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Tetrahedron 60 (2004) 4693–4704
Tetrahedron

Computer-assisted design and lactonization of model *seco*-acid derivatives of lankanolide☆

Tatsuo Hamada,* Mitsugu Kiyokawa, Yukinari Kobayashi, Toshikazu Yoshioka, Junichiro Sano and Osamu Yonemitsu†

Faculty of Pharmaceutical Sciences, Hokkaido University, N-12, W-6, KITAKU, Sapporo 060-0812, Japan

Received 22 May 2003; revised 21 March 2004; accepted 22 March 2004

Abstract—In some cases, *seco*-acid derivatives (a precursor of macrolactone) did not cyclize to form the corresponding macrolactone. To design easily cyclizable *seco*-acid derivatives of lanaknolide, the conformation of several model *seco*-acids was calculated, and lactonization experiments of the *seco*-acids prepared from oleandomycin were carried out to elucidate the efficiency of the cyclization of the model *seco*-acid. The easily cyclable *seco*-acid was designed to be C8 exomethylene derivative of lankanolide *seco*-acid. On the other hand, *seco*-acid derivative having tertiary alcohol at C8 was predicted not to cyclize to form macrolactone.

1. Introduction

The target molecule, lankanolide **2**, is the aglicone of 14-membered macrolide lankamycin **1**. Lankamycin was isolated in 1960 by Gaumann et al.,[2] and the relative stereostructure of the macrolide was determined in 1972 by Keller-Schlierlein et al.[3] Since then, there has appeared no report of the total synthesis of this macrolide, while synthetic efforts have been carried out.[4] We are interested in the effect of the structure of the *seco*-acid derivative on the efficiency of macrolactonization (Fig. 1). In some cases, *seco*-acid derivatives did not cyclize to give macrolactone derivatives.[5] To avoid such a case, we decided to design the target *seco*-acid derivatives by computer-aided simulation before starting the synthesis.[6] In our design, there are two routes depending on whether before cyclization, C8 is quaternalized (route a) or after cyclization, an asymmetric center at C8 is introduced (route b). Route a is via *seco*-acid **II** which has tertiary alcohol at C8 position. In route b, macrolactone **IV** is oxidized to prepare a tertiary alcohol at C8 after cyclization. The critical point of these two routes will be the reactivity of *seco*-acids **II** and **V** Scheme 1. To predict the reactivity of *seco*-acids **II** and **V**, first, we calculated the conformation of the methyl ester of model *seco*-acid derivatives (**4**, **6** and **8**) corresponding to *seco*-acids **II** and **V**, and the lactones (**3**, **5**, and **7**) (Fig. 2).

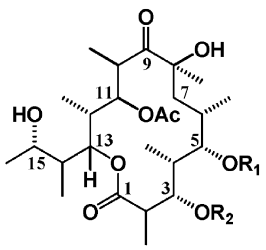

Figure 1. Lankamycin and lankanolide. Lankamycin (**1**): R_1=D-chalcose, R_2=acetylarcanose. Lankanolide (**2**): R_1=H, R_2=H.

2. Results and discussions

2.1. Computer-assisted design of model *seco*-acid

Recently, Goto et al. developed a conformational search method of chain compounds by stepwise bond rotation (conflex).[7] First, we calculated the conformations of *seco*-acid derivatives (**4**, **6**, and **8**) by using 'CONFLEX' and the obtained conformers were classified to conformation cluster (experimental detail was shown in Section 3.4). Similar conformation (differences of all dihedral angle to be compared are less than 10°) is classified in one cluster. The similarity of the clusters between *seco*-acid derivative and the corresponding lactone was also calculated, and the similarity was shown as cluster distance. The more similar the conformation of the cluster to be compared is, the

☆ See Ref. 1.

Keywords: Conformation calculation; *seco*-Acid; Lactonization; Lankanolide.
* Corresponding author. Tel./fax: +81-11-706-3980; e-mail address: hamada@pharm.hokudai.ac.jp
† Present address: Department of Chemistry, Okayama University of Science, Okayama 700-0005, Japan.

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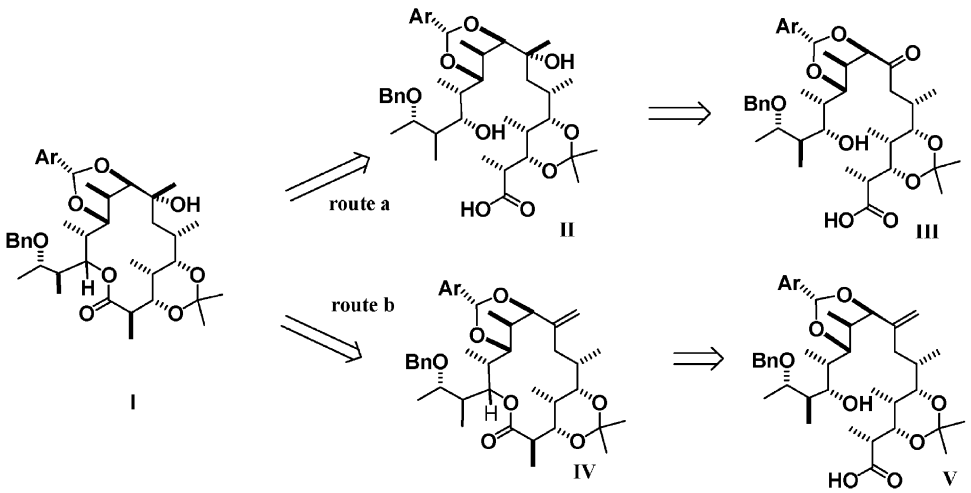
doi:10.1016/j.tet.2004.03.061



Scheme 1. Retro synthetic analysis of lankanolide.

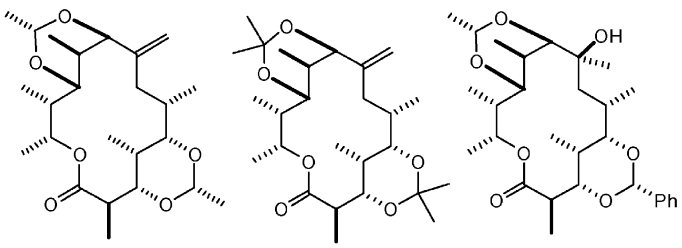


Figure 2. Model *seco*-acids and lactones for conformation calculation.

smaller the conformation distance is.[8] Obtained number of conformers having more than 0.01% population are shown below: 120 for **4**, 256 for **6**, 153 for **8**, 2 for **3**, 4 for **5**, 11 for **7**.

The results were shown in Table 1 (clustering results of conformers generated by conformation search) and Table 2 (cluster distance; cluster similarity between starting *seco*-acid and the corresponding cyclized lactone) and Figure 3. As shown in Figure 3, the simulated conformation of the methyl ester of *seco*-acid **4** showed a conformation cluster (#2, 15.2%) of the *seco*-acid is similar conformation to the corresponding cluster of lactone **3** (conformation distance=8.7).[8,9] On the other hand, the calculated conformation of diacetonide *seco*-acid **6** showed no similar conformation to the major cluster corresponding to lactone **5**. It is well known that the 6-membered ketal of anti-1,3-diol prefers twist-boat type,[10] and the most preferable conformer of 6-membered ketal of anti-1,3-diol (C9, C11) of model *seco*-acid **6** was also twist-boat (Fig. 3). However, most of the conformations of the corresponding lactone **5** was chair type (Fig. 3). Therefore, twist-boat conformer has to change to the more unstable chair conformer before cyclization. However, in the case of *seco*-acid **6**, there is a cluster (#11, population 1.5%) close to the lactone **5**, although population is not high.[9] The simulated conformation of **8** methyl ester also did not contain a similar conformation to the corresponding lactone **7** (conformation distance between the closest conformation of **8** was 49.7). Most of the conformation of model compound **8** is locked as shown in Figure 3, mainly becouse of hydrogen bonding between the tertiary alcohol at C8 and ether oxygen of 6-membered ketal of C3 and C5 diol. Because of the locked

Table 1. Major conformation clusters of model *seco*-acids (**4**, **6**, and **8**) and corresponding lactones (**3**, **5**, and **7**)

	Size[a]	Pop[b] (%)	Size	Pop (%)
Rank	**4**		**3**	
1	126	70.78	4	99.99
2	57	15.18	2	0.01
3	29	3.21		
4	62	2.90		
5	64	2.77		
Rank	**6**		**5**	
1	82	56.2	5	99.7
2	40	16.1	5	0.3
3	19	4.0		
4	28	3.4		
5	4	1.7		
11	14	1.5		
Rank	**8**		**7**	
1	23	99.2	32	99.9
2	2	0.8	27	0.1

[a] Number of conformers comprising a cluster.
[b] Combined percentage population of the component conformers.

Table 2. Cluster distance analysis of the model *seco*-acids and the corresponding lactones

	4	1	2	3	4	5	6	7	8	9	10	
3												
1		72.13	**8.72**	79.26	65.34	84.77	62.89	64.92	47.24	83.94	82.59	
2		81.25	42.25	86.16	72.81	90.3	76.95	75.59	62.56	91.69	87.34	
	6	1	2	3	4	5	6	7	8	9	10	11
5												
1		79.33	71.62	65.82	72.08	47.39	79.47	73.81	82.27	86.14	83.05	**6.44**
2		73.48	89.92	64.46	48.8	11.73	96.1	52.17	69.05	79.96	81.86	33.51
	8	1	2									
7												
1		49.77	48.69									

Close distances (less than 10) are printed in bold letters.

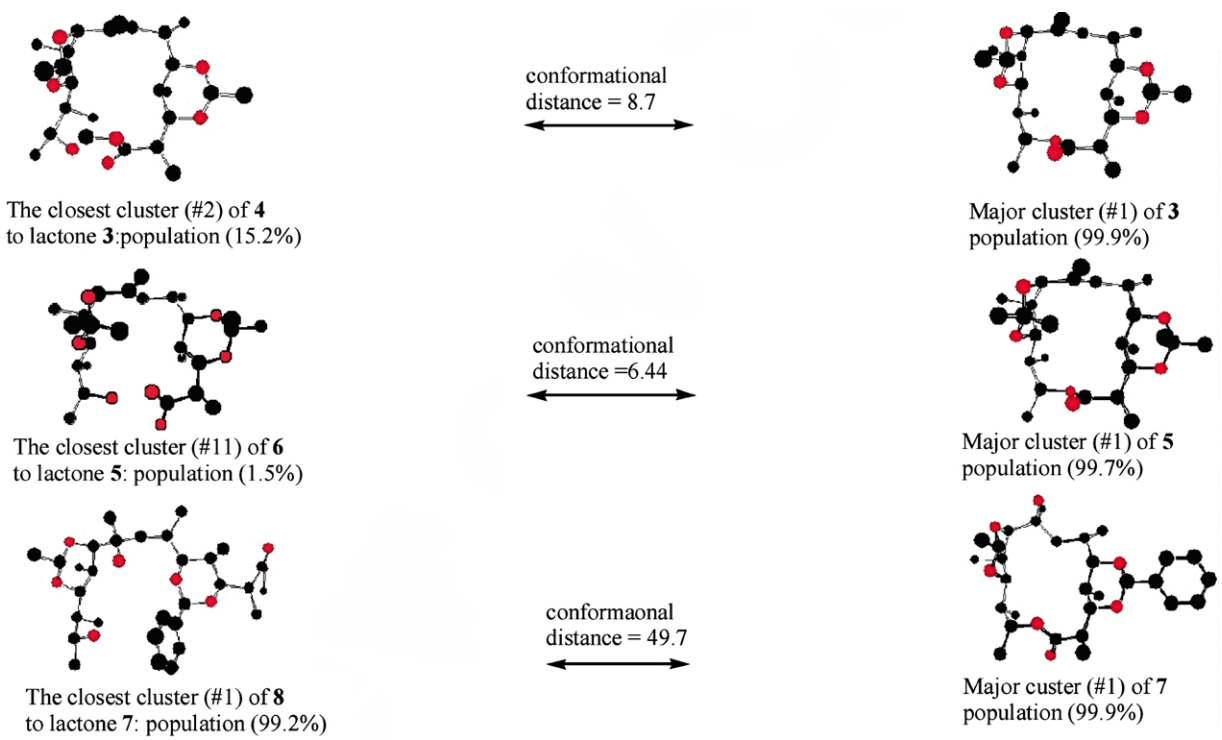
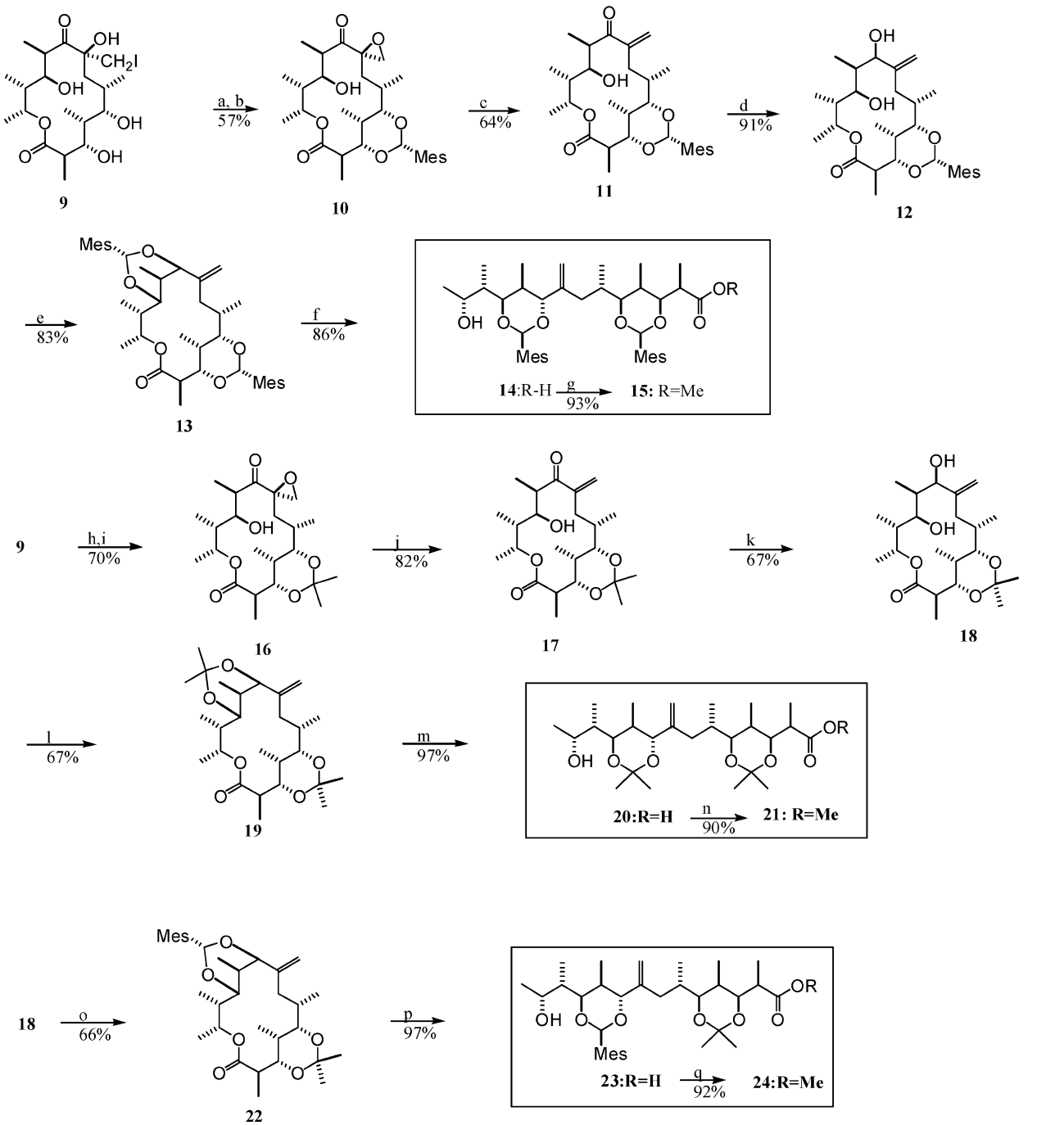


Figure 3. Conformational distance between the cluster of lactone (**3**, **5** and **7**) and the corresponding *seco*-acid (**4**, **6** and **8**).

structure, the reaction point (alcohol at C13 and terminal carboxylic acid) can not approach each other. This result suggests that *seco*-acid **4** having a similar conformation to the corresponding lactone will easily cyclize to form macrolactone.[9] The diacetonide *seco*-acid **6** will cyclize slowly in low yield. The *seco*-acid having a tertiary alcohol at C8 (**8**) can be predicted not to cyclize because unfavorable conformation to cyclize is locked by hydrogen bonding. To test the predicted reactivity of these three types of *seco*-acids, we synthesized several model *seco*-acids, and performed cyclization experiments.

2.2. Synthesis of model *seco*-acids (14, 20, 23, and 32)

seco-Acids (**14**, **20**, **23**, and **32**) were prepared starting from the known intermediate **9** reported by Paterson et al.[11] as shown in Schemes 2 and 3. The iodide **9** was converted to epoxy-ketone **10** via acetalization with mesitaldehyde dimethylacetal and cyclization of iodohydrin with $NaHCO_3$. The epoxide of **10** was deoxygenated to form *exo*-olefin **11**, followed by 1,2-reduction of enone to give diol **12** as a single diastereomer. Acetalization of diol of **12** and hydrolysis of lactone gave *seco*-acid **14**. *seco*-Acid **20** and **23** were synthesized by a similar method. Acetalization of **9** and epoxide formation gave **16** and deoxigenation of **16** gave **17**, then 1,2-reduction afforded diol **18** as a single isomer. The diol of **18** was protected as an acetonide and hydrolyzed with NaOH to form *seco*-acid **20**. Similar treatment of **18** with mesitaldehyde dimethylacetal, and hydrolysis of lactone gave *seco*-acid **23**. *seco*-Acid **32** was also synthesized starting from **9** as shown in Scheme 3. The diol of **9** was protected as a mesitilidene acetal, following reduction of ketone, and the resulting diol was again protected as a mesitilidene acetal to give **28**. The lactone and epoxide were reduced with LAH to form a triol. The primary alcohol of the triol was protected as a TBDMS



Scheme 2. Preparation of model *seco*-acid derivatives **14**, **20** and **23**. Reagents and conditions: (a) $MesCH(OMe)_2$, CSA, CH_2Cl_2, rt, 6 h; (b) 8% aq-$NaHCO_3$, THF, rt, 20 min; (c) $CrCl_2$, acetone–H_2O (2:1), 0 °C, 3 h; (d) $BaBH_4$, $CeCl_3$,THF, −25 °C, 4.5 h; (e) $MesCH(OMe)_2$, CSA, rt, 24 h; (f) 5 N-NaOH, DMSO, 90 °C, 5 h; (g) Me_3SiCHN_2, benene, rt, 1 h; (h) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt, 1 h; (i) 10% aq-$NaHCO_3$, THF, rt, 40 min; (j) $CrCl_2$, acetone–H_2O (2:1), 0 °C, 30 min; (k) $NaBH_4$, $CeCl_3$, −25 °C, 4.5 h; (l) 2-Methoxypropene, PPTS, CH_2Cl_2, 0 °C, 1.25 h; (m) 5 N-NaOH, DMSO, 90 °C, 7 h; (n) Me_3SiCHN_2, benzene, rt, 45 min; (o) $MesCH(OMe)_2$, CH_2Cl_2, CSA, rt, 6 h; (p) 5 N-NaOH, DMSO, 90 °C, 12 h; (q) Me_3SiCHN_2, benzene, rt, 45 min.

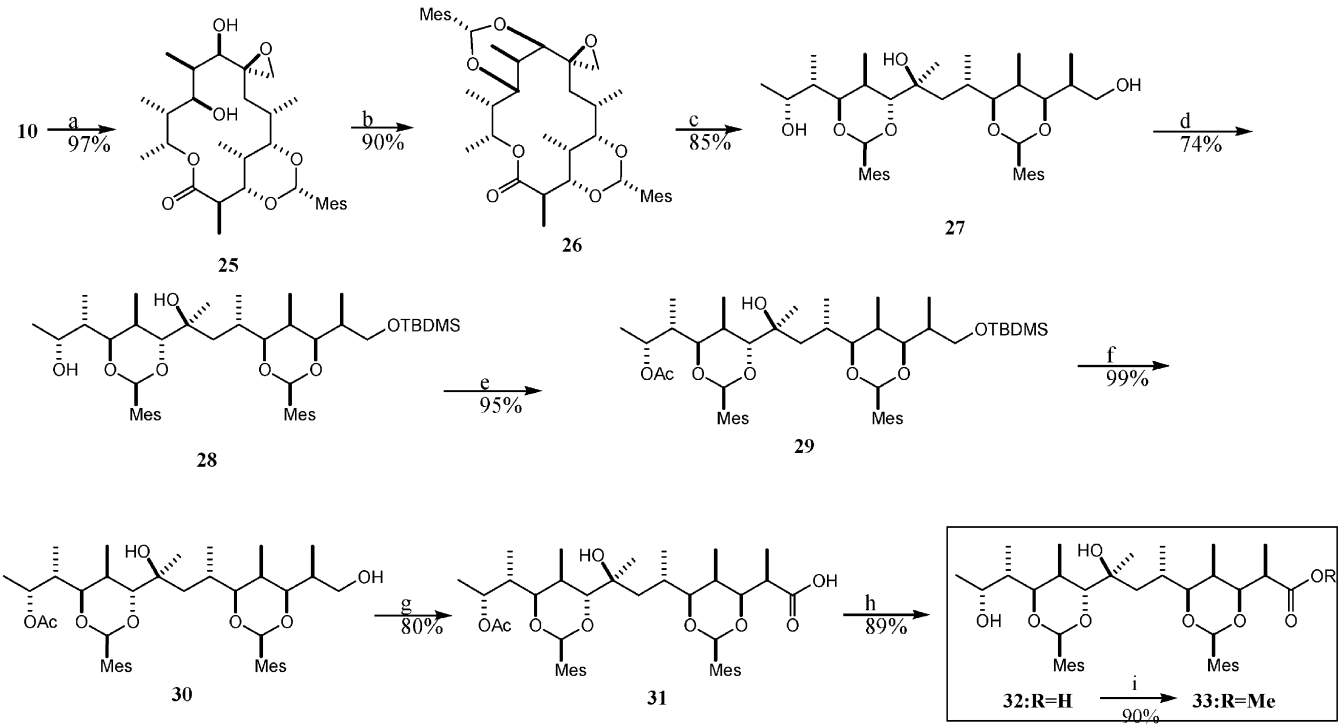
ether, and the secondary alcohol was acetylated to give **29**. Deprotection of TBDMS and Jones oxidation followed by deacetylation gave *seco*-acid **32**.

2.3. Cyclization experiments of the model *seco*-acids

seco-Acids (**14**, **20**, **23**, and **32**) were subjected to macrolactonization. The results of cyclization experiments are shown in Table 3 and Scheme 4. As we predicted, *seco*-acid **14** and **23** cyclize smoothly to give macrolactones **13** and **22** in high yield, even under the normal concentration conditions. On the other hand, *seco*-acid **20** (diacetonide) cyclized sluggishly to form lactone **19** in low yield even under the high dilution condition. *seco*-Acid **32** did not give **34** at all even under the high-dilution condition (Table 3 and Scheme 4).

2.4. Conclusion

The compatibility between computer-simulated reactivity



Scheme 3. Preparation of *seco*-acid derivative **32**. Reagents and conditions: (a) $NaBH_4$, *i*-PrOH-AcOEt (2:1), rt, 20 min. (b) $MesCH(OMe)_2$, CSA, CH_2Cl_2, rt, 5 h. (c) $LiAlH_4$, Et_2O, 30 °C, 2 h. (d) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 24 h. (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 33 h;. (f) n-Bu_4NF, THF, rt, 3.5 h. (g) Jones reagent, acetone, −30 °C, 5 h. (h) 15% NaOH, MeOH, rt, 24 h. (i) Me_3SiCHN_2, benzene, rt, 1 h.

and chemical reactivity is so important that the computer-simulated conformation analysis may predict the reactivity of intramolecular cyclization, and the most preferable model *seco*-acid to synthesize lankanolide is *seco*-acid **23**. In some cases, computer-assisted conformation analysis of model *seco*-acid may complement synthetic design. We are continuing research along this line, and we reported a successful example of total synthesis of lankanolide **2** via the *seco*-acid designed according to the model *seco*-acid **23**.[12]

3. Experimental

3.1. General procedures

All reactions were carried out under argon atmosphere unless otherwise specified. CH_2Cl_2, DMSO and triethylamine were distilled from $CaCl_2$ and stored on molecular sieves. Ether and THF were distilled from sodium-benzophenone ketyl, and used freshly. Optical rotations were measured with a JASCO DIP-370 polarimeter, and P-1030 polarimeter. IR spectra were recorded with a JASO FT/IR-5300 spectorometer. Proton and carbon NMR were recorded with JEOL-EX-270, JEOL-EX-400 and Bruker ARX-500 spectrometers, using tetramethylsilane as an internal standard. Mass spectra were recorded with JEOL JMS-700 TZ and JEOL HMS-HX1100. Column chromatographies were performed on Kanto silicagel 60N (spherical, neutral; 40–100 μm). Merk precoated silicagel $60F_{254}$ plates (0.25 mm thickness) were used for analytical thin-layer chromatography.

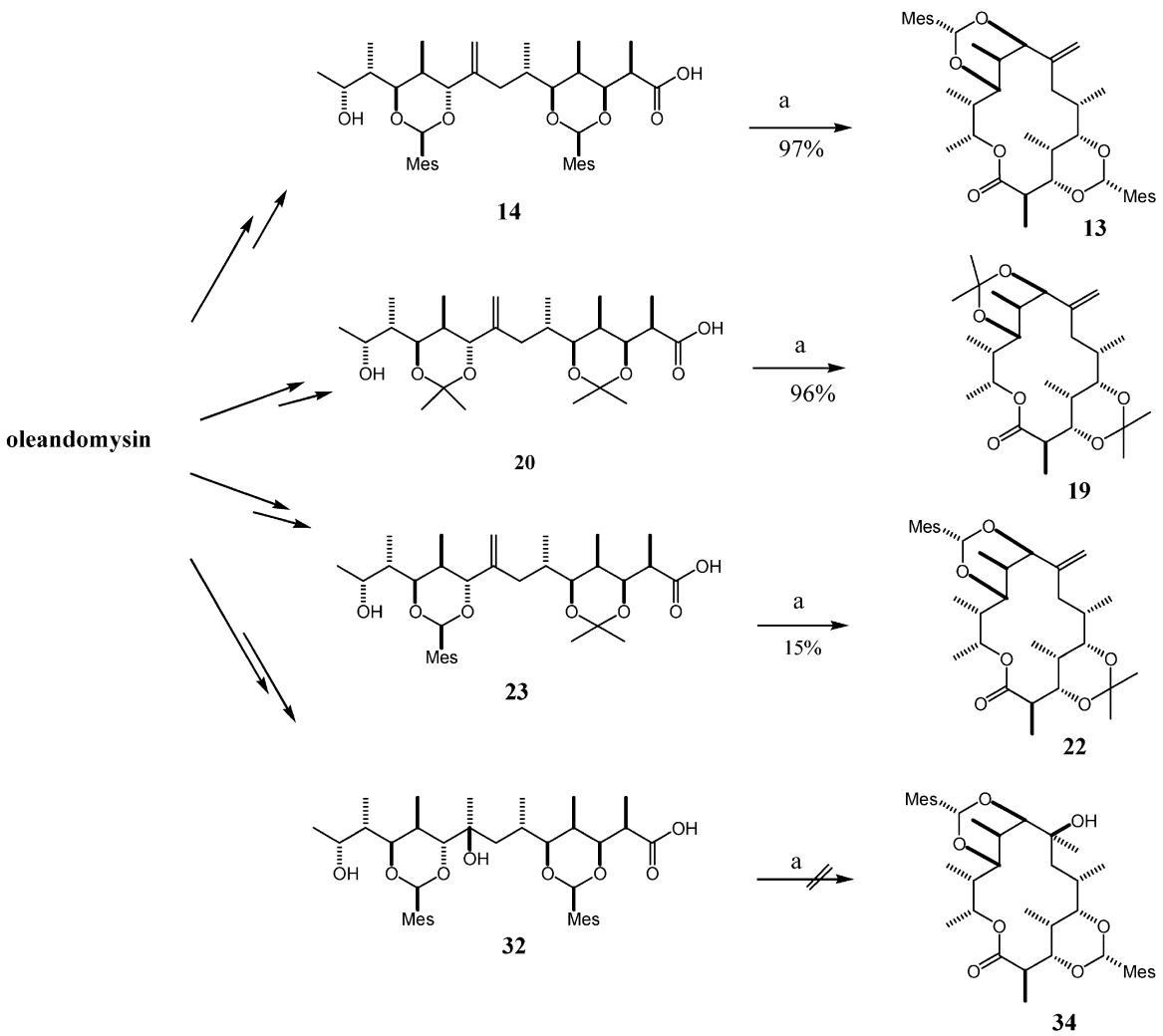
3.2. Preparation of *seco*-acids 14, 20, and 33

3.2.1. 3,5-*O*-(2,4,6-Trimethylbenzylidene)-oleandonolide (10). A solution of **9** (264 mg, 0.51 mmol) and mesitaldehyde dimethylacetal (63 mg, 1.02 mmo0l) and camphorsulfonic acid (3 mg, 13 μmol) in CH_2Cl_2 (4 ml) was stirred for 6 h and then treated with sat. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined extract was washed with brine, dried over Na_2SO_4, and evaporated to

Table 3. Cyclization reactions of several *seco*-acids

seco-Acid (mM)	Cyclization method[a]	DMAP (mol equiv.)	Reaction temp (°C)	Reaction time (h)	Yield (%)
14 (1.0)	A	2.5	130	43	97
14 (6.6)	B	3	rt	3	82
23 (1.0)	A	2.5	130	11	96
23 (1.0)	B	3	rt	3	81
20 (1.0)	A	2.5	130	43	15
20 (1.0)	B	2.5	rt	43	0
32 (1.0)	A	2.5	130	43	0

[a] A; High-dilution condition: To a 6 mM toluene solution of DMAP in toluene, was added slowly a 2 mM toluene solution of the mixed anhydride prepared from *seco*-acid and 2,4,6-trichlorbenzoyl chloride. B: Normal condition: DMAP was added to a 10 mM toluene solution of the mixed unhydride.



Scheme 4. Effect of C8 functional groups on macrolactonization. Reagents and conditions: (a) to a solution of DMAP was added slowly a dilute solution of the mixed anhydride prepared from *seco*-acid (**14**, **20**, **23** and **32**) and 2,4,6-trichlorobenzoyl chloride.

dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (3:1) to give iodohydrin (187 mg, 57%) as an amorphous solid.

$[\alpha]_D^{22}=-46.0°$ (c=0.98, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 6.81 (2H, s), 5.80 (1H, s), 5.63 (1H, dq, J=2.0, 6.9 Hz), 3.93 (1H, dd, J=10.3, 3.4 Hz), 3.84 (1H, dd, J=6.0, 1.3 Hz), 3.80 (1H, s), 3.69 (1H, t, J=6.0 Hz), 3.59 (1H, dd, J=5.2, 0.9 Hz), 3.58 (1H, t, J=6.5 Hz), 3.53 (1H, d, J=10.3 Hz), 3.42 (1H, d, J=10.3 Hz), 3.12 (1H, q, J=6.9 Hz), 3.11 (1H, d, J=3.0 Hz), 2.84 (1H, dq, J=10.3, 6.7 Hz), 2.57 (1H, m), 2.45 (6H, s), 2.23 (3H, s), 2.21 (1H, m), 2.01 (1H, q, J=6.5 Hz), 1.84 (1H, d, J=14.5 Hz), 1.82 (1H, dd, J=14.5, 6.1 Hz), 1.70–1.58 (2H, m), 1.25 (3H, d, J=6.7 Hz), 1.16 (3H, d, J=6.6 Hz), 1.36 (3H, d, J=6.7 Hz), 1.08 (3H, d, J=7.0 Hz), 1.06 (3H, d, J=7.4 Hz), 0.93 (3H, d, J=7.3 Hz). MS (EI) m/z 644 (M^+). HRMS (EI) m/z Calcd for $C_{30}H_{45}O_7I$ (M^+) 644.2228, found 644.2205.

A cooled (0 °C) mixture of the above iodohydrin (151.2 mg, 0.23 mmol) in THF (25 ml) and 8% aq. $NaHCO_3$ (25 ml) was stirred for 20 min and then treated with phosphate buffer (pH 6.86, 25 ml). After stirring for further 5 min, the mixture was extracted with CH_2Cl_2 and the combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (3:1) to give **10** (118 mg, quant.) as an amorphous solid.

$[\alpha]_D^{25}=-52.0°$ (c=0.77, $CHCl_3$). IR (neat) 1740 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 6.77 (2H, s), 6.06 (1H, dq, J=1.0, 0.6 Hz), 5.98 (1H, s), 4.46 (1H, dq, J=2.0, 6.4 Hz), 4.01 (1H, dd, J=1.5, 7.3 Hz), 3.89 (1H, dd, J=1.5, 10.7 Hz), 2.91 (1H, d, J=4.9, 6.8 Hz), 2.77 (1H, d, J=4.4 Hz), 2.66 (1H, dd, J=2.0, 6.4 Hz), 2.55 (6H, s), 2.29–2.34 (1H, m), 2.30 (1H, d, J=3.9 Hz), 2.13 (3H, s), 1.95 (1H, dd, J=12.2, 15.6 Hz), 1.77–1.88 (1H, m), 1.47–1.55 (1H, m), 1.42 (1H, dd, J=2.0, 15.6 Hz), 1.37 (3H, d, J=6.8 Hz), 1.36 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6.3 Hz), 1.10 (3H, d, J=6.3 Hz), 1.10 (3H, d, J=6.3 Hz), 1.05 (3H, d, J=7.3 Hz), 0.76 (3H, d, J=6.8 Hz). ^{13}C NMR (100.4 Hz, C_6D_6) δ 204.9, 173.9, 137.9, 137.1, 132.1, 130.1, 127.9, 103.9, 85.2, 70.1, 69.9, 63.5, 47.2, 46.5, 41.7, 33.3, 32.3, 21.0, 20.9, 18.4, 16.6, 13.3, 9.7, 6.4. MS (EI) m/z 516 (M^+). HRMS (EI) m/z Calcd for $C_{30}H_{44}O_7$ (M^+) 516.3087, found 516.3068.

3.2.2. 8,8a-Deoxa-3,5-*O*-(2,4,6-trimethylbenzylidene)-oleandonolide (11). To a cooled (0 °C) solution of **10** (428 mg, 0.83 mmol) in acetone (7 ml) was added dropwise $CrCl_2$ (306 mg, 2.49 mmol) in H_2O 3.5 ml, and the solution was treated with sat. $NaHCO_3$, and extracted with ether. The combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate to give *exo*-olefin **11** (266 mg, 64%) as an amorphous solid.

$[\alpha]_D^{22}=-55.7°$ (c=0.98, $CHCl_3$). IR (neat) 1740, 1702, 1620 cm^{-1}. ^1H NMR (400 MHz, C_6C_6) δ 6.78 (2H, s), 6.05 (1H, s), 5.95 (1H, s), 5.76 (1H, dq, J=1.0, 6.4 Hz), 5.13 (1H, s), 4.03 (1H, dd, J=1.0, 6.4 Hz), 3.80 (1H, dd, J=5.4, 8.8 Hz), 3.68 (1H, dd, J=1.5, 10.8 Hz), 2.89 (1H, dq, J=1.0, 6.8 Hz), 2.82 (1H, dq, J=6.4, 10.8 Hz), 2.71 (1H, d, J=5.4 Hz), 2.56 (6H, s), 2.48–2.56 (1H, m), 2.15 (3H,s), 2.13–2.18 (1H, m), 1.98 (1H,dd, J=6.8, 13.7 Hz), 1.91 (1H, dd, J=2.4, 18.1 Hz), 1.38–1.47 (1H, m), 1.34 (3H, d, J=6.8 Hz), 1.29 (3H, d, J=6.4 Hz), 1.17 (3h, d, 6.4 Hz), 1.15 (3H, d, J=7, 3 Hz), 1.06 (3H, d, J=6.4 Hz), 0.72 (3H, d, J=7.3 Hz). ^{13}C NMR (100.4 MHz, C_6D_6) δ 204.79, 174.5, 146.8, 138.0, 137.1, 131.9, 130.2, 127.9, 121.0, 104.0, 85.2, 80.8, 70.6, 43.6, 42.6, 41.6, 34.0, 33.1, 33.0, 21.0, 20.9, 18.5, 16.6, 13.3, 9.8, 9.0, 6.6. MS (EI) m/z 500 (M^+). HRMS (EI) m/z Calcd for $C_{30}H_{44}O_6$ (M^+) 500.3184, found 500.3137.

3.2.3. (9*R*)-3,5-*O*-(2,4,6-Trimethylbenzylidene)-8,8a-deoxa-9-dehydro-oleandonolide (12). To a cooled (−25 °C) solution of **11** (266 mg, 0.53 mmol) in THF (8 ml) was added $CeCl_3.H_2O$ (102 mg, 0.27 mmol) and after stirring for 30 min, $NaBH_4$ 38 mg, (1.00 mmol) was added to the suspension and the mixture was stirred for 4.5 h at −25 °C and treated with sat. NH_4Cl and extracted with ether. The combined extract was washed with brine and dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (3:1) to afford diol **12** (230 mg, 91%) as an amorphous solid.

$[\alpha]_D^{23}=-28.0°$ (c=0.98, $CHCl_3$). IR (neat) 1730, 1660, 1620 cm^{-1}. ^1H NMR (400 MHz, C_6C_6) δ 6.80 (1H,s), 6.02 (1H, s), 5.64–5.67 (1H, m), 5.61 (1H, s), 5.14 (1H, s), 4.35 (1H, dd, J=1.5, 114 Hz), 3.75–3.82 (3H, m), 3.56–3.62 (2H, m), 2.78–2.97 (3H, m), 2.59 (6H, s), 2.15 (1H, s), 1.59–1.90 (4H, m), 1.34 (3H, d, J=7.0 Hz), 1.31 (3H, d, J=6.6 Hz), 1.20 (3H, d, J=7.3 Hz), 1.14 (3H, d, J=7.0 Hz), 1.04 (3H, d, J=6.6 Hz), 0.68 (3H, d, J=7.0 Hz). MS (EI) m/z 502 (M^+); HRMS (EI) m/z Calcd for $C_{30}H_{46}O_6$ (M^+) 502.3230, found 502.3322.

3.2.4. (9*R*)-3,5:9,11-Bis-*O*-(2,4,6-trimethylbenzylidene)-8,8a-deoxa-9-dihydro-oleandonolide (13). A solution of the above diol **12** (72 mg, 0.14 mmol) and mesitaldehyde dimethylacetal (82 mg, 0.92 mmol) and camphorsulfonic acid (3 mg) was stirred for 24 h and then treated with sat. $NaHCO_3$. The mixture was extracted with ether and the extract was washed with brine and dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with benzene hexane (1:1) to hexane and ethyl acetate (9:1) to give dimesitilidene acetal **13** (73 mg, 86%) as an amorphous solid.

$[\alpha]_D^{22}=-67.4°$ (c=1.02, $CHCl_3$). IR (neat) 1720, 1630, 1630 cm^{-1}. ^1H NMR (400 MHz, C_6C_6) δ 6.80 (4H, d, 10.0 Hz), 6.48 (1H, s), 6.15 (1H, s), 5.86 (1H, dq, J=0.9, 6.6 Hz), 5.73 (1H, s), 5.28 (1H,s), 4.43 (1H, dd, J=2.0, 7.0 Hz), 4.36 (1H, br. s). 3.96 (1H, d, J=10.9 Hz), 3.63 (1H, dd, J=1.0, 10.0 Hz), 2.88 (6H, s), 2.84–2.90 (1H, m), 2.73–2.78 (1H, s), 2.57 (1H,s), 2.13 (6H, d, J=6.8 Hz), 1.88–2.01 (2H, m), 1.92 (1H, dd, J=17.5, 12.0 Hz), 1.69 (1H, br d, J=17.5 Hz), 1.50–1.56 (1H, m), 1.40 (3H, d, J=6.6 Hz), 1.39 (3H, d, J=6.8 Hz), 1.33 (3H, d, J=6.6 Hz), 1.23 (3H, d, J=7.1 Hz), 0.91 (3H, d, J=7.3 Hz), 0.77 (3H, d, J=7.3 Hz). MS (EI) m/z (M^+) 630. HRMS (EI) m/z Calcd for $C_{40}H_{56}O_6$ (M^+) 632.4077, found 632.4080.

3.2.5. (9*R*)-3,9:9,11-Bis-*O*-(2,4,6-trimethylbenzylidene)-8,8a-deoxa-9-dihydrooleandonolide *seco*-acid (14). A solution of **13** (175 mg, 0.28 mmol)and 5-N NaOH (1.6 ml, 8 mmol) in DMSO (3.8 ml)was stirred for 5 h at 90 °C and then cooled to room temperature and extracted with ether. The aqueous layer was neutralized with 10% aq. HCl (6 ml). The mixture was extracted with ether and the combined extract was washed with brine and dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on a silicagel column eluted with hexane and ethyl acetate (1:2) to give *seco*-acid **14** (154 mg, 86%) as an amorphous solid. Because NMR of the *seco*-acid showed peak broadening, the *seco*-acid was characterized as its methyl ester **15**.

$[\alpha]_D^{23}=-57.9°$ (c=0.50, $CHCl_3$). IR (neat) 1720, 1630, 1620 cm^{-1}. MS (EI) m/z 650 (M^+). HRMS (EI) m/z Calcd for $C_{40}H_{58}O_7$ (M^+) 640.4183, found 650.4166.

3.2.6. (9*R*)-3,5:9,11-Bis-*O*-(2,4,6-trimethylbenzylidene)-8,8a-deoxa-9-dihydrooleandonolide *seco*-acid methyl ester (15). To a solution of **14** (12.0 mg, 1.5 μmol) in benzene 1.0 ml) was added MeOH (200 μl) and 10% hexane solution of trimethylsilyldiazomethane (200 μl, 176 μmol) and the solution was stirred for 1 h and then treated with acetic acid and the solution was diluted with ether and washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (4:1) to give methyl ester **15** (11.4 mg, 93%) as an amorphous solid.

^1H NMR (400 MHz, C_6C_6) δ 6.73 (4H, m) 6.15 (1H,s), 5.79 (1H, s), 5.11 (1H,s), 4.29 (1H, br s), 4.20 (1H, dd, J=2.0, 10.3 Hz), 3.98 (1H, dq, J=2.1, 6.6 Hz), 3.93 (1H, dd, J=2.1, 10.1 Hz), 3.35 (3H, s), 3.17 (1H, dd, J=2.1, 9.7 Hz), 3.00 (1H, br dd, J=3.0, 15.0 Hz), 2.87 (1H, dq, J=6.8, 10.1 Hz), 2.54 (3H, s), 2.39 (3H, s), 2.19 (3H, s), 2.10–2.04 (1H, m), 1.00–2.04 (1H, m), 1.78–1.89 (3h, M), 1.32 (3h, D, J=6.8 Hz), 1.28 (3H, d, J=6.8 Hz), 1.14 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=6.6 Hz), 0.80 (3H, d, J=6.8 Hz), 0.66 (3H, d, J=7.1 Hz).

3.2.7. 3,5-*O*-(Isopropylidene)-oleandonolide (16). Compound **16** was prepared following the known method by Paterson et al.[11] To a solution of **9** (130 mg, 0.273 mmol)

and 2,2-dimethoxpropane (6 ml, 48.9 mmol) in CH_2Cl_2 (10 ml) was added PPTS (7 mg, 0.028 mmol) at rt. The solution was stirred for 1 h at rt, then treated with phosphate buffer (pH 7.0), and extracted with CH_2Cl_2. The combined extract was concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (2:1) to give acetonide (105 mg, 75%). To a cooled (0 °C) solution of the acetonide (460 mg, 0.830 mol) in THF (75 ml) was added 10% aq.$NaHCO_3$ (75 ml), and the mixture was stirred for 40 min, then treated with phosphate buffer (pH7.0). The mixture was extracted with CH_2Cl_2 and the combined extract was dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (2:1) to give **16** (355 mg, quantitative yield) as an amorphous solid.

$[\alpha]_D^{23}=-50.1°$ (c=1.20, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.76 (1H, dq, J=1.2, 6.6 Hz), 4.36 (1H, m), 4.01 (1H, dd, J=1.3, 6.9 Hz), 3.74 (1H, J=1.3, 10.7 Hz), 3.10 (1H, d, J=4.2 Hz), 3.03 (1H, dq, J=1.8, 6.5 Hz), 2.96 (1H, d, J=4.2 Hz), 2.75 (1H, dq, J=6.6, 10.6 Hz), 2.41 (1H, d, J=5.5 Hz), 2.24 (1H. dd, J=12.4, 15.7 Hz), 1.96–2.08 (2H, m), 1.65 (1H, m), 1.42 (3H, s), 1.41 (3H, s), 1.28 (3H, d, J=6.6 Hz), 1.16 (3H, d, J=6.5 Hz), 1.07 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.5 Hz), 1.03 (3H, d, J=7.2 Hz), 1.01 (3H, d, J=7.2 Hz).

3.2.8. 8,8a-Deoxa-3,5-*O*-(2,4,6-isopropylidene)-oleandonolide (17). To a cooled (0 °C) solution of **16** (2.03g, 4.76 mmol) in acetone (40 ml) was added dropwise $CrCl_2$ (1.76 g, 14.28 mmol) in H_2O (20 ml). After stirring for 30 min, the solution was treated with sat. $NaHCO_3$, extracted with brine and dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate to give *exo*-olefin **17** (1.60 g, 82%) as an amorphous solid.

$[\alpha]_D^{24}=-30.9°$ (c=1.00, $CHCl_3$). IR (neat) 1720 cm$^-$ ^{1}H NMR (400 MHz, C_6C_6) δ 6.00 (1H,s), 5.74 (1H, dq, J=1.5, 6.00 Hz), 5.08 (1H, s), 4.10 (1H, dd, J=1.5, 6.2 Hz), 3.72–3.79 (2H, m), 2.72–2.90 (3, m), 1.79–2.36 (5H, m), 1.33 (3H, d, J=6.6 Hz), 1.24 (6H, s), 1.17 (3H, d, J=6.6 Hz), 1.15 (3H, d, J=6.6 Hz), 1.10 (3H, d, J=6.2 Hz), 0.69 (3, d, J=7.0 Hz). MS (EI) m/z 410 (M^+). IHRMS (EI) m/z Calcd for $C_{23}H_{38}O_6$ (M^+) 410.2669, found 410.2643.

3.2.9. (9*R*)-3,5-*O*-Isopropylidene-8,8a-deoxa-9-dihydro-oleandonilide (18). To a cooled (−25 °C) solution of **17** 200 mg, 0.49 mmol) in THF (7.5 ml) was added $CeCl_3$. $7H_2O$ (94 mg, 0.54 mmol) and after stirring for 1 h, $NaBH_4$ 30 mg, (0.79 mmol) was added to the suspension and the mixture was stirred for 4.5 h at −25 °C and treated with sat. NH_4Cl and extracted with ether. The combined extract was washed with brine and dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (3:1) to afford diol **18** (205 mg, quantitative yield) as an amorphous solid.

$[\alpha]_D^{21}=25.0°$ (c=1.20). ^{1}H NMR (400 MHz, C_6D_6) δ. 5.48 (1H, s), 5.46 (1H, dd, J=6.6, 1.0 Hz), 5.07 (1H, s), 4.33 (1H, dd, J=6.6, 1.0 Hz), 4.00 (1H, br. s), 3.62 (1H, dd, J=10.5, 1.0 Hz), 3.46 (1H, m), 3.37 (1H, d, J=8.0 Hz), 3.03 (1H, d, J=4.0 Hz), 2.63 (1H, dd, J=11.5, 6.8 Hz), 2.50 (1H, m), 2.04 (1H, m), 1.97 (1H, dd, J=17.0, 11.5 Hz), 1.50–1.61 (2H, m), 1.44 (6H, s), 1.25 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=6.8 Hz), 1.03 (3H, d, J=7.3 Hz), 0.98 (3H, d, J=6.8 Hz), 0.98 (3H, d, J=7.3 Hz). ^{13}C NMR (100.4 MHz, C_6D_6), δ 175.8, 147.6, 109.2, 100.6, 72.972.5, 72.1, 69.5, 42.6, 41.6, 35.3, 34.6, 32.4, 32.0, 29.7, 19.9, 18.7, 16.3, 13.2, 9.6, 8.7, 7.7. MS (EI) m/z 412 (M^+). HRMS (EI) m/z Calcd for $C_{23}H_{40}O_6$ (M^+) 412.2825, found 412.2838.

3.2.10. (9*R*)-3,5:9,11-Bis-*O*-isopropylidene-8,8a-deoxa-9-dihydrooleandonolide (19). A solution of the above diol **18** (112 mg, 0.27 mmol) in CH_2Cl_2 was added 2-methoxy-propene (80 ml, 0.81 mmol) and PPTS (20 mg, 85 μmol) at 0 °C and the solution was stirred for 1.25 h and then treated with sat. $NaHCO_3$ and extracted with ether. The combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane ethyl acetate (8:1) to give diacetonide **19** (85 mg, 70%) as an amorphous solid.

$[\alpha]_D^{19}=-26.6°$ (c=0.23, $CHCl_3$). IR (neat) 1730, 1640, 1620 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6) δ 5.62 (1H, s), 5.47 (1H, dq, J=1.0, 6.8 Hz), 5.22 (1H, br. s), 4.24 (1H, br. s), 4.19 (1H, dd, J=1.5, 6.4 Hz), 3.57 (1H, dd, J=1.0, 10.7 Hz), 3.43 (1H, d, J=9.3 Hz), 2.68 (1H, ddq, J=6.8, 2.5, 10.7 Hz), 2.49–2.56 (1H, m), 2.11 (1h, DD, J=6.5, 13.5 Hz), 1.94–1s.96 (2H, m), 1.69 (1H, dd, J=6.5, 13.5 Hz), 1.49–1.53 (1H, m), 1.45 (3H, s), 1.44 (3H, s), 1.40 (3H.s), 1.29 (3H, s), 1.22 (3H, d, J=6.8 Hz), 1.13 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.04, (3H, d, J=6.4 Hz), 0.93 (3H, d, 6.7 Hz). ^{13}C NMR (100.4 Hz, C_6D_6) δ 174.0, 144.8, 113.9, 100.8, 100.2, 80.8, 77.2, 71.9, 69.6, 68.5, 41.0, 40.2, 33.7, 32.5, 32.4, 31.0, 29.8, 29.0, 26.8, 19.7, 18.6, 16.2, 13.0, 11.7, 7.8, 7.4. MS (EI) m/z 452 (M^+). HRMS (EI) m/z Calcd for $C_{26}H_{44}O_6$ (M^+) 452.3138, found 452.3120.

3.2.11. (9*R*)-3,5:9,11-Bis-*O*-isopropilidene-8,8a-deoxa-9-dihydrooleandonolide *seco*-acid (20). A solution of the above diacetonide lactone **19** (121 mg, 0.29 mmol) and 5 N-NaOH (1.7 ml) in DMSO (3.9 ml) was stirred for 7 h at 90 °C. After cooling to room temperature, the solution was extracted with ether. The combined organic layer was washed with sat. $NaHCO_3$ and water and the combined aqueous layer was neutralized with 10% HCl and extracted with ether and the extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (1:2) to give *seco*-acid **20** (91 mg, 66%) as an amorphous solid. Because NMR spectrum of the *seco*-acid showed peak broadening, the *seco*-acid was characterized as its methyl ester **21**.

3.2.12. (9*R*)-3,5:9,11-Bis-*O*-isopropilidene-9-dihydro-oleandonolide *seco*-acid methyl ester (21). To a solution of **20** (10.0 mg, 21.3 μmol) in benzene 1.0 ml) was added MeOH (200 μl) and 10% hexane solution of trimethyl-silyldiazomethane (200 μl, 176 μmol) and the solution was stirred for 45 min and then treated with acetic acid and the

solution was diluted with ether and washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (4:1) to give methyl ester **21** (10.3 mg, quantitative) as an amorphous solid.

$[\alpha]_D^{21}=-20.0°$ (c=0.78). ^{1}H NMR (400 MHz, C_6D_6) δ 5.08 (1H, br. s), 4.92 (1H, br. s), 4.13 (1H, br. s). 4.06 (1H, dd, J=2.0, 5.0 Hz), 4.02 (1H, dd, J=4.4, 10.7 Hz), 3.87 (1H, d, J=7.3 Hz), 3.37 (3H, s), 3.35 (1H, dd, J=2.0, 10.3 Hz), 3.09 (1H, br. d, J=14.2 Hz), 2.87 (1H, m), 2.22–2.28 (1H, m), 2.05–2.15 (2H, m), 1.78–1.88 (2H, m), 1.64 (1H, dd, J=10.7, 13.7 Hz), 1.49 (3H, s), 1.43 (3H, s), 1.39 (3H, d, J=6.8 Hz), 1.36 (3h, S), 1.30, 3h, S), 1.15 (3H, d, J=6.4 Hz), 1.13 (3H, d, J=7.3 Hz), 0.91 (3H, d, J=6.8 Hz), 0.80 (3H, d, J=6.4 Hz), 0.67 (3H, d, J=7.3 Hz). MS (EI) m/z 484 (M^+). HRMS (EI) m/z Calcd for $C_{27}H_{48}O_7$ (M^+) 484.3400, found 484.3410.

3.2.13. 3,5-*O*-Isopropylidene-9,11-*O*-(2,4,6-trimethylbenzylidene)-(9*R*)-8,8a-deoxa-9-dihydrooleandonolide (22). A solution of diol **18** (205 mg, 0.50 mmol) and mesitaldehyde dimethylacetal (291 mg, 1.50 mmol) and camphorsulfonic acid (3 mg) was stirred for 6 h at room temperature. The solution was treated with sat. $NaHCO_3$ and extracted with CH_2Cl_2 and the combined extract was washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate to give **22** (180 mg, 66%) as an amorphous solid.

$[\alpha]_D^{23}=-39.2°$ (c=0.31, $CHCl_3$). IR (neat) 1720, 1630, 1610 cm^{-1}. ^{1}H NMR (400 MHz, C_6C_6) δ 6.82 (2H, s), 6.44 (1H, s), 5.86 (1H, dq, J=7.0, 1.0 Hz), 5.74 (1H, br. s), 5.28 (1H, br. s), 4.48 (1H, dd, J=2.0, 7.0 Hz), 4.37 (1H, br. s), 3.97 (1H, dd, 1.0, 10.7 Hz), 3.61 (1H, d, J=1.0, 9.8 Hz), 2.88 (6H, s), 2.80–2.85 (1H, m), 2.57–2.63 (1H, m), 2.13 (3H, s), 1.93 (1H, dd, J=6.8, 13.2 Hz), 1.80–1.87 (3H, m), 1.67 (1H, dd, J=17.1, 2.5 Hz), 1.58 (3H, s), 1.52 (1H, m), 1.45 (3H, s), 1.39 (3H, d, J=6.8 Hz), 1.36 (3H, d, J=6.3 Hz), 1.21 (3H, d, J=6.8 Hz), 1.19 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz), 0.73 (3H, J=7.3 Hz). ^{13}C NMR (100.4 MHz, C_6D_6) δ 174.4, 143.1, 138.1, 137.7, 132.1, 130.2, 128.6, 127.9, 111.8, 100.5, 98.0, 82.4, 78.1, 72.3, 69.3, 41.9, 70.3, 34.1, 32.6, 30.1, 29.5, 20.9, 19.6, 18.2, 16.4, 13.7, 13.1, 7.98, 7.14. MS (EI) m/z 542 (M^+). HRMS (EI) m/z Calcd for $C_{33}H_{50}O_6$ (M^+) 542.3608542, found 542.3608.

3.2.14. (9*R*)-3,5-*O*-Isopropylidene-9,11-*O*-(2,4,6-trimethylbenzylidene)-8,8a-deoxa-9-dihydrooleandonolide *seco*-acid (23). A solution of the **22** 160 mg, 0.30 mmol) and 5 N-NaOH (1.7 ml, 8.5 mmol) was stirred for 12 h at 90 °C, and after cooling to rt, was extracted with ether. The aqueous layer was neutralized with 10% HCl and extracted with ether. The combined extract was washed with water and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate to give *seco*-acid **23** 163 mg, 97%) as an amorphous solid. Because NMR spectrum of the *seco*-acid **23** showed peak broadening, the *seco*-acid was characterized as its methyl ester **24**.

$[\alpha]_D^{23}=-51.4°$ (c=1.00, $CHCl_3$). IR (neat) 1710, 1640, 1610 cm^{-1}. MS (EI) m/z 560 (M^+). HRMS (EI) m/z Calcd for $C_{33}H_{52}O_7$ (M^+) 560.3713, found 560.3738.

3.2.15. (9*R*)-3,5-*O*-Isopropylidene-9,11-*O*-(2,4,6-trimethylbenzylidene)-8,8a-deoxa-9-dihydrooleandonolide *seco*-acid methyl ester (24). A solution of **23** (20.0 mg, 35.7 μmol) and MeOH (400 μl) and 10% hexane solution of Me_3SiCHN_2 (400 μl, 35.7 μmol) was stirred for 45 min at room temperature and then treated with acetic acid and the solution was diluted with ether and washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (4:1) to give methyl ester **24** (18 mg, 88%) as an amorphous solid.

$[\alpha]_D^{21}=-49.3°$ (c=0.67, $CHCl_3$). EIMS m/z 574 EIHRMS m/z 574.3852 $(M+H)^+$ [Calcd for $C_{34}H54O_7$ (M^+) 574.3870]. ^{1}H NMR (400 MHz, C_6C_6) δ 6.75 (2H, s), 6.23 (1H, s), 5.21 (1H, s), 5.17 (1H, s), 4.39 (1H, s), 4.25 (1H, dd, J=2.0, 9.8 Hz), 4.01–4.06 (1H, m), 3.99 (1H, dd, J=1.5, 10.3 Hz), 3.36 (1H, s), 3.27 (1H, dd, J=8.3, 1.5 Hz), 2.93 (1H, d, J=14.2 Hz), 2.81 (1H, dq, J=10.0, 6.8 Hz), 2.65 (6H, s), 2.11 (3H,s), 2.07 (1H, dd, J=6.3, 12.7 Hz), 1.85–1.97 (2H, m), 1.69–1.75 (2H, m), 1.38–1.42 (1H, m), 1.35 (3H, d, J=6.8 Hz), 1.31 (3H, s), 1.23 (3H, s), 1.02–1.06 (6H, m), 0.78 (3H, d, J=6.8 Hz), 0.71 (3H, d, J=6.8 Hz). ^{13}C (100.4 MHz, C_6D_6) δ 174.7, 146.5, 137.1, 130.1, 128.6, 127.9, 114.0, 99.3, 81.2, 78.4, 75.7, 67.8, 51.1, 42.5, 40.0, 38.2, 32.8, 32.0, 29.8, 29.2, 20.9, 19.9, 19.6, 15.4, 14.0, 13.8, 9.5, 5.4. MS (EI) m/z 574 (M^+). HRMS (EI) m/z Calcd for $C_{33}H_{52}O_7$ (M^+) 574.3870, found 574.3852.

3.2.16. (9*R*)-9-Dihydro-3,5-*O*-(2,4,6-trimethylbenzylidene)-oleandonolide (25). To a cooled (0 °C) solution of **10** in *iso*-propanol and ethyl acetate (1:2, 48 ml) was added sodium borohydride (60.4 mg, 1.60 mmol), and the solution was stirred for 15 min at room temperature, and treated with sat. NH_4Cl and extracted with CH_2Cl_2 and the combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (2:1) to give **25** (399 mg, 97%) as an amorphous solid.

$[\alpha]_D^{21}=-6.47$ (c=0.66, $CDCl_3$). IR (neat) 1735, 1620 cm^{-1}. ^{1}H NMR (270 MHz, C_6D_6) δ 6.78 (2h, S), 6.08 (1h, s), 5.70 (1H, dq, J=0.8, 6.8 Hz), 4.21 (1H, dd, J=1.1, 7.3 Hz), 4.10 (1H, m), 4.03 (1H, dd, J=1.5, 10.8 Hz), 3.75 (1H, d, J=10.2 Hz), 3.54 (1H, dd, J=3.5, 10.2 Hz), 3.22 (1H, d, J=5.8 Hz), 3.14 (1H, d, J=5.3 Hz), 2.90 (1H, dq, J=6.6, 10.8 Hz), 2.57 (6H, s), 2.32 (1H, d, J=5.3 Hz), 2.21 (1H, m), 2.13 (3H,s), 1.94–2.09 (2H, m), 1.84 (1H, m), 1.66 (1H, dd, J=12.5, 15.6 Hz), 1.37 (3H, d, J=6.6 Hz), 1.36 (3H, d, J=6.8 Hz), 1.17 (3H, d, J=6.7 Hz), 1.11 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.8 Hz), 0.74 (3H, d, J=7.0 Hz). MS (EI) m/z 518 (M^+). HRMS (EI) Calcd for $C_{30}H_{46}O_7$ (M^+) 518.3241, found 518.3291.

3.2.17. (9*R*)-9-Dihydro-3,5:9,11-bis-*O*-(2,4,6-trimethylbenzylidene)-oleandonolide (26). A solution of **25** (250 mg, 482 mmol) and mesitaldehyde dimethylacetal (118 mg, 965 mmol) and camphorsulfonic acid (10 mg, 43 mmol) in CH_2Cl_2 (5 ml) was stirred for 5 h at room temperature, and then treated with excess triethylamine. The reaction mixture was concentrated in vacuo and the residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (15:1 to 1:1) to give **26** (188 mg, 90% based on reacted **25**) as an amorphous solid and recovered **25** (75.5 mg, 33%) as an amorphous solid.

$[\alpha]_D^{23}=-75.8$ (c=0.63, $CDCl_3$).IR (neat) 1730 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 7.17 (1H, s), 6.78 (2H, s), 6.77 (2H, s), 6.10 (1H, s), 5.88 (1H, dq, J=0.7, 6.7 Hz), 4.61 (1H, dd, J=0.8, 5.2 Hz),4.22 (1H, dd, J=1.1, 10.8 Hz), 4.01 (1H, dd, J=1.1, 9.3 Hz), 3.78 (1H, s), 2.94 (1H, dq, J=6.8, 10.8 Hz), 2.91 (6H, s), 2.72 (1H, d, J=5.4 Hz), 2.53 (6H, s), 2.20 (1H, m), 2.18 (1H, d, J=5.4 Hz), 2.12 (3H, s), 2.10 (3H, s), 2.05 (1H, m), 1.90–2.00 (2H, m), 1.57 (1H,), 1.44 (3H, d, J=6.8 Hz), 1.41 (3H, d, J=6.8 Hz), 1.38 (3H, d, J=6.8 Hz), 1.13 (3H, d, J=6.4 Hz), 0.94 (3H, d, J=6.7 Hz), 0.88 (3H, d, J=7.3 Hz). MS (EI) m/z 648 (M^+). HRMS (EI) m/z Calcd for $C_{40}H_{56}O_7$ (M^+) 648.4023, found 648.4030.

3.2.18. (2*S*,3*R*,4*S*,5*R*,6*R*,8*S*,10*R*,11*S*,12*R*,13*R*)-2,4,6,8,10,12-Hexamethyl-3,5:9,11-bis-(2,4,6-trimethylbenzylidenedioxy)-tetradecane-1,8,13-triol (27). To a solution of lactone **26** (343 mg, 529 mmol) in ether (10 ml) was added $LiAlH_4$ (60.2 mg, 1.59 mmol) in ether (1 ml), the reaction mixture was stirred for 2 h at 30 °C. To the mixture was added water (60 μl) and 15% NaOH (60 μl) and water (180 μl) consecutively. The reaction mixture was stirred for 1 h, and dried over Na_2SO_4. After stirring over night, an insoluble material was filtered thru a pad of celite and washed with ether. The combined filtrate was concentrated to dryness and the residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (1:1) to give **27** (294 mg, 85%).

^1H NMR (400 MHz, C_6D_6) δ 6.95 (1H, s), 6.73 (2H, s), 6.71 (2H, s), 5.79 (1H, s), 4.64 (1H, dd, J=2.8, 10.8 Hz), 3.94 (1H, m), 3.82 (1H, s), 3.52 (1H, dd, J=2.0, 9.3 Hz), 3.31 (1H, s), 3.26 (1H, dd, J=4.8, 11.0 Hz), 3.20 (1H, dd, J=4.8, 11.0 Hz), 3.09 (1H, dd, J=2.1, 10.1 Hz), 2.78 (1H, d, J=9.5 Hz), 2.51 (6H, s), 2.15 (1H, m), 2.12 (3H, s), 2.06 (1H, m), 1.85 (1H, ddd, J=2.9, 6.9, 10.8 Hz), 1.66–1.79 (2H, m), 1.46 (1H, dd, J=10.8, 13.5 Hz), 1.38 (3H, s), 1.38 (3H, d, J=6.9 Hz), 1.11 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=6.7 Hz), 1.03 (3H, d, J=6.7 Hz), 0.73 (3H, d, J=7.0 Hz), 0.39 (3H, d, J=7.2 Hz). MS (EI) m/z 653 (M^+-1)). HRMS (EI) m/z Calcd for $C_{40}H_{61}O_7$ 653. (M^+-1) 4414, found 653.4408.

3.2.19. (2*R*,3*R*,4*S*,5*R*,6*R*,7*S*,9*R*,10*R*,11*S*,12*R*,13*S*)-14-[(*t*-Butyl)dimetylsilyloxy]-3,5,7,9,11,13-hexamethyl-4,6:10,12-bis-(2,4,6-trimethylbenzylidenedioxy)-tetradecane-2,7-diol (28). A solution of **27** (185 mg, 238 μmol) and triethylamine (66.3 μl, 476 μmol) and *t*-butyldimethylsilyl chloride (59.8 mg, 397 μmol) and DMAP (4 mg, 32.7 μmol) in CH_2Cl_2 (5 ml) was stirred for 32 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with sat. $NaHCO_3$ and sat. NH_4Cl and brine consecutively, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried on $MgSO_4$ and the residue was concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (10:1) to give **28** (160 mg, 74%) as an amorphous solid.

^1H NMR (400 MHz, C_6D_6) δ 6.96 (1H, s), 6.73 (2H, s), 6.71 (2H, s), 5.87 (1H, s), 4.65 (1H, dd, J=2.5, 10.3 Hz), 3.94 (1H, m), 3.85 (1H, s), 3.64 (1H, dd, J=2.1, 9.4 Hz), 3.37 (1H, dd, J=4.3, 10.2 Hz), 3.54 (1H, dd, J=4.3, 10.2 Hz), 3.31 (1H, s), 3.22 (1H, dd, J=2.1, 9.7 Hz), 2.89 (1H, d, J=9.8 Hz), 2.69 (6H, s), 2.16 (1H, m), 2.12 (3H, s), 2.11 (3H, s), 2.08 (1H, m), 1.72–1.92 (3H, m), 1.40 (3H, s), 1.40 (3H, d, J=7.0 Hz), 1.14 (3H, d, J=6.8 Hz), 1.14 (3H, d, J=6.8 Hz), 1.12 (3H, d, J=7.2 Hz), 1.02 (9H, s), 0.80 (3H, d, J=7.0 Hz), 0.34 (3H, d, J=7.1 Hz), 0.08 (3H, s), 0.07 (3H, s). MS (EI) m/z 768 (M^+). HRMS (EI) m/z Calcd for $C_{46}H_{76}O_7Si$ (M^+) 768.5360, found 768.5412.

3.2.20. (2*R*,3*R*,4*S*,5*R*,6*R*,7*S*,9*R*,10*R*,11*S*,12*R*,13*S*)-2-Acetoxy-14-[(*t*-butyl)dimethylsilyloxy]-3,5,7,9,11,13-hexamethyl-4,6:10,12-bis-(2,4,6-trimethylbenzylidenedioxy)-tetradecane-7-ol (29). A solution of **28** (137 mg, 178 μmol) and triethylamine (81 μl, 582 μmol) and acetic anhydride (22 μl, 235 μmol) and DMAP (5 mg, 41 μmol) in CH_2Cl_2 was stirred for 33 h at room temperature. The solution was washed with sat. $NaHCO_3$, and sat NH_4Cl, and the combined aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried on $MgSO_4$ and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (10:1) to give **29** (137 mg, 95%) as an amorphous solid.

$[\alpha]_D^{21}=-23.2$ (c=1.06, $CDCl_3$).IR (neat) 1740 cm^{-1}. ^1H NMR (270 MHz, C_6D_6) δ 6.80 (2H, s), 6.75 (1H, s), 6.72 (2H, s), 5.89 (1H, s), 5.59 (1H, dq, J=1.7, 6.8 Hz), 4.34 (1H, dd, J=2.2, 10.8 Hz), 3.65 (1H, dd, J=1.5, 9.2 Hz), 3.55 (1H, dd, J=4.1, 10.3 Hz), 3.43 (1H, s), 3.38 (1H, dd, J=4.1, 10.3 Hz),3.37 (1H, s), 3.25 (1H, dd, J=1.5, 10.4 Hz), 2.79 (6H, s), 2.52 (6H, s), 2.17 (1H, m), 2.12 (6H, s), 1.85 (3H, s), 1.78–1.94 (3H, m), 1.62 (1H, m), 1.42 (3H, s), 1.36 (3H, d, J=7.1 Hz), 1.16 (3H, d, J=6.7 Hz), 1.15 (3H, d, J=6.78 Hz), 1.03 1.02 (3H, d, J=7.0 Hz), 0.81 (3H, d, J=6.9 Hz), 0.44 (3H, s), 0.43 (1H, d, J=6.8 Hz), 0.08 (3H, s), 0.07 (3H, s). MS (FAB) m/z 811 (M^++1). HRMS (FAB) m/z Calcd for $C_{48}H_{79}O_8Si$ (M^++1) 811.5540, found 811.5545.

3.2.21. (2*S*,3*R*,4*S*,5*R*,6*R*,8*S*,9*R*,10*R*,11*S*,12*R*,13*R*)-13-Acetoxy-2,4,6,8,10,12-hexamethyl-3,5:9,11-bis-(2,4,6-trimethylbenzylidenedioxy)-tetradecane-1,8-diol (30). To a solution of **29** (131 mg, 161 μmol) in THF (5 ml) was added 1 M THF solution of TBAF (320 μl, 320 μmol), and the solution was stirred for 3.5 h at room temperature and treated with brine and extracted with CH_2Cl_2. The extract was dried on $MgSO_4$ and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel eluting with hexane and ethyl acetate (2:1) to give **30** (111 mg, 99%) as an amorphous solid.

$[\alpha]_D^{21}=-18.8$ (c=1.22, $CDCl_3$). IR (neat) 1740 cm^{-1}. ^1H NMR δ 6.68 (2H, s), 6.74 (1H, s), 6.71 (2H, s), 5.81 (1H, s), 5.59 (1H, dq, J=2.3, 6.7 Hz), 4.34 (1H, dd, J=2.6, 10.3 Hz), 3.52 (1H, dd, J=1.9, 9.8 Hz), 3.43 (1H, s), 3.28 (1H, s), 3.25 (1H, dd, J=4.7, 10.4 Hz), 3.18 (1H, dd, J=4.7, 10.4 Hz), 3.10 (1H, dd, J=1.8, 9.7 Hz), 2.78 (6H, s), 2.52 (6H, s), 2.12 (6H, s), 2.11 (1H, m), 1.91 (1H, dq, J=2.1, 7.0 Hz) 1.85 (3H, s), 1.40 (3H, s), 1.34 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=6.8 Hz), 1.05 (3H, d, J=6.7 Hz), 1.03 (3H, d, J=6.8 Hz), 0.72 (3H, d, J=7.1 Hz), 0.45 (3H, d, J=7.0 Hz). MS (EI) m/z 696 (M^+). HRMS (EI) m/z Calcd for $C_{42}H_{64}O_8$ (M^+) 696.4601, found 696.4622.

3.2.22. (8*S*,9*R*)-13-*O*-Acetyl-3,5-*O*-isopropylidene-9,11-*O*-(2,4,6-trimeethylbenzylidene)-8-hydroxy-8,8a-deoxa-9-dihydro-oleandonolide *seco*-acid (31). To a cooled (−40 °C) solution of **30** (102 mg, 146 μmol) in acetone (3.5 ml) was added 2.67 M Jones reagent (106 μl. 283 μmol) and the solution was stirred for 5 h at −30 °C, then treated with isopropanol and diluted with water, and extracted with CH_2Cl_2. The combined extract was dried on $MgSO_4$ and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (1:2) to give **31** (83 mg, 80%) as an amorphous solid.

IR (neat) 1745 cm^{-1}. ^1H NMR δ 6.81 (2H, s), 6.72 (3H, s), 5.79 (1H, s), 5.59 (1H, dq, J=2.2, 6.6 Hz), 4.31 (1H, dd, J=2.5, 10.7 Hz), 3.86 (1H, dd, J=2.1, 9.8 Hz), 3.39 (1H, s), 3.09 (1H, dd, J=1.8, 9.7 Hz), 2.86 (1H, dq, J=6.7, 10.6 Hz), 2.78 (6H, s), 2.48 (6H, s), 2.13 (6H, s), 2.02–2.18 (2H, m), 1.83–1.90 (1H, m), 1.87 (3H, s), 1.56–1.79 (2H, m), 1.37 3H, s), 1.34 (3H, d, J=7.1 Hz), 1.29 (3H, d, J=7.0 Hz), 1.17 (3H, d, J=6.8 Hz), 1.03 (3H, d, J=6.6 Hz), 0.67 (3H, d, J=7.1 Hz), 0.45 (3H, d, J=7.1 Hz). MS (EI) m/z 710 (M^+). HRMS (EI) m/z Calcd for $C_{42}H_{62}O_9$ (M^+) 710.4394, found 710.4432.

3.2.23. (8*S*,9*R*)-3,5-*O*-Isopropylidene-9,11-*O*-(2,4,6-trimeethylbenzylidene)-8-hydroxy-8,8a-deoxa-9-dihydro-oleandonolide *seco*-acid (32). To a solution of **31** (55 mg, 77.5 μmol) in MeOH (3 ml) was added 15% NaOH (0.6 ml, 2.25 mol). The reaction mixture was stirred for 24 h and then treated with phosphate buffer (pH7), extracted with ether and the extract was washed with brine and dried over $MgSO_4$ and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with MeOH and CH_2C_2 (1:50) to give *seco*-acid **32** (48 mg, 93%) as an amorphous solid. Because this *seco*-acid could not be purified completely, analytical data was taken after conversion to its methyl ester **33**.

IR (neat) 1735 cm^{-1}. ^1H NMR (400 MHz, C_6D_6) δ 6.92 (1H, s), 6.74 (2H, s), 6.71 (2H, s), 5.76 (1H, s), 4.62 (1H, dd, J=2.5, 9.7 Hz), 3.96 (1H, dq, J=2.4, 6.6 Hz), 3.83 (1H, dd, J=1.8, 10.2 Hz), 3.29 (1H, s), 3.07 (1H, dd, J=1.8, 10.5 Hz), 2.81 (1H, dq, J=7.0, 10.3 Hz), 2.66 (6H, s), 2.46 (6H, s), 2.12 (3H, s), 2.11 (3H, s), 2.01–2.13 (2H, m), 1.89 (1H, m), 1.82 (1H, dq, J=2.5, 7.0 Hz), 1.34 (3H, d, J=7.1 Hz), 1.28 (3H, d, J=6.9 Hz), 1.13 (3H, d, J=6.9 Hz), 1.11 (3H, d, J=6.6 Hz), 0.67 (3H, d, J=6.8 Hz), 0.35 (3H, d, J=7.0 Hz). MS (EI) m/e 668 (M^+).

3.2.24. (8*S*,9*R*)-3,5-*O*-Isopropylidene-9,11-*O*-(2,4,6-trimeethylbenzylidene)-8-hydroxy-8,8a-d4eoxa-9-dihydro-oleandonolide *seco*-acid methyl ester (33). To a solution of **32** (17 mg, 25.4 μmol) in benzene (1.0 ml) was added MeOH (200 μl) and 10% hexane solution of trimethylsilyldiazomethane (200 μl, 176 μmol) and the solution was stirred for 1 h and then treated with acetic acid and the solution was diluted with ether and washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (4:1) to give methyl ester **33** (15.6 mg, 90%) as an amorphous solid.

$[\alpha]_D^{19}=-16.9$ (c=0.76, $CDCl_3$). IR (neat) 1720 cm^{-1}. ^1H NMR (500 MHz, C_6D_6) 6.95 (1H, s), 6.73 (2H, s), 6.70 (2H, s), 5.76 (1H, s), 4.69 (1H, dd, J=10.6, 2.4 Hz), 3.98 (1H, dd, J=10.1, 6.8 Hz), 3.95 (1H, broad s), 3.69 (1H, s), 3.36 (3H, s), 3.09 (1H, dd, J=10.2, 6.8 Hz), 2.86 (1H, dq, J=6.8, 10.1 Hz), 2.67 (6H, s), 2.48 (6H, s), 2.12 (3H, s), 2.11 (3H, s), 2.10 (1H, m), 1.86 (1H, m), 1.69 (1H, dd, J=14.4, 5.4 Hz), 1.38 (3H, d, J=7.2 Hz), 1.34 (3H, s), 1.29 (3H, d, J=6.8 Hz), 1.13 (3H, d, J=6.9 Hz), 1.11 (3H, d, J=6.6 Hz), 1.00 (1H, dd, J=14.0, 2.7 Hz), 0.66 (3H, d, J=7.1 Hz), 0.37 (3H, d, J=7.1 Hz). ^{13}C NMR (125 MHz, C_6D_6) 174.29, 139.61, 137.57, 136.92, 132.75, 130.80, 130.34, 13o.12, 128.26, 127.44, 102.63, 96.78, 87.67, 86.30, 83.56, 78.70, 79.64, 70.46, 59.97, 51.20, 46.18, 42.64, 39.77, 32.10, 39.14, 29.47, 28.49, 24.16, 20.85, 20.79, 20.60, 18.70, 18.08, 15.30, 15.15, 14.14, 10.93, 6.71. MS (FAB) m/e 683 (M^++1). EXMS (FAB) m/z Calcd for $C_{41}H_{63}O_8$ 683.4544 (M^++1), found 683.4555.

3.3. General methods of lactonization of *seco*-acid 14, 20, 23 and 32

3.3.1. Lactonization under the high dilution condition. To a solution of *seco*-acid (1, 20, 33) (0.047 mmol) in THF (0.95 ml) was added triethylamine (7.2 μl, 52 μmol) and 2,4,6-trichlorobenzoyl chlodide (7.4 μl, 0.047 mmol) and the solution was stirred for 19.5 h and then diluted with toluene (24 ml) and transferred to a syringe. The solution in the syringe was added to a solution of DMAP (139 mg, 1.18 mol) in toluene (20 ml) at 130 °C over 5 h with micro feeder syringe pump. The resulting mixture was stirred for further 6 h at 130 °C. After cooling to rt, the mixture was concentrated to dryness in vacuo and the residue was treated with sat. NH_4Cl and extracted with ether and the combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (10:1) to give lactone **13** (97%) from**14**, **19** (15%) from **20**, **22** (96%) from **23**, and **34** (0%) from **32**.

3.3.2. Lactonization under the normal condition. To a solution of *seco*-acid (35.7 μmol) in THF (3.5 ml) was added triethylamine (5.5 μl, 40 μmol) and 2,4,6-trichlorobenzoyl chloride (5.6 μl, 36 μmol) at room temperature and the solution was stirred for 17 h and then to the mixture was added DMAP (13.2 mg, 108 μmol), and after stirring for further 3 h the mixture was concentrated to dryness in vacuo and the residue was treated with sat. NH_4Cl and extracted with ether. The combined extract was washed with brine and dried over Na_2SO_4 and concentrated to dryness in vacuo.

The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (10:1) to give lactone **13** (82%), **19** (0%), and **22** (81%).

3.3.3. The attempted lactonization of *seco*-acid 32 (34). To a solution of *seco*-acid **33** (15.4 mg, 23 μmol) in THF (0.5 ml) was added triethylamine (5.2 μl, 34.5 μmol), and 2,4,6-trichlorobenzoyl chloride (5.4 μl, 11.5 μmol), and then the solution was stirred for 20 h at rt, and diluted with toluene (10 ml). The solution was transferred to syringe, added over 8.5 h with a syringe pump to a refluxed solution of DMAP (65 mg, 530 μmol) in toluene (20 ml), the mixture was stirred for 11.5 h under reflux. The mixture was cooled to rt, and concentrated to dryness in vacuo. The residue was treated with sat. NH_4Cl and extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$. The residue was chromatographed on a silicagel column eluting with hexane and ethyl acetate (10:1 to 1:1) to give complicated product and the desired lactone **33** (0%) (Scheme 4).

3.4. Conformation calculations of model *seco*-acids (4, 6 and 8) and corresponding lactones (3, 5, 7), and clustering of conformers

Conformation calculation of model *seco*-acids and the corresponding lactones were carried out by a conformational space searching algorism 'CONFLEX ver.4' working on PC-unix (Linux). Extended MM2 was used as the energy minimizer. The conformers obtained by conformation search were classified into clusters using the single lincage algorithm accelelated by the doubly linked list method.[8a,b] The conformational similarity between a pair of conformers (clusters) A and B was measured by conformational distance, d_{AB}, defined as the root-mean-square difference in the major backbone and ring dihedral angles (Eq. 1):[8c]

$$d_{AB} = \sqrt{\frac{\sum_{i=1}^{17} (w_i^A - w_i^B)^2}{17}} \quad (1)$$

where w_i^A and w_i^B are the *i*-th dihedral angle of conformers A and B, respectively. Seventeen dihedral angle used in Eq. 1 refer to nine backbone bonds along the segment of C3–C4–C5–C6–C7–C8–C9–C10–C11–C12, and to four each along the two dioxane rings, C3–O3–C (acetal or ketal carbon)–O5–C5 and C9–O9–C (acetal or ketal carbon)–O11–C11. The end portions, C3–C2–C1–OMe and C12–C13–OH and OH and phenyl group rotation, was not included in the cluster analysis, although all these bonds were rotated during the conformation search. When a pair of conformers have a conformational distance d_{AB} shorter than 10°, they belong to the same cluster.

References and notes

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9. Conformations of the 6-membered acetal and ketal of *syn*-1,3-diol (C3,C5) of *seco*-acids **4**, **6** and **8** were shown to be fixed to chair conformation.[10] The substituents (methyl, phenyl or dimethl group) on the 6-membered ring of the *syn*-1,3-diol are far from the backbone chain, we can conclude that the difference in the substituents does not affect the backbone conformation.
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