Stereoselective Total Synthesis of 16-Membered Macrolide Aglycons, Leuconolides and Maridonolides. Macrocyclic Stereocontrol Based on Conformational Analysis of the 16-Membered Macrolide Ring[1)]

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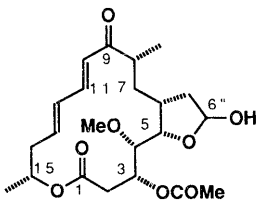
Sixteen-membered macrolide aglycons with different oxidation levels, leuconolide A_1 (3a), leuconolide A_3 (3b), midecanolide A_1 (3c), maridonolide II (4a), and maridonolide I (4b), were synthesized from two carbonolide type compounds (1, 2) by stereoselective reduction and epoxidation on the 16-membered ring system. The conformational analysis of macrolide rings based on nuclear magnetic resonance measurements and MMP2 calculations is also discussed in relation to the stereoselective synthesis of the five macrolide aglycons (3a—4b).

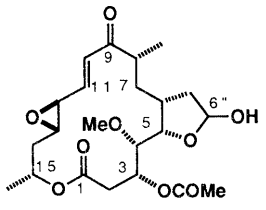
Keywords macrolide aglycon; total synthesis; leuconolide; maridonolide; conformation; conformational analysis; stereoselective reduction; NOE; MMP2 calculation

Macrolides and polyether antibiotics are interesting synthetic targets, and new synthetic methodologies have been developed to achieve their total synthesis, *i.e.* acyclic and macro ring stereocontrol, use of protecting groups, macrolactonization, *etc.*

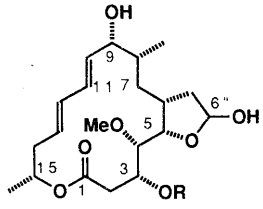
Recently[1,2)] we reported the total synthesis of 16-membered macrolide aglycons,[3)] carbonolide B (**1**) and carbonolide A (**2**), by virtue of the MPM (4-methoxyphenylmethyl) protection of hydroxy functions[4)] and some stereocontrolled reactions in an acyclic system. During the synthesis of **2**, we have been able to analyze the conformation of a 16-membered dienone compound using the combination of nuclear Overhauser enhancement (NOE) data and X-ray crystallography. The methodology was extended to the total synthesis of five 16-membered macrolide aglycons, leuconolide A_1 (**3a**),[5)] leuconolide A_3 (**3b**),[6)] midecanolide A_1 (**3c**),[7)] maridonolide I (**4b**), and maridonolide II (**4a**).[8,9)] Since these aglycons (**1**—**4**) have the same skeleton and only differ in their oxidation levels, the aglycons (**3**, **4**) were expected to be synthesized from the carbonolides (**1**, **2**) by stereoselective reduction and epoxidation. The conformational analysis of the 16-membered macrolide rings allowed us to achieve stereoselective synthesis of the five macrolide aglycons (**3a**—**4c**). The conformation of the 16-membered lactone ring plays a very important role in the stereoselectivity in such a large ring system.[10)] We focused on how to control the conformation by variation of the protection pattern of C3, C5, and C6″ hydroxy groups to obtain the desired stereoselection in reduction and epoxidation.



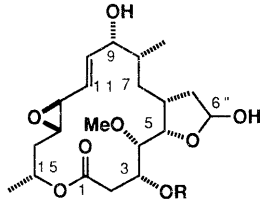
1: carbonolide B



2: carbonolide *A*



3a: R=H leuconolide A_1
3b: R=COMe leuconolide A_3
3c: R=COEt midecanolide A_1



4a: R=COMe maridonolide II
4b: R=COEt maridonolide I

Fig. 1

Results and Discussion

Conformational Analysis of 16-Membered Macrolide Rings Combined with C9 Carbonyl Reduction[11)] The synthesis of leuconolides (**3a**—**c**) and maridonolides (**4a**, **b**) by the reduction of carbonolide B 4-methoxybenzylacetal (**5**) and carbonolide A 4-methoxybenzylacetal (**8**) was first examined.[12)] When **5** was treated with tetrabutylammonium borohydride in MeOH at 0 °C, a 1 : 1.8 mixture of the desired 9*R* alcohol (**6**)[13)] and its 9*S* isomer (**7**) was obtained. Reduction of **8** under the same conditions gave mainly the undesired 9*S* alcohol (**10**) with 22 : 1 selectivity. The stereochemistry of C9-alcohols was confirmed by comparing their *J*9,10 values with those in the reports by Grieco *et al.*[14)] and Freiberg *et al.*[15)]

On the basis of NOE and NOE spectroscopy (NOESY) measurements,[16)] this disappointing selectivity can be explained in terms of the unfavorable 9,10-*s-cis*, 11,12-*s-trans* (A) conformation. As can be seen from Fig. 2, the dienone group is almost at right angles to the 16-membered ring plane, so the inside of the ring (*si* face) is completely blocked. The reduction of the C9 ketone occurred from the less hindered peripheral (*re*) face to give mainly the undesired 9*S* alcohol (**7**). The hydride attack on the C9

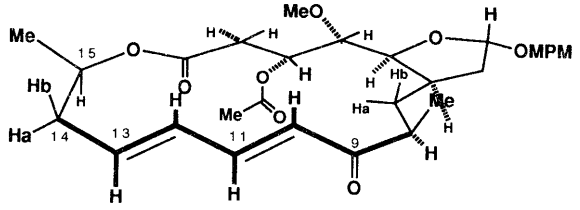


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Fig. 2

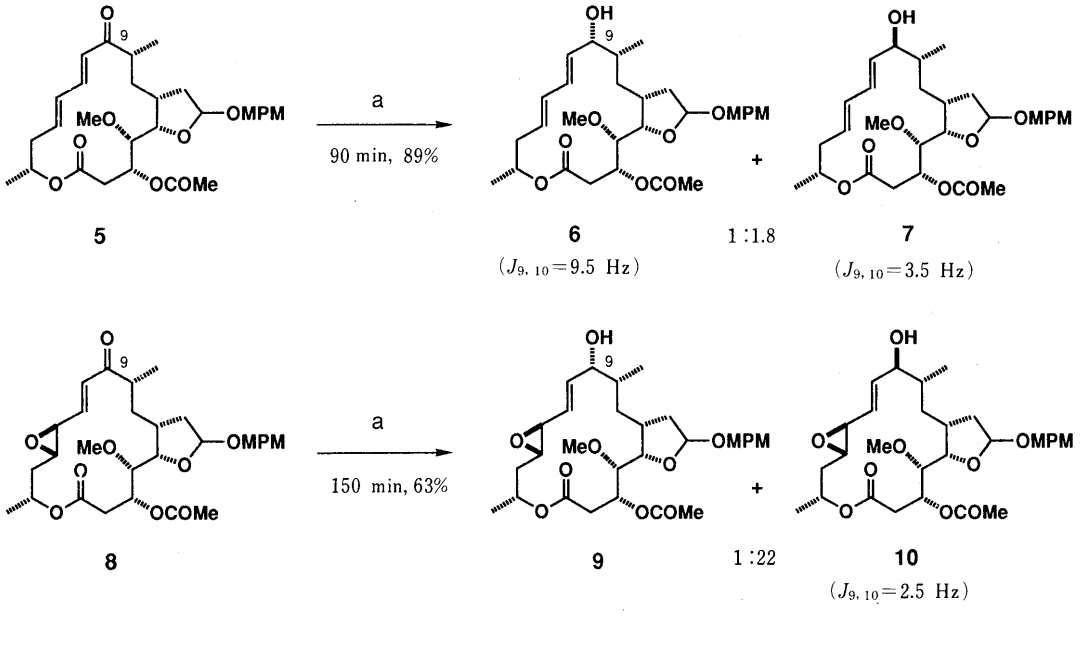


Chart 1

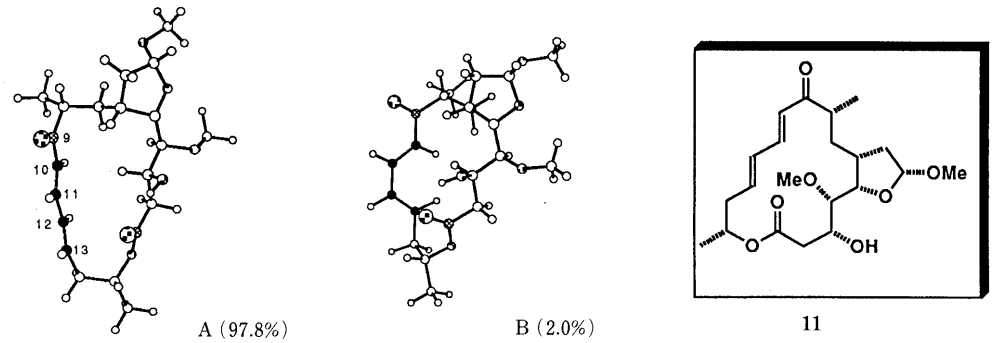


Fig. 3. MMP2–CONFLEX 2 Calculation of **11**

carbonyl was, however, hindered by the C8-methyl group and required a long reaction time. The MMP2 calculation combined with a systematic structure generation algorithm (CONFLEX)[17] supported this conclusion. Niddanolide methylacetal (**11**), with the same system, was calculated[18] to exist mainly in the A conformation (97.8%) together with the B conformer (9,10-*s*-*cis*, 11,12-*s*-*cis*; 2.0%) (Fig. 3).

We should completely reverse the stereoselectivity of the reduction to obtain the desired 9*R*-alcohol. In the 3,5-acetonide compound (**12**), A, B, C (9,10-*s*-*trans*, 11,12-*s*-*trans*), and A′ (the dienone portion inside out) conformers were observed by NOE and NOESY measurements (Fig. 4, 5). This result was supported by the MMP2–CONFLEX2 calculation for the 6-methyl 3,5-acetonide compound (**13**).[19] Compound **13** has interconvertible A (67.9%), B (10.5%), C (10.5%) and A′ (13H, 14Hb: *syn*, 8.8%) conformers. Typical computer drawings of conformers A, B, C, and A′ are shown in Fig. 6. In contrast to the A conformer giving the undesired 9*S* alcohol, the A′, B, and C conformers should be reduced much faster than the A conformer from the back side (*si* face) without steric hindrance to afford the desired 9*R* alcohol (Fig. 7). More than 30% of the 3,5-acetonide was found to exist as the desired conformers.

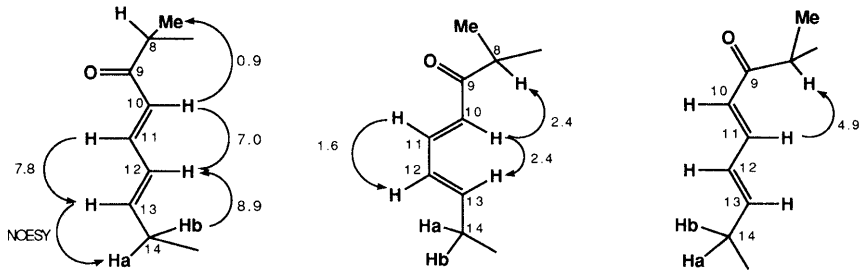
Synthesis of Leuconolides A_1 and A_3, and Midecanolide A_1 We sought to synthesize leuconolides A_1 (**3a**) and A_3 (**3b**), and midecanolide A_1 (**3c**) using reduction of the 6″-*O*-MPM-protected C3,C5-acetonide compound (**12**), which was synthesized from D-glucose *via* Yamaguchi's esterification of two fragments, **14** (C1—C10) and **15** (C11—C16), followed by Wittig–Horner cyclization as described in the previous paper.[1] When **12** was treated with sodium borohydride ($NaBH_4$) in methanol at 0 °C, a rapid reduction occurred stereoselectively to give the desired 9*R* alcohol (**16**) in 97% yield, and none of the stereoisomer was detected in the crude product. Chloroacetyl protection of **16** followed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation gave the primary alcohol (**18**) in 91% yield. The Swern oxidation and acid treatment with 1 N HCl–tetrahydrofuran (THF) (1 : 3) gave the hemiacetal compound (**20**), as a 1 : 1 mixture of anomers. The chloroacetyl group was hydrolyzed to afford leuconolide A_1 (**3a**) in 98% yield. Acetylation of the hemiacetal (**20**) gave the diacetates (**21**α, β), which were converted to leuconolide A_3 (**3b**) in 83% yield by careful alkaline treatment. Similarly, midecanolide A_1 (**3c**) was synthesized

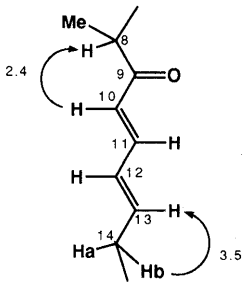
NOE observed (%)

Signal irradiated

	1	2a	2b	3	4	5	6	7a	7b	8	8Me	9	10	11	12	13	14a	14b	15	16
1																				
2a			25.4																	
2b		19.5		3.0												3.2			2.2	
3			2.7		5.4	2.7														
4				6.5		5.4							2.7	1.1						
5				7.2	6.5		7.0			5.9										
6						NOE				NOE										
7a					NOE				NOE				NOE							
7b																				
8						NOE			NOE				NOE	NOE						
8Me										3.2			1.4							
9																				
10					2.4			3.2		2.4	0.9					7.0	2.4			
11										4.9						1.6	7.8			
12														NOE						
13																				
14a																NOE		NOE	NOE	
14b															8.9	3.5				2.0
15															1.9	3.2	3.2			1.6
16																			2.8	

Fig. 4. The Matrix of ^{1}H-NOE Obtained for **12** in $CDCl_3$ (NOE: Exact Measurement of NOE % Is Not Possible for Unresolved Peaks)





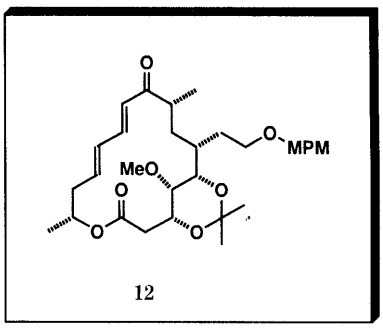


Fig. 5. NOE Correlation for the Conformational Isomers of **12** in $CDCl_3$

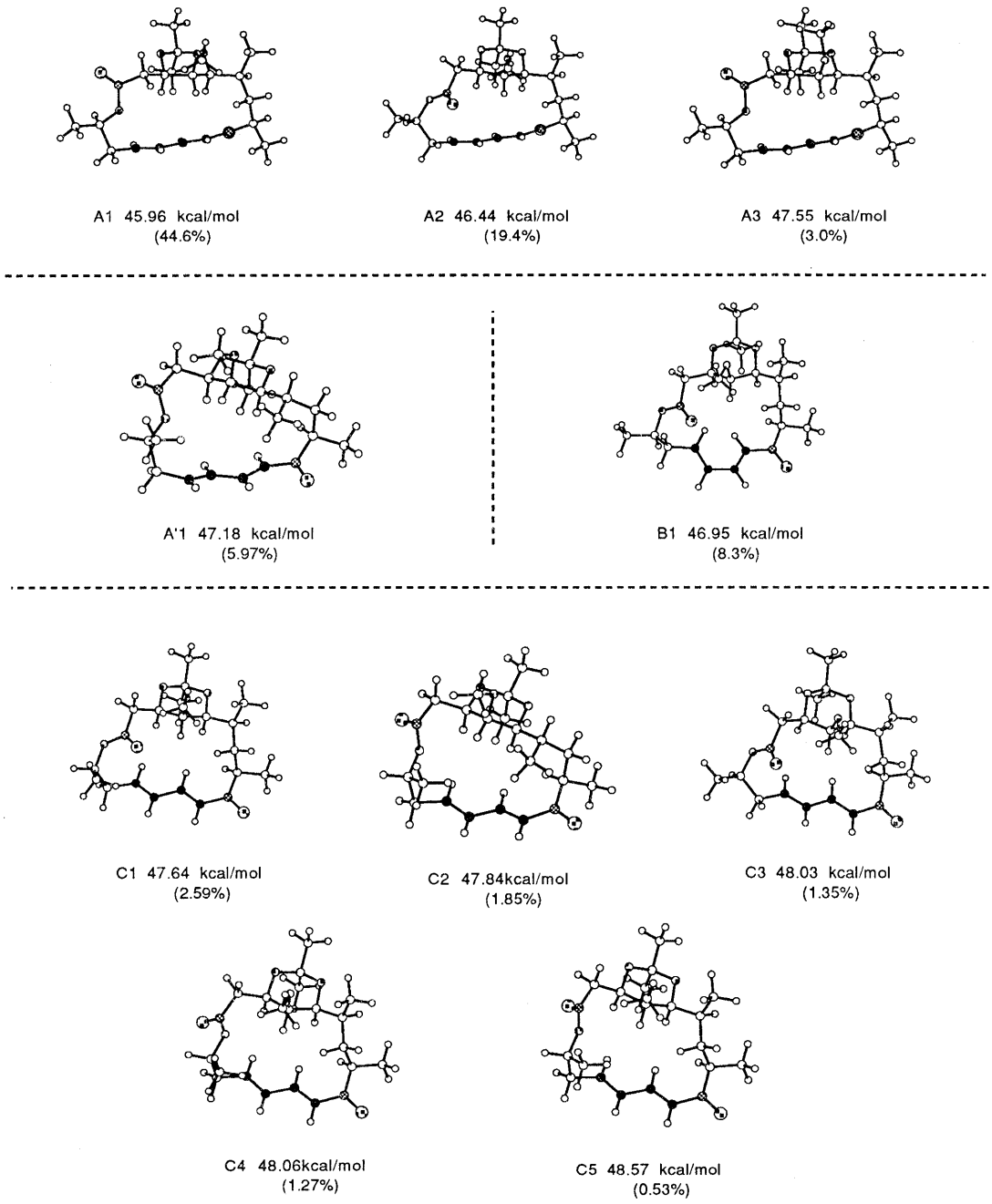


Fig. 6. Structures and Populations of Conformers by MMP2–CONFLEX 2 Calculation

from the dipropionates (**22**α, β).[20]

Synthesis of Maridonolides I and II We have succeeded in the total synthesis of carbonolide A (**2**), leuconolides (**3a**, **b**), and midecanolide A_1 (**3c**) based on the conformation-controlled reactions of 16-membered macrolide rings. This methodology has now been extended to the synthesis of maridonolide II (**4a**) and maridonolide I (**4b**), which are the aglycons of maridomycins II and I isolated from *Streptomyces hygroscopicus* No. B-5050.[8]

In order to synthesize maridonolides, two different routes, reduction of the epoxyenone (**23**) and epoxidation of the diene alcohols (**21**, **22**), were examined. Epoxidation of **12** with *meta*-chloroperbenzoic acid (MCPBA) gave the epoxide (**23**) in 22% yield, and the C10,11–C12,13-di-epoxide was concomitantly formed. A better result was obtained by using three conventional reactions; hydrolysis of the C3,C5-acetonide of **12** with 10-camphorsulfonic acid (CSA) in MeOH, MCPBA oxidation giving the desired β-epoxide in 56% yield, and acetonide formation with 2-methoxypropene and 0.1 eq of CSA to afford **23**.[21] When **23** was reduced with $NaBH_4$ in MeOH at 0 °C, the expected 9*R* alcohol (**24**) was obtained in quantitative yield. The alcohol was protected with a chloroacetyl group, and converted to the aldehyde (**27**) by DDQ deprotection of the MPM group and Swern oxidation. Careful hydrolysis of **27** to avoid opening of the epoxide ring with 2 N sulfuric acid–THF (1 : 20) at 0 °C for 10 h gave the hemiacetal (**28**), as a 1 : 1 mixture of anomers. The hemiacetal (**28**) was converted to the diacetate (**29**α, β) in the usual way, and then easily converted to maridonolide II (**4a**) by selective deprotection of the C9 chloroacetyl and C6″ acetyl groups under alkaline conditions. Maridonolide I (**4b**) was similarly

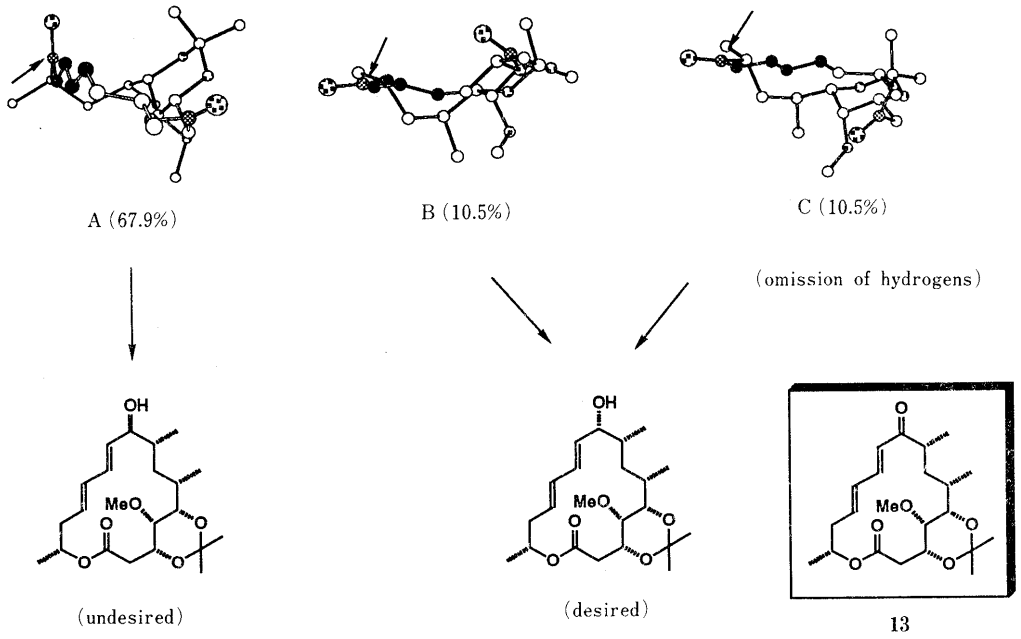
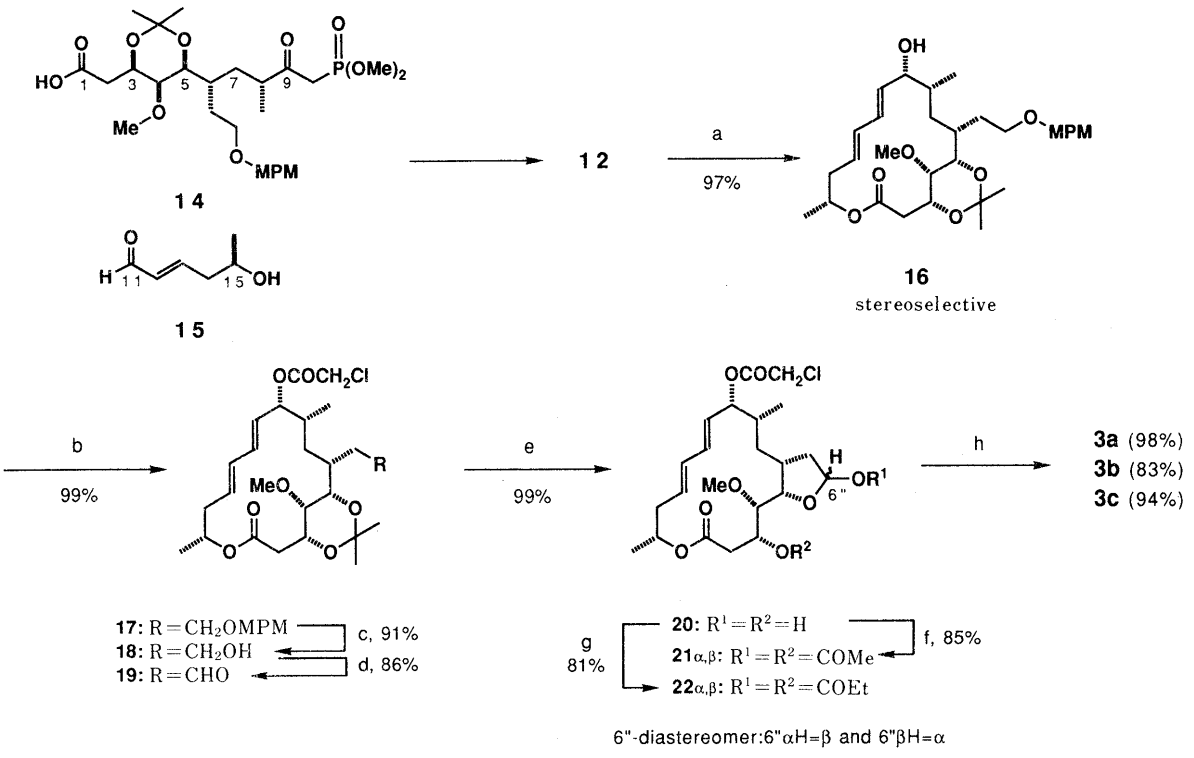


Fig. 7. Reduction of **13**

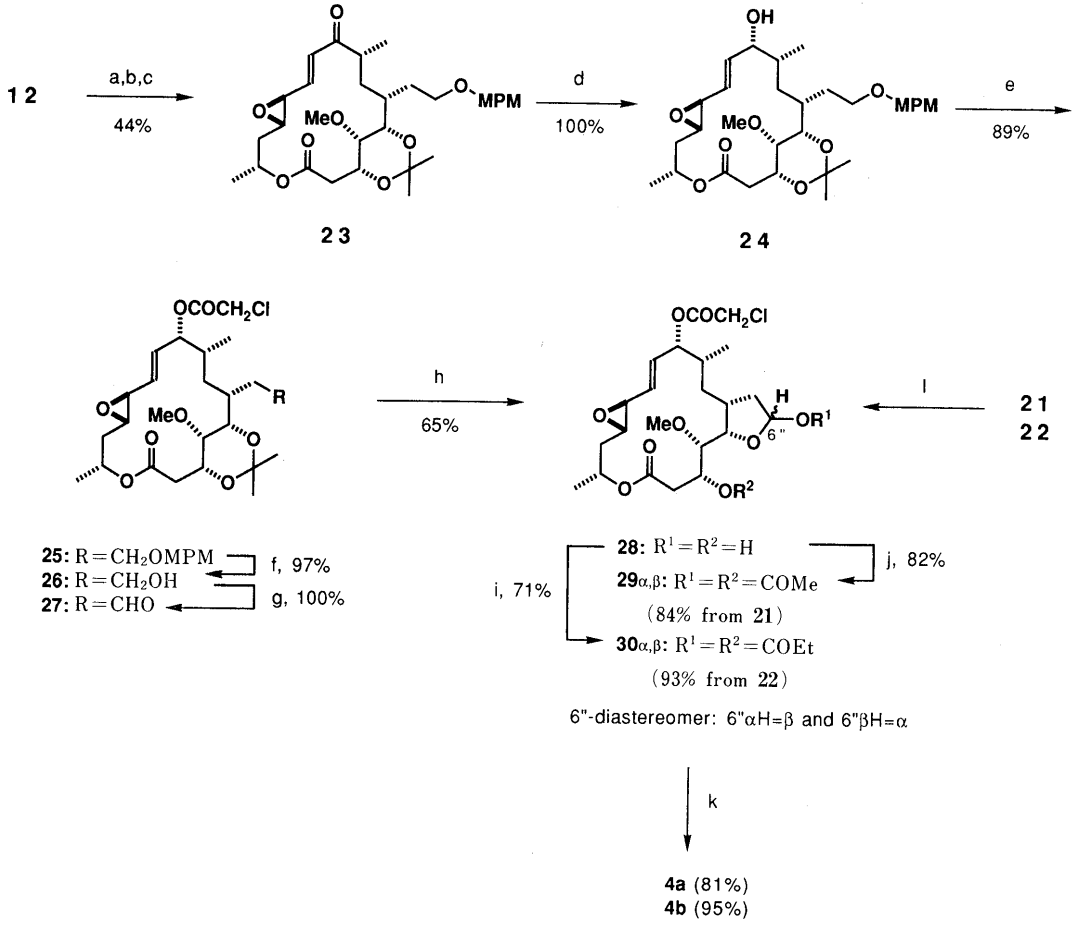


a) $NaBH_4$, MeOH, 0°C; b) $(ClCH_2CO)_2O$, py. DMAP; c) DDQ, CH_2Cl_2-H_2O (20:1); d) $(COCl)_2$, DMSO, Et_3N
e) 1 N HCl-THF (3:1); f) Ac_2O, Et_3N, DMAP, CH_2Cl_2; g) $(EtCO)_2O$, Et_3N, DMAP, CH_2Cl_2;
h) K_2CO_3 (3 eq), MeOH, 0°C

Chart 2

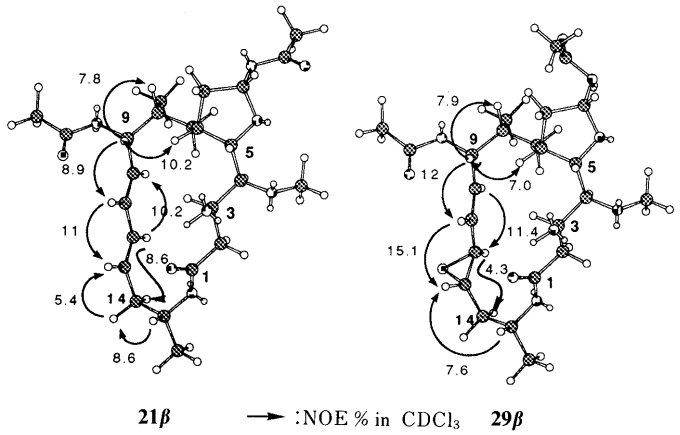
synthesized from **30α, β**.[22]

Epoxidation on the diene part to the 9*R*(α) alcohol compounds was next examined. From the nuclear magnetic resonance (NMR) spectra (coupling constants and NOE) of **21** and **29**, the most probable conformations of **21** and **29** were estimated to be as shown in Fig. 8. The diene is approximately perpendicular to the plane of the 16-membered ring and the H-9 lies nearly in the plane of the diene system. Therefore, epoxidation of the C10,11-double bond would be strongly hindered by the protective group of the C-9 hydroxy group, and the C12,13-β-epoxide was expected to be formed selectively. When the MPM-leuconolide A_3 (**6**) was treated with MCPBA in dichloromethane, a 1:2.3 regioisomeric mixture of the C10,11-β-



a) CSA, MeOH; b) MCPBA, $NaHCO_3$, CH_2Cl_2; c) $Me(MeO)C=CH_2$, PPTS, CH_2Cl_2; d) $NaBH_4$, MeOH, 0°C
e) $(ClCH_2CO)_2O$, py. DMAP; f) DDQ, CH_2Cl_2-H_2O (10:1); g) $(COCl)_2$, DMSO, Et_3N; h) 2 N H_2SO_4-dioxane (1:10)
i) Ac_2O, Et_3N, DMAP, CH_2Cl_2; j) $(EtCO)_2O$, Et_3N, DMAP, CH_2Cl_2; k) K_2CO_3 (3 eq), MeOH, 0°C
l) MCPBA (1.5eq), CH_2Cl_2

Chart 3



21β → :NOE % in $CDCl_3$ **29β**

Fig. 8. Estimated Conformations of **21β** and **29β**

and C12,13-β-epoxides was obtained. Also 3,5-acetonide compound (**17**) gave a 1 : 1 regioisomeric mixture of the β-epoxides. On the other hand, the diacyl compounds, **21** and **22**, were selectively epoxidized to give the C12,13-β-epoxides, **29** and **30**, in 84% and 93% yields, respectively.

Leuconolide A_3, midecanolide A_1, and maridonolide II were identical [NMR, infrared (IR) mass, $[\alpha]_D$] with the degradation products of natural leucomycin A_3 (josamycin), midecamycin A_1 and maridomycin IV, respectively.

Experimental

All melting points were measured with Yamato melting point apparatus model MP-21 and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. IR spectra were recorded in $CHCl_3$ or neat on a JASCO IRA-2-spectrometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL FX-100, JEOL JNM GX-270, or JEOL JNM GX-500 instrument. Low- and high-resolution mass spectra (MS) were taken on a JEOL JMS HX-110 or JEOL JMS DX-303 spectrometer. Ultraviolet (UV) spectra were obtained on a Varian Cary 219 spectrophotometer using ethanol as a solvent.

Reduction of Carbonolide B 4-Methoxybenzylacetal (5) and Carbonolide A 4-Methoxybenzylacetal (8) (1) A stirred ethanol (1 ml) solution of **5** (20.0 mg, 37 μmol) was treated with *n*-Bu_4NBH_4 (9.5 mg, 37 μmol) at 0 °C for 60 min. *n*-Bu_4NBH_4 (9.5 mg, 37 μmol) was added to the reaction mixture and stirring was continued for an additional 30 min. Solid NH_4Cl was added to the reaction mixture to quench the reaction, and the solvent was removed. The residue was extracted with CH_2Cl_2, and the whole was washed with saturated aqueous NaCl, and dried over $MgSO_4$. The solvent was removed *in vacuo*, the residue was purified on a silica gel preparative thin layer chromatography (TLC) plate with hexane–AcOEt (3 : 2) to afford leuconolide A_1 4-methoxybenzylacetal (**6**) (6.4 mg, 32%) and 9*S* leuconolide A_1 4-methoxybenzylacetal (**7**) (11.4 mg, 57%). The ratio of **6** and **7** (1 : 1.8) was determined from the isolation yields.

Leuconolide A_1 4-Methoxybenzylacetal (**6**): $[\alpha]_D^{13}+67°$ ($c=0.624$, $CHCl_3$). ^{1}H-NMR δ: 0.99 (3H, d, $J=7.0$ Hz), 1.01—1.10 (2H, m), 1.26 (3H, d, $J=6.0$ Hz), 1.50—1.60 (1H, m), 1.82—1.92 (1H, m), 2.07—2.15

(2H, m), 2.12 (3H, s), 2.15—2.25 (2H, m), 2.22 (1H, dd, J=14.2, 1.5 Hz), 2.47 (1H, dt, J=13.0, 3.5 Hz), 2.93 (1H, dd, J=14.2, 11.5 Hz), 3.17 (1H, d, J=9.2 Hz), 3.99 (1H, dd, J=9.5, 4.0 Hz), 4.24 (1H, dd, J=9.5, 4.0 Hz), 4.42 (1H, d, J=11.5 Hz), 4.69 (1H, d, J=11.5 Hz), 5.07 (1H, m), 5.10 (1H, d, J=11.5 Hz), 5.22 (1H, dd, J=5.5, 4.2 Hz), 5.61 (1H, dd, J=15.5, 9.5 Hz), 5.63 (1H, ddd, J=15.5, 11.0, 4.0 Hz), 6.03 (1H, dd, J=15.5, 10.5 Hz), 6.50 (1H, dd, J=15.5, 10.5 Hz), 6.86—6.89 (2H, m), 7.26—7.29 (2H, m). MS m/z (relative intensity): 546 (M^+, 0.2%), 528 (M^+-18, 0.25%), 409 (1.7), 175 (5.2), 138 (6.3), 121 (100), 111 (7.7), 95 (9.6). Exact MS Calcd for $C_{30}H_{40}O_8$: 528.2723. Found: 528.2701. IR ν (neat) cm^{-1}: 3450, 1735, 1725. TLC Rf=0.30 (30% EtOAc/hexane).

9*S*-Leuconolide A_1 4-Methoxybenzylacetal (**7**): ^{1}H-NMR δ: 0.91 (3H, d, J=7.0 Hz), 1.24 (1H, d, J=6.2 Hz), 1.73—1.86 (1H, m), 1.92—1.98 (1H, m), 1.97—2.03 (1H, m), 2.06 (1H, ddd, J=13.8, 10.6, 9.50 Hz), 2.16 (1H, dd, J=15.5, 1.8 Hz), 2.30—2.40 (1H, m), 2.45 (1H, ddd, J=13.8, 4.5, 3.0 Hz), 2.73 (1H, dd, J=15.5, 10.5 Hz), 2.96 (1H, dd, J=9.2, 0.5 Hz), 3.49 (3H, s), 3.73 (3H, s), 3.79 (1H, br d, J=10.5 Hz), 4.08—4.11 (1H, m), 4.11 (1H, dd, J=9.0, 4.3 Hz), 4.65 (1H, d, J=11.5 Hz), 5.10 (1H, dd, J=5.5, 1.5 Hz), 5.05—5.14 (1H, m), 5.52 (1H, ddd, J=15.0, 10.5, 5.0 Hz), 5.68 (1H, dd, J=15.0, 4.0 Hz), 6.01 (1H, dd, J=15.0, 10.5 Hz), 6.26 (1H, ddd, J=15.0, 10.5, 1.5 Hz). TLC Rf=0.37 (30% EtOAc/hexane).

(2) A stirred ethanol (1 ml) solution of **8** (2.8 mg, 5.5 μmol) was treated with n-Bu_4NBH_4 (3.0 mg, 11 μmol) at 0 °C for 150 min. Solid NH_4Cl was added to the reaction mixture to quench the reaction, and the solvent was removed. The residue was extracted with CH_2Cl_2, and the whole was washed with saturated aqueous NaCl, dried over $MgSO_4$. After removal of the solvent, the residue was passed through a short silica gel column with hexane–AcOEt (2 : 1) to afford maridonolide II 4-methoxybenzylacetal (**9** and **10**) (1.9 mg, 63%, **9** : **10** = 1 : 22). The ratio of alcohols was determined from the NMR signals (methoxy peaks of δ 3.62 *vs.* δ 3.66 and δ 3.80 *vs.* δ 3.90).

9*S*-Maridonolide II 4-Methoxybenzylacetal (**10**): ^{1}H-NMR δ: 0.98 (3H, d, J=7.3 Hz), 1.28 (3H, d, J=6.2 Hz), 1.87—1.96 (2H, m), 1.96—2.07 (1H, m), 2.08—2.17 (2H, m), 2.09 (3H, s), 2.33 (1H, d, J=14.0 Hz), 2.35 (1H, dd, J=14.3, 1.8 Hz), 2.45—2.57 (1H, m), 2.99 (1H, dd, J=14.3, 11.4 Hz), 3.17 (2H, q, J=7.0 Hz), 3.62 (3H, s), 3.80 (3H, s), 4.02 (1H, dd, J=9.1, 4.0 Hz), 4.24 (1H, m), 4.43 (1H, d, J=11.3 Hz), 4.68 (1H, d, J=11.3 Hz), 5.07 (1H, ddd, J=11.0, 6.2, 2.8 Hz), 5.22 (1H, dd, J=5.5, 4.0 Hz), 5.27 (1H, d, J=10.4 Hz), 5.70 (1H, ddd, J=15.2, 9.0, 2.0 Hz), 6.17 (1H, dd, J=15.4, 3.9 Hz).

6″-Dihydro-3,5-isopropylidene-6″-*O*-(4-methoxybenzyl) Leuconolide A_1 (16) $NaBH_4$ (2.1 mg, 0.054 mmol) was added to a stirred solution of **12** (29.6 mg, 0.054 mmol) in MeOH (2 ml) at 0 °C and the reaction mixture was stirred for 5 min. Powdered NH_4Cl was added to the reaction mixture to quench the reaction and the solvent was evaporated off *in vacuo*. The residue was extracted with AcOEt, and the extract was washed with saturated aqueous NH_4Cl and dried. After removal of the solvent, the residue was chromatographed on a silica gel column with AcOEt–hexane (2 : 1) as the eluant to give the 9*R* alcohol **16** (28.6 mg, 97%) as a colorless oil. $[\alpha]_D^{13}$ +32° (c=0.7, $CHCl_3$). ^{1}H-NMR δ: 1.07 (3H, d, J=6.5 Hz), 1.28 (3H, d, J=6.5 Hz), 1.40 (3H, s), 1.44 (3H, s), 1.54 (1H, t, J=13.0 Hz), 2.20 (1H, ddd, J=15.5, 10.5, 9.0 Hz), 2.34 (1H, dd, J=15.0, 2.2 Hz), 2.41—2.54 (1H, m), 2.48 (1H, dd, J=14.0, 3.0 Hz), 2.81 (1H, dd, J=15.0, 10.5 Hz), 2.82 (1H, s), 3.41—3.55 (2H, m), 3.45 (3H, s), 3.76 (1H, d, J=5.0 Hz), 3.79 (3H, s), 4.23 (1H, d, J=11.0 Hz), 4.25 (1H, s), 4.38 (1H, d, J=11.3 Hz), 4.45 (1H, d, J=11.3 Hz), 5.35 (1H, ddq, J=8.5, 2.5, 6.5 Hz), 5.65 (1H, ddd, J=15.0, 10.0, 3.5 Hz), 5.66 (1H, dd, J=15.0, 5.0 Hz), 5.99 (1H, dd, J=15.5, 10.5 Hz), 6.12 (1H, ddd, J=15.5, 10.5, 0.5 Hz), 6.84—6.87 (2H, m), 7.24—7.27 (2H, m) MS m/z (relative intensity): 546 (M^+, 0.3%) 531 (0.4), 488 (0.8), 456 (1.3), 438 (1.0), 398 (1.0), 367 (1.7), 317 (1.5), 233 (4.2), 135 (4.6), 121 (100). Exact MS m/z Calcd for $C_{31}H_{46}O_8$ (M^+): 546.3192. Found: 546.3181. IR ν (neat) cm^{-1}: 3500, 1735, 1620.

9-*O*-Chloroacetyl-6″-dihydro-3,5-isopropylidene-6″-*O*-(4-methoxybenzyl) Leuconolide A_1 (17) Chloroacetic anhydride (23.4 mg, 0.14 mmol) was added to a stirred solution of **23** (25.0 mg, 0.046 mmol) and 4-dimethylaminopyridine (DMAP) (16.7 mg, 0.046 mmol) in pyridine (1 ml). Stirring was continued for 20 min at 5 °C, then the reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl–brine (3 : 1) and brine. The organic layer was dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (3 : 1) as the eluant to give **17** as a colorless oil (27.7 mg, 99%). $[\alpha]_D^{13}$ +39.4° (c=0.72, $CHCl_3$). ^{1}H-NMR δ: 1.0 (3H, d, J=6.5 Hz), 1.28 (3H, d, J=6.5 Hz), 1.3—1.5 (2H, m), 1.41 (3H, s), 1.44 (3H, s), 1.64 (1H, t, J=13.0), 1.8—1.9 (1H, m), 2.18 (1H, dt, J=15.5, 10.5 Hz), 2.34 (1H, dd, J=15.5, 2.0 Hz), 2.42—2.55 (2H, m), 2.78 (1H, s), 2.80 (1H, dd, J=15.5, 10.5 Hz), 3.40—3.57 (2H, m), 3.47 (3H, s), 3.75 (1H, d, J=5.0 Hz), 3.80 (3H, s), 4.04 (2H, s), 4.12 (1H, br d, J=11.0 Hz), 4.39 (1H, d, J=12.5 Hz), 4.45 (1H, d, J=12.5 Hz), 5.30 (1H, ddq, J=8.8, 2.2, 6.5 Hz, 5.38 (1H, d, J=6.2 Hz), 5.59 (1H, dd, J=15.5, 6.0 Hz), 5.69 (1H, ddd, J=15.5, 9.5, 3.2 Hz), 5.92 (1H, ddd, J=15.5, 10.0, 0.5 Hz), 6.10 (1H, dd, J=10.5 Hz), 6.84—6.87 (2H, m), 7.24—7.27 (2H, m). MS m/z (relative intensity): 622 (M^+, 0.3%) 564 (0.8), 533 (3.0), 514 (0.5), 470 (0.9), 438 (1.0), 421 (0.75), 407 (1.36), 349 (2.0), 334 (1.3), 317 (2.0), 303 (2.5), 233 (10.4), 121 (100), 71 (100). Exact MS m/z Calcd for $C_{33}H_{47}ClO_9$ (M^+): 622.2908. Found: 622.2908. IR ν (neat) cm^{-1}: 1760, 1720 (CO), 1610 (C=C).

9-*O*-Chloroacetyl-6″-dihydro-3,5-isopropylideneleuconolide A_1 (18) DDQ (30.0 mg, 0.13 mmol) was added to a stirred solution of **17** (27.5 mg, 0.044 mmol) in CH_2Cl_2 (1 ml) and H_2O (0.05 ml). After being stirred for 40 min, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, and brine. The extract was dried over $MgSO_4$ and concentrated to leave an oil, which was chromatographed on a silica gel column with hexane–AcOEt (2 : 1) as the eluant to give **18** as a colorless oil (20.2 mg, 91%). $[\alpha]_D^{13.5}$ +29.2° (c=0.85, $CHCl_3$). ^{1}H-NMR δ: 1.04 (3H, d, J=6.5 Hz). 1.29 (3H, d, J=6.5 Hz), 1.35—1.48 (2H, m), 1.44 (3H, s), 1.47 (3H, s), 1.58—1.60 (1H, m), 1.77 (1H, t, J=13.5 Hz), 1.86—1.96 (1H, m), 2.19 (1H, dt, J=15.2, 10.0 Hz), 2.28 (1H, ddd, J=10.5, 8.0, 6.5 Hz), 2.29—2.36 (1H, m), 2.36 (1H, dd, J=15.2, 2.0 Hz), 2.50 (1H, d, J=15.2 Hz), 2.80 (1H, s), 2.81 (1H, dd, J=15.2 Hz, 11.0 Hz), 3.48 (3H, s), 3.55 (1H, ddd, J=10.2, 8.0, 5.2 Hz), 3.74 (1H, t, J=5.5 Hz), 3.77 (2H, q, J=5.5 Hz), 4.09 (2H, s), 4.26 (1H, dt, J=10.0, 1.5 Hz), 5.32 (1H, ddq, J=11.0, 2.2, 6.5 Hz), 5.39 (1H, d, J=6.0 Hz), 5.60 (1H, dd, J=15.5, 5.5 Hz), 5.70 (1H, ddd, J=15.0, 9.5, 3.5 Hz), 5.94 (1H, ddd, J=15.0, 10.0, 0.5 Hz), 6.12 (1H, dd, J=15.5, 10.0 Hz). MS m/z (relative intensity): 504 (M^++2, 0.5%), 502 (M^+, 1.4), 489 (3.0), 487 (8.2), 446 (3.8), 444 (9.8), 426 (6.5), 393 (6.0), 350 (12), 310 (26), 301 (42), 234 (100), 148 (50), 123 (52), 94 (84). Exact MS m/z Calcd for $C_{25}H_{39}ClO_8$ (M^+): 502.2333. Found: 502.2335. IR ν (neat) cm^{-1}: 3600, 1755, 1720.

9-*O*-Chloroacetyl-3,5-isopropylideneleuconolide A_1 (19) Dry dimethyl sulfoxide (DMSO) (24 μl, 0.34 mmol) in dry CH_2Cl_2 (0.5 ml) was added dropwise during 15 min to an efficiently stirred solution of oxalyl chloride (15 μl, 0.15 mmol) in dry CH_2Cl_2 (0.5 ml) at −78 °C under an argon atmosphere. After 15 min at −78 °C, a solution of **18** (42.5 mg, 0.085 mmol) in CH_2Cl_2 (1 ml) was added to the mixture during 5 min. Stirring was continued at −78 °C for 15 min, then Et_3N (70 μl, 0.51 mmol) was added dropwise, and after removal of the cooling bath, the reaction mixture was allowed to warm to room temperature (over *ca.* 1 h). Then H_2O was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 ml × 2). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (2 : 1) as the eluant to give the aldehyde (**19**) as a colorless oil (36.2 mg, 86%). $[\alpha]_D^{17}$ +33.8° (c=1.45, $CHCl_3$). ^{1}H-NMR δ: 1.09 (3H, d, J=6.5 Hz), 1.29 (3H, d, J=6.2 Hz), 1.39 (3H, s), 1.45 (3H, s), 1.72 (1H, t, J=13.0 Hz), 2.14 (1H, ddd, J=16.0, 10.5, 9.5 Hz), 2.26 (1H, ddd, J=10.5, 8.5, 2.5 Hz), 2.37 (1H, dd, J=16.0, 2.5 Hz), 2.45—2.55 (2H, m), 2.80 (1H, s), 2.80 (1H, dd, J=16.0, 11.0 Hz), 3.19 (1H, dd, J=4.5, 1.0 Hz), 3.26 (1H, dd, J=4.5, 1.0 Hz), 3.51 (3H, s), 3.84 (1H, dd, J=5.5, 0.5 Hz), 4.07 (2H, s), 4.27 (1H, d, J=10.0 Hz), 5.32 (1H, ddq, J=11.0, 2.2, 6.2 Hz), 5.38 (1H, d, J=6.0 Hz), 5.59 (1H, dd, J=15.5, 6.0 Hz), 5.71 (1H, ddd, J=15.5, 9.5, 3.5 Hz), 5.92 (1H, ddd, J=16.0, 10.0, 1.5 Hz), 6.12 (1H, dd, J=16.0, 10.0 Hz), 9.73 (1H, d, J=2.5 Hz), MS m/z (relative intensity); 500 (M^+, 1.4%) 485 (M^+ − Me, 1.2), 442 (1.6), 424 (1.0), 406 (2.4), 391 (4.7), 348 (12.5), 326 (12), 299 (8.3), 232 (32.3), 148 (26), 123 (51.3), 71 (100), 43 (57). Exact MS m/z Calcd for $C_{25}H_{37}ClO_8$ (M^+): 500.2177. Found: 502.2190. IR ν (neat) cm^{-1}: 1750, 1720 (CO).

9-*O*-Chloroacetylleuconolide A_1 Hemiacetal (20) A solution of **19** (17 mg, 0.034 mmol) in 1 N HCl (0.3 ml) and THF (1 ml) was stirred at room temperature for 40 min. After neutralization with solid $NaHCO_3$, the reaction mixture was evaporated to dryness. CH_2Cl_2 and H_2O were added to the residue, and the CH_2Cl_2 layer was separated. The aqueous layer was extracted again with CH_2Cl_2, and the organic layers were combined, and dried over $MgSO_4$. After evaporation of the solvent, purification of the residue on a silica gel column with hexane–AcOEt (1 : 2) as the eluant afforded **20** as a colorless oil (15.5 mg, 99%). $[\alpha]_D^{17}$ +35.4° (c=1.08, $CHCl_3$). ^{1}H-NMR δ: 1.04 (3H, d, J=6.5 Hz), 1.13 (1H, t, J=7.0 Hz), 1.30 (1.5H, d, J=6.5 Hz), 1.31 (1.5H, d, J=6.5 Hz), 1.48—1.55 (1H, m), 1.65—1.83 (1H, m), 1.85—2.04 (1H, m), 2.09 (0.5H, dd, J=11.0, 2.9 Hz), 2.14—2.16 (0.5H, m), 2.19 (0.5H, dd, J=11.0, 2.9 Hz), 2.25 (0.5 H, dd, J=15.0, 3.0 Hz), 2.25—2.35 (0.5H, m), 2.39 (0.5H, dd, J=14.0, 8.0 Hz),

2.45—2.57 (1.5H, m), 2.55 (0.5H, dd, J=17.0, 8.0 Hz), 2.68 (0.5H, dd, J=6.2, 6.0 Hz), 2.77 (0.5H, dd, J=15.0, 10.5 Hz), 2.97 (0.5H, d, J=8.0 Hz), 3.07 (0.5H, d, J=4.0 Hz), 3.53 (1H, s), 3.62 (1H, s), 3.75 (0.5H, dd, J=2.2, 0.5 Hz), 4.04 (1.5H, s), 4.07 (1.5H, s), 4.47 (0.5H, dd, J=8.5, 4.0 Hz), 5.14—5.29 (1H, m), 5.36 (1H, dd, J=9.4, 4.2 Hz), 5.36—5.39 (0.5H, m), 5.43—5.46 (0.5H, m), 5.57 (0.5H, dd, J=15.5, 9.5 Hz), 5.58 (0.5H, dd, J=15.5, 9.5 Hz), 5.65 (0.5H, ddd, J=11.5, 8.5, 2.0 Hz), 5.72 (0.5H, ddd, J=15.5, 10.5, 4.0 Hz), 5.96 (0.5H, dd, J=15.0, 11.5 Hz), 6.00 (0.5H, dd, J=15.0, 11.5 Hz), 6.21 (0.5H, dd, J=15.0, 10.5 Hz), 6.35 (0.5H, dd, J=15.0, 10.5 Hz). MS m/z (relative intensity): 442 (M^+, 5.8%), 366 (3.8), 348 (23), 326 (18), 308 (11), 232 (47), 148 (44), 124 (100), 94 (97), 71 (95). Exact MS m/z Calcd for $C_{22}H_{31}ClO_7$ (M^+): 442.1759. Found: 442.1735. IR ν (neat) cm^{-1}: 3400, 1750, 1720, 1700.

Leuconolide A_1 Hemiacetal (3a) A solution of **20** (12.2 mg, 0.0265 mmol) in 1 ml of MeOH was treated with K_2CO_3 (5.5 mg, 0.04 mmol) at 0 °C for 10 min. After evaporation of the solvent, CH_2Cl_2 was added to the reaction mixture and precipitate was filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–AcOEt (1 : 3) as the eluant to give **3a** as a colorless solid (10 mg, 98%). $[\alpha]_D^{19}$ +43.6° (c=0.5, $CHCl_3$). ^{1}H-NMR δ: 1.02 (1.5H, d, J=7.0 Hz), 1.09 (1.5H, d, J=7.0 Hz), 1.29 (1.5H, d, J=7.0 Hz), 1.30 (1.5H, d, J=7.0 Hz), 1.36—1.45 (0.5H, m), 1.45—1.55 (0.5H, m), 1.55—1.7 (1H, m), 1.81—1.91 (1H, m), 2.13 (0.5H, dt, J=10.5, 3.0 Hz), 2.19 (0.5H, dt, J=10.5, 3.0 Hz), 2.25—2.35 (1H, m), 2.27 (0.5H, dd, J=15.0, 3.2 Hz), 2.37 (0.5H, dd, J=8.0, 6.5 Hz), 2.48 (1H, t, J=14.5 Hz), 2.64 (1H, d, J=7.7 Hz), 2.76 (0.5H, dd, J=15.0, 10.0 Hz), 2.97 (0.5H, d, J=8.2 Hz), 3.08 (0.5H, d, J=3.0 Hz), 3.53 (1.5H, s), 3.62 (1.5H, s), 3.79 (0.5H, dd, J=10.0, 2.5 Hz), 3.90—4.02 (0.5H, m), 4.02—4.12 (0.5H, m), 4.15 (0.5H, dd, J=9.5, 3.3 Hz), 4.19 (0.5H, dd, J=9.5, 7.2 Hz), 4.22 (0.5H, dd, 8.5, 4.0 Hz), 4.20—4.32 (0.5H, m), 4.42 (0.5H, dd, J=8.2, 4.5 Hz), 5.18—5.30 (1H, m), 5.42 (0.5H, s), 5.60 (0.5H, ddd, J=15.5, 6.0, 4.0 Hz), 5.67 (1H, dd, J=15.5, 9.5 Hz), 5.71 (0.5H, ddd, J=15.5, 9.5, 7.0 Hz), 5.98 (0.5H, dd, J=15.5, 9.5 Hz), 6.01 (0.5H, dd, J=15.5, 9.5 Hz), 6.14 (0.5H, dd, J=15.5, 9.5 Hz), 6.18 (0.5H, dd, J=15.5, 9.5 Hz). MS m/z (relative intensity): 384 (M^+, 0.1%), 366 (5.6), 349 (1.9), 232 (4.8), 211 (8.6), 155 (14), 123 (100), 95 (56), 43, (49). Exact MS m/z Calcd for $C_{20}H_{32}O_7$ (M^+): 384.2148. Found: 384.2127. IR ν (neat) cm^{-1}: 3400, 1730, 1700.

9-*O*-Chloroacetylleuconolide A_3 Acetoxyacetal (21) Acetic anhydride (50 μl) was added to a stirred solution of **20** (20 mg, 45 μmol), Et_3N (150 μl), and DMAP (1 mg) in CH_2Cl_2 (0.5 ml) at room temperature, and the solution was stirred for 10 h. The reaction mixture was evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (3 : 1) as the eluant to give the diacetate **21β** as a colorless oil (12 mg, 51%). $[\alpha]_D^{20}$ +32.5° (c=1.43, $CHCl_3$). ^{1}H-NMR δ: 1.02 (3H, d, J=6.5 Hz), 1.09—1.13 (1H, m), 1.27 (3H, d, J=6.2 Hz), 1.95—2.16 (4H, m), 2.05 (3H, s), 2.14 (3H, s), 2.22 (1H, dd, J=14.5, 1.7 Hz), 2.30 (1H, dd, J=14.5, 6.0 Hz), 2.30—2.40 (1H, m), 2.47 (1H, ddd, J=13.0, 3.0, 2.5 Hz), 2.93 (1H, dd, J=14.5, 11.5 Hz), 3.13 (1H, d, J=9.5 Hz), 3.54 (3H, s), 4.00 (1H, dd, J=9.5, 3.8 Hz), 4.04 (2H, s), 5.01 (1H, m), 5.04 (1H, dd, J=11.0, 0.5 Hz), 5.36 (1H, dd, J=9.5, 4.0 Hz), 5.55 (1H, dd, J=15.0, 9.5 Hz), 5.72 (1H, ddd, J=15.0, 11.0, 3.2 Hz), 6.03 (1H, ddd, J=15.0, 10.5, 0.5 Hz), 6.28 (1H, dd, J=5.5, 4.5 Hz), 6.63 (1H, dd, J=15.0, 10.5 Hz). MS m/z (relative intensity): 544 (M^+, 0.2%), 509 (0.26), 485 (6.3), 390 (8.3), 350 (4.6), 308 (6.3), 232 (12), 215 (13.5), 199 (8.8), 175 (13), 147 (12.5), 135 (29), 124 (29), 105 (30), 95 (34), 81 (34), 71 (34), 55 (50), 43 (100). Exact MS m/z Calcd for $C_{26}H_{37}ClO_{10}$: 544.2075. Found: 544.2057. IR ν (neat) cm^{-1}: 1750, 1740, 1730, 1720.

Continued elution provided **21α** as a colorless oil (8.0 mg, 34%). $[\alpha]_D^{19}$ +18.7° (c=0.6, $CHCl_3$). ^{1}H-NMR δ: 1.02 (3H, d, J=7.0 Hz), 1.27 (3H, d, J=6.2 Hz), 1.54 (1H, ddd, J=14.0, 13.0, 3.2 Hz), 2.03 (3H, s), 2.05—2.35 (5H, m), 2.10 (3H, s), 2.22 (1H, dd, J=14.0, 2.0 Hz), 2.48 (1H, dd, J=14.0, 4.0, 3.0 Hz), 2.92 (1H, dd, J=14.0, 11.5 Hz), 3.19 (1H, d, J=10.0 Hz), 3.55 (3H, s), 3.84 (1H, dd, J=10.0, 4.2 Hz), 4.05 (2H, s), 4.98 (1H, ddq, J=11.0, 3.0, 6.0 Hz), 5.05 (1H, d, J=11.2 Hz), 5.36 (1H, dd, J=10.0, 4.0 Hz), 5.56 (1H, dd, J=15.0, 10.0 Hz), 5.73 (1H, ddd, J=15.0, 11.5, 3.6 Hz), 6.05 (1H, ddd, J=15.0, 10.5, 0.5 Hz), 6.20 (1H, d, J=4.5 Hz), 6.61 (1H, dd, J=15.0, 10.5 Hz). MS m/z (relative intensity): 546 (M^++2, 0.15%), 544 (M^+, 0.3), 484 (6.3), 390 (7.5), 308 (8.3), 232 (12.5), 215 (12.5), 199 (10), 188 (8.7), 175 (13.5), 148 (11.5), 135 (25), 124 (30), 105 (29), 95 (29), 81 (29), 71 (29). Exact MS m/z Calcd for $C_{24}H_{33}ClO_8$ (M^+−60): 484.1864. Found: 484.1854. IR ν (neat) cm^{-1}: 1750, 1735, 1725, 1720.

9-*O*-Chloroacetylmidecanolide A_1 Propionyloxy Acetal (22) Propionic anhydride (25 μl) was added to a stirred solution of **20** (10.0 mg, 0.022 mmol), Et_3N (83 μl), and DMAP (4 mg) in CH_2Cl_2 (1 ml) at room temperature, and the solution was stirred for 13 h, then evaporated *in vacuo*. The residue was chromatographed on a silica gel columnn with hexane–AcOEt (3 : 1) as the eluant to give the dipropionate **22β** as a colorless oil (6.9 mg, 58%). $[\alpha]_D^{19}$ −19.3° (c=0.46, $CHCl_3$). ^{1}H-NMR δ: 1.02 (3H, d, J=7.0 Hz), 1.12 (3H, t, J=7.0 Hz), 1.16 (3H, t, J=7.0 Hz), 1.26 (3H, d, J=6.2 Hz), 1.98 (1H, ddd, J=14.2, 7.0, 4.8 Hz), 2.02—2.09 (1H, m), 2.14 (1H, dt, J=13.5, 11.5 Hz), 2.30 (1H, dd, J=14, 2.0 Hz), 2.315 (2H, q, J=7.0 Hz), 2.320 (1H, q, J=7.0 Hz), 2.41 (1H, d, J=7.0 Hz), 2.415 (1H, q, J=7.0 Hz), 2.47 (1H, ddd, J=13.5, 5.0, 3.0 Hz), 2.47—2.50 (1H, m), 2.89 (1H, ddd, J=14.0, 11.5 Hz), 3.15 (1H, dd, J=9.6, 1.0 Hz), 3.53 (3H, s), 3.98 (1H, dd, J=9.0, 6.0 Hz), 4.04 (2H, s), 4.99 (1H, ddd, J=11.6, 2.7, 6.2 Hz), 5.06 (1H, ddd, J=11.5, 2.0, 1.0 Hz), 5.37 (1H, dd, J=9.5, 3.5 Hz), 5.54 (1H, dd, J=15.5, 9.5 Hz), 5.73 (1H, ddd, J=15.0, 11.0, 3.5 Hz), 6.03 (1H, ddd, J=15.5, 10.5 Hz). MS m/z (relative intensity): 572 (M^+, 0.02%), 516 (0.015), 499 (14.2), 422 (1.3), 404 (9.5), 382 (2.5), 350 (4.0), 326 (5.1), 308 (7.6), 232 (18.3), 215 (15.6), 189 (15), 171 (9.6), 148 (12.9), 124 (20.8), 93 (22.9), 57 (108). Exact MS m/z Calcd for $C_{28}H_{41}ClO_{10}$ (M^+): 572.2388. Found: 572.2391.

Continued elution provided **22α** as a colorless oil (2.8 mg, 23%). ^{1}H-NMR δ: 1.02 (3H, d, J=7.0 Hz), 1.11 (3H, t, J=7.5 Hz), 1.12 (3H, t, J=7.5 Hz), 1.27 (3H, d, J=7.5 Hz), 2.05—2.20 (2H, m), 2.17 (1H, dt, J=14.0, 1.0 Hz), 2.22 (1H, br d, J=13.5, 1.5 Hz), 2.24—2.33 (1H, m), 2.30 (2H, q, J=7.5 Hz), 2.38 (1H, q, J=7.5 Hz), 2.40—2.49 (1H, m), 2.48 (1H, ddd, J=14.0, 4.0, 3.0 Hz), 2.92 (1H, dd, J=13.5, 1.5 Hz), 3.19 (1H, d, J=10.0 Hz), 3.53 (3H, s), 3.83 (1H, dd, J=9.6, 4.2 Hz), 4.05 (2H, s), 4.94 (1H, ddq, J=11.0, 3.5, 4.2 Hz), 5.06 (1H, dd, J=9.0, 4.2 Hz), 5.38 (1H, dd, J=9.5, 4.0 Hz), 5.56 (1H, dd, J=15.0, 9.8 Hz), 5.73 (1H, ddd, J=15.0, 11.0, 3.8 Hz), 6.05 (1H, ddd, J=15.2, 10.5, 1.0 Hz), 6.23 (1H, d, J=4.5 Hz), 6.64 (1H, dd, J=15.2, 10.5 Hz). MS m/z (relative intensity): 572 (M^+, 0.014%), 516, (0.04), 509 (0.14), 499 (5.5), 404 (4.4), 392 (2.5), 350 (9.4), 326 (6.3), 308 (6.3), 232 (16.5), 215 (9.6), 189 (15), 171 (7.5), 148 (13.0), 135 (41.7), 124 (26.0), 105 (28.1), 93 (29.2), 71 (37), 57 (108). Exact MS m/z Calcd for $C_{28}H_{41}ClO_{10}$ (M^+): 572.2388. Found: 572.2365. IR ν (neat) cm^{-1}: 1750, 1735, 1725 (CO), 1460, 1420, 1300, 1280, 1180, 1125, 1080, 1050.

Leuconolide A_3 Hemiacetal (3b) A solution of **21α,β** (10.0 mg, 0.0184 mmol) in 1 ml of MeOH was treated with K_2CO_3 (7.6 mg, 0.05 mmol) at 0 °C for 25 min. Solid NH_4Cl was added to the solvent, and the precipitate was filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with hexane–AcOEt (2 : 1) as the eluant to give **3b** as a colorless solid (6.5 mg, 83%). mp 95—96.6 °C (amorphous solid). $[\alpha]_D^{19}$ +35.3° (c=0.81, $CHCl_3$). ^{1}H-NMR δ: 1.00 (2H, d, J=7.0 Hz), 1.04 (1H, d, J=7.0 Hz), 1.27 (3H, d, J=6.5 Hz), 1.75—1.96 (2H, m), 2.10 (1H, s), 2.13 (2H, s), 2.19 (1H, dt, J=8.0, 2.8 Hz), 2.30—2.37 (1H, m), 2.42—2.75 (1H, m), 2.48—2.33 (1H, m), 2.77 (0.3H, dd, J=15.5, 8.0 Hz), 2.92 (0.7H, dd, J=14.0, 10.0 Hz), 3.14 (0.7H, d, J=9.2 Hz), 3.18 (0.3H, dd, J=6.2, 1.5 Hz), 3.55 (0.7H, s), 3.60 (0.3H, s), 4.06 (1H, dd, J=9.0, 4.0 Hz), 4.25 (1H, dd, J=9.5, 4.0 Hz), 4.97—5.13 (1H, m), 5.08 (0.3H, ddd, J=11.0, 2.0, 1.0 Hz), 5.28 (0.3H, dd, J=8.2, 4.5 Hz), 5.39—5.45 (0.3H, s), 5.61 (0.7H, ddd, J=16.0, 10.0, 4.5 Hz), 5.62 (1H, dd, J=16.0, 10.0 Hz), 5.69 (0.3H, ddd, J=16.0, 10.0, 4.5 Hz), 6.03 (1H, dd, J=15.0, 10.5 Hz), 6.35 (0.3H, dd, J=15.0, 10.5 Hz), 6.49 (0.7H, dd, J=15.0, 10.5 Hz). MS m/z (relative intensity): 426 (M^+, 0.3%), 408 (8.9), 368 (3.2), 253 (6.4), 232 (1.7), 211 (11), 155 (15), 123 (77), 43 (100). Exact MS m/z Calcd for $C_{22}H_{34}O_8$ (M^+): 426.2254. Found: 426.2227. Calcd for $C_{22}H_{32}O_7$ (M^+−18): 408.2148. Found: 408.2123. IR ν (neat) cm^{-1}: 3400, 1740, 1730.

Midecanolide A_1 Hemiacetal (3c) A solution of **21α,β** (4.3 mg, 0.0075 mmol) in 1 ml of MeOH was treated with K_2CO_3 (3.1 mg, 0.022 mmol) at 0 °C for 60 min. Solid NH_4Cl was added to the reaction mixture and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 and the precipitate was filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–MeOH (20 : 1) as the eluant to give **3c** as a colorless solid (3.1 mg, 94%). mp 80—81 °C (amorphous solid). $[\alpha]_D^{19}$ +31.6° (c=0.58, $CHCl_3$). ^{1}H-NMR δ: 1.00 (2.1H, d, J=7.0 Hz), 1.04 (0.9H, d, J=7.0 Hz), 1.14 (0.9H, t, J=7.0 Hz), 1.16 (2.1H, t, J=7.0 Hz), 1.26 (3H, d, J=6.2 Hz), 1.75—1.97 (2H, m), 2.12 (0.3H, dd, J=11.5, 2.5 Hz), 2.21 (0.7H, dd, J=14.0, 6.5 Hz), 2.23 (0.7H, dd, J=14.5, 2.0 Hz), 2.34 (0.3H, q, J=7.0 Hz), 2.35 (0.3H, q, J=7.0 Hz), 2.38 (0.7H, q, J=7.0 Hz), 2.39 (0.7H, q, J=7.0 Hz), 2.50 (0.3H, dd, J=10.5, 5.5 Hz), 2.75 (0.3H, dd, J=15.5, 8.0 Hz), 2.91 (0.7H, dd, J=14.0, 11.2 Hz), 3.14 (0.3H, dd, J=9.5, 0.5 Hz), 3.19 (0.3H, dd, J=9.0, 2.0 Hz), 3.54 (2.1H, s), 3.59 (0.9H, s), 3.84 (0.3H, t, J=5.5 Hz), 4.04 (0.3H, dd, J=9.2, 4.2 Hz), 4.28 (0.7H, dd, J=9.2, 4.2 Hz), 4.97—5.10 (1H, m), 5.08 (0.7H, ddd, J=11.0, 2.3, 1.5 Hz),

5.25—5.30 (0.3H, m), 5.29—5.32 (0.3H, m), 5.62 (0.7H, dd, J=15.5, 10.5 Hz), 5.64 (0.3H, dd, J=15.5, 11.5 Hz), 5.63 (0.7H, ddd, J=15.5, 10.5, 4.2 Hz), 5.79 (0.3H, ddd, J=15.5, 10.5, 4.2 Hz), 6.03 (0.7H, ddd, J=9.5, 4.0, 0.5 Hz), 6.22 (0.3H, ddd, J=9.5, 4.0, 0.5 Hz), 6.35 (0.3H, dd, J=15.5, 10.0 Hz), 6.52 (0.7 H, dd, J=15.5, 10.0 Hz). MS m/z (relative intensity): 440 (M^+, 0.4%), 422 (M^+-18, 7.2), 348 (2.1), 252 (4.3), 232 (5.7), 211 (11), 155 (13), 123 (72), 95 (51), 57 (100). Exact MS m/z Calcd for $C_{23}H_{34}O_7$ (M^+-18): 422.2305. Found: 422.2289. IR ν (neat) cm^{-1}: 3400, 1740, 1730, 1720, 1460, 1360, 1310, 1280, 1180, 920, 865, 740.

6″-Dihydro-12*S*,13*R*-epoxy-3,5-isopropylidene-6″-*O*-(4-methoxybenzyl)-niddanolide (23) CSA (0.7 mg) was added to a solution of **12** (17.0 mg, 0.031 mmol) in MeOH (0.5 ml) at room temperature. After 30 min, Et_3N (50 μl) was added, and the reaction mixture was evaporated *in vacuo*. The residue was chromatographed on a preparative TLC plate with hexane–AcOEt (1 : 3) as the developer to give 6″-dihydro-6″-*O*-(4-methoxybenzyl)niddanolide as a colorless oil (13.0 mg, 83%). $[\alpha]_D^{24}$ +14.5° (c=0.64, $CHCl_3$). ^{1}H-NMR δ: 1.18 (3H, d, J=7.0 Hz), 1.31 (3H, s), 1.32 (3H, d, J=6.2 Hz), 1.33 (3H, s), 1.37—1.45 (2H, m), 1.49 (1H, dd, J=7.0, 2.0 Hz), 1.62 (1H, d, J=4.0 Hz), 1.75 (1H, dd, J=14.5, 8.8 Hz), 1.65—1.95 (2H, m), 2.22 (1H, d, J=15.0 Hz), 2.35—2.62 (2H, m), 2.78 (1H, dd, J=16.1, 11.0 Hz), 2.94 (1H, dd, J=9.5, 1.5 Hz), 3.46—3.54 (2H, m), 3.72 (1H, dd, J=11.0, 1.5 Hz), 3.80 (3H, s), 3.99 (1H, d, J=8.4 Hz), 4.43 (2H, dd, J=16.5, 11.7 Hz), 5.20—5.30 (1H, m), 6.08—6.19 (2H, m), 6.31 (1H, d, J=15.0 Hz), 6.80—6.95 (2H, m), 7.20 (1H, d, J=15.0 Hz), 7.26—7.30 (2H, m). MS m/z (relative intensity): 504 (M^+, 0.3%), 399 (0.1), 384 (0.6), 366 (5.2), 351 (0.8), 334 (0.8), 261 (0.6), 249 (1.3), 234 (2.7), 150 (4.2), 137 (8.3), 121 (100). Exact MS m/z Calcd for $C_{28}H_{40}O_8$ (M^+): 504.2723. Found: 504.2709.

MCPBA (81.4 mg, 0.40 mmol; 85% activity) was added to a stirred solution of 6″-dihydro-6″-*O*-(4-methoxybenzyl)niddanolide (65.6 mg, 0.13 mmol), $NaHCO_3$ (40 mg) in CH_2Cl_2 (3 ml) at room temperature. After 20.5 h, the solution was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). After removal of the solvent, the crude epoxide was chromatographed on a silica gel column with hexane–AcOEt (1 : 3) as the eluant to give 6″-dihydro-12*S*,13*R*-epoxy-6″-*O*-(4-methoxybenzyl)niddanolide as a colorless oil (37.8 mg, 56%). $[\alpha]_D^{24}$ +9.45° (c=0.74, $CHCl_3$). ^{1}H-NMR δ: 1.17 (3H, d, J=7.0 Hz), 1.24—1.26 (1H, m), 1.31 (3H, s), 1.39—1.92 (5H, m), 2.31 (1H, dd, J=16.1, 1.1 Hz), 2.39 (1H, dd, J=12.1, 2.2 Hz), 2.61—2.63 (1H, m), 2.82 (1H, dd, J=16.1, 11.0 Hz), 3.00—3.15 (2H, m), 3.08 (1H, dd, J=10.3, 2.2 Hz), 3.14 (1H, dd, J=9.2, 1.8 Hz), 3.42—3.56, (2H, m), 3.60, (3H, s), 3.74—3.76 (1H, m), 3.80 (3H, s), 3.98 (1H, d, J=9.8 Hz), 4.43 (1H, dd, J=16.5, 11.4 Hz), 5.28—5.30 (1H, m), 6.49 (1H, dd, J=16.5, 11.4 Hz), 6.84—6.87 (2H, m), 7.20—7.23 (2H, m). MS m/z (relative intensity): 520 (M^+, 0.4%), 383 (1.0), 383 (12.5), 350 (1.7), 336 (0.9), 318 (1.7), 249 (1.3), 234 (3.8), 223 (2.1), 195 (1.7), 181 (3.4), 150 (98.3), 121 (100). Exact MS m/z Calcd for $C_{28}H_{40}O_9$ (M^+): 520.2673. Found: 520.2701. IR ν (neat) cm^{-1}: 3450, 1720, 1685, 1620, 1510, 1450, 1350, 1300, 1180, 1100, 1040, 1010, 980.

2-Methoxypropene (20 μl, 0.21 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (1 mg) were added to a solution of the above epoxide (9.1 mg, 17.5 mmol) in CH_2Cl_2 (1 ml) at room temperature under an argon atmosphere. After 5 min, Et_3N (50 μl) was added, and the reaction mixture was evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (1 : 1) as the eluant to give **23** as a colorless oil (9.2 mg, 94%). $[\alpha]_D^{22}$ −7.0° (c=0.83, $CHCl_3$). ^{1}H-MMR δ: 0.87—0.88 (0.5H, m), 0.95 (1.8H, d, J=6.6 Hz), 1.02—1.09 (0.5H, m), 1.12 (1.2H, d, J=6.6 Hz), 1.24 (1.8H, s), 1.26 (1.2H, s), 1.28 (1.8H, s), 1.30 (1.2H, s), 1.33 (1.2H, d, J=6.2 Hz), 1.40 (1.8H, d, J=7.0 Hz), 1.76—1.90 (2.5H, m), 1.94 (0.5H, dd, J=6.0, 3.5 Hz), 1.99 (0.5H, dd, J=6.0 Hz, 3.5 Hz), 2.24—2.40 (3H, m), 2.36 (0.5H, dd, J=14.7, 2.9 Hz), 2.55 (0.5H, dd, J=14.7, 4.5 Hz), 2.72 (0.5H, dd, J=14.7, 4.4 Hz), 2.85 (0.5H, dd, J=14.7, 9.2 Hz) 2.82—2.92 (5H, m), 3.045 (0.5H, s), 3.05 (0.5H, s), 3.30—3.36 (1.5H, m), 3.40—3.60 (5H, m), 3.46 (2H, s), 3.52 (1H, s), 3.72 (1H, d, J=9.2 Hz), 3.80 (2H, s), 3.81 (1H, s), 3.98—3.99 (0.5H, m), 4.22 (1H, ddd, J=9.5, 4.2, 1.0 Hz), 4.40 (0.5H, d, J=11.7 Hz), 4.49 (1H, d, J=11.7 Hz), 5.08 (0.5H, m), 5.25 (0.5H, m), 6.42 (0.5H, d, J=15.5 Hz), 6.49 (0.5H, d, J=15.5 Hz), 6.64 (0.5H, dd, J=15.5, 6.0 Hz), 6.85—7.23 (4H, m), 6.90 (0.5H, dd, J=15.4, 2.9 Hz). MS m/z (relative intensity): 560 (M^+, 0.07%), 502 (0.2), 471 (0.5), 421 (1.0), 406 (0.3), 366 (2), 348 (0.75), 334 (1.1), 150 (4.8), 137 (8.8), 121 (100). Exact MS m/z Calcd for $C_{31}H_{44}O_9$ (M^+): 560.2985. Found: 560.2963. IR ν (neat) cm^{-1}: 1725, 1695, 1635, 1620, 1300.

6″-Dihydro-12*S*,13*R*-epoxy-3,5-isopropylidene-6″-*O*-(4-methoxybenzyl)-leuconolide A_1 (24) A stirred MeOH solution of **23** (31.5 mg, 0.056 mmol in 1.5 ml of MeOH) was treated with $NaBH_4$ (5.2 mg, 0.138 mmol) at 0 °C for 10 min. Solid NH_4Cl was added to the reaction mixture to quench the reaction, and the solvent was removed to dryness. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NH_4Cl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column with hexane–AcOEt (1 : 1) to afford **24** as a colorless oil (31.6 mg, 100%). $[\alpha]_D^{23}$ +14.9° (c=0.66, $CHCl_3$). ^{1}H-NMR δ: 0.80—0.90 (2H, m), 1.08 (3H, d, J=5.5 Hz), 1.32 (3H, d, J=6.6 Hz), 1.42 (3H, s), 1.44 (3H, s), 1.23—1.81 (6H, m), 1.89 (1H, m), 2.07—2.09 (1H, m), 2.34 (1H, d, J=7.7 Hz), 2.41—2.51 (1H, m), 2.44 (1H, dd, J=16.5, 2.6 Hz), 2.90 (1H, dd, J=16.1, 11.0 Hz), 2.92 (1H, s), 2.98—3.08 (1H, m), 3.05 (1H, dd, J=6.6, 1.8 Hz), 3.51 (3H, s), 3.80 (1H, dd, J=6.6, 1.8 Hz), 4.21—4.28 (2H, m), 4.39 (1H, d, J=11.7 Hz), 4.46 (1H, d, J=11.7 Hz), 5.24—5.26 (1H, m), 5.53 (1H, dd, J=16.0, 6.6 Hz), 6.03 (1H, dd, J=16.0, 6.2 Hz), 6.86—6.88 (2H, m), 7.24—7.27 (2H, m). MS m/z (relative intensity): 562 (M^+, 0.03%), 544 (0.14), 486 (0.36), 472 (1.5), 365 (0.42), 249 (2.6), 234 (2.3), 202 (2.5), 121 (100), 98 (0.46). Exact MS m/z Calcd for $C_{31}H_{46}O_9$ (M^+): 562.3142. Found: 562.3172. IR ν (neat) cm^{-1}: 3450, 1740, 1625.

9*R*-*O*-Chloroacetyl-6″-dihydro-12*S*,13*R*-epoxy-3,5-isopropylidene-6″-*O*-(4-methoxybenzyl)leuconolide A_1 (25) Chloroacetic anhydride (26.1 mg, 0.153 mmol) was added to a stirred solution of **24** (28.4 mg, 0.051 mmol) and DMAP (6.0 mg, 0.049 mmol) in a 1 : 1 mixture of pyridine and CH_2Cl_2 (1 ml). Stirring was continued for 30 min at room temperature, then the reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl–brine (1 : 1) and brine. The organic layer was dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (1 : 1) as the eluant to give **25** as a colorless oil (28.6 mg, 88.6%). $[\alpha]_D^{23}$ +18.9° (c=0.72, $CHCl_3$). ^{1}H-NMR δ: 1.00 (3H, d, J=6.6 Hz), 1.32 (3H, d, J=6.6 Hz), 1.35—1.45 (1H, m), 1.89—1.95 (1H, m), 2.07 (1H, d, J=15.2 Hz), 2.44 (1H, dd, J=5.5, 2.9 Hz), 2.40—2.55 (1H, m), 2.88 (1H, dd, J=16.1, 11.0 Hz), 2.90—3.05 (3H, m), 3.51 (3H, s), 3.44—3.57 (3H, m), 3.78 (1H, d, J=5.9 Hz), 3.80 (3H, s), 4.02 (2H, s), 4.26 (1H, dd, J=11.3, 2.2 Hz), 4.45 (1H, d, J=11.5 Hz), 5.21—5.27 (1H, m), 5.41 (1H, d, J=6.2 Hz), 5.52 (1H, dd, J=15.4, 6.6 Hz), 5.93 (1H, dd, J=15.4, 6.6 Hz), 6.87—6.89 (2H, m), 7.25—7.27 (2H, m). MS m/z (relative intensity): 638 (M^+, 0.07%), 620 (M^+-18, 0.07), 580 (0.3), 564 (0.2), 549 (0.9), 487 (0.4), 459 (0.3), 444 (0.4), 319 (0.6), 301 (0.4), 249 (1.5), 234 (1.0), 217 (1.9), 189 (2.3), 175 (2.7), 137 (4.2), 121 (100), 109 (4.2). Exact MS m/z Calcd for $C_{33}H_{47}ClO_{10}$ (M^+): 638.2857. Found: 638.2819. IR ν (neat) cm^{-1}: 1755, 1725, 1610, 1580, 1455, 1380, 1360, 1300, 1250, 1200, 1180, 1120, 1080, 1035, 975.

9*R*-*O*-Chloroacetyl-6″-dihydro-12*S*,13*R*-epoxy-3,5-isopropylideneleuconolide A_1 (26) DDQ (22.2 mg, 0.094 mmol) was added to a stirred solution of **25** (22.2 mg, 0.035 mmol) in CH_2Cl_2 (1 ml) and H_2O (0.05 ml). After being stirred for 40 min, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$, and brine. The extract was dried over Na_2SO_4 and concentrated to leave an oil, which was purified by silica gel column chromatography with hexane : AcOEt = 1 : 1 as an eluant to give **26** as a colorless oil (17.4 mg, 97%). $[\alpha]_D^{23}$ +10.5° (c=0.56, $CHCl_3$). ^{1}H-NMR δ: 1.03 (3H, d, J=6.6 Hz), 1.32 (3H, d, J=6.2 Hz), 1.20—1.80 (11H, m), 1.93—1.99 (1H, m), 2.10 (1H, ddd, J=13.2, 1.8, 1.5 Hz), 2.31—2.33 (1H, m), 2.48 (1H, dd, J=16.1, 2.9 Hz), 2.89 (1H, dd, J=16.1, 11.0 Hz), 2.95—3.05 (2H, m), 3.03 (1H, d, J=6.2 Hz), 3.50—3.62 (2H, m), 3.53 (3H, s), 3.75 (1H, t, J=5.5 Hz), 3.80 (1H, d, J=5.1 Hz), 4.09 (2H, s), 4.27 (1H, dd, J=11.0, 1.8 Hz), 5.25 (1H, m), 5.44 (1H, d, J=6.6 Hz), 5.55 (1H, dd, J=15.8, 6.6 Hz), 5.95 (1H, dd, J=15.8, 6.6 Hz). MS m/z (relative intensity): 503 (M^+-15, 0.1%), 460 (0.09), 442 (1), 366 (0.08), 349 (0.08), 317 (2), 251 (5.2), 233 (12.5), 163 (9.4), 121 (12.5), 109 (28), 98 (100). Exact MS m/z Calcd for $C_{24}H_{36}ClO_9$ (M^+-15): 503.2048. Found: 503.2075. IR ν (neat) cm^{-1}: 3400, 1750, 1720, 1450, 1375, 1360, 1300, 1280, 1260, 1200, 1175, 1120, 1080, 1040, 970.

9*R*-*O*-Chloroacetyl-12*S*,13*R*-epoxy-3,5-isopropylideneleuconolide A_1 (27) Dry DMSO (17 μl, 0.239 mmol) in dry CH_2Cl_2 (0.5 ml) was added dropwise during 15 min to a well stirred solution of oxalyl chloride (10 μl, 0.115 mmol) in dry CH_2Cl_2 (0.5 ml) cooled to below −73 °C under an argon atmosphere. After 15 min at −73 °C, a solution of **26** (12.7 mg, 0.024 mmol) was added to the mixture during 5 min. Stirring was continued at −73 °C for 15 min, then Et_3N (0.048 ml, 0.345 mmol) was added dropwise, and after removal of the cooling bath, the reaction mixture was allowed to warm to room temperature (over *ca.* 1 h). Then saturated aqueous NH_4Cl (5 ml) was added, the organic layer was separated, and the aqueous layer was re-extracted with ether (5 ml × 2). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column with hexane–AcOEt (1 : 1) as the eluant to give the aldehyde as a colorless oil (12.7 mg, 100%). $[\alpha]_D^{24}$ +3.05° (c=0.75, $CHCl_3$). ^{1}H-NMR δ: 1.09 (3H,

d, J=6.0 Hz), 1.32 (3H, d, J=6.6 Hz), 1.40 (3H, s), 1.44 (3H, s), 1.52—1.71 (5H, m), 2.11 (1H, d, J=16.5 Hz), 2.28 (1H, dq, J=8.2, 2.2 Hz), 2.48 (1H, dd, J=16.5, 2.9 Hz), 2.96 (1H, d, J=16.5 Hz), 3.01 (1H, d, J=7.3 Hz), 3.03—3.06 (1H, m), 3.22 (1H, ddd, J=17.2, 3.7, 1.5 Hz), 3.56 (3H, s), 3.86 (1H, d, J=6.2 Hz), 4.07 (2H, s), 4.27 (1H, dd, J=11.0, 2.2 Hz), 5.21—5.30 (1H, m), 5.42 (1H, d, J=6.0 Hz), 5.52 (1H, dd, J=16.1, 7.0 Hz), 5.95 (1H, dd, J=16.1, 7.0 Hz), 9.74 (1H, s). MS m/z (relative intensity): 501 (M^+-15, 0.07%), 458 (0.98), 442 (0.2), 431 (0.27), 407 (0.48), 364 (4.2), 249 (9.2), 175 (6.3), 163 (6.8), 147 (10), 121 (17), 98 (100). Exact MS m/z Calcd for $C_{24}H_{34}ClO_9$ (M^+-15): 501.1891. Found 501.1892. IR ν (neat) cm^{-1}: 1750, 1720, 1710, 1450, 1410, 1370, 1300, 1280, 1260, 1200, 1170, 1075, 970, 910.

9*R*-*O*-Chloroacetylmaridonolide II Acetoxyacetal (29) (a) A solution of **27** (9.3 mg, 0.018 mmol) in 1 ml of 2 N H_2SO_4–THF (1 : 10) was stirred at room temperature for 30 min. After dilution of the solvent with CH_2Cl_2, the reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4, and evaporated. Purification of the residue on a silica gel column with hexane–AcOEt (1 : 3) as the eluant gave recovered **27** (3.6 mg, 39%) and 9*R*-*O*-Chloroacetyl-12*S*,13*R*-epoxyleuconolide A_1 hemiacetal (**28**) as a colorless oil (3.4 mg, 40%). $[\alpha]_D^{24}$ +5.94° (c=0.42, $CHCl_3$). IR ν (neat) cm^{-1}: 3400, 1750, 1725, 1720, 1460, 1380, 1260, 1200, 1080, 1040. A solution of **28** (4.8 mg, 0.01 mmol) in pyridine (0.5 ml) and CH_2Cl_2 (0.5 ml) was treated with acetic anhydride (10 μl, 0.106 mmol) and DMAP (1 mg). Stirring was continued for 40 min, then the reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified on a silica gel column with hexane–AcOEt (1 : 1) as the eluant, affordeding **29α**, **β** as a colorless oil (4.6 mg, 82%).

(b) MCPBA (4.4 mg, 0.021 mmol; 85% activity) was added to a stirred solution of **21** (7.8 mg, 0.0143 mmol) and K_2CO_3 (2 mg) in CH_2Cl_2 (0.5 ml) at room temperature. After 16.5 h, the solution was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave the crude epoxide, which was chromatographed on a silica gel column with hexane–AcOEt (2 : 1) as the eluant to give the epoxide **29α**, **β** as a colorless oil (6.7 mg, 84%). ^{1}H-NMR δ: 1.07 (3H, d, J=7.0 Hz), 1.28 (3H, d, J=6.0 Hz), 1.97—2.17 (2H, m), 2.06 (1H, dd, J=11.5, 8.5 Hz), 2.06 (3H, s), 2.10 (3H, s), 2.20—2.37 (3H, m), 2.34 (1H, dd, J=12.5, 1.0 Hz), 2.93 (1H, dd, J=12.5, 11.5 Hz), 3.11 (1H, dd, J=9.2, 2.0 Hz), 3.15 (1H, dt, J=10.5, 1.0 Hz), 3.16 (1H, dd, J=9.0, 0.5 Hz), 3.56 (3H, s), 3.59 (1H, t, J=6.9 Hz), 4.04—4.08 (1H, m), 4.05 (2H, s), 4.99 (1H, ddq, J=8.5, 3.0, 6.0 Hz), 5.06 (1H, dd, J=11.0, 1.5 Hz), 5.39 (1H, dd, J=9.5, 3.5 Hz), 5.78 (1H, dd, J=15.5, 8.5 Hz), 5.99 (1H, dd, J=15.5, 9.5 Hz), 6.29 (1H, dd, J=6.0, 4.5 Hz). MS m/z (relative intensity): 560 (M^+, 0.36%), 501 (4.8), 472 (0.9), 440 (0.7), 407 (1.2), 249 (4.2), 231 (6.3), 175 (17), 98 (84), 43 (100). Exact MS m/z Calcd for $C_{26}H_{37}ClO_{11}$ (M^+): 560.2024. Found: 560.2012. IR ν (neat) cm^{-1}: 1750, 1740, 1730.

9*R*-*O*-Chloroacetylmaridonolide I (30) (a) A solution of **28** (4.2 mg, 9 μmol), Et_3N (32 μl), propionic anhydride (15 μl, 0.117 mmol) and DMAP (1 mg) in CH_2Cl_2 was stirred at room temperature for 90 min, then diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic layer was dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified on a silica gel column with hexane–AcOEt (1 : 1) as the eluant to give **30** as a colorless oil (3.7 mg, 71%).

(b) MCPBA (5 mg, 0.029 mmol; 85% activity) was added to a stirred solution of **22** (10 mg, 0.0174 mmol) and K_2CO_3 (4 mg) in CH_2Cl_2 (1 ml) at room temperature. After 8.5 h, the solution was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated *in vacuo* to leave the crude epoxide, which was chromatographed on a silica gel column with hexane–AcOEt (2 : 1) as the eluant to give the epoxide **30** as a colorless oil (9.5 mg, 93%). $[\alpha]_D^{22.5}$ +22.4° (c=0.81, $CHCl_3$). ^{1}H-NMR δ: 1.07 (3H, d, J=6.5 Hz), 1.13 (6H, t, J=7.3 Hz), 1.28 (3H, d, J=6.2 Hz), 1.46 (1H, ddd, J=14.2, 12.0, 9.8 Hz), 2.01 (1H, ddd, J=14.0, 6.8, 4.8 Hz), 2.02—2.12 (1H, m), 2.20—2.42 (4H, m), 2.33 (2H, q, J=7.3 Hz), 2.37 (2H, q, J=7.3 Hz), 2.38 (2H, q, J=7.3 Hz), 2.93 (1H, ddd, J=14.0, 11.6 Hz), 3.12 (1H, dd, J=10.5, 5.5 Hz), 3.18 (1H, dd, J=9.6, 1.0 Hz), 3.55 (3H, s), 4.03 (1H, dd, J=9.3, 4.2 Hz), 4.05 (2H, s), 4.96 (1H, ddq, J=12.2, 3.4, 6.2 Hz), 5.11 (1H, d, J=10.5 Hz), 5.39 (1H, dd, J=9.5, 3.5 Hz), 5.80 (1H, dd, J=15.5, 9.0 Hz), 6.00 (1H, dd, J=15.5, 9.6 Hz), 6.31 (1H, dd, J=5.8, 5.0 Hz). MS m/z (relative intensity): 590 (M^++2, 0.1%), 588 (M^+, 0.2), 515 (4.7), 495 (0.3), 421 (0.7), 231 (2.7), 189 (6.3), 147 (3.5), 121 (6.5), 109 (11.3), 98 (27.9), 81 (12.0), 71 (22.6), 57 (100), 41 (9.2). Exact MS m/z Calcd for $C_{28}H_{41}ClO_{11}$ (M^+): 588.2337. Found: 588.2344. IR ν (neat) cm^{-1}: 1750, 1730, 1720, 1460, 1280, 1180, 1130, 1080, 970.

Maridonolide II Hemiacetal (4a) A solution of **29α**, **β** (13 mg, 0.023 mmol) in 0.5 ml of MeOH was treated with K_2CO_3 (10 mg, 0.072 mmol) at 0 °C for 20 min. After evaporation of the solvent, the residue was taken up in CH_2Cl_2, and the precipitate was filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–MeOH (20 : 1) as the eluant to give **4a** as a colorless solid (8.3 mg, 81%). mp 94—95 °C (amorphous solid). $[\alpha]_D^{19}$ −4.6° (c=0.56, $CHCl_3$). ^{1}H-NMR δ: 1.05 (2.1H, d, J=7.0 Hz), 1.07 (0.9H, d, J=7.0 Hz), 1.28 (2.1H, d, J=6.2 Hz), 1.30 (0.9H, d, J=6.2 Hz), 1.40 (1H, dt, J=11.5, 2.5 Hz), 1.81 (1H, dd, J=7.5, 3.5 Hz), 1.86 (1H, dd, J=7.0, 4.5 Hz), 1.92—2.05 (1H, m), 2.076 (0.9H, s), 2.084 (2.1H, s), 2.11 (1H, dd, J=12.0, 8.0 Hz), 2.19 (0.7H, ddd, J=11.5, 3.5, 1.5 Hz), 2.20 (0.7H, dd, J=8.2, 5.0 Hz), 2.28 (0.3H, ddd, J=7.5, 3.5, 1.5 Hz), 2.34 (0.7H, dd, J=13.0, 2.8 Hz), 2.53 (0.3H, dd, J=14.2, 4.2 Hz), 2.62 (0.7H, br d, J=2.5 Hz), 2.86 (0.3H, dd, J=14.0, 9.5 Hz), 2.94 (0.7 H, dd, J=13.5, 11.5 Hz), 3.12 (1H, d, J=9.2 Hz), 3.19 (0.7H, dd, J=9.2, 0.5 Hz), 3.30 (0.3H, dd, J=7.5, 2.0 Hz), 3.57 (2.1H, s), 3.62 (0.9H, s), 3.89 (0.3H, dd, J=7.2, 5.0 Hz), 4.12 (1H, dd, J=9.5, 4.0 Hz), 4.24 (1H, dd, J=9.0, 3.5 Hz), 4.95—5.17 (1H, m), 5.15 (0.7H, ddd, J=11.0, 2.2, 1.5 Hz), 5.23 (0.3H, ddd, J=9.8, 4.2, 2.0 Hz), 5.46 (0.3H, t, J=4.0 Hz), 5.55—5.65 (0.7H, m), 5.62 (0.7H, dd, J=15.5, 8.5 Hz), 6.07 (0.7H, dd, J=15.5, 8.5 Hz), 6.08 (0.3 H, dd, J=15.5, 8.5 Hz). MS m/z (relative intensity): 442 (M^+, 0.07%), 424 (M^+-18, 0.9), 382 (1.2), 364 (2.2), 350 (2.6), 249 (8.0), 179 (17), 117 (36), 98 (99), 71 (66), 43 (100). Exact MS m/z Calcd for $C_{22}H_{32}O_8$ (M^+): 424.2097. Found: 424.2095. IR ν (neat) cm^{-1}: 3400, 1730.

Maridonolide I Hemiacetal (4b) A solution of **30α**, **β** (6.8 mg, 0.012 mmol) in 1 ml of MeOH was treated with K_2CO_3 (6 mg, 0.043 mmol) at 0 °C for 60 min. After evaporation of the solvent, CH_2Cl_2 was added to the reaction mixture and precipitate was filtered off. The filtrate was evaporated *in vacuo* to leave an oil, which was chromatographed on a silica gel column with CH_2Cl_2–MeOH (20 : 1) as the eluant to give **4b** as a colorless solid (5.0 mg, 95%). mp 91—92.5 °C (amorphous solid). $[\alpha]_D^{19}$ = −6.4° (c=1.90). ^{1}H-NMR δ: 1.05 (2.1H, d, J=7.0 Hz), 1.07 (0.9H, d, J=7.0 Hz), 1.12 (3H, t, J=7.0 Hz), 1.28 (0.9H, d, J=6.2 Hz), 1.30 (2.1H, d, J=6.2 Hz), 1.39—1.49 (1H, m), 1.79—1.85 (1H, m), 1.82—1.90 (1H, m), 1.91—2.01 (1H, m), 2.10—2.20 (1H, m), 2.17 (0.3H, s), 2.21 (1H, dd, J=7.8, 5.0 Hz), 2.28 (0.3H, dd, J=6.0, 3.2 Hz), 2.36 (2H, dt, J=2.0, 6.2 Hz), 2.53 (0.3H, dd, J=14.5, 4.2 Hz), 2.63 (0.7H, d, J=3.5 Hz), 2.85 (0.3H, dd, J=14.0, 9.5 Hz), 2.93 (0.7H, dd, J=12.5, 11.5 Hz), 3.08—3.17 (0.3H, m), 3.13 (1H, d, J=9.0 Hz), 3.17 (0.7H, dd, J=9.2, 0.5Hz), 3.31 (0.3H, dd, J=7.0, 2.0 Hz), 3.56 (2.1H, s), 3.62 (0.9H, s), 3.89 (0.3H, dd, J=7.0, 5.0 Hz), 4.11 (1H, dd, J=9.0, 4.0 Hz), 4.24 (1H, dd, J=9.0, 3.5 Hz), 4.93—5.74 (1H, m), 5.12 (0.7H, ddd, J=11.8, 2.5, 1.0 Hz), 5.24 (0.3H, ddd, J=8.5, 4.0, 1.8 Hz), 5.44 (0.3H, t, J=5.0 Hz), 5.58 (0.7H, dd, J=8.0, 6.0 Hz), 5.62 (0.3H, dd, J=15.5, 8.5 Hz), 5.65 (0.7H, dd, J=15.5, 8.5 Hz), 6.06 (0.3H, dd, J=15.5, 9.5 Hz), 6.08 (0.7H, dd, J=15.5, 9.5 Hz). MS m/z (relative intensity): 456 (M^+, 0.04%), 438 (M^+-18, 0.48), 249 (4.3), 189 (8.9), 98 (60), 71 (57), 57 (100). Exact MS m/z Calcd for $C_{23}H_{34}O_8$ (M^+-18): 438.2101. Found: 438.2271. IR ν (neat) cm^{-1}: 3400, 1730.

References and Notes

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9) The first synthesis of **3a**—**4b** has been completed in this work.
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11) Unless otherwise noted, the numberings are based on those of **1**—**4**.
12) Compound **6** was converted to leuconolide A_3 by treatment with 80% trifluoroacetic acid in 61% yield.
13) There are two precedents for the reduction of such a 16-membered macrolide. Grieco *et al.*[14] reported the reduction of tylonolide *O*-methylacetal to the 9*S*-alcohol selectively and Freiberg *et al.*[15] obtained the 9*R*-alcohol (josamycin) from carbomycin B in moderale selectivity.
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