Oxidative Coupling of (-)-Sclareol and Related Diols Leading to Oxepane Terpenoids

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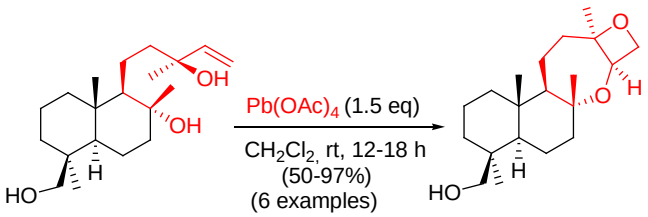


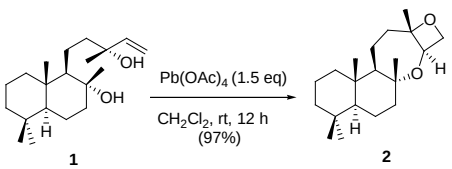
ABSTRACT: Treatment of (-)-sclareol and related compounds with lead tetraacetate affords tetracyclic compounds bearing a 2,8-dioxabicyclo[5.2.0]nonane moiety, with complete regio- and stereoselectivity. This process, which is also applicable to 1,5-diols with a similar substitution pattern, facilitates the development of efficient syntheses towards oxepane terpenoids, such as aplysistatin derivatives.

Natural products are frequently utilized as the starting material for synthesizing valuable compounds, providing various advantages in this respect. These processes make use of the stereochemistry and other structural features of the natural precursor, which makes it feasible to achieve the target compound in an efficient and economical way. One such natural compound is (-)-sclareol (**1**).[1] This labdane diterpene, which is the main component of the aerial parts of the clary sage *Salvia sclarea*, satisfies all the requisites for this purpose. Compound **1**, which has a *trans*-decalinic system with five stereogenic centres, is an inexpensive, commercially-available compound. The use of this diterpene as a starting material usually involves the degradative oxidation of the carbon side chain and the suitable transformation of the C-8 hydroxyl group. The oxidant systems most often utilized for this purpose are $RuCl_3/3H_2O/NaIO_4$[2] or $OsO_4/NaIO_4$,[3,5a] or the more classic reagent $KMnO_4$.[4]

Continuing our research into the oxidation of (-)-sclareol (**1**), we were interested in exploring processes involving radical species, which have received very little research attention. Indeed, only two articles in this respect have been published. Decorzant et al. reported the preparation of the odorant (-)-ambrox from diterpene **1**. Treatment with hydrogen peroxide in an acid medium produced a mixture of hydroperoxides and manoyl oxides; the degradation of 13-hydroperoxide epimers with Fe (II) and Cu (II) salts, via an alkoxy radical, afforded the target compound in 52% global yield.[5] In addition, our group described a very efficient synthesis of manoyl oxide,[6] after treatment of diterpene **1** with cerium ammonium nitrate; the participation of oxygen radicals was postulated for the cyclization process.[7] In general, chemical processes involving alkoxy radicals have been little studied, probably due to their high reactivity, particularly in the case of those derived from primary and secondary alcohols, and to the ready oxidation of this type of alcohols. Mihailovic reported the use of $Pb(OAc)_4$ to convert different types of alcohols into variable mixtures of cyclic ethers and other oxidation products.[8]

The treatment of (-)-sclareol (**1**) with $Pb(OAc)_4$ (1.5 eq) in dichloromethane at room temperature for 12 h gave the tetracyclic diether **2** in high yield (Scheme 1). When the reaction was performed in benzene, a mixture of compounds resulted. When $PhI(OAc)_2$ was utilized as the oxidant, the starting material remained unaltered.

Scheme 1. Reaction of (-)-sclareol (**1**) with $Pb(OAc)_4$.



This unexpected result prompted us to explore the use of this reaction for the efficient preparation of terpenes bearing an oxepane moiety.[9] Some interesting examples of this type of compound are found in nature, including sesquiterpenes, such as the cytotoxic (-)-aplysistatin (**3**)[10] and (+)-palisadin B (**4**),[11] the bromoditerpene **5**, and the related oxocane **6,**[12] the sesterterpene (+)-luffalactone (**7**)[13] or the merosesquiterpene bis(sulfate)-cyclosiphonodictyol A (**8**).[14] (Figure 1).

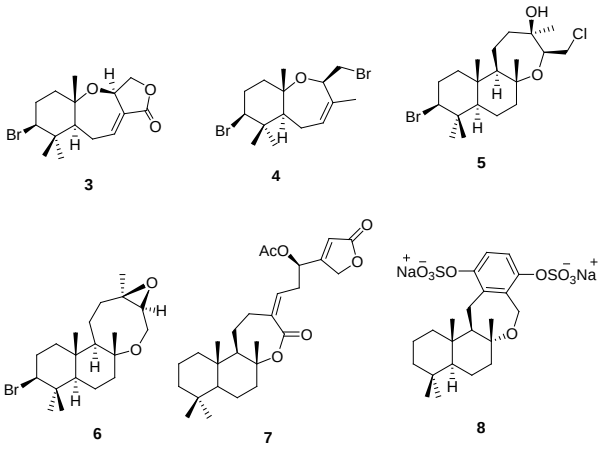
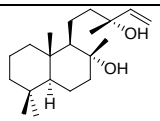
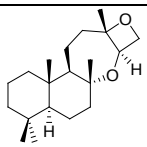
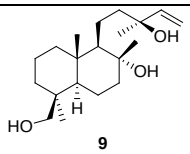
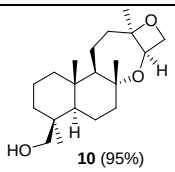
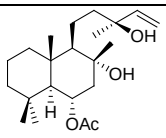
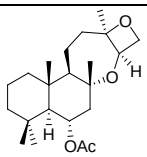
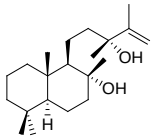
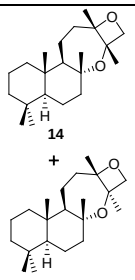
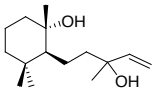
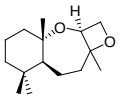
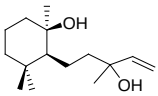
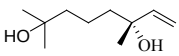
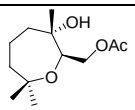


Figure 1. Some natural oxepane terpenes and related compounds.

In order to establish the scope of this oxidation, other diols with a substitution pattern similar to that of (-)-sclareol (**1**) were assayed (Table 1).

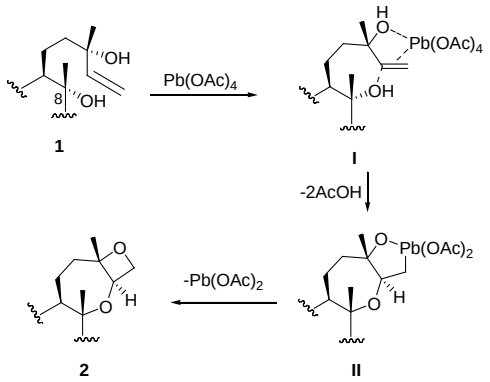
Table 1. Treatment of (-)-sclareol (**1**) and related diols with $Pb(OAc)_4$.

Entry	Diol[15]	t	Product[a]
1	 **1**	12h	 **2** (97%)
2	 **9**	12h	 **10** (95%)
3	 **11**	12h	 **12** (92%)
4	 **13**	18h	 **14** + **15** (73% global)
5	 **16**	12h	 **17** (93%)
6	 **18**	24h	No reaction
7	 **19**	14h	 **20** (50%)

[a]The relative stereochemistry of the resulting compounds was established on the basis of NOE experiments.

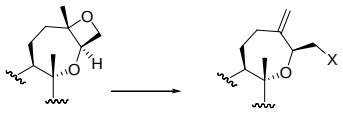
As can be seen, diols **1**, **9**, **11**, **13** and **16** gave the corresponding diethers **2**, **10**, **12**, **14**, **15** and **17**, having a 2,8-dioxabicyclo[5.2.0]nonane moiety, with complete regio- and stereoselectivity. This process could involve the Pb(IV) approach to the carbon-carbon double bond, probably assisted by the allyl hydroxyl group,[16] to produce a complex, which undergoes the attack of the C_8-hydroxyl group leading to intermediate **II**, which after C-O reductive elimination will gave the bicyclic ether **2** (Scheme 2**).** At this point, we cannot rule out the intermediacy of radical or cationic species.[17] On the other hand, intermediates are not detected in the course of the reaction, and a concerted process should not be excluded. It is important to note that diol **18**, the epimer of compound **16**, remains unaltered under the reaction conditions; in this case, the tricylic intermediate similar to **II** cannot be formed, due to the 1,3-diaxial interaction between methyl groups. In the case of acyclic diol **19**, the 2,8-dioxabicyclo[5.2.0]nonane fragment is not present in the final compound, probably due to the flexibility of the monocyclic oxepane, which is unfavourable to the formation of the oxetane ring.

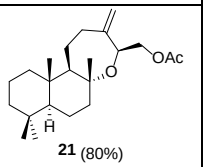
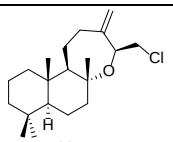
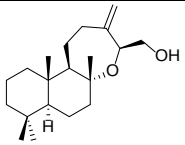
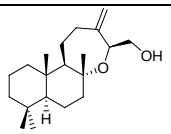
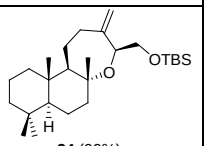
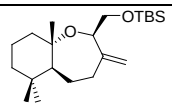
Scheme 2. A possible transformation of (-)-sclareol (**1**) into tetracyclic ether **2** *via* intermediate **II**.



After obtaining the tetracyclic diether **2,** we studied the oxetane ring opening, in order to prepare synthetic intermediates of oxepane terpenoids related to compounds **3-8**. We then examined the nucleophilic oxetane ring opening of compounds **2** and **17**. The most significant results obtained are shown in table 2.

Table 2. Nucleophilic oxetane ring opening for compounds **2** and **17**.



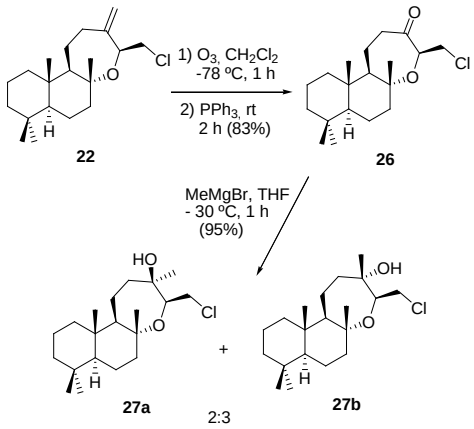
Entry	Conditions	t	Product
1	**2**,CH_3COCl, N,N-dimethylaniline, CH_2Cl_2, rt	72h	 **21** (80%)
2	**2**, $POCl_3$, pyridine, 0 °C	15h	 **22** (56%)
3	**2**, $SOCl_2$, NEt_3, - 30 °C	3 h	Complex mixture
4	**2**, LiBr, DMF, 70 °C	72h	 **23** (30%)
5	**2**, CH_2=CHMgBr, THF, reflux	72h	Starting material
6	**2**, $MgBr_2$, toluene, reflux	15h	Complex mixture
7	**2**, TMSOTf, Et_2NPr^i, CH_2Cl_2, 0 °C,	5min	 **23** (97%)
8	**2**, TBSOTf, Et_2NPr^i, CH_2Cl_2, 0 °C,	5min	 **24** (99%)
9	**17**, TBSOTf, Et_2NPr^i, CH_2Cl_2, 0 °C,	15min	 **25** (97%)

As can be seen, even though the treatment of diether **2** with LiBr gave alcohol **23** in low yield (entry 4), this compound was obtained in high yield when the oxetane ring opening was realized with TMSOTf (entry 7).

Compounds **21-25** appear to be suitable intermediates to prepare oxepane terpenoids related to the above natural products.

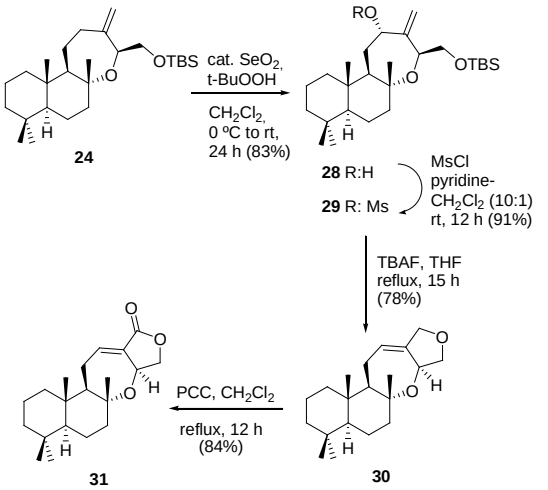
Thus, the chloroderivative **22** was transformed into chloroalcohol **27a**, the corresponding 3-debromoderivative of natural oxepane **5** (Scheme 3).

Scheme 3. Synthesis of chloroalcohols **27a-b** from oxepane **22**.



The homoallyl alcohol moiety presented by compounds **21** and **23-25** can also be easily converted into the γ-butyrolactone fragment of aplysistatins and related compounds. Thus, oxepane **24** was efficiently transformed into lactone **31**, a tetracyclic analogue of 3-debromoaplysistatin (Scheme 4).

Scheme 4. Synthesis of lactone **31** from oxepane **24**.



Following the same synthetic sequence, compound **25** could be readily converted into the corresponding tricyclic lactone (3-debromoaplysistatin).

In summary, (-)-sclareol (**1**) and related 1,5-diols with a similar substitution pattern undergo an oxidative coupling process after treatment with lead tetraacetate, affording diethers bearing a 2,8-dioxabicyclo[5.2.0]nonane moiety. The oxetane ring opening of these compounds provides suitable intermediates for synthesizing oxepane terpenoids, such as aplysistatin derivatives.

EXPERIMENTAL SECTION

General methods.

Unless stated otherwise, reactions were performed in oven-dried glassware under an argon atmosphere using dry solvents. Solvents were dried as follows: THF and MeOtBu-over Na–benzophenone, benzene over Na, DCM and MeOH over CaH_2. Dimethylformamide (DMF) was dried over 4Å molecular sieves. Thin-layer chromatography (TLC) was performed using F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching and phosphomolybdic acid solution staining. Flash chromatography was performed on silica gel (230-400 mesh) Chromatography separations were carried out by conventional column on silica gel 60 (230-400 Mesh), using Hexanes-MeOtBu (H-E) mixtures of increasing polarity.^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. $CDCl_3$ was treated with K_2CO_3. Chemical shifts (δ H) are quoted in parts per million (ppm) referenced to the appropriate residual solvent peak and tetramethylsilane. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), with the abbreviations s, br s, d, br d, t, q, and m denoting singlet, broad singlet, doublet, broad doublet, triplet, quartet and multiplet respectively. J = coupling constant in Hertz (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0) and the signals were assigned utilizing DEPT experiments and on the basis of heteronuclear correlations.Infrared spectra (IR) were recorded as thin films or as solids on a FTIR spectrophotometer with samples between sodium chloride plates or as potassium bromide pellets and are reported in frequency of absorption (cm^{-1}). Only selected absorbances (ν_{max}) are reported. ($[\alpha]^D$) measurements were carried out in a polarimeter; utilizing a 1dm length cell and $CHCl_3$ as a solvent. Concentration is expressed in mg/mL. HRMS were recorded on a spectrometer, utilizing a quadrupole MS/MS analyzer, and using FAB with thioglicerol or glycerol matrix doped in NaI 1%.

General procedure for the reaction of diols with $Pb(OAc)_4$. Lead tetraacetate (2 mmol) was added to a solution of diol (2 mmol) in dichloromethane (10 mL) and the resulting mixture was stirred at room temperature for the specified time, and the course of the reaction was monitored by TLC. When the starting material was consumed, the mixture was filtered on a silicagel pad and the solvent was evaporated. The crude residue was dissolved in ether (10 mL) and the organic solution was successively washed with 5% aq. $NaHSO_3$ (3 x 10 mL), H_2O (4 x 10 mL) and brine (10 mL). The organic phase was dried over anh. Na_2SO_4 and evaporated to give the bicyclic ether.

(4a*S*, 6a*R*, 7a*R*, 9a*S*, 11a*R*, 11b*S*)-4, 4, 6a, 9a, 11b-Pentamethyltetradecahydro-1H-naphtho[2, 1-b]oxeto [2, 3-f]oxepine (2). Colourless oil, 963 mg, 97%. $[\alpha]_D^{25}$ +6.4 (c 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.78 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 1.10 (ddd, *J* = 16.8, 13.3, 4.2 Hz, 1H), 1.27 (s, 3H), 1.40 (s, 3H), 1.33 - 1.69 (m, 14H), 2.51 (ddd, *J* = 17.4, 17.1, 6.6 Hz, 1H), 4.16 (dd, *J* = 5.8, 3.4 Hz, 1H), 4.19 (dd, *J* = 7.2, 3.4 Hz, 1H), 4.68 (dd, *J* = 7.2, 5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.4 (CH_3), 18.7 (CH_2), 18.7 (CH_2), 20.2 (CH_2), 21.5 (CH_3), 22.6 (CH_3), 23.7 (CH_3), 31.7 (CH_2), 33.3 (C), 33.4 (CH_3), 38.4 (C), 38.7 (CH_2), 40.3 (CH_2), 41.7 (CH_2), 52.4 (CH), 56.4 (CH), 71.5 (CH), 72.0 (CH_2), 79.5 (C), 90.4 (C). IR (film): 1594, 1457, 1386, 1214, 1160, 1103, 1084, 973, 926, 875, 772, 665 cm^{-1}. HRMS (FAB) m/z: calcd for $C_{20}H_{34}O_2Na$ (M+Na+) 329.2457, found: 329.2463.

((4*S*,4a*R*,6a*R*,7a*R*,9a*R*,11a*R*,11b*S*)-4,6a,9a,11b-Tetramethyltetradecahydro-1H-naphtho[2,1-b]oxeto[2,3-f]oxepin-4-yl)methanol (10). Colourless oil, 198 mg, 95%. $[\alpha]_D^{25}$ +7.06 (c 0.11, $CHCl_3$). ^{1}H- NMR ($CDCl_3$, 500 MHz) δ: 0.82 (s, 3H), 0.99 (s, 3H), 1.27 (s, 3H), 1.43 (s, 3H), 0.88 - 1.81 (m, 15H), 2.54 (td, *J* = 11.9, 11.4, 7.5 Hz, 2H), 3.44 (d, *J* = 10.9 Hz, 1H), 3.69 (d, *J* = 10.9 Hz, 1H), 4.18 (dd, *J* = 5.9, 3.4 Hz, 1H), 4.22 (dd, *J* = 7.3, 3.4 Hz, 1H), 4.70 (dd, *J* = 7.3, 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz,) δ: 15.9 (CH_3), 18.4 (CH_2), 18.9 (CH_2), 20.4 (CH_2), 22.7 (CH_3), 23.6 (CH_3), 27.0 (CH_3), 31.7 (CH_2), 35.4 (CH_2), 38.4 (C), 38.6 (C), 39.1 (CH_2), 40.4 (CH_2), 52.5 (CH), 57.0 (CH), 65.3 (CH_2), 71.5 (CH), 72.1 (CH_2), 79.3 (C), 90.2 (C). IR (film): 2959, 1426, 1255, 1125, 1075, 960, 754, 613 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_3Na$ ($M+Na^+$) 345.2406, found: 345.2398.

(*4aS*, 5*S*, 6a*R*, 7a*R*, 9a*R*, 11a*R*, 11b*S*)- 4, 4, 6a, 9a, 11b-Pentamethyltetradecahydro-1H-naphtho[2, 1-b]oxeto[2, 3-f]oxepin-5-yl acetate (12). Colourless oil, 228 mg, 92%. $[\alpha]_D^{25}$ +21.8 (c 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.83 (s, 3H), 0.84 (s, 3H), 1.03 (s, 3H), 1.23 (s, 3H), 1.40 (s, 3H), 0.88 – 2.21 (m, 14H), 2.02 (s, 3H), 4.25 (t, *J* = 5.9 Hz, 1H), 4.33 (dd, *J* = 5.9, 5.3 Hz, 1H), 4.52 (dd, *J* = 7.3, 5.3 Hz, 1H), 5.04 (dd, *J* = 7.3, 5.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ : 17.4 (CH_3), 18.6 (CH_2), 19.7 (CH_2), 20.6 (CH_3), 22.0 (CH_3), 22.3 (CH_3), 24.7 (CH_3), 33.5 (C), 36.1 (CH_3), 38.6 (CH_2) 39.2 (C), 40.1 (CH_2), 43.1 (CH_2), 49.5 (CH_2), 58.1 (CH), 64.0 (CH), 70.9 (CH_2), 70.9 (CH), 72.8 (CH), 79.2 (C), 91.4 (C), 170.3 (C). IR (film): 1736, 1458, 1367, 1245, 1166,

1106, 1029, 975 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_4Na$ ($M+Na^+$) 387.2511, found: 387.2526.

(4a*S*, 6a*R*, 7a*S*, 9a*S*, 11a*R*, 11b*S*)-4, 4, 6a, 7a, 9a, 11b-Hexamethyl tetradecahydro-1H-naphtho[2, 1-b]oxeto[2, 3-f]oxepine (14). Colourless oil, 73 mg, 32%. $[\alpha]_D^{25}$ +7.4 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (s, 6H), 0.85 (s, 3H), 1.13 (s, 3H), 1.31 (s, 3H), 1.33 (s, 3H), 0.76 - 1.68 (m, 15H), 2.37 (m, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.6 (CH_3), 18.6 (CH_2), 19.2 (CH_3), 19.5 (CH_2), 20.6 (CH_2), 21.3 (CH_3), 23.5 (CH_3), 33.3 (C), 37.9 (CH_2), 39.0 (CH_2), 39.2 (C), 39.9 (CH_2), 42.0 (CH_2), 49.4 (CH_3), 56.3 (CH), 58.0 (CH), 64.2 (C), 65.5 (CH_2), 65.9 (C), 72.8 (C), 79.4 (C). IR (film): 1594, 1458, 1385, 1261, 1082, 801 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{36}O_2Na$ ($M+Na^+$) 343.2613, found: 343.2622.

(4a*S*, 6a*R*, 7a*R*, 9a*S*, 11a*R*, 11b*S*)-4, 4, 6a, 7a, 9a, 11b-Hexamethyltetradecahydro-1H-naphtho[2, 1-b]oxeto[2, 3-f]oxepine (15). Colourless oil, 94 mg, 41%. $[\alpha]_D^{25}$ +5.4 (c 0.16, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (s, 3H), 0.78 (s, 3H), 0.87 (s, 3H), 1.18 (s, 3H), 1.36 (s, 3H), 1.55 (s, 3H), 0.75 – 1.80 (m, 14H), 2.16 (m, 1H), 2.34 (m, 1H), 3.89 (d, *J* = 5.0 Hz, 1H), 4.40 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.0 (CH_3), 18.8 (CH_2), 19.6 (CH_2), 20.0 (CH_2), 21.9 (CH_3), 22.8 (CH_3), 25.2 (CH_3), 33.4 (CH_3), 38.4 (C), 39.2 (CH_2), 40.1 (CH_2), 41.8 (CH_2), 44.4 (CH_2), 49.4 (CH), 55.9 (CH), 64.7 (CH), 72.8 (C), 76.9 (C), 81.0 (C), 81.3 (CH_2), 92.5 (C). IR (film): 1706, 1460, 1379, 1194, 1086, 973 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{36}O_2Na$ ($M+Na^+$) 343.2613, found: 343.2622.

(2a*S*,3a*S*,7a*S*)-3a,7,7,9a-Tetramethyldecahydro-2H-benzo[b]oxeto[2,3-f]oxepine (17). Colourless oil, 249 mg, 93%. $[\alpha]_D^{25}$ -53.9 (c 0.12, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (s, 3H), 0.92 (s, 3H), 1.29 (s, 3H), 1.41 (s, 3H), 1.20 – 1.65 (m, 11H), 4.18 – 4.24 (m, 2H), 4.70 (dd, *J* = 7.1, 5.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8 (CH_2), 20.3 (CH_2), 20.9 (CH_3), 22.7 (2 x CH_3), 32.0 (CH_2), 33.2 (CH_3), 35.0 (C), 37.9 (CH_2), 41.9 (CH_2), 48.3 (CH), 71.7 (CH), 72.1 (CH_2), 79.5 (C), 90.4 (C). IR (film) : 1463, 1426, 1380, 1274, 1123, 1073, 1039, 959 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{15}H_{26}O_2Na$ ($M+Na^+$) 261.1830, found: 261.1842.

((2*R*, 3*S*)-3-Hydroxy-3, 7, 7-trimethyloxepan-2-yl) methyl acetate (20). Colourless oil, 267 mg, 50%. $[\alpha]_D^{25}$ -3.5 (c 0.13, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.14 (s, 3H), 1.17 (s, 3H), 1.20 (s, 3H), 1.21 - 1.74 (m, 7H), 2.05 (s, 3H), 3.60 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.97 (dd, *J* = 11.3, 9.0 Hz, 1H), 4.31 (dd, *J* = 11.3, 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.4 (CH_2), 21.2 (CH_3), 24.7 (CH_3), 27.2 (CH_3), 28.4 (CH_3), 40.4 (CH_2), 45.6 (CH_2), 63.9 (CH_2), 72.1 (C), 73.4 (CH), 75.8 (C), 171.2 (C). IR (film): 2968, 2928, 1739, 1599, 1463, 1368, 1123 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{12}H_{22}O_4Na$ ($M+Na^+$) 253.1416, found: 253.1404.

((4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-5a,8,8,11a-Tetramethyl-3-methylenetetradecahydronaphtho[2,1-b]oxepin-4-yl)methyl acetate (21). N,N-dimethylaniline (4 mL, 32 mmol) and CH_3COCl (1.15 mL, 16.3 mmol) were added to a solution of **2** (1 g, 3.26 mmol) in anhydrous CH_2Cl_2 (30 mL), and the mixture was kept stirring at room temperature under argon atmosphere for 72 h. Then, the reaction was quenched with water (10 mL), and ether was added (30 mL). The organic solution was washed with 10% HCl (6 x 15 mL) and brine (2 x 15 mL), dried over anh. Na_2SO_4, and evaporate to yield **21** (900 mg, 80%). $[\alpha]_D^{25}$ +27.8 (c 0.11, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.78 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 1.18 (s, 3H), 1.18 - 1.61 (m, 14H), 2.05 (s, 3H), 1.88 - 1.97 (m, 1H), 2.63 (m, 1H), 3.91 (dd, *J* = 11.3, 8.5 Hz, 1H), 4.13 (dd, *J* = 11.3, 3.4 Hz, 1H), 4.43 (brs, 1H), 4.74 (s, 1H), 4.87 (s, 1H). ^{13}C NMR ($CDCl_3$,400 MHz) δ: 16.2 (CH_3), 18.9 (CH_2), 20.5 (CH_2), 21.2 (CH), 21.6 (CH_3), 22.8 (CH_2), 23.7 (CH_3), 31.0 (CH_2), 33.5 (C), 33.6 (CH_3), 38.3 (C), 38.6 (CH_2), 40.5 (CH_2), 42.1 (CH_2), 53.4 (CH), 56.3 (CH), 68.0 (CH_2), 70.1 (CH), 79.1 (C), 107.9 (CH_2), 150.8 (C), 171.2 (C). IR (film): 1743, 1457, 1381, 1232, 1105, 1040 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{22}H_{36}O_3Na$ ($M+Na^+$) 371.2562, found: 371.2555.

(4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-4-(Chloromethyl)-5a,8,8,11a-tetramethyl-3-methylenetetradecahydronaphtho[2,1-b]oxepine (22). Pyridine (1 mL) and $POCl_3$ (0.5 mL) were added to a solution of **2** (100 mg, 0.326 mmol) previously cooled at 0º C and the mixture was kept stirring under argon atmosphere for 15 h. Then, the reaction was carefully quenched at 0º C with water (1mL), and ether was added (25 mL). The organic solution was washed with 10% HCl (3 x 10 mL) and brine (3 x 10 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (30% ether/hexane) to yield **22** (40 mg, 56%). $[\alpha]_D^{25}$ + 68.9 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.78 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 1.23 (s, 3H), 1.25 – 1.69 (m, 14H), 2.03 (dd, *J* = 11.9, 8.3 Hz, 1H), 2.62 (q, *J*= 10.1, 1H), 3.41 (dd, *J* = 11.2, 8.9 Hz, 1H), 3.53 (dd, *J* = 11.2, 3.1 Hz, 1H), 4.37 (d, *J* = 8.2 Hz, 1H), 4.73 (s, 1H), 4.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2 (CH_3), 18.9 (CH_2), 20.4 (CH_2), 21.6 (CH_3), 22.8 (CH_2), 23.7 (CH_3), 31.0 (CH_2), 33.4 (C), 33.6 (CH_3), 38.3 (C), 38.5 (CH_2), 40.5 (CH_2), 42.0 (CH_2), 49.1 (CH_2), 53.4 (CH), 56.4 (CH), 72.5 (CH), 79.3 (C), 108.5 (CH_2), 151.8 (C). IR (film): 1637, 1457, 1383, 1130, 1100, 1038, 946, 894, 746, 664 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{33}ClONa$ ($M+Na^+$) 347.2118, found: 347.2131.

((4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-5a,8,8,11a-Tetramethyl-3 methyl-enetetradecahydronaphtho[2,1-b]oxepin-4-yl)methanol (23). LiBr (903 mg, 10.4 mmol) was added to a solution of **2** (80 mg, 2.6 mmol) in anhydrous DMF (10 mL) and the mixture was kept stirring at 70º C under argon atmosphere for 72 h. Then, the reaction was quenched with water (1 mL), and ether was added (30 mL). The organic solution was washed with water (4 x 25 mL) and brine (3 x 20 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (30% ether/hexane) to yield **23** (50 mg, 30%). Colorless oil. $[\alpha]_D^{25}$ + 70.9 (c 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.79 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 1.06 (ddd, *J* = 13.4, 13.4, 4.1 Hz, 1H), 1.22 (s, 3H), 1.19 – 1.70 (m, 14H), 2.03 (ddd, *J* = 10.7, 8.3, 1.5 Hz, 1H), 2.11 (brs, 1H), 2.57 (m, 1H), 3.37 (dd, *J* = 11.0, 9.0 Hz, 1H), 3.49 (dd, *J* = 11.0, 4.0 Hz, 1H), 4.31 (m, 1H), 4.65 (s, 1H), 4.82 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2 (CH_2), 18.9 (CH_2), 20.5 (CH_2), 21.6 (CH_3), 22.8 (CH_2), 23.9 (CH_3), 30.8 (CH_2), 33.5 (C), 33.6 (CH_3), 38.4 (C), 39.1 (CH_2), 40.5 (CH_2), 42.0 (CH_2), 53.5 (CH), 56.4 (CH), 66.2 (CH_2), 72.8 (CH), 79.3 (C), 107.0 (CH_2), 151.0 (C). IR (film): 3461, 1643, 1454, 1412, 1095, 1041, 888, 756 cm^{-1}.

HRMS (FAB) *m/z*: calcd for $C_{20}H_{34}O_2Na$ ($M+Na^+$) 329.2457, found: 329.2442.

Treatment of compound 2 with TMSOTf. Obtention of alcohol 23. N,N-Diisopropylethylamine (0.26 mL, 1.47 mmol) and TMSOTf (0.21 mL, 1.17 mmol) were added to a solution of **2** (300 mg, 0.98 mmol) in anhydrous CH_2Cl_2 (15 mL), and the mixture was kept stirring at 0º C under argon atmosphere for 5 min. Then, the reaction was carefully quenched with water (0.5 mL), and ether (20 mL) was added. The organic solution was washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to yield alcohol **23** (359 mg, 97%) as colorless oil.

***tert*-Butyldimethyl(((4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-5a,8,8,11a-tetramethyl-3-methylenetetradecahydronaphtho[2,1-b]oxepin-4-yl)methoxy)silane (24).** N,N-Diisopropylethylamine (1.7 mL, 9.8 mmol) and TBSOTf (0.9 mL, 4.9 mmol) were added to a solution of **2** (1 g, 4.9 mmol) in anhydrous CH_2Cl_2 (30 mL), and the mixture was kept stirring at 0º C under argon atmosphere for 5 min. Then, the reaction was carefully quenched with water (2 mL), and ether (30 mL) was added. The organic solution was washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to yield **24** (1.36 g, 99%) as colorless oil. $[\alpha]_D^{25}$ +45.9 (c 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.06 (s, 6H), 0.78 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.89 (s, 9H), 1.12 (ddd, *J* = 13.5, 13.3, 4.0 Hz,1H), 1.13 (s, 3H), 1.21 - 1.67 (m, 13H), 1.97 (ddd, *J* = 9.2, 5.7, 1.4, 1H), 2.58 (q, *J* = 10 Hz, 1H), 3.48 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.52 (dd, *J* = 10.5, 6.3 Hz, 1H), 4.22 (t, *J* = 5.8 Hz, 1H), 4.69 (t, *J* = 1.36 Hz, 1H), 4.81 (d, *J* = 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.1 (CH_3), -4.8 (CH_3), 16.3 (CH_3), 18.6 (CH_2), 19.0 (C), 20.6 (CH_2), 21.6 (CH_3), 22.9 (CH_2), 23.8 (CH_3), 26.1 (3 CH_3), 31.0 (CH_2), 33.5 (CH_3), 33.6 (C), 38.3 (CH_2), 38.7 (C), 40.5 (CH_2), 42.1 (CH_2), 53.4 (CH), 56.4 (CH), 67.9 (CH_2), 73.3 (CH), 78.7 (C), 107.1 (CH_2), 151.9 (C). IR (film): 1461, 1381, 1252, 1122, 1085, 836, 775 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{26}H_{48}O_2SiNa$ ($M+Na^+$) 443.3321, found: 443.3312.

***tert*-Butyldimethyl(((2*R*,5a*S*,9a*S*)-6,6,9a-trimethyl-3-methylenedecahydrobenzo[b]oxepin-2-yl)methoxy)silane (25)**. N,N-Diisopropylethylamine (0.22 mL, 1.26 mmol) and TBSOTf (0.36 mL, 1.57 mmol) were added to a solution of **11** (250 mg, 1.05 mmol) in anhydrous CH_2Cl_2 (15 mL) cooled at 0 ºC, and the mixture was kept stirring at this temperature under argon atmosphere for 15 min. Then, the reaction was carefully quenched with water (1 mL), and ether (20 mL) was added. The organic solution was washed with water (3 x 10 mL) and brine (2 x 10 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (5% ethyl acetate/hexane) to yield **25** (359 mg, 97%) as colorless syrup. $[\alpha]_D^{25}$ -20.4 (c 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.07 (s, 3H), 0.82 (s, 3H), 0.88 (s, 3H), 0.89 (s, 9H), 1.20 (s, 3H), 1.59 – 1.40 (m, 9H), 2.60 (brdt , *J* =15.2, 10.8 Hz, 2H), 3.56 – 3.45 (m, 2H), 4.22 (brdd, *J* = 6.2 Hz, 1H), 4.72 (d, *J* = 1.6 Hz, 1H), 4.81 (d, *J* = 1.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: -5.0 (CH_3), -4.7 (CH_3), 18.6 (C), 20.8 (CH_2), 21.6 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 26.1 (3 CH_3), 31.2 (CH_2), 33.6 (CH_3), 34.9 (C), 37.8 (CH_2), 42.0 (CH_2), 49.2 (CH), 67.9 (CH_2), 73.5 (CH), 78.6 (C), 107.3 (CH_2), 151.7 (C). IR (film): 1722, 1426, 1255, 1124, 1074, 960 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{21}H_{40}O_2SiNa$ ($M+Na^+$) 375.2695, found: 375.2709.

(4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-4-(Chloromethyl)-5a,8,8,11a-tetramethyldodecahydronaphtho[2,1-b]oxepin-3(2H)-one (26). Ozone stream was bubbled into a solution of **22** (80 mg, 0.246 mmol) in anhydrous CH_2Cl_2 previously cooled at -78º C for 1 h. When the reaction finished, an argon stream was bubbled for eliminate ozone excess. Then, PPh_3 was added to the cooled solution and the mixture was kept stirring for 2 h. Solvent was evaporated to afford a crude product that was purified by flash chromatography on silica gel (10% ether/hexane) to yield **26** (66 mg, 83%). $[\alpha]_D^{25}$ +78.5 (c 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.79 (s, 3H), 0.85 (s, 3H), 0.86 (s, 3H), 1.25 (s, 3H), 1.40 – 1.78 (m, 14H), 2.18 (ddd, *J* = 11.4, 10.9, 2.0 Hz, 1H), 3.22 (q, *J* = 10.3 Hz, 1H), 3.63 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.67 (dd, *J* = 11.2, 2.8 Hz, 1H), 4.02 (dd, *J* = 6.2, 3.0 Hz, 1H). ^{13}C NMR (CDCl3, 125 MHz) δ: 15.6 (CH_3), 18.4 (CH_2), 18.8 (CH_2), 20.3 (CH_2), 21.5 (CH_3), 23.5 (CH_3), 33.4 (C), 33.5 (CH_3), 38.0 (CH_2), 38.5 (CH_2), 38.7 (C), 40.3 (CH_2), 41.8 (CH_2), 45.6 (CH_2), 53.7 (CH), 56.3 (CH), 76.4 (CH), 80.1 (C), 215.6 (C). IR (film): 1747, 1697, 1616, 1457, 1370, 1222, 1125, 1056, 1009, 930, 771, 665 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{19}H_{31}ClO_2Na$ ($M+Na^+$) 349.1910, found: 349.1902.

(3*R*,4*S*,5a*R*,7a*S*,11a*S*,11b*R*) -4- (Chloromethyl)-3,5a,8,8,11a-pentamethyltetradecahydronaphtho[2,1-b]oxepin-3-ol (27a) and (3*S*,4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-4-(chloromethyl)- 3,5a,8,8,11a-pentamethyltetradecahydronaphtho[2,1-b]oxepin-3-ol (27b). A CH_3MgBr solution (0.18 mL, 1.4 M THF/Toluene, 0.18 mmol) was added to a solution of **27** (120 mg, 0.36 mmol) in anhydrous THF (15 mL) previously cooled at -30º C and the mixture was kept stirring under argon atmosphere for 1 h. Then 10% HCl (1 mL) was added and the mixture was kept stirring for 5 min more. The solvent was evaporated and ether was added (30 mL). The organic solution was washed with water (3 x 10 mL) and brine (15 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (5% ether /hexane) to yield **27a** (49 mg, 38%) and **27b** (70 mg, 57%). **Compound 27a**. $[\alpha]_D^{25}$ +26.6 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.77 (s, 3H), 0.78 (s, 3H), 0.86 (s, 3H), 0.84 – 0.93 (m, 1H), 1.15 s, 3H), 1.18 (s, 3H), 1.23 – 1.84 (m, 15H), 3.21 (brs, 1H), 3.35 (dd, *J* = 11.0, 9.7 Hz, 1H), 3.80 (dd, *J* = 9.4, 1.8 Hz, 1H), 3.97 (dd, *J* = 11.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2 (CH_3), 18.5 (CH_2), 19.1 (CH_2), 20.89 (CH_2), 21.1 (CH_3), 21.7 (CH_3), 24.1, (CH_3), 33.3 (C), 33.3 (CH_3), 39.0 (C), 39.3 (CH_2), 39.7 (C), 42.0 (CH_2), 45.6 (CH_2), 47.5 (CH_2), 56.3 (CH), 58.3 (CH), 75.3 (C), 76.0 (CH), 78.7 (C). HRMS (FAB) *m/z*: calcd for $C_{20}H_{35}ClO_2Na$ ($M+Na^+$) 365.2223, found: 365.2236. **Compound 27b**. $[\alpha]_D^{25}$ +7.9 (c 0.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.79 (s, 3H), 0.85 (s, 3H), 0.86 (s, 3H), 1.10 (ddd, *J* = 11.4, 10.9, 2.3 Hz, 1H), 1.25 (s, 3H), 1.36 (s, 3H), 1.40 – 1.78 (m, 14H), 2.18 (ddd, *J* = 11.4,10.9, 2.0 Hz, 1H), 3.22 (q, *J* = 10.3 Hz, 1H), 3.63 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.67 (dd, *J* = 11.2, 2.8 Hz, 1H), 4.02 (dd, *J* = 6.2, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.2 (CH_3), 18.1 (CH_2), 18.5 (CH_2), 20.9 (CH_2), 21.1

(CH_3), 24.1 (CH_3), 24.9 (CH_3), 33.3 (C), 33.30 (CH_3), 39.0 (C), 39.1 (CH_2), 39.6 (CH_2), 42.1 (CH_2), 44.8 (CH_2), 45.5 (CH_2), 56.3 (CH), 58.1 (CH), 72.7 (C), 74.4 (CH), 79.3 (C). HRMS (FAB) *m/z*: calcd for $C_{20}H_{35}ClO_2Na$ ($M+Na^+$) 365.2223, found: 365.2215.

(2*S*,4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5a,8,8,11a-tetramethyl-3-methylenetetradecahydronaphtho[2,1-b]oxepin-2-ol (28). *tert*-Butyl hydroperoxide (0.22 mL, 1.2 mmol) was added to a solution of **24** (500 mg, 1.2 mmol) in anhydrous CH_2Cl_2 previously cooled at 0º C and the mixture was kept stirring under argon atmosphere for 5 min. Then, catalytic SeO_2 was added (1.3 mg, 0.12 mmol) and the mixture was kept stirring for 24 h. The solvent was evaporated, and ether was added (15 mL). The organic solution was washed with water (3 x 5 mL) and brine (5 mL), dried over anh. Na_2SO_4, and evaporated to afford a crude product that was purified by flash chromatography on silica gel (30% AcOEt /hexane) to yield **28** (400 mg, 83%). $[\alpha]_D^{25}$ +58.3 (c 0.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.04 (s, 6H), 0.77 (s, 3H), 0.82 (s, 3H), 0.84 (s, 3H), 0.88 (s, 9H), 1.11 (ddd, *J* = 13.4, 13.4, 4.0 Hz, 1H), 1.17 (s, 3H), 1.26 - 1.64 (m, 12H), 2.04 (ddd, *J* = 12.6, 12.6, 8.0 Hz, 1H), 3.52 (d, *J* = 10.5 Hz, 1H), 3.55 (s, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 4.27 (brs, 1H), 4.81 (dd, *J* = 8.0, 8.0 Hz, 1H), 4.83 (s, 1H), 5.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.2 (CH_3), -4.9 (CH_3), 16.0 (CH_3), 18.3 (C), 18.6 (CH_2), 20.3 (CH_2), 21.3 (CH_3), 23.4 (CH_3), 25.9 (3 CH_3), 33.20 (CH_2), 33.26 (C), 33.3 (CH_3), 37.5 (CH_2), 37.9 (C), 40.2 (CH_2), 41.8 (CH_2), 52.9 (CH), 56.0 (CH), 67.8 (CH_2), 69.1 (CH), 72.0 (CH), 78.0 (C), 104.3 (CH_2), 153.7 (C). IR (film): 3412, 1646, 1462, 1383, 1253, 1122, 836, 776 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{26}H_{48}O_3SiNa$ ($M+Na^+$) 459.3270, found: 459.3259.

(2*S*,4*S*,5a*R*,7a*S*,11a*S*,11b*R*)-4-(((Tert-butyldimethylsilyl)oxy)methyl)-5a,8,8,11a-tetramethyl-3-methylenetetradecahydronaphtho[2,1-b]oxepin-2-yl methanesulfonate (29). MsCl (124 mg, 1.08 mmol) and pyridine (5 mL) were added to a solution of **28** (200 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (15 mL), and the mixture was kept stirring under argon atmosphere for 12 h. Then, ether was added (50 mL) and the organic solution was washed with 10% HCl (10 mL), water (2 x 10 mL) and brine (10 mL), dried over anh. Na_2SO_4, and evaporate to yield **29** (210 mg, 91%). $[\alpha]_D^{25}$ -31.8 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.04 (s, 6H), 0.77 (s, 3H), 0.82 (s, 3H), 0.85 (s, 3H), 0.88 (s, 9H), 1.17 (s, 3H), 1.72-1.21 (m, 12H), 2.09-2.01 (m, 2H), 3.62 (d, *J* = 10.5 Hz, 1H), 3.63 (d, *J* = 10.5 Hz, 1H), 4.27 (m, 1H), 4.83 (brs, 1H), 5.05 (brs, 1H), 5.50 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: -5.1 (2 CH_3), 16.0 (CH_3), 18.4 (C) 18.6 (CH_2), 20.2 (CH_2), 21.3 (CH_3), 23.5 (CH_3), 25.8 (3 CH_3), 31.5 (CH_2), 33.2 (C), 33.3 (CH_3), 37.3 (CH_2), 37.9 (C), 40.1 (CH_2), 41.7 (CH_2), 52.5 (CH_3), 52.8 (CH), 56.0 (CH), 67.9 (CH_2), 71.2 (CH), 78.3 (C), 80.3 (C), 107.1 (CH_2), 147.8 (C). IR (film): 1727, 1631, 1462, 1385, 1359, 1253, 1177, 1122, 1082, 954, 836, 761 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{27}H_{50}O_5SSiNa$ ($M+Na^+$) 537.3046, found: 537.3061.

(4a*S*,6a*R*,7a*S*,12a*R*,12b*S*)-4,4,6a,12b-Tetramethyl-1,2,3,4,4a,5,6,6a,7a,8,10,12,12a,12b-tetradecahydrofuro[3,4-b]naphtho[1,2-f]oxepine (30). TBAF (74.6 mg, 0.28 mmol) was added to a solution of **29** (120 mg, 0.24 mmol) in anhydrous THF (10 mL), and the reflux mixture was kept stirring for 15 h. Then, the solvent was evaporated and ether was added (25 mL). The organic solution was washed with water (3 x1 0 mL) and brine (10 mL), dried over anh. Na_2SO_4, and evaporated to yield **30** (80 mg, 78%). $[\alpha]_D^{25}$ -14.1 (c 0.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.80 (s, 6H), 0.88 (s, 3H), 0.91 (dd, *J* = 12.9, 3.9 Hz, 1H), 1.15 (ddd, *J* = 14.7, 13.4, 2.7 Hz, 1H), 1.24 (s, 3H), 1.31 - 1.41 (m, 3H), 1.45 (dt, *J* = 13.3, 3.4 Hz, 1H), 1.56 - 1.79 (m, 5H), 1.90 (dd, *J* = 8.6, 2.8 Hz, 2H), 2.18 – 2.23 (m, 2H), 3.44 (t, *J* = 8.3 Hz, 1H), 4.06 (t, *J* = 8.1 Hz, 1H), 4.34 (dd, *J* = 12.7, 2.2 Hz, 1H), 4.40 (brd, *J* = 12.7 Hz, 1H), 4.86 (brs, 1H), 5.53 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.1 (CH_3), 18.7 (CH_2), 20.6 (CH_2), 21.3 (CH_3), 23.1 (CH_3), 23.8 (CH_2), 33.3 (CH_3), 33.4 (C), 37.9 (CH_2), 38.8 (C), 39.9 (CH_2), 41.9 (CH_2), 55.8 (CH), 56.1 (CH), 69.9 (CH), 71.0 (CH_2), 72.1 (CH_2), 79.3 (C), 121.6 (CH), 141.8 (C). IR (film): 1732, 1461, 1384, 1106, 1060, 926, 755 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{32}O_2Na$ ($M+Na^+$) 327.2300, found: 327.2286.

(4a*S*,6a*R*,7a*S*,12a*R*,12b*S*)-4,4,6a,12b-Tetramethyl-1,3,4,4a,5,6,6a,7a,8,12,12a,12b-dodecahydrofuro[3,4-b]naphtho[1,2-f]oxepin-10(2H)-one (31). Excess of PCC was added to a solution of **30** (50 mg, 0.165 mmol) in anhydrous CH_2Cl_2 (10 mL) and the reflux mixture was kept stirring under argon atmosphere for 12 h. When the reaction finished, the mixture was filtered on silica gel to afford a crude product that was purified by flash chromatography on silica gel (10% ether /hexane) to yield **31** (40 mg, 84%). $[\alpha]_D^{25}$ +6.4 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.80 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.14 (ddd, *J* = 13.5, 13.4, 4.1 Hz, 1H), 1.26 (s, 3H), 1.29 - 1.87 (m, 11H), 2.37 (m, 1H), 2.48 (dd, *J* = 19.8, 6.3 Hz, 1H), 3.86 (dd, *J* = 8.9, 7.3 Hz, 1H), 4.47 (t, *J* = 8.1 Hz, 1H), 5.15 (m, 1H), 6.96 (brd, *J* = 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.0 (CH_3), 18.5 (CH_2), 20.5 (CH_2), 21.2 (CH_3), 22.7 (CH_3), 24.8 (CH_2), 33.3 (CH_3), 33.4 (C), 38.1 (CH_2), 38.9 (C), 39.8 (CH_2), 41.8 (CH_2), 55.2 (CH), 56.1 (CH), 66.7 (CH), 70.0 (CH_2), 80.3 (C), 131.8 (C), 144.1 (CH), 169.5 (C). IR (film): 1764, 1682, 1457, 1386, 1210, 1190, 1114, 1018, 772, 668 cm^{-1}. HRMS (FAB) *m/z*: calcd for $C_{20}H_{30}O_3Na$ ($M+Na^+$) 341.2093, found: 341.2105.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
^{1}H and ^{13}C NMR spectra for all new compounds.

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