo,[†] Jesús F. Arteaga,[‡] José Luis López Pérez,[§] Rafael Peláez,[§] José F. Quílez del Moral,*[,†] and Alejandro F. Barrero*[,†]

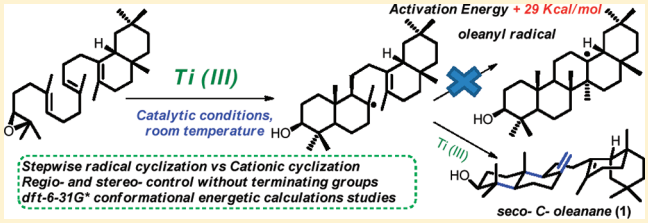
[†]Department of Organic Chemistry, Institute of Biotechnology, University of Granada, Avda. Fuentenueva, 18071 Granada, Spain

[‡]Department of Chemical Engineering, Physical Chemistry and Organic Chemistry, University of Huelva, Campus el Carmen, 21071 Huelva, Spain

[§]Department of Pharmaceutical Chemistry, University of Salamanca, Campus M. Unamuno, 37007 Salamanca, Spain

Supporting Information

ABSTRACT: An asymmetric concise total synthesis of the (+)-*seco*-C-oleanane **1** was accomplished. The successful route to this natural product involves as the key step a stepwise regio- and stereocontrolled catalytic radical polyene cascade cyclization from preoleanatetraene oxide (**16**), a process mediated by Cp_2TiCl. The use of this single-electron-transfer complex permits mild cyclization conditions without using unnecessary prefunctionalizations and stops the process at the bicyclic level. Theoretical data revealed high activation energy for the third ring closure, which would account for the control of the cyclization. This process also led to natural (−)-achilleol B, camelliol A, and (+)-*seco*-β-amyrin as minor compounds.



INTRODUCTION

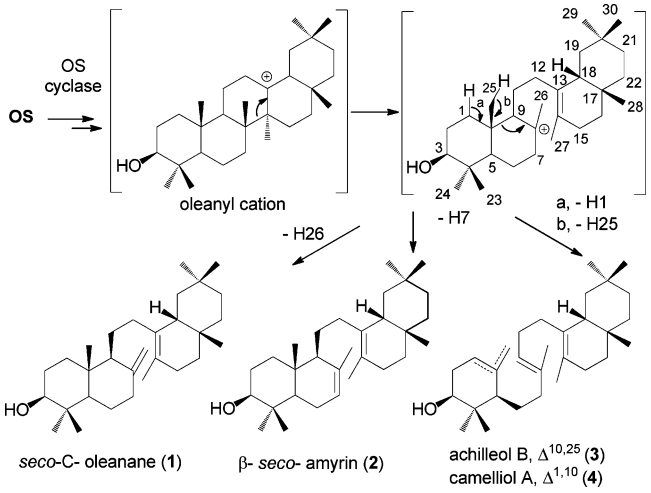
The biosynthesis of β-amyrin, in which 2,3-oxidosqualene (OS) possessing one stereogenic center is transformed into a pentacyclic triterpene containing eight stereogenic centers, constitutes one of the most impressive examples of efficiency in biosynthesis. Over the last 20 years, remarkable progress has been achieved in the understanding of the fascinating mechanism of triterpene formation, although the degree of enzymatic assistance still remains difficult to determine.[1] The potential of metabolic engineering to produce alternative natural products or to increase the yields of those of "commercial value" has renewed interest in these kinds of compounds.[2] In this sense, the recent report by Ebizuka et al. describing an OS cyclase homologue that is capable of cleaving preformed ring systems, in addition to produce polycyclic systems, further increases the diversity of structures produced by OS cyclases.[3] In this context, some triterpenes from higher plants or mutagenesis studies such as the *seco*-C-oleananes **1**[4] and **2**,[3] achilleol B (**3**),[5] and camelliol A (**4**)[6] are proposed to derive from the oleanyl cation which suffers retrocyclization processes (Scheme 1).[7]

During the writing of this paper, Hoshino et al. reported the existence of achilleol B synthase, an enzyme encoded by AK070534 gene from *Oryza sativa*.[8] This *seco*-type triterpene cyclase produces achilleol B (**3**) as the main product (ca. 90%).

RESULTS AND DISCUSSION

From the work of pioneers, including those of van Tamelen and Johnson,[9] to the recent progresses reported by Corey,[10] chemists' efforts to mimic the enzymatic cyclization of 2,3-(*R*)-OS in tetra- and pentacyclic triterpenes in a single step have culminated in a number of impressive syntheses of triterpenes, most of them sharing a cation−olefin polyannulation strategy.[11] Nevertheless, this synthetic strategy involves certain drawbacks, such as the need to attach extra groups to the polyene substrate

Scheme 1. Natural Triterpenes 1−4 and Their Proposed Biosynthetic Origin



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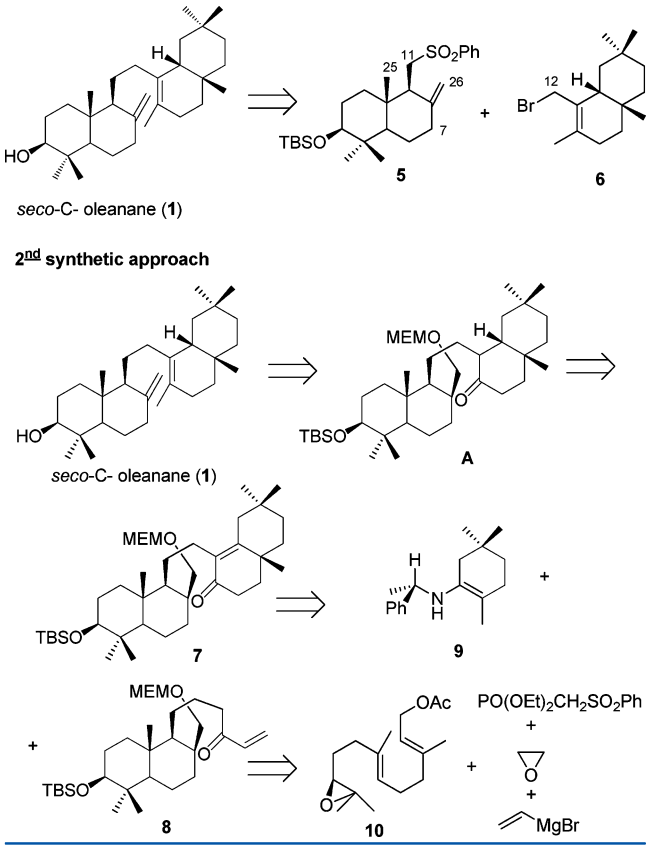
to stabilize carbocationic intermediates and the control of the termination steps.[12] In contrast to these acid-catalyzed cyclizations, other approaches using radical transformations exploited successfully in several polycarbocyclizations have received less attention.[13] In this sense, the work reported by Breslow some 40 years ago showing that terpene skeletons are accessible by radical cyclizations deserved to be underlined.[13j] More recently, it has been established that the Ti(III)-mediated opening of epoxypolyprenes—a strategy reported by our group[14a]—may well be efficiently used for the preparation of polycyclic structures.[14j−o] Interested in the so-called "unusually cyclized triterpenes",[7] we report herein the enantioselective synthesis of the *seco*-C-oleanane **1**, a metabolite isolated from *Stevia viscida* and *S. eupatoria*,[4] and collaterally those of *seco*-triterpenes **2**−**4**.

In our efforts to synthesize **1**, two "dead-end" routes were tried prior to the successful approach (Scheme 2).

Scheme 2. Unsuccessful Approaches to (+)-*seco*-C-Oleanane (1)



The first route was based on the convergent coupling of two C15 synthons, **5** and **6**, which we previously prepared in an enantiopure form.[14o,n] This strategy failed most likely due to the large steric repulsions originating in the C11−C12 approach.

In order to overcome this steric hindrance posed by C11 and C12 in the carbon−carbon coupling, we planned a second route where the target *seco*-C-oleanane could be obtained from ketone **A**, after incorporation of a methyl group from the corresponding enol triflate. Ketone **A** would be produced after stereoselective cis hydrogenation of enone **7**. The construction of the tetracyclic backbone in **7** would be the result of an enantioselective variation of the Robinson annulation, employing bicyclic compound **8** as the chiral Michael acceptor and enamine **9**. Finally, compound **8** was envisaged as being accessible by C5 homologation of the C15 bicyclic compound resulting from the Ti(III)-mediated cyclization of the chiral monoepoxy derivative of farnesol **10**, a transformation previously reported by some of us.[14o]

In this regard, we obtained adequately the advanced tetracyclic intermediate **7**, but we failed in achieving the stereoselective conjugate reduction of the tetrasubstituted conjugated enone to produce the desired *cis*-decalin (Scheme 3). This substrate remained unaltered by a variety of reducing reagents and conditions, including copper hydrides generated in situ,[15] commercial Stryker's reagent,[16] Raney nickel,[17a] Crabtree's catalyst,[17b] and dozens of hydrogenations with varying loads of catalyst (Pd or Pt), solvent, pH, or pressure.[17c]

Finally, after getting enough topological information from our unsuccessful routes, we anticipated that target **1** could be produced via cyclization of epoxypreoleanatetraene **16**, assuming that the process would stop after the second cyclization (Scheme 4). Two reasons led us to envision this truncated cyclization: on the one hand, the recently reported theoretical calculations supporting the nonconcerted nature of the radical cyclization of a C15-epoxypolyprene,[18] and on the other, the existence of different examples where the Ti(III)-promoted cyclization failed when the acceptor double bond possessed a *Z* geometry.[14a] In contrast to what we expected using radical chemistry, at this point, it should be noted that Van Tamelen et al. described the racemic epoxide **16**, which was transformed into *dl*-*δ*-amyrin by treatment with stannic chloride−CH_3NO_2 at 0 °C.[19] In the same sense, the transformation of **16** by a cyclase from *Pysum sativum* led directly to *β*-amyrin[20] (Scheme 4). These results coincided with recent experimental[10a,b] and theoretical[21] data in that the carbocationic cyclization of polyprenes led to tricyclic structures without the intermediacy of mono- or bicyclic carbocations. With all these data in mind, the crux of our strategy was to know whether the radical cyclization of key intermediate **16** would lead to the desired bicyclization process or the cyclization would progress to produce the pentacyclic oleanane skeleton (Scheme 4).

In order to gain more data to evaluate the feasibility of our radical approach, theoretical studies were undertaken to provide reaction and activation energies of the radicals which are intermediates along the pathway connecting the starting bicyclic radical **I**, resulting from the Ti(III)-mediated homolytic opening of the oxirane ring in **16**, to the potential pentacyclic radical **IV**.

Focusing on the third key radical cyclization, the computational studies showed not only that this process is thermodynamically unfavorable by 6.7 kcal/mol but also that the activation energy for cyclization is higher than 29 kcal/mol, which is a considerable energetic barrier, not easily reachable at room temperature. This high barrier is most likely due to an important increase of the steric hindrance and steric congestion when evolving from the most stable conformer of radical **III** to pentacyclic radical **IV**. In this sense, it should be noted that the approach of carbons 8 and 14 in the transition state leading from **III** to **IV** forced a rotation of the C11−C12 bond (Figure 1). Furthermore, the theoretical calculations also showed a slight D-ring rotation in the transition state conformation in comparison to that of **IV**, which results in a destabilizing decrease in the Me-26−Me-28 distance (Figure 2).

At this point, we also examined the conformational strain in the cations corresponding to **III** (**IIIc**), **IV** (**IVc**), and the transition state (Figure 3). The data shown in Figure 3 indicate

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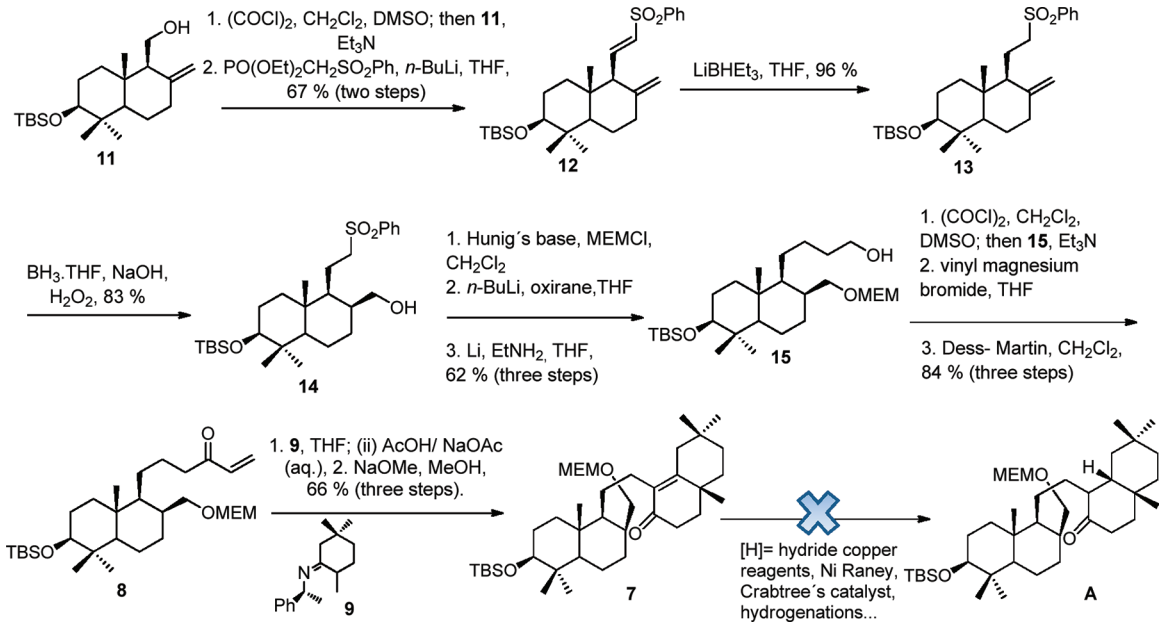
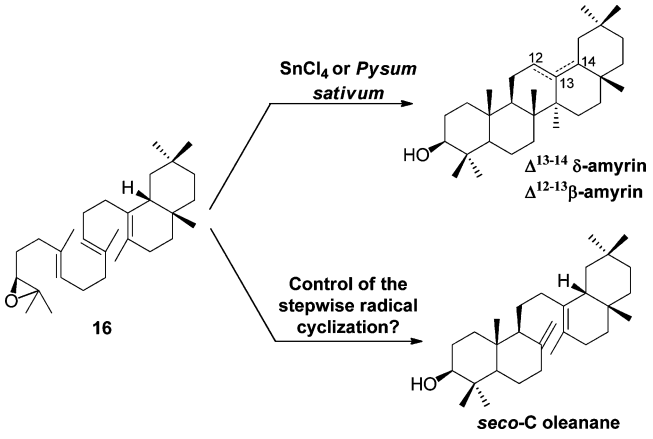
Scheme 3. Second Approach to (+)-*seco*-C-Oleanane



Scheme 4. Carbocationic versus Radical Cyclizations Starting from 16



that the formation of the C ring is thermodynamically unfavorable by about 2 kcal/mol, although in this case, this cyclization was calculated to proceed with activation energies of about 10 kcal/mol, thus suggesting that the cationic approach may well lead to pentacyclic structures, as proven experimentally by Van Tamelen.

Encouraged by the computational results, we went on to address the experimental studies that should corroborate the applicability of our synthetic proposal. In designing a synthetic route toward key intermediate **16**, we envisioned a convergent approach based on the coupling of two chiral synthons, namely bicyclic allyl bromide **6** and polyprenated (*E*)-allyl sulfone **19** (Scheme 5). The route to **19** commenced from commercially available farnesol, which was protected as its acetate form and exposed to asymmetric dihydroxylation conditions to afford the corresponding chiral diol in a 43% yield, based on recovered starting material (96% ee).[14o] After acetonide protection with 2,2-dimethoxypropene, exposure of **18** to palladium-catalyzed allylic sulfonation conditions[22] led to the formation of **19** as a single isomer in 98% yield on a gram scale. Anionic alkylation of the asymmetric intermediate **6**[16] with acyclic moiety **19** afforded, gratifyingly, a diasteromeric mixture of sulfones which after reductive desulphonation furnished **20** in 58% overall yield. Deprotection of acetonide **20** under acidic conditions, treatment of the corresponding diol with mesyl chloride, and subsequent oxirane closure with base gave rise to enantiopure preoleanatetraene oxide (**16**) in 60% global yield (Scheme 5).

With this polyprene precursor in our hands without the use of further functionalizations to promote the radical cascade, we proceeded to carry out the key Ti(III)-mediated cyclization. Gratifyingly, exposure of **16** to 2 equiv of Cp_2TiCl led to *seco*-C-oleanane **1** as the major product (39%), along with the minor tricyclic triterpenes achilleol B (**3**) and camelliol A (**4**) in 7 and 3% yields,[23] respectively. The physical and spectral properties of synthetic **1** turned out to be identical with those of an authentic sample. The signs of the optical rotation $[\alpha]_D$ of both synthetic (+23°, *c* 1.0, $CHCl_3$) and natural *seco*-C-oleanane (+30°, *c* 1.0, $CHCl_3$) matched, thus confirming the absolute configuration of the natural compound. Achilleol B (**3**) was first isolated by our group from *Achillea odorata*,[5] whereas camelliol A (**4**) was identified from *Camellia sasanqua*.[6] Both achilleol B (**3**) and camelliol A (**4**) were formed as a consequence of a premature trapping of the achilleyl radical **II** (Figure 1) by a second molecule of Cp_2TiCl, followed by a β-elimination process. Whereas previous to this work one enantioselective synthesis of achilleol B (**3**) was reported,[14n] the minor camelliol A (**4**) has not been prepared before.

At this point, the feasibility of overcoming the energy barrier leading to the pentacyclic skeleton was tested by conducting the cyclization reaction in refluxing THF−toluene. In this reaction, no pentacyclic compound was detected, with the results obtained being comparable to those obtained at room temperature.

Bearing in mind that it has been reported that in some cases the use of catalytic Ti(III) improved to some degree the results obtained with the stochiometric protocol,[14j−p,18] we decided to treat epoxide **16** with 0.2 equiv of Cp_2TiCl_2 and Mn in excess (8 equiv) in the presence of 7 equiv of the Ti(III) regenerator TMSCl−collidine.[14i] Under these conditions, the efficiency of

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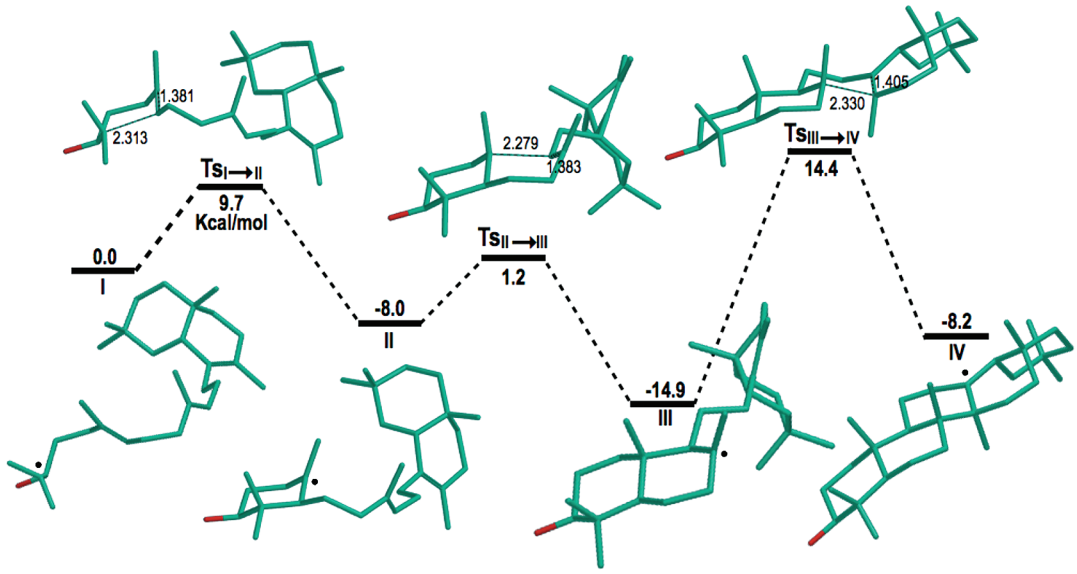

Figure 1. Energy profile of the radical cyclization reaction from bicyclic radical **I** to the oleanyl radical **IV**. Geometries were optimized by UB3LYP/6-31+G(d) basis set. Energies relative to that of **I** (kcal/mol) including zero-point energy corrections are shown. Distances are given in Å.

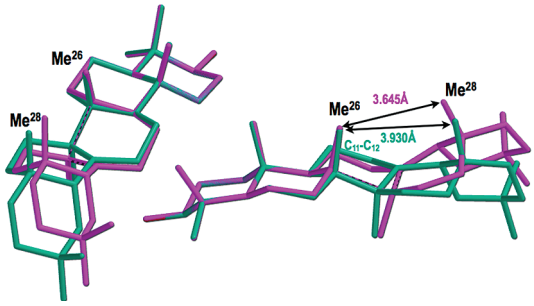

Figure 2. Superposition of radical **IV** (green) and the **III** to **IV** transition state (pink) structures.

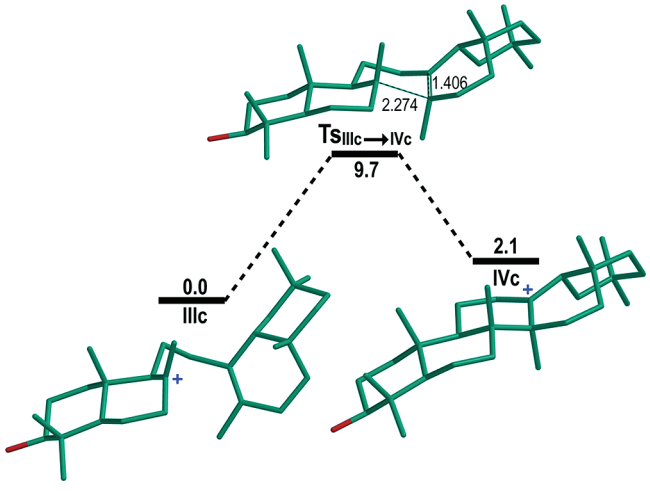

Figure 3. Energy profile of the cyclization reaction from cation **IIIc** to the oleanyl cation **IVc**. Geometries were optimized by the UB3LYP/6-31+G(d) basis set. Energies relative to that of **IIIc** (kcal/mol) including zero-point energy corrections are shown. Distances are given in Å.

the cyclization increased and the targeted *seco*-C-oleanane **1** was obtained in 44% yield after TBAF-mediated desilylation (Scheme 6), a yield that could be considered more than acceptable considering the number of bonds and stereocenters created. Together with **1**, a minor isomer (8%), C-ring *seco*-β-amyrin **2**, was also obtained in the cyclization. Compound **2** was recently reported to be produced by a triterpene synthase encoded by *Atlg*78500, one of the OSC homologous genes of *Arabidopsis thaliana*.[3] As was the case for compound **1**, the sign of the optical rotation $[\alpha]_D$ of both synthetic (+10.1°, *c* 0.1, $CHCl_3$) and natural **2** (+12°, *c* 1.0, $CHCl_3$) coincided. Thus, the formation of **2** in the cyclization of epoxypolyprene **16** also permitted us to confirm the structure and stereochemistry of this *seco*-triterpene.

Finally, with the ultimate goal of confirming the differences between the radical and cationic outcomes of the cyclization of preoleanatetraene **16**, we performed a preliminary test repeating the Van Tamelen experiment. In this reaction, treatment of epoxide **16** with $SnCl_4$ led to a complex mixture of compounds, where no *seco*-C-oleananes were detected, which confirms the different behavior of the corresponding cations and radicals.

CONCLUSION

We have achieved the first enantioselective synthesis of *seco*-C-oleanane **1** and the related *seco*-triterpenes **2**–**4**. The use of a Ti(III)-mediated radical polyannulation reaction as the key step to produce these molecules demonstrated the synthetic efficiency of this strategy, whereas the cationic version of these cyclizations or other approaches failed. In addition to a minimal use of protecting group chemistry and high stereocontrol over the six stereocenters created, we supported these results with radical computational calculations, which also confirmed the nonconcerted nature of these radical cyclizations.

EXPERIMENTAL SECTION

((2*S*,4a*S*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5-((phenylsulfonyl)methyl)naphthalen-2-yloxy)(*tert*-butyl)-dimethylsilane (5). A mixture of alcohol **11** (529 mg, 1.5 mmmol) and diphenyl disulfide (981 mg, 4.5 mmol) in pyridine (1.5 mL) was stirred at room temperature for 1 h before tributylphosphine (1.11 mL, 4.5 mmol) was added. After the mixture was stirred for an additional 4 h, EtOAc (100 mL) and water (50 mL) were added and the resulting layers separated. The organic layer was washed with

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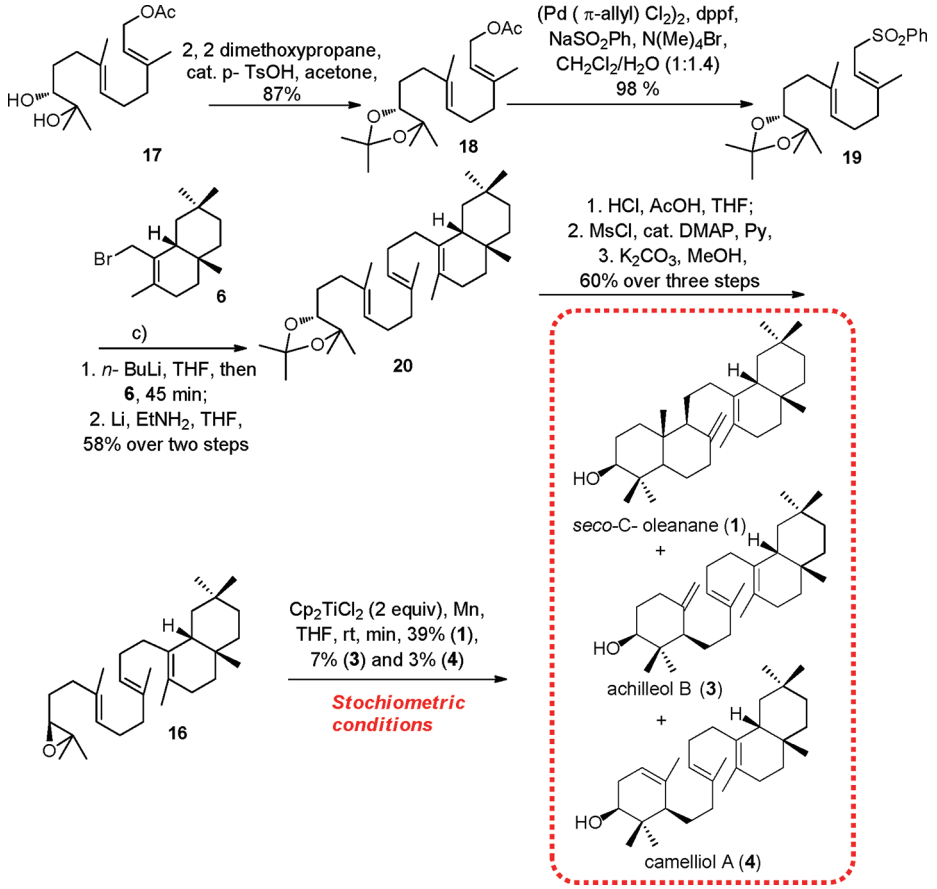
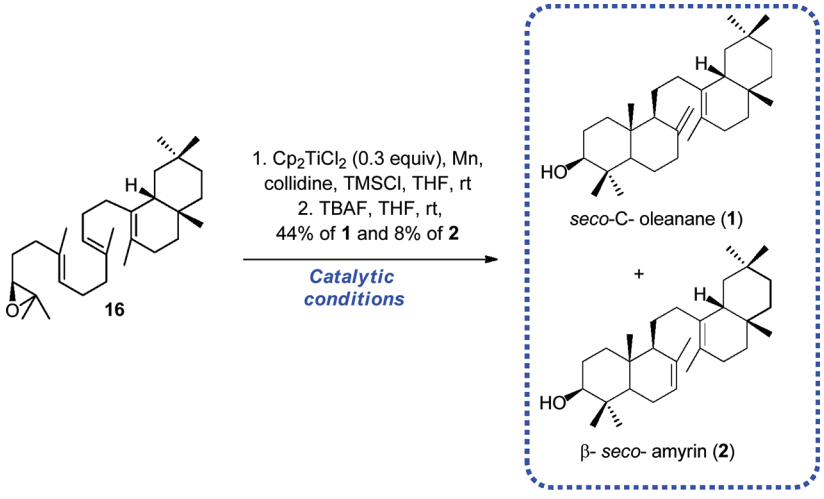
Scheme 5. Synthesis of (+)-*seco*-C-Oleanane and Related Triterpenes



Scheme 6. Synthesis of (+)-*seco*-C-Oleanane using Catalytic Ti(III)



10% HCl(aq) (25 mL), 10% NaOH(aq) (25 mL), and brine (25 mL), dried (Na_2SO_4), and evaporated under vacuum. The resulting crude product was purified by column chromatography on silica gel (5/1 hexane/*t*-BuOMe) to afford the corresponding sulfide (521 mg, 78%). To a solution of this sulfide (215 mg, 0.484 mmol) in DCM (12 mL) at −78 °C was added dropwise a 0.1 M solution of MCPBA (0.5 mL, 1.21 mmol). The resulting mixture was stirred for 45 min until starting material consumption (TLC analysis). Then, the reaction mixture was diluted with DCM and the organic layer was washed with $NaHCO_3$ (3 × 80 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (5/1 hexanes/*t*-BuOMe) to afford the corresponding sulfone **5** (166 mg, 72%): white foam, TLC (hexanes/*t*-BuOMe, 2/1 v/v) R_f = 0.62; $[\alpha]_D$ = +15.2° (*c* 1, CH_2Cl_2); IR (film) ν_{max} 2948, 2855, 1737, 1648, 1472, 1446, 1307, 1252, 1144, 1100, 885, 774, 731, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, *J* = 8 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 4.73 (brs, 1H), 4.42 (br s, lH), 3.35 (dd, *J* = 14.6, 8.8 Hz, 1H), 3.23−3.16 (m, 2H), 2.37 (bt, *J* = 9.8 Hz, 1H), 1.97 (bt, *J* = 13.2, 4.6 Hz, 1H), 1.73 (dt, *J* = 13.2, 2.8 Hz, 1H), 1.59−1.52 (m, 4H), 1.38−1.21 (m, 2H), 1.15 (dd, *J* = 13.2, 2.8 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 9H), 0.70 (s, 3H), 0.61 (s, 3H), −0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.5, 140.3, 133.6, 129.2 (2C), 128.3 (2C), 108.0, 79.0, 54.4, 52.5, 50.6, 39.9, 39.6, 37.6, 36.7, 28.7, 28.1, 26.0 (3C), 23.8, 18.2,

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15.9, 15.2, −3.6, −4.8; HRFABMS calcd for $C_{28}H_{46}NaO_3SSi$ $[M + Na]^+$ 513.2835, found 513.2841.

((2*S*,4a*S*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5-((*E*)-2-(phenylsulfonyl)vinyl)naphthalene-2-yloxy)(*tert*-butyl)-dimethylsilane (12). Oxalyl chloride (3.8 mL, 2.0 M in CH_2Cl_2, 7.5 mmol) was added to a solution of dry DMSO (1.2 mL, 15 mmol) in dry CH_2Cl_2 (27 mL) at −60 °C, under argon. The mixture was stirred for 30 min, and a solution of alcohol **11** (880 mg, 2.5 mmol) in CH_2Cl_2 (9 mL) was added. After additional stirring for 30 min at −60 °C, Et_3N (3.5 mL, 25 mmol) was added, and the mixture was warmed to 0 °C. The reaction mixture was then poured into ice-cold water, diluted with CH_2Cl_2 (150 mL), washed with brine (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the corresponding crude product, which was directly used in the next step. To a solution of diethyl (phenylsulfonylmethyl)-phosphonate (870 mg, 3.0 mmol) in THF (7 mL) was added *n*-butyllithium (2 M solution in hexanes, 1.5 mL, 3.0 mmol) at −78 °C. The resulting yellow mixture was stirred for 10 min, and then a solution of the aldehyde in THF (7 mL) was added dropwise. The mixture was stirred for 12 h until starting material consumption (TLC analysis) and then diluted with *t*-BuOMe and quenched with NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with *t*-BuOMe (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (3/1 hexanes/*t*-BuOMe) to afford the corresponding vinyl sulfone **12** (813 mg, 67%): white solid, TLC (hexanes/*t*-BuOMe, 3/1 v/v) R_f = 0.50; $[\alpha]_D$ = +31.5° (*c* 1, CH_2Cl_2); IR (film) 2934, 2854, 1639, 1319, 1146, 1088, 835, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.04 (dd, *J* = 15.0, 10.6 Hz, 1H), 6.3 (d, *J* = 15.0 Hz, 1H), 4.78 (brs, 1H), 4.36 (brs, 1H), 3.17 (dd, *J* = 11.2, 4.4 Hz, 1H), 2.41 (bd, *J* = 11.2 Hz, 1H), 1.99 (dt, *J* = 13.8, 5.5 Hz, 1H), 1.70 (dt, *J* = 13.1, 2.6 Hz, 1H), 1.61−1.39 (m, 4H), 1.33 (dt, *J* = 13.3, 3.3 Hz, 1H), 1.08−0.98 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.87 (s, 9H), 0.76 (s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.2, 145.5, 140.8, 133.3, 132.7, 129.4 (2C), 127.6 (2C), 109.3, 79.2, 59.6, 53.7, 39.9, 39.2, 38.4, 28.7, 27.9, 25.9 (3C), 22.9, 18.1, 17.1, 16.1, 15.0, −3.7, −4.9.

((2*S*,4a*R*,5*S*)-Decahydro-1,1,4a-trimethyl-6-methylene-5-(2-(phenylsulfonyl)ethyl)naphthalen-2-yloxy)(*tert*-butyl)-dimethylsilane (13). A 1 M solution of $LiBH(Et)_3$ in THF (1.77 mL, 1.7 mmol) was added to a solution of vinyl sulfone **12** (702 mg, 1.4 mmol) in THF (40 mL) at 0 °C under argon, and then the resulting yellow mixture was stirred for 3 h at room temperature before quenching with water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The resulting crude was purified by flash column chromatography on silica gel (3/1 hexanes/*t*-BuOMe) to afford the corresponding sulfone **13** (634 mg, 96%) as a white foam: TLC (hexanes/*t*-BuOMe, 3/1 v/v) R_f = 0.55; $[\alpha]_D$ = +14.6° (*c* 1, CH_2Cl_2); IR (film) 2952, 2934, 2854, 1641, 1461, 1307, 1150, 1088, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 4.70 (brs, 1H), 4.19 (brs, 1H), 3.18 (ddd, *J* = 14.4, 10.4, 4.4 Hz, 1H), 3.11 (dd, *J* = 9.6, 5.7, 1H), 2.81 (ddd, *J* = 14.1, 9.9, 6.0 Hz, 1H), 2.26 (ddd, *J* = 12.9, 4.0, 2.3 Hz, 1H), 1.89 (m, 1H), 1.80 (dt, *J* = 13.0, 5.0 Hz, 1H), 1.67−1.46 (m, 6H), 1.27 (dt, *J* = 12.7, 4.1 Hz, 1H), 1.09−1.03 (m, 1H), 0.94 (dd, *J* = 12.5, 2.6 Hz, 1H), 0.80 (s, 9H), 0.81 (s, 3H), 0.64 (s, 3H), 0.57(s, 3H), −0.03(s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 147.1, 139.9, 133.6, 129.3 (2C), 127.9 (2C), 107.0, 79.1, 55.3, 54.6, 39.7, 39.4, 37.9, 36.9, 28.7, 28.2, 27.0, 25.9 (3C), 24.1, 18.1, 17.1, 15.9, 14.3, −3.7, −4.9; HRFABMS calcd for $C_{28}H_{46}NaO_3SSi$ $[M + Na]^+$ 513.2835, found 513.2841.

Compound 14. A solution of **13** (789 mg, 1.6 mmol) in anhydrous THF (69 mL) was cooled to 0 °C under argon and treated with BH_3·THF (3.2 mL, 1 M in THF, 3.2 mmol). The reaction mixture was warmed slowly to room temperature over 4 h. It was then cooled to 0 °C and treated with a premixed solution of 3 M NaOH (1.3 mL, 3.9 mmol) and 30% aqueous H_2O_2 (1.3 mL, 3.9 mmol). After 1 h at 0 °C, the reaction mixture was stirred for 3 h at room temperature and quenched with saturated NH_4Cl solution (25 mL). The mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic extracts were washed with brine (15 mL) and dried. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with *t*-BuOMe to afford the corresponding hydroxy sulfone **14** (675 mg, 83%) as a white foam: TLC (EtOAc/*t*-BuOMe, 1/1 v/v) R_f = 0.75; $[\alpha]_D$ = +12.6° (*c* 1, CH_2Cl_2); IR (film) 3453, 2931, 2854, 1642, 1469, 1447, 1304, 1145, 1085, 835, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.90 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 2H), 3.54−3.48 (m, 2H), 3.22 (ddd, *J* = 13.7, 11.4, 5 Hz, 1H), 3.12 (dd, *J* = 10.8, 5.2, 1H), 2.96 (ddd, *J* = 13.7, 11.0, 4.9 Hz, 1H), 1.99−1.92 (m, 2H), 1.71−1.45 (m, 7H), 1.36−1.27 (m, 2H), 1.23 (dt, *J* = 11.3, 4 Hz, 1H), 0.93 (dt, *J* = 12.8, 4.5 Hz, 1H), 0.76 (brd, *J* = 9.7 Hz, 1H), 0.87 (s, 12H), 0.70 (s, 3H), 0.67 (s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 133.7, 129.3 (2C), 128.0 (2C), 79.1, 61.3, 55.5, 55.3, 52.01, 39.6, 39.2, 37.8, 37.4, 29.5, 28.5, 27.7, 25.9 (3C), 18.7, 18.1, 17.6, 15.9, 15.7, −3.7, −4.9; HRFABMS calcd for $C_{28}H_{48}NaO_4SSi$ $[M + Na]^+$ 531.2940, found 531.2945.

Compound 15. Hydroxysulfone **14** (383 mg, 0.76 mmol) was dissolved in 15.8 mL of CH_2Cl_2, and *N*,*N*-diisopropylethylamine (0.40 mL, 2.28 mmol) and MEMCl (0.23 mL, 1.98 mmol) were added at 0 °C. The mixture was stirred for 3 h at room temperature and then partitioned between H_2O (50 mL) and DCM (50 mL). The aqueous layer was extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. To a solution of the crude residue obtained above in THF (6.7 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi (0.5 mL, 0.84 mmol). The resulting yellow mixture was stirred for 30 min, and then oxirane (30 equiv) was added. The reaction mixture was stirred for 10 min and then quenched by the dropwise addition of a saturated aqueous solution of NH_4Cl (3 mL). The reaction mixture was partitioned between EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the organic solvent gave a mixture of diastereomers which was used directly without further purification. A solution of lithium (9 mg, 1.2 mmol) in ethylamine (10 mL) at −78 °C under argon was stirred for 30 min until the solution turned dark blue. Then, the crude bis-homologated compound obtained above in THF (6 mL) at −78 °C was added. The mixture was stirred for 10 min (TLC monitoring), and then the reaction was quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (3 mL). The resulting mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1/1 hexanes/*t*-BuOMe) to afford the primary alcohol **15** (236 mg, 62%) as a colorless oil: TLC (*t*-BuOMe) R_f = 0.50; $[\alpha]_D$ = +14.3° (*c* 1, CH_2Cl_2); IR (film) 3422, 2933, 2856, 1461, 1253, 1095, 1053, 835, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.71 (d, *J* = 6.8, 1H), 4.69 (d, *J* = 6.8, 1H), 3.73−3.55 (m, 7H), 3.44 (t, *J* = 9.7 Hz, 1H), 3.39 (s, 3H), 3.15 (dd, *J* = 11.1, 4.7 Hz, 1H), 1.96 (m, 2H), 1.64 (dt, *J* = 13.0, 3.3 Hz, 1H), 1.60−1.15 (m, 12H), 0.94 (dt, *J* = 13.1, 3.8 Hz, 1H), 0.88 (s, 3H), 0.87(s, 9H), 0.79 (brd, *J* = 9.2 Hz, 1H), 0.73 (s, 3H), 0.71 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 95.6, 79.4, 71.9, 67.0, 66.7, 62.8, 59.1, 55.7, 52.9, 39.6, 37.6, 37.5, 36.1, 33.1, 30.1, 28.6, 27.9, 25.9 (3C), 25.2, 24.1, 18.2, 17.8, 15.9 (2C), −3.7, −4.8; HRFABMS calcd for $C_{28}H_{56}NaO_5Si$ $[M + Na]^+$ 523,3795, found 523.3799.

Compound 8. Oxalyl chloride (0.76 mL, 2.0 M in CH_2Cl_2, 1.52 mmol) was added to a solution of dry DMSO (0.23 mL, 3.04 mmol) in dry CH_2Cl_2 (5.4 mL) at −60 °C, under argon. The mixture was stirred for 30 min, and a solution of alcohol **15** (254 mg, 0.50 mmol) in CH_2Cl_2 (1.8 mL) was added. After additional stirring for 30 min at −60 °C, Et_3N (0.7 mL, 5 mmol) was added. The mixture was warmed to 0 °C, poured into ice-cold water, diluted with CH_2Cl_2, and worked up in the usual way to give the corresponding crude aldehyde, directly

used in the next step. To a solution of the aforementioned aldehyde dissolved in THF (4.4 mL) at 0 °C was added vinylmagnesium bromide (0.557 mL) dropwise. The reaction mixture was stirred for 10 min at 0 °C and then quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was separated and extracted with *t*-BuOMe (2 × 20 mL). The combined organic layer was washed with brine (25 mL) and dried over Na_2SO_4 to give a mixture of epimers, which were used in the next step without purification. To a solution of the allylic alcohols in CH_2Cl_2 (16 mL) was added Dess–Martin periodinane (299 mg, 0.70 mmol) at 0 °C. The ice bath was removed and the solution was stirred at room temperature while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting alcohol (30 min), the reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$·$NaHCO_3$ (5 mL) diluted in CH_2Cl_2 (20 mL) and the organic layer was washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (25 mL) and dried over Na_2SO_4. Volatiles were removed in vacuo, and the crude material was purified by silica gel flash chromatography (1/1 hexanes/*t*-BuOMe) to afford enone **8** (224 mg, 84%) as a yellowish oil: TLC (hexanes/*t*-BuOMe, 1/1 v/v) R_f = 0.55; $[\alpha]_D$ = +10.9° (*c* 1, CH_2Cl_2); IR (film) 2932, 2853, 1640, 1461, 1252, 1111, 1087, 1052, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.33 (dd, *J* = 17.6, 10.5 Hz, 1H), 6.19 (dd, *J* = 17.6, 1.1 Hz, 1H), 5.79 (dd, *J* = 10.5, 1.1 Hz, 1H), 4.71 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 3.69–3.53 (m, 5H), 3.46 (t, *J* = 9.6 Hz, 1H), 3.38 (s, 3H), 3.14 (dd, *J* = 11.1, 4.9 Hz, 1H), 2.56 (dt, *J* = 7.5, 3.1 Hz, 2H), 1.96 (brt, *J* = 7.4 Hz, 2H), 1.75–1.68 (m, 1H), 1.60 (dt, *J* = 9.4, 3.5 Hz, 1H), 1.54–1.15 (m, 10 H) 0.94 (dt, *J* = 13.1, 3.9 Hz, 1H), 0.87 (s, 12H), 0.78 (brt, *J* = 5.8 Hz, 1H), 0.71 (s, 3H), 0.68 (s, 3H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 136.6, 127.9, 95.6, 79.3, 71.9, 66.9, 66.7, 59.1, 55.6, 52.9, 39.9, 39.6, 37.6, 37.5, 36.3, 31.5, 30.0, 28.6, 27.8, 25.9 (3C), 25.2, 22.6, 18.2, 17.7, 15.9, −3.7, −4.8.

Compound 7. To a solution of compound **8** (224 mg, 0.43 mmol) in THF (1.5 mL) was added imine **9**[15] (207 mg, 0.85 mmol) at 0 °C. The resulting mixture was stirred for 17 h at the same temperature and concentrated under reduced pressure. H_2O (6.0 mL) and AcOH (1.0 mL) were added to the residue at room temperature. The mixture was then stirred for 4 h, poured into brine (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was treated with a 30% w/w solution of NaOMe (0.17 mL, 0.94 mmol) in MeOH (1 mL) at reflux for 5 h, while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting diketone, the solvent was removed in vacuo and partitioned between saturated aqueous 2 N HCl (50 mL) and *t*-BuOMe (50 mL) and the aqueous layer extracted with *t*-BuOMe (2 × 25 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL) and dried over Na_2SO_4. Volatiles were removed under reduced pressure, and the crude material was purified by silica gel flash chromatography (1/1 hexanes/*t*-BuOMe) to afford enone **7** (183 mg, 66% overall yield). TLC (hexanes/*t*-BuOMe, 1/1 v/v): R_f = 0.45; $[\alpha]_D$ = +0.3° (*c* 1, CH_2Cl_2); IR (film) 2930, 2855, 1665, 1459, 1252, 1112, 1086, 1051, 835, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.79 (d, *J* = 6.7 Hz, 1H), 4.74 (d, *J* = 6.7 Hz, 1H), 3.77–3.54 (m, 6H), 3.4 (s, 3H), 3.15 (dd, *J* = 10.9, 5.2 Hz, 1H), 2.48 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.45 (dd, *J* = 14.5, 5.4 Hz, 1H), 2.40–2.31 (m, 2H), 2.03–1.96 (m, 4H), 1.79 (dt, *J* = 13.5, 4.2 Hz, 1H), 1.73 (ddd, *J* = 8.4, 5.3, 3.1 Hz, 1H), 1.66–1.20 (m, 11 H), 1.19 (s, 3H), 1.05 (s, 3H), 1.01–0.94 (m, 1H) 0.89 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.72 (s, 3H), 0.67 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 161.6, 135.3, 95.8, 79.4, 71.9, 67.3, 66.7, 59.1, 55.7, 53.7, 40.9, 39.6, 38.4, 37.8, 37.6, 37.5, 36.5, 35.6, 34.8, 34.2, 33.8, 32.5, 30.1, 28.6, 27.8, 26.0 (3C), 25.7, 25.1, 24.2, 22.7, 18.2, 17.8, 16.0, 15.9, −3.7, −4.8; HREIMS (*m*/*z*) calcd for $C_{39}H_{70}O_5Si$ $[M - H]^+$ 645.4993, found 645.4994.

(2*E*,6*E*)-3,7-Dimethyl-9-((*R*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienyl Acetate (18). 2,2-Dimethoxypropane (2.9 mL, 24 mmol) was added to a cooled (0 °C) solution of **16**[14] (500 mg, 1.6 mmol) and catalytic *p*-TsOH in acetone (30 mL). The reaction mixture was removed from the ice bath and stirred at room temperature for 30 min. It was then quenched with saturated aqueous $NaHCO_3$. The resulting solution was poured into *t*-BuOMe (150 mL), and the aqueous layer was extracted with *t*-BuOMe (2 × 50 mL). The combined organic extract was washed with water (150 mL) and brine (150 mL) and dried over Na_2SO_4. Volatiles were removed under vacuum, and the crude material was purified by silica gel flash chromatography (hexanes/*t*-BuOMe 1/2) to afford acetonide **17** (535 mg, 87%): TLC (hexanes/*t*-BuOMe, 1/1 v/v) R_f = 0.75; $[\alpha]_D$ = +3.3° (*c* 1, MeOH); IR (film) 2982, 1742, 1377, 1369, 1232, 1114, 1023, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.33 (dt, *J* = 7.1, 1.2 Hz, 1H); 5.14 (dt, *J* = 6.9, 1.1 Hz, 1H), 4.6 (d, *J* = 7.1 Hz, 2H), 3.65 (dd, *J* = 9.2, 3.6 Hz, 1H), 2.22–1.98 (m, 6H), 2.05 (s, 3H), 1.70 (s, 3H), 1.64–1.57 (m, 1H), 1.61 (s, 3H), 1.49–1.43 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 142.2, 134.9, 124.2, 118.4, 106.5, 82.9, 80.2, 61.5, 39.6, 36.7, 28.6, 27.8, 26.9, 26.3, 26.2, 23.0, 21.1, 16.6, 16.1.

(*R*)-2,2,4,4-Tetramethyl-5-((3*E*,7*E*)-3,7-dimethyl-9-(phenylsulfonyl)nona-3,7-dienyl)-1,3-dioxolane (19). A solution of $(Pd(\pi\text{-allyl})Cl)_2$ (23 mg, 0.06 mmol) and dppf (102 mg, 0.18 mmol) in 3.5 mL of CH_2Cl_2 was added to a flask containing $NaSO_2Ph$ (854 mg, 5.2 mmol), tetramethylammonium bromide (42 mg, 0.27 mmol), and **17** (1.19 g, 3.06 mmol), in a mixture of degassed water (10 mL) and CH_2Cl_2 (7 mL). The reaction was stirred at room temperature for 2.5 h, at which time the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extract was dried over Na_2SO_4, concentrated under reduced pressure, and purified via silica gel flash chromatography (2/1 hexanes/*t*-BuOMe) to afford the corresponding sulfone **18** (1.26 g, 98%): TLC (hexanes/*t*-BuOMe, 1/1 v/v) R_f = 0.62; $[\alpha]_D$ = +0.63° (*c* 1, CH_2Cl_2); IR (film) 2979, 2932, 2855, 1447, 1371, 1234, 1150, 1128, 100, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.84 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 5.17 (t, *J* = 7.9 Hz, 1H), 5.07 (bt, *J* = 6.3 Hz, 1H), 3.77 (d, *J* = 7.9 Hz, 2H), 3.61 (dd, *J* = 9.3, 3.3 Hz, 1H), 2.20–2.15 (m, 1H), 2.03–1.96 (m, 5H), 1.61–1.53 (m, 1H), 1.58 (s, 3H), 1.47–1.41 (m, 1H), 1.39 (s, 3H), 1.29 (s, 6H), 1.21 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 146.3, 138.7, 135.1, 133.5, 129.0 (2C), 128.546 (2C), 123.7, 110.3, 106.4, 82.9, 80.1, 56.1, 39.6, 36.7, 28.6, 27.7, 26.9, 26.1, 26.0, 22.9, 16.2, 16.0; HRFABMS calcd for $C_{24}H_{36}NaO_4S$ $[M + Na]^+$ 443.2232, found 443.2235.

(*R*)-5-((3*E*,7*E*)-10-((4a*S*,8a*R*)-1,2,3,4,4a,5,6,8a-Octahydro-2,2,4a,7-tetramethylnaphthalen-8-yl)-3,7-dimethyldeca-3,7-dienyl)-2,2,4,4-tetramethyl-1,3-dioxolane (20). To a solution of sulfone **18** (850 mg, 2.02 mmol) in THF (9.6 mL) was added *n*-butyllithium (2 M solution in hexane, 1.01 mL, 2.02 mmol) at −78 °C. The resulting yellow mixture was stirred for 10 min, and a solution of bromide **6** (192 mg, 0.67 mmol) in THF (20 mL) was added dropwise. The mixture was warmed for 4 h and then diluted with *t*-BuOMe (100 mL) and quenched with water. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica chromatography (hexane/*t*-BuOMe, gradient from 3/1 to 1/1) afforded the corresponding epimeric mixture of sulfones (326 mg, 78%). To a solution of Li (10 mg) in $EtNH_2$ (15 mL) was added at −78 °C a solution of the sulfones (326 mg, 0.522 mmol) in THF (8 mL). The mixture was stirred for 20 min. Saturated NH_4Cl was then added slowly, and the mixture was further stirred for 10 min. The aqueous layer was extracted with *t*-BuOMe (2 × 100 mL), and the combined organic extract was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by silica gel flash chromatography (5/1 hexanes/*t*-BuOMe) to afford acetonide **19** (187 mg, 74%): TLC (hexanes/*t*-BuOMe, 4/1 v/v) R_f = 0.85; $[\alpha]_D$ = +5.3° (*c* 1, CH_2Cl_2); IR (film) 2969, 2914, 2857, 1458, 1369, 1215, 1113, 1002 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.09 (t, *J* = 8.1 Hz, 1H), 5.08 (t, *J* = 7.3 Hz, 1H), 3.59 (dd, *J* = 9.2, 3.5 Hz, 1H), 2.17–2.10 (m, 2H), 2.04–1.77 (m, 10H), 1.66–1.56 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.45–1.36 (m, 3H), 1.35 (s, 3H), 1.32 (d, *J* = 2.5 Hz, 1H), 1.31 (d, *J* = 2.7 Hz, 1H), 1.30 (m, 1H),

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1.25 (s, 3H), 1.17 (s, 3H), 1.13 (t, J = 3.2 Hz, 1H), 1.03 (s, 3H), 0.89 (t, J = 13 Hz, 1H), 0.88 (d, J = 9.2 Hz, 1H), 0.82 (s, 3H), 0.80 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.8, 134.4, 133.8, 125.0, 124.9, 124.1, 106.6, 83.1, 80.2, 43.2, 42.6, 39.9, 36.8 (2C), 34.8, 32.3, 31.9, 31.6, 31.1, 29.7, 28.7, 28.0, 27.3, 27.1, 27.0, 26.8 (2C), 26.3, 24.4, 23.1, 18.7, 16.1 (2C); HREIMS (m/z) $[M]^+$ calcd for $C_{33}H_{56}O_2$ 484.4280, found 484.4277.

Preoleanatetraene Oxide (16). To a solution of **20** (127 mg, 0.26 mmol) and 80% aqueous AcOH (2.5 mL) in THF (4 mL) was gradually added 2 M HCl (2 mL) at room temperature for 30 min, and the whole mixture was stirred for 12 h at the same temperature. The reaction mixture was diluted with brine and extracted with *t*-BuOMe (100 mL). The combined organic extract was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL) and dried over Na_2SO_4. Evaporation of the organic solvent gave a residue, which was chromatographed on silica gel (hexane/*t*-BuOMe, 2/1) to give the corresponding diol (92 mg, 80%). To a solution of the aforementioned diol (142 mg, 0.32 mmol) and catalytic DMAP in anhydrous pyridine (5 mL), cooled to −12 °C under an argon atmosphere, was added dropwise MsCl (0.15 mL, 1.92 mmol). After 40 min (TLC monitoring), the mixture was diluted with *t*-BuOMe and treated with saturated $NaHCO_3$ solution. After an additional 15 min of stirring at room temperature, the mixture was extracted with Et_2O (3 × 50 mL) and the organic layer was washed with 1 N HCl (1 × 50 mL) and brine (1 × 50 mL), dried over anhydrous Na_2SO_4, and finally concentrated under reduced pressure. The mesylated crude product was dissolved in 5 mL of MeOH, and K_2CO_3 (176 mg, 1.25 mmol) was added. After the mixture was stirred for 20 min, the formation of epoxide was complete (TLC monitoring). Then, the reaction was quenched by diluting with H_2O and *t*-BuOMe. The organic layer wa washed with 1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel (hexane/*t*-BuOMe, 1/2) to afford 101 mg of the corresponding epoxide **16** (74% yield over two steps): colorless oil, TLC (hexanes/*t*-BuOMe, 1/2 v/v) R_f = 0.50; $[\alpha]_D$ = +2.9° (c 1, CH_2Cl_2); IR (film) 2944, 2917, 2858, 1451, 1377, 1121, 1033, 967, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (t, J = 6.6 Hz, 1H), 5.15 (t, J = 6.6 Hz, 1H), 2.69 (t, J = 6.3 Hz, 1H), 2.22−1.83 (m, 14H), 1.73−1.64 (m, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.48 (dt, J = 13.7, 4.3 Hz, 1H), 1.41−1.33 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H), 1.23−1.09 (m, 1H), 0.95 (t, J = 13 Hz, 1H), 0.94 (d, J = 9.2 Hz, 1H), 0.89 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.6, 133.9, 133.5, 124.9, 124.7, 123.8, 64.1, 58.2, 42.9, 42.2, 39.6, 36.5, 36.3, 34.6, 33.1, 31.6, 31.4, 30.9, 29.5, 27.5, 27.1, 26.9, 26.6, 26.5, 24.9, 24.2, 18.7, 18.6, 16.0, 15.9; HREIMS (m/z) $[M + H]^+$ calcd for $C_{30}H_{50}O$ 427.3861, found 427.3867.

***seco*-C-Oleanane (1), Achilleol B (3), and Camelliol A (4).** A mixture of Cp_2TiCl_2 (138 mg, 0.557 mmol) and Mn dust (61 mg, 1.11 mmol) in strictly deoxygenated THF (6 mL) under an Ar atmosphere was stirred at room temperature until the red solution turned green. Then, a solution of 119 mg (0.278 mmol) of preoleanatetraene oxide in THF (6 mL) was added. The reaction mixture was stirred for 20 min (TLC monitoring), quenched with 1 N HCl, extracted with *t*-BuOMe (50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 10/1 to 4/1 v/v hexanes/*t*-BuOMe) to afford 51 mg (49%) of an inseparable mixture of triterpenes by classic chromatography, namely, *seco*-C-oleanane (**1**), achilleol B (**3**), and camelliol A (**4**), in a 81/13/6 ratio, respectively, calculated by GC-MS analyses: TLC (hexanes/*t*-BuOMe, 4/1 v/v) R_f = 0.30. This mixture was subjected to column chromatography on $AgNO_3$ (20%)−silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 5/1 to 2/1 hexanes/*t*-BuOMe v/v) to afford two main fractions, the first (35 mg) constituted by a mixture of the three triterpenes (hexanes/*t*-BuOMe, 3/1 v/v), and the second (15 mg) enriched in *seco*-C-oleanane (**1**) and achilleol B (**3**) (hexanes/*t*-BuOMe, 2/1 v/v). The latter fraction was subjected to HPLC (6/1 hexanes/*t*-BuOMe) to obtain pure *seco*-C-oleanane (**1**; 7 mg) and achilleol B (**3**; 2 mg) (t_r = 25.3 and 26.2 min, respectively). *seco*-C-oleanane (**1**): colorless oil; $[\alpha]_D$ = +23° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3610, 3450, 1644, 1384, 892 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.86 (1H, d, J = 1.5 Hz, H-26), 4.63 (1H, d, J = 1.0 Hz, H-26′), 3.25 (1H, dd, J = 11.7, 4.4 Hz, H-3), 2.41 (1H, dq, J = 12.7, 2.4 Hz, H-7), 2.32 (1H, m, H-12), 1.99 (1H, m, H-7′), 1.99 (1H, m, H-15), 1.88 (1H, m, H-15′), 1.89 (1H, m, H-16), 1.79 (1H, m, H-1), 1.75 (1H, m, H-6), 1.69 (1H, m, H-2), 1.60 (1H, m, H-9), 1.59 (1H, m, H-2′), 1.55 (1H, m, H-18), 1.56 (3H, s, Me-27), 1.49 (1H, m, H-11), 1.48 (1H, m, H-22), 1.47 (1H, m, H-12′), 1.38 (1H, m, H-6′), 1.33 (1H, m, H-11′), 1.33 (1H, m, H-21), 1.33 (1H, m, H-19), 1.21 (1H, m, H-22′), 1.17 (1H, m, H-1′), 1.12 (1H, m, H-21′),1.10 (1H, m, H-5), 0.93 (1H, m, H-19′), 0.99 (3H, s, Me-23), 0.88 (3H, s, Me-30), 0.87 (3H, s, Me-29), 0.85 (3H, s, Me-28), 0.81 (1H, m, H-16′), 0.77 (3H, s, Me- 24), 0.67 (3H, s, Me-25); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 148.3, 134.2, 123.5, 106.5, 78.9, 56.9, 54.6, 42.9, 42.9, 39.5, 39.1, 38.2, 36.8, 36.5, 34.5, 33.1, 31.5, 30.9, 30.8, 29.4, 28.3 27.9, 27.2, 26.4, 24.0, 24.0, 22.8, 18.7, 15.3, 14.4; HREIMS m/z 426.3868 (calcd for $C_{30}H_{50}O$ 426.3865). Achilleol B (**3**): $[\alpha]_D$ = −10.9° (c 0.9, $CHCl_3$); IR ($CHCl_3$) 3394, 3080, 1662, 1644, 1385, 1365, 1195, 1085, 892; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (1H, t, J = 7.0 Hz), 4.88 (1H, bs), 4.62 (1H, bs), 3.40 (1H, dd, J = 10.0, 4.5 Hz), 2.32 (1H, dt, J = 13.2, 4.5 Hz), 2.21 (1H, ddd, J = 13.1, 10.0, 6.6 Hz), 2.08 (1H, ddd, J = 13.2, 10.3, 3.8 Hz), 2.02−1.82 (7H, m), 1.80−1.44 (8H, m), 1.61 (3H, s), 1.58 (3H, s), 1.39 (1H, ddd, J = 13.0, 3.7, 2.6 Hz), 1.35 (1H, dd, J = 13.8, 3.9 Hz), 1.23 (1H, dt, J = 13.3, 3.5 Hz), 1.12 (1H, m), 1.04 (3H, s), 0.97 (1H, t, J = 13.0 Hz), 0.90 (3H, s), 0.88 (3H, s), 0.82 (3H, s), 0.82 (1H, m), 0.72 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 135.2, 133.8, 124.8, 124.1, 108.6, 77.5, 51.3, 43.2, 42.5, 40.8, 38.9, 36.8, 34.8, 33.4, 33.3, 32.4, 31.9, 31.6, 31.2, 29.7, 27.4, 27.2, 26.7, 26.1, 24.4, 24.0, 18.9, 16.2, 15.7.

***seco*-C-oleanane (1) and C-Ring *seco*-β-Amyrin (2).** A mixture of Cp_2TiCl_2 (18 mg, 0.071 mmol) and Mn dust (104 mg, 1.896 mmol) in strictly deoxygenated THF (4 mL) under an argon atmosphere was stirred at room temperature until the red solution turned green. Then, a solution of 101 mg (0.237 mmol) of preoleanatetraene oxide **16** and 2,4,6-collidine (0.220 mL, 1.659 mmol) and Me_3SiCl (0.12 mL, 0.946 mmol) were added. The reaction mixture was stirred for 3.30 h (TLC monitoring), quenched with 1 N HCl, extracted with *t*-BuOMe (50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in THF (3 mL) and stirred with Bu_4NF (0.704 mL, 0.704 mmol) for 30 min. Then, THF was removed, and the mixture was diluted with *t*-BuOMe (50 mL), washed with brine (50 mL), and dried over anhydrous Na_2SO_4 and the solvent was removed. The resulting crude product was purified by column chromatography on silica gel using hexanes/*t*-BuOMe mixtures of increasing polarity as eluents to afford 59 mg (51%) of the exo and endo isomers *seco*-C-oleanane (**1**) and *seco*-β-amyrin (**2**) in a 7/1 ratio, respectively (NMR integration): TLC (hexanes/*t*-BuOMe, 4/1 v/v) R_f = 0.30. This mixture was subjected to column chromatography on $AgNO_3$ (20%)−silica gel using mixtures of hexanes and *t*-BuOMe as eluent (gradient from 5/1 to 2/1 hexanes/*t*-BuOMe v/v) to obtain a fraction enriched in *seco*-β-amyrin (**2**; 30 mg) (hexanes/*t*-BuOMe, 2/1 v/v) and 19 mg of **1** (hexanes/*t*-BuOMe, 2/1 v/v). A 15 mg amount of the fraction enriched in *seco*-β-amyrin (**2**) was subjected to HPLC (4/1 hexanes/*t*-BuOMe) to obtain 3 mg of pure *seco*-β-amyrin (**2**) (t_r = 17.3 min): $[\alpha]_D$ = +10.1° (c 0.1, $CHCl_3$); IR ($CHCl_3$) 3610, 3450, 1644, 1384, 892 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.40 (1H, brs, H-7), 3.25 (1H, dd, J = 10.9, 4.9 Hz, H-3), 2.41 (1H, dt, J = 13.0, 5.8 Hz, H-12), 1.98 (1H, m, H-15), 1.97 (1H, m, H-6, H-6′), 1.92 (1H, m, H-1), 1.87 (1H, m, H-15′), 1.75 (3H, brs, Me-26), 1.70−1.55 (2H, m, H-2, H-2′), 1.63 (1H, m, H-18), 1.58 (1H, m, H-9), 1.58 (1H, m, H-12′), 1.57 (3H, s, Me-27), 1.51 (1H, m, H-22), 1.42 (1H, m, H-11), 1.38 (1H, m, H-19), 1.35 (1H, m, H-21), 1.23 (1H, m, H-22′),1.20 (1H, m, H-5), 1.19 (1H, m, H-1′), 1.14 (1H, m, H-11′), 1.13 (1H, m, H-21′), 0.98 (1H, m, H-19′), 0.98 (3H, s, Me-23), 0.88 (3H, s, Me-29), 0.88 (3H, s, Me-30), 0.86 (3H, s, Me-24), 0.84 (3H, s, Me-28), 0.76 (3H, s, Me-25); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.40, 134.3, 123.6, 121.8, 79.2, 55.7, 49.7, 43.0, 42.8, 38.7, 37.2, 37.0, 36.5,

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34.9, 34.6, 33.2, 31.5, 31.0, 29.4, 27.9, 27.5, 27.1, 26.5, 26.0, 24.0, 23.5, 22.1, 18.8, 15.1, 13.7. HREIMS m/z 426.3855 (calcd for $C_{30}H_{50}O$, 426.3862).

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and tables giving computational methods and ^{1}H and ^{13}C NMR spectra of **1**−**5**, **8**, **9**, **12**−**16**, and **18**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: afbarre@ugr.es (A.F.B.); jfquilez@ugr.es (J.F.Q.d.M.).

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