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# Acid Cyclization of 5-Ketogermacren-6,12-olides. A Reactivity and Conformational Study

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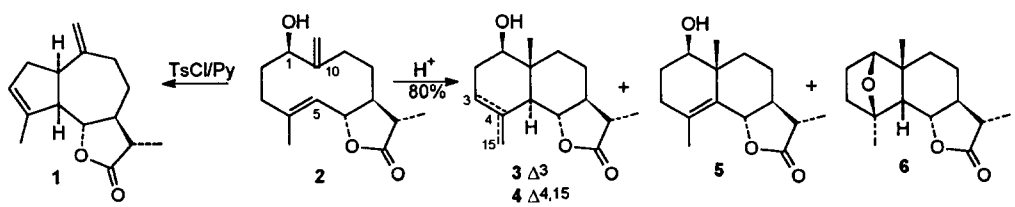
*Abstract*: The acid cyclization of three related 5-ketogermacren-6,12-olides has been studied. All products have been identified and their stereochemistries established. The conformation of the germacrenolides and of the protonated derivatives have been studied in order to provide an explanation for the stereochemical course of the reaction. Copyright © 1996 Elsevier Science Ltd

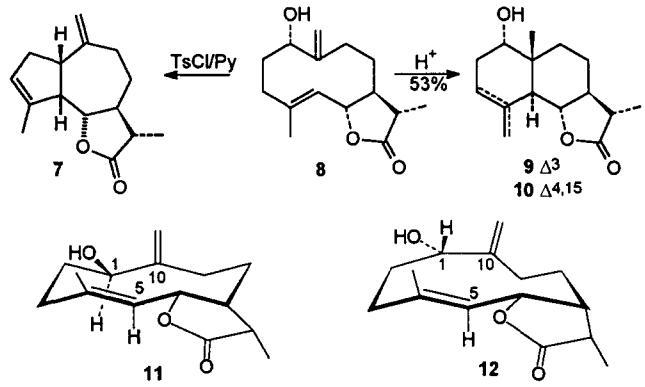
The reactivity and conformational behaviour of the germacrenes and related compounds have been studied over the years due to their central role in the biogenesis of other sesquiterpenes, such as eudesmanes, guaianes and elemanes.[1]

Several studies have linked the preferred conformation of the germacrane with the type or with the stereochemistry of the products formed in the different reactions tried. Thus, conformational analysis has been used, for example, in studies of the acid cyclization of germacrenes,[2] their diimide reduction[3] and their Cope rearrangement to elemanes.[4]

In most cases, a correlation between the lowest energy conformer and the resulting products was used to explain the experimental results.

A few years ago,[5] we studied the acid cyclization of gallicin **2**, a germacranolide isolated from *Artemisia maritima gallica*, which upon treatment with chloroform saturated with gaseous hydrogen chloride yielded mainly the eudesmanolides **3-6**. Its epimer at the C-1 position, 1-epigallicin (**8**), showed a similar behaviour,[6] yielding the eudesmanolides **9** and **10** under the same conditions.

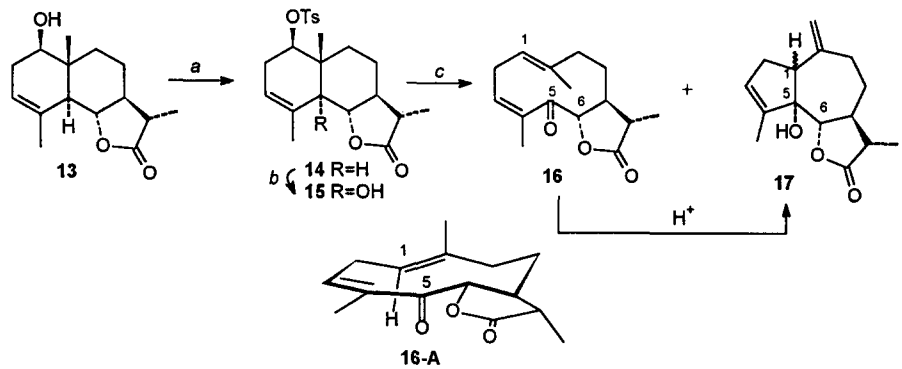





A conformational analysis of gallicin (**2**) and 1-epigallicin (**8**) using lanthanide-induced shift (LIS) studies and molecular mechanics allowed us to correlate the lowest energy conformation of these compounds **11** and **12**, with the stereochemistry of the cyclization products.

When the intramolecular nucleophilic displacement reaction of the tosylates of **2**[7] and **8**[8] was studied, it was observed that the stereochemistry of the resulting guaianolides, **1** and **7** respectively, also correlated well with conformations such as **11** and **12**.

Following our studies of the cyclization of germacrenes, we then focused our attention on the 5-ketogermacranolides such as **16**.[9] This compound, prepared as shown in Scheme 1 from **13**,[5] was highly unstable. All purification attempts resulted in its partial transformation into a new compound **17**. Upon stirring with silica gel, total conversion to **17** was achieved.




a) TsCl, Py, 48h (92%); b) $SeO_2$, *t*-BuOOH, $CH_2Cl_2$, 72 h (95%); c) $NaHCO_3$,$H_2O$, EtOH, reflux, 2h (79%)

Scheme 1

The guaiane skeleton of the cyclization product was deduced from its spectroscopic data, and the disposition of the hydroxyl group at C-5 was established by comparison of the $^1$H-NMR spectrum taken in $CDCl_3$ with the one taken in Py-$d_5$.[10] The small $\Delta\delta$ value ($\Delta\delta=\delta_{CDCl_3}-\delta_{Py\text{-}d_5}$) of -0.09 ppm for H-6 seemed to indicate that the hydroxyl group is disposed in $\alpha$.

The stereochemistry at C-1 was proposed as α by a conformational analysis carried out on the precursor **16**. A LIS study suggested a *syn* relationship between H-1 and the carbonyl oxygen at C-5 on **16**,[9] which upon cyclization should yield the proposed *cis* stereochemistry.

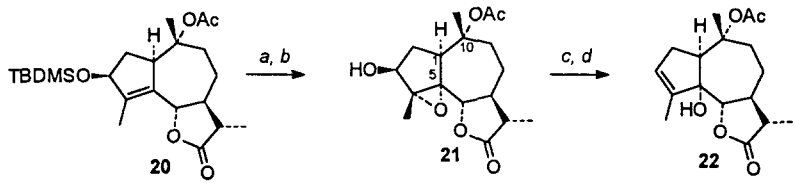
This conformation was in good agreement with the lowest energy conformer of **16** found in a molecular mechanics study (**16-A**).

This proposal was, however, in contrast with the stereochemistry of the cyclization product of a closely related germacranolide, reported by Fujimoto et al.[11]

In order to determine unambigously the stereochemistry of **17** at the C-1 position, we decided to synthesize the proposed compound, that is, the cis-[1α-H;5α-OH]-guaianolide.

The starting material chosen was the lactone **20**, previously prepared in our laboratories[12] from the isophotosantonic lactone, a product of the photolysis of α-santonine whose structure and stereochemistry was established by X-ray.[13]

Our initial strategy was first to transform the A ring, introducing the $\Delta^3$ double bond and the 5α-OH group. Subsequently, hydrolysis of the C-10 acetate and elimination of the resulting hydroxyl should afford the desired product.

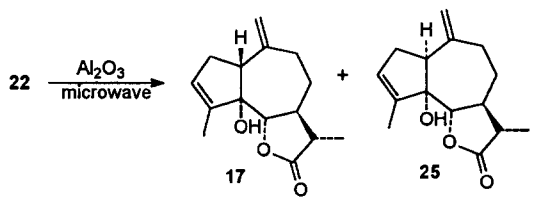



a)m-CPBA, $NaHCO_3$, $CH_2Cl_2$, (85%); b)TBAF, THF, (98%); c)MsCl, $Et_3N$, $CH_2Cl_2$ ,(79%); d)Zn, NaI, glyme, reflux, 4 h, (78%)

Scheme 2

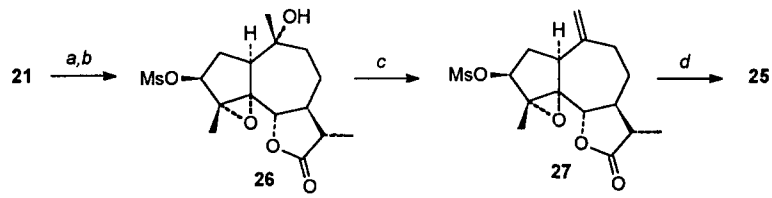
The first part of the projected transformations was carried out as shown in Scheme 2. When the removal of the acetate on **21** was attempted, however, we found that this was a difficult task and all reaction conditions assayed failed to effect the desired transformation. These included a variety of acids and bases in different solvents and at different temperatures, treatment with exchange resins and others. In most cases, the starting compound was recovered unaltered. Only upon treatment with tetrabutylammonium hydroxide, a very low yield of the desired alcohol was obtained. All attempts to improve the yield of this reaction failed, and thus this route was abandoned.

An interesting reaction was observed, however, when the acetate **22** was absorbed in neutral alumina and placed in a microwave oven in an attempt to induce the direct elimination of the acetate. After 7 minutes, a mixture of two compounds in a 1:1 ratio was obtained (Scheme 3).




Scheme 3

After HPLC separation NMR revealed that one of the compounds was identical with the cyclization product **17**. The other one (**25**), however, appeared to be an isomer at the ring junction. In fact, a careful re-examination of the $^1$H NMR spectrum of the crude of the acid cyclization reaction of **16** allowed us to find the isomeric compound **25** in a very minor proportion. The comparison of the $^1$H-NMR spectra in $CDCl_3$ and Py-$d_5$ of **25** indicated that the C-5 hydroxyl group was in the same α disposition as in **17**. Since we now had the two isomers at the C-1 position and in a sufficient amount, a spectroscopic study was undertaken. The proposed structures were confirmed by different experiments, including COSY, HMQC and ROESY. This last one showed a correlation between H-6 and H-1 in **17**, indicating that the stereochemistry at the ring junction in the cyclization product is *trans*-[1β-H; 5α-OH]. The absence of such a correlation in **25** indicated that this was the *cis*-[1α-H;5β-OH] isomer. Thus, the stereochemistry proposed for the cyclization product on the basis of the conformation of the germacrane from which it originated was not the right one. This was confirmed by the synthesis of the *cis*-[1α-H;5α-OH] compound, which was achieved by the sequence shown in Scheme 4.




a) MsCl, $CH_2Cl_2$, $Et_3N$ (79%); b) KOH, $H_2O$ (66%); c) $SO_2Cl$, Py, -55°C (65%); d) Zn, NaI, glyme, reflux, 4h (80%)

Scheme 4

The hydrolysis of the acetate and its removal were carried out on the epoxide mesylate **26**, yielding after rearrangement, a compound identical with **25** and not with the cyclization major product **17**. The formation of the two guaianes **17** and **25** in the microwave treatment of **22** can be explained as the rearrangement of **22** aided by the Lewis acid character of the alumina, which will give the germacrane **16**. This compound, after some equilibration can yield the observed products. The high proportion of **25** when compared to the acid cyclization of **16**, can be explained either by a combination of mechanisms (direct elimination of the acetate together with an acid cyclization) or by restricted conformational mobility of the germacrane due to the fact that it is adsorbed on alumina.

Since the low stability of **16** made it very difficult to study its conformation and reactivity in more detail, we decided to study a closely related compound which had shown greater stability.

The compound chosen was the keto-germacradienolide **28**, whose preparation has been previously reported.[14]

The conformation of **28** was studied in solution by different techniques. LIS studies pointed to a *syn* relationship between H-1 and the carbonyl oxygen at C-5.[14] The circular dichroism spectrum shows a band at 255 nm (K band) with a $\Delta\varepsilon_{max}$= +8.95 which indicates that the α,β-unsaturated ketone must exist in a transoid arrangement with a positive sign of the torsion angle,[15] as shown in Figure 1. The ROESY spectrum showed correlations between H-6 the C-10 methyl group and one of the exocyclic methylenic hydrogens (H-15). All

these data indicate that the preferred conformation in solution for **28** must be the one depicted in Figure 1 as **28-A** (a "crown" conformation). This is the same conformation found for the solid state in an X-ray analysis.[14]

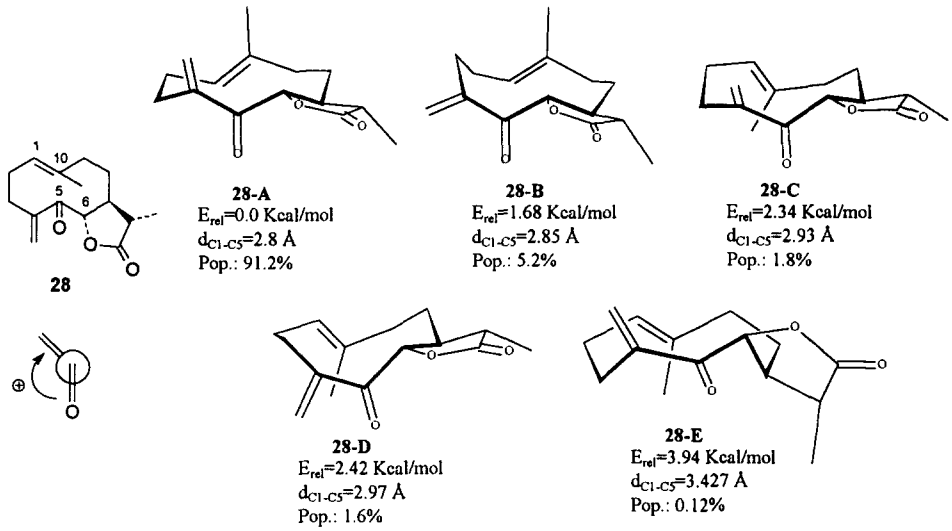



Figure 1

The $^{13}$C-NMR spectrum in $CDCl_3$ taken at 300 K shows, however, a clear broadening of several signals, most notably those assigned to C-1, C-9 and the C-10 methyl group. These signals became sharper when the probe temperature was raised to 330 K. Lowering the temperature to 253 K also resulted in the sharpening of the signals with slight changes in the chemical shift, all the above indicating that some conformational equilibrium exists for **28** in solution.

When **28** was treated with chloroform saturated with gaseous hydrogen chloride, four new compounds **29-32** were obtained in 19%, 21%, 28% and 12% yield, respectively. Compound **29** decomposed to **30** and **31** in deuterochloroform solution or upon standing with silica gel, and its structure was deduced from its $^1$H-NMR spectrum and by comparison with the other compounds obtained in the reaction. The other three products were stable, and a complete spectroscopic study allowed us to assign them the guaiane skeleton and the structures shown in Figure 2.

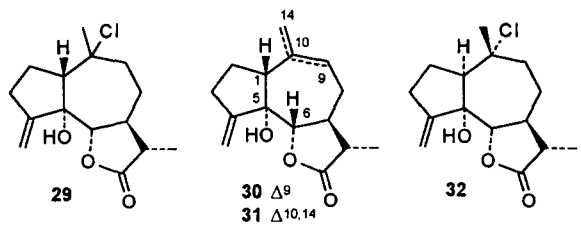



Figure 2

The stereochemistry at the A/B ring junction was established by a combination of correlations found in the ROESY spectrum and the study of the pyridine-induced solvent shift of the signals in the $^1$H-NMR spectrum.

A clear correlation between H-1 and H-6 was observed in the ROESY spectra for **30** and **31**, indicating that H-1 was β-disposed in both compounds and hence in **29**. That correlation was absent in **32**. The difference in chemical shifts for H-1 and H-6 when the NMR solvent was changed from $CDCl_3$ to Py-$d_5$ was then studied, and the results are shown in Table 1. The value for H-6 was quite similar in the three compounds studied, probably due to the proximity of the oxygen atoms of the lactone ring. The effect of the pyridine in H-1 was, however, more marked, clearly indicating that the hydroxyl group was *anti* to H-1 in **30** and **31**, and *syn* in **32**.

Table 1. Observed ROESY correlations and pyridine-induced solvent shifts.

| | Corr. | $\Delta\delta^b$ | |
|---|---|---|---|
| | H-1/H-6[a] | H-1 | H-6 |
| **30** | √ | 0.03 | -0.09 |
| **31** | √ | 0.0 | -0.11 |
| **32** | - | -0.23 | -0.15 |
| **36** | √ | 0.13 | -0.08 |
| **37** | √ | 0.05 | -0.08 |
| **38** | - | | |
| **40** | - | -0.25 | -0.03 |
| **41** | - | -0.32 | -0.12 |
| **42** | √ | -0.04 | -0.18 |
| **43** | √ | -0.08 | -0.22 |
| **44** | - | -0.25 | -0.15 |
| **45** | - | -0.38 | -0.18 |

a) (√) observed correlation, (-) no observed. b) $\Delta\delta = \delta_{CDCl_3} - \delta_{Py\text{-}d_5}$

Thus, the stereochemistry of the A/B ring junction was established as *trans*-[1β-H;5α-OH] for **29**, **30** and **31**, and *cis*-[1α-H;5α-OH] for **32**. The disposition of the C-10 methyl group on **32** was deduced from a correlation found in the ROESY spectrum between this group and H-6.

From the study of the cyclization reactions of this 5-keto germacranolide **28**, it can be seen that the major conformation in solution (**28-A**) does not account for the stereochemistry of the cyclization products, and thus a lower energy pathway must exist involving other higher energy conformers present in the equilibrium mixture.

In order to provide an explanation for the stereochemical course of the cyclization of this type of compounds, we decided to carry out a molecular mechanics study. The conformations of **28** were explored by minimization of all the structures generated in a systematic conformational search by stepwise rotation of all single bonds of the ten-membered ring. All conformers were then minimized using the MMX force field as implemented in the program PCMODEL,[16] and those with energies within 4 Kcal/mol of the minimum were considered.

The lowest energy conformer found for **28** in the molecular mechanics calculations (**28-A**) was consistent with the one deduced from the experimental data in solution and in solid state. All conformers found within the 4 Kcal/mol limit showed a relative disposition of H-1 and the C-5 carbonyl either *syn*-α,α (**28-A**, **28-B**) or *anti*-β, α (**28-C**, **28-D**, **28-E**) (Figure 1). The calculated population for **28-A**, 91.2%, is also consistent with the spectroscopic data, which points to the existence of one major conformer together with other minor ones in the equilibrium mixture.

Since the transannular cyclization reaction takes place in the protonated species, we carried out a similar analysis on the cationic compound **33**. In this case, however, a complete parametrization was not available for the force field used, and thus we decided to minimize all conformers using the semiempirical package MOPAC.[17] Using the AM1 Hamiltonian, the conformers found were quite similar to those for the neutral ketone **28**, having relative stereochemistries between H-1 and the C-5 carbonyl group either *syn*-α,α or *anti*-β,α.

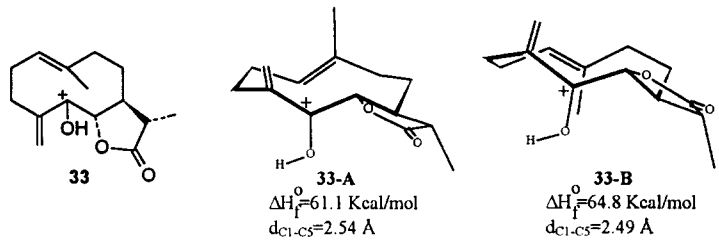



Figure 3

We then looked at the distance between the reacting centres in all the protonated conformers as the criterion for reactivity.[18] With this criterion, conformer **33-B** (distance between C-1 and C-5 2.49 Å) (Figure 3) and not the lowest energy one **33-A**, should be considered the most reactive, and it can be seen that it should yield, after cyclization, a *trans*-[1β-H;5α-OH] guaianolide, in good agreement with that experimentally observed.

The cyclization of other two keto-germacranolides derived from **28**, **34** and **35,** was then carried out. The preparation of these two compounds from **28** by $NaBH_4$ reduction and catalytic hydrogenation respectively, has been reported previously.[14,19]

The acid treatment of **34**, under the same conditions as described for **28**, gave the following six compounds: **36**, in a 20.9 % yield; **37**, in 13.6 % yield; **38**, in 4.1% yield; **39**, in 4.6% yield; **40**, in 33.4% yield; and **41** in 1.1% yield. **39** decomposed quickly to a mixture of **36** and **37** upon stirring with silica gel, and its stereochemistry was deduced from that of those two compounds.

The acid treatment of **35** yielded four compounds with a 5-hydroxyguaianolide skeleton: **42** in a 46% yield; **43** in a 26 % yield; **44** in a 6% yield; and **45** in a 6% yield.

The structures and stereochemistries found for all compounds are shown in Figure 4. Table 1 shows the data used for the stereochemical assignments.

It can be seen that also in the cyclization of these two compounds, the major products are those with a *trans*-[1β-H;5α-OH] stereochemistry at the A/B ring junction, although in the case of the cyclization of **34** the *cis/trans* ratio is almost 1:1.

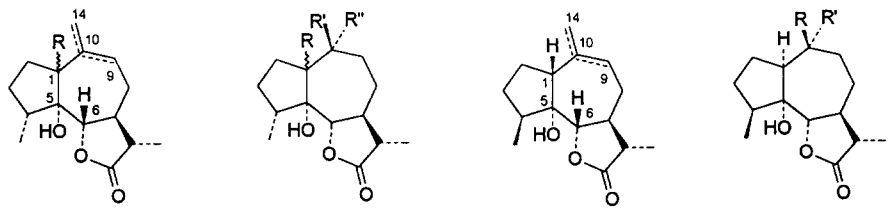



Figure 4

The conformational behaviour shown by **34** and **35** in solution was similar to that of **28**, that is a major conformer with LIS and ROESY data compatible with a "crown" conformation, and a clear broadening of the signals in the $^{13}$C-NMR spectra, indicative of a conformational equilibrium. Those effects were more marked for **35**. In this case, the broadening of the signals was also visible in the $^{1}$H-NMR spectrum.

The molecular mechanics calculations on **34** indicated the presence of a major conformer with a population of 87.1 % (Figure 5). The relative disposition of the H-1 and the C-5 carbonyl group is *syn*-α,α and *anti*-β,α for all conformers within 4 Kcal/mol of the minimum.

The semiempirical calculations carried out on the protonated compounds **44** (Figure 5) show that the conformers are similar to those found for **34**. The one with the shortest distance between C-1 and C-5 (**44-B**) should give a *trans*-[1β-H;5α-OH] guaianolide upon cyclization.

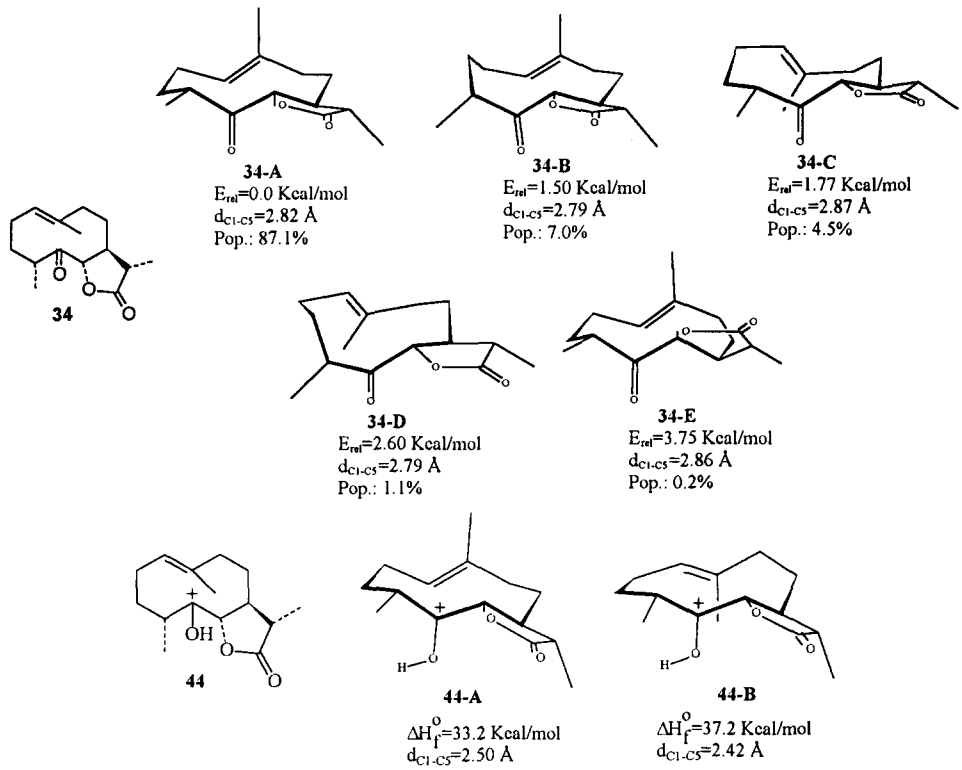



Figure 5

Similar calculations on **35** (Figure 6) indicated that this compound has a greater conformational mobility, since a larger number of conformers were found by molecular mechanics. Also, the conformers within 4 Kcal/mol of the minimum present all four possible relative dispositions of H-1 and the C-5 hydroxyl group. There is a second conformer (**35-B**) close to the minimum energy one (**35-A**). The MOPAC calculations on the protonated compound **45** indicated that although the conformers are again quite similar to those of the neutral compound **35**, the two with the lowest energy are interchanged, the most stable being the one with the equatorial C-4 methyl group. The conformation with the shortest C-1/C-5 distance found (**45-C**) also possesses an *anti*-β,α disposition between H-1 and the C-5 hydroxyl group, which should give a *trans*-[1β-H;5α-OH] guaianolide upon cyclization.

It can be seen that the calculations are in good agreement with the observed behaviour of all three 5-keto germacranolides studied. The lowest energy conformers found by molecular mechanics are consistent with the

experimental data for the conformation in solution and, in one case, identical with the conformation in solid state. On the other hand, the conformer with the shortest distance between C-1 and C-5 in the protonated species can explain the stereochemical course of the acid cyclizations of these compounds.

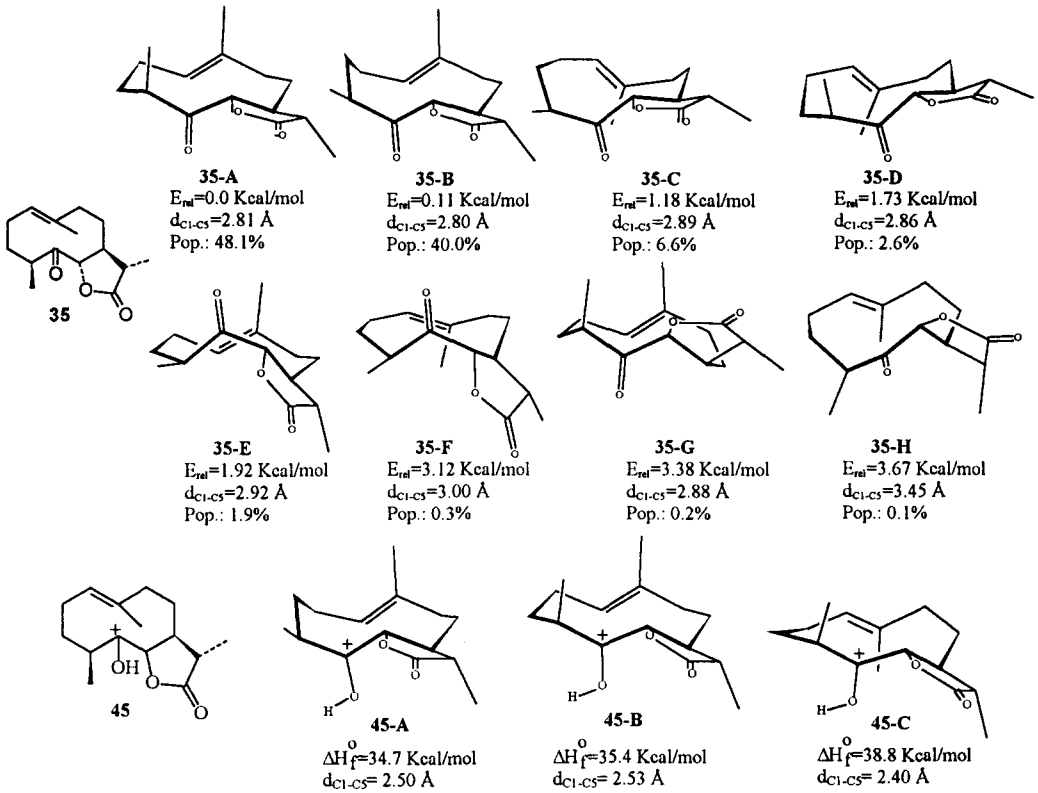



Figure 6

## EXPERIMENTAL

*General*

Solvents used were purified and dried by the standard procedures before use. $^{1}$H-NMR spectra were recorded at 200 or 400 MHz, and $^{13}$C-NMR at 50 or 100 MHz. Column chromatography was performed using silica gel 60 (230-400 mesh). HPLC was performed using a μ-Porasil column (300 x 7.8 mm i.d.).

*1-p-Toluenesulfonyloxy- eudesman-3-en-6,12-olide (14)*

p-Toluenesulfonyl chloride (624 mg, 3.27 mmol) was added to a cold (0°C) solution of **13** (682 mg, 2.73 mmol) in dry pyridine (2 mL). The reaction was allowed to stand at room temperature for 48 h., and then ice and a saturated solution of $NaHCO_3$ were added. The reaction was extracted with $CH_2Cl_2$, the extracts washed with

2N HCl, saturated solution of $NaHCO_3$ and water. The concentrated extract was chromatographed on silica gel using EtOAc 20% on hexanes yielding 1.027 g of **14** (92%).
m.p. 160-162°C; $[\alpha]_D^{25}$ +81 (c 0.28, $CHCl_3$); IR ($CHCl_3$) 1770, 1590 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.86 (d , *J*=9 Hz, 2H), 7.40 (d, *J*=9 Hz, 2H), 5.45-5.12 (m, 1H), 4.52 (dd, *J*=8, 8 Hz, 1H), 3.95 (dd, *J*=9, 10 Hz, 1H), 2.50 (s, 3H), 1.82 (s, 3H), 1.22 (d, *J*=7 Hz, 3H), 0.98 (s, 3H); MS (EI) m/z (rel intensity) 232 ( $M^+$-TsOH, 1), 217 (5).

*1-p-Toluenesulfonyloxy-5-hydroxy-eudesman-3-en-6,12-olide (15)*

*tert*-Butylhydroperoxide 90% (4 mL, 3.6 mmol) was added to a stirred solution of $SeO_2$ (69 mg, 0.62 mmol) in $CH_2Cl_2$ (15 mL). After 15 min at 25°C, 500 mg of **14** (1.24 mmol) were added. After 72 h, the $CH_2Cl_2$ was removed and 30 mL of ethyl ether were added. The organic layer was washed with 4.5 mL of KOH (10%) and concentrated. The concentrate was dissolved in cold AcOH (2 mL) and $Me_2S$ (1 mL) was then added. After 4 h, the solution was neutralized with $K_2CO_3$ (20%). The aqueous layer was then extracted with ether, dried, concentrated and chromatographed to give 498 mg of **15** (95%).
m.p. 117-118°C; $[\alpha]_D^{25}$ +17.7 (c 0.30, $CHCl_3$); IR ($CHCl_3$) 3600, 1770, 1590 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.87 (d, *J*=9 Hz, 2H), 7.40 (d , *J*=9 Hz, 2H), 5.42 (m, 1H), 5.12 (dd, *J*=9, 9 Hz, 1H), 4.05 (d, *J*=10 Hz, 1H), 2.49 (s, 3H), 1.87 (s, 3H), 1.20 (d, *J*=7 Hz, 3H), 1.01 (s, 3H); MS (EI) m/z (rel intensity) 420 ($M^+$, 1), 248 (3).

*Preparation of* ***16***

To a solution of **15** (100 mg, 0.24 mmol) in EtOH (5 mL) were added 2 mL of an aqueous saturated solution of $NaHCO_3$. After refluxing for 2 h, the mixture was cooled, neutralized with HCl (10%) and extracted with $CH_2Cl_2$, giving 47 mg (79%) of a mixture of **16** and **17** (approx. 2:1).
**16**: IR ($CHCl_3$) 1770, 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.45 (bs, 1H), 5.32 (bs, 1H), 4.50 (d, *J*=8 Hz, 1H), 1.88 (bs, 3H), 1.60 (bs, 3H), 1.33 (d, *J*=6 Hz, 3H).
**17**: IR ($CHCl_3$) 3590, 1770 $cm^{-1}$; $^1H$ NMR δ 5.66 (d, *J*=1.2 Hz, 1H), 5.23 (s, 1H), 5.10 (s, 1H), 3.88 (d, *J*=10.2 Hz, 1H), 2.75 (m, 1H), 2.67-2.44 (m, 3H), 2.29-2.21 (m, 2H), 2.01-1.91 (m, 2H), 1.88 (d, *J*=1.2 Hz, 3H), 1.67-1.56 (m, 2H), 1.21 (d, *J*=7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 178.3, 144.8, 142.6, 129.5, 114.7, 88.8, 79.4, 49.4, 44.1, 41.2, 35.0, 32.9, 24.5, 14.7, 12.3; MS (EI) m/z (rel intensity) 248 (24), 230 (4), 217 (25); HRMS (CI) calcd. for $C_{15}H_{20}O_3$ ($M^+$) 248.14124, found 248.14098.

*Preparation of* ***21***

a) To a mixture of **20** (118 mg, 0.28 mml) and $NaHCO_3$ (94 mg) in 7 mL of $CH_2Cl_2$ , 96 mg of *m*-chloroperbenzoic acid 80% (96 mg, 0.56 mmoles) were added. After stirring for 23 h at room temperature, ice-water was added and the reaction was extracted with $CH_2Cl_2$. Chromatography on silica gel using 15% EtOAc in hexane gave 104 mg (85% yield) of epoxide as a colourless oil; $R_f$=0.35 (silica, 20% EtOAc in hexane); $[\alpha]_D^{25}$ + 19.4° (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 2900, 1780, 1725, 1460, 1370 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.29 (d, *J*=10.4 Hz, 1H), 4.14 (d, *J*=6.6Hz, 1H), 3.37 (d, *J*=8.3Hz, 1H), 2.43 (dt, *J*=13.5, 4.4 Hz, 1H), 2.25-2.18 (m, 3H), 2.15-1.97 (m, 3H), 1.96 (s, 3H), 1.66 (d, *J*=15Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.25 (d, *J*=6.4 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 177.1, 169.9, 85.0, 78.6, 74.8, 70.3, 69.3, 50.3, 47.6, 41.4, 38.4, 34.9, 26.8, 25.8, 22.4, 21.1, 18.0, 12.7, 11.0, -4.9. -5.0; MS (EI) m/z (rel intensity) 439 ($M^+$+1, 1), 363 (3); HRMS (CI) calcd for $C_{19}H_{29}O_6Si$ ($M^+$ - $C_4H_9$) 381.17334, found 381.17261.

b) Tetrabutylammonium fluoride (1M solution in THF, 0.7 mL, 0.7 mmol) was added to a stirred solution of the epoxide of **20** (250 mg, 0.57 mmol) in THF (6 mL) at 0°C. The reaction mixture was stirred overnight at room temperature and then poured onto ice-water. The aqueous solution was extracted with $CH_2Cl_2$, dried and concentrated under vacuum. Chromatography over silica gel (50% EtOAc in hexane) yielded 181 mg (98%) of **21** as a crystalline solid; $R_f$= 0.26 (silica, 50% EtOAc in hexane); m.p. 204-207°C, $[\alpha]_D^{25}$ + 13.8° (*c* 0.13, $CHCl_3$); IR ($CHCl_3$), 3600, 2900, 1770, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.31 (d, *J*=10.4 Hz, 1H), 4.22 (dd, *J*= 6.6, 3.9 Hz, 1H); 3.40 (dd, *J*= 9.7, 2.4 Hz, 1H); 2.43 (dt, J= 13.5, 4.4 Hz, 1H); 2.27 - 2.02 (m, 5H); 1.98 (s, 3H); 1.95 (d, *J*=3.9 Hz, 1H); 1.77 (d, *J*= 13.4 Hz, 1H), 1.63 (s, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.26 (d, *J*=6.4 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 177.1, 170.0, 85.0, 78.5, 74.3, 70.2, 69.3, 50.4, 47.6, 41.3, 38.4, 34.5, 26.8, 22.5, 21.0, 12.7, 10.7, MS (EI) m/z (rel intensity) 264 (1), 247 (3); HRMS (CI) calcd. for $C_{15}H_{20}O_4$ ($M^+$-$C_2H_4O_2$), 264.13616, found 264.13561.

*Preparation of 26*

a) To a solution of 185 mg (0.57 mmol) of **21** in 6 mL of dichloromethane were added 0.09 mL (1.2 mmol) of methanesulfonyl chloride and 0.17 mL (1.25 mmol) of triethylamine. The mixture was stirred for 6 h at 25°C and then water was added and the pH was adjusted to 7 with 10% HCl solution. The organic layer was washed with water, dried and concentrated. The crude product was chromatographed on silica gel (50% EtOAc in hexane) to afford 181 mg (79%) of mesylate as a colourless oil; $R_f$= 0.3 (silica, 50% EtOAc in hexane); $[\alpha]_D^{25}$ + 27.8(c 0.14, $CHCl_3$); IR ($CHCl_3$) 1780, 1730, 1370, 1180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 4.98 (d, *J*=6.7 Hz, 1H), 4.28 (d, *J*= 10.4 Hz, 1H), 3.43 (dd, *J*= 9.5, 2.2 Hz, 1H), 3.05 (s, 3H), 2.37 (dt, *J*= 13.4, 4.3 Hz, 1H), 2.28 - 2.02 (m, 6H), 1.96 (s, 3H), 1.54 (s, 3H), 1.45 - 1.42( m, 1H), 1.37 (s, 3H), 1.23 (d, *J*= 6.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.7, 170.0, 84.2, 82.6, 77.7, 69.4, 68.0, 50.1, 47.5, 41.0, 38.3, 38.2, 32.6, 26.4, 22.3, 21.0, 12.5, 10.7; MS (EI) m/z (rel intensity) 360 (1), 306 (1) , 247 (100); HRMS (CI) calcd. for $C_{16}H_{24}O_7S$ ($M^+$ + 1-$C_2H_3O$) 360.12428, found 360.12204.

b) A suspension of 97 mg (0.24 mmol) of mesylate in 14 mL of 5% aqueous KOH was stirred for 3 h at room temperature. The reaction mixture was diluted with water and the pH was adjusted to 7 with 10% HCl solution. After extracting with EtOAc, the organic layer was dried and concentrated. Chromatography over silica gel (70% EtOAc in hexane) yielded 58 mg (66%) of **26** as a white solid; $R_f$= 0.31 (silica, 75% EtOAc in hexane); m.p. 110-112°C; $[\alpha]_D^{25}$ + 59.4 (c 0.23, $CHCl_3$); IR ($CHCl_3$) 3600, 2950, 1780, 1360 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.0 (d, *J*= 6.8 Hz, 1H), 4.31 (d, *J*= 10.5 Hz, 1H), 3.06 ( s, 3H), 2.58 (d, *J*= 8.0 Hz, 1H), 2.39 (d, *J*= 16.3 Hz, 1H), 2.29-2.0 (m, 5H), 1.75-1.67 (m, 2H), 1.58 (s, 3H), 1.49-1.38 (m, 1H), 1.26 (d, *J*= 6.8 Hz, 3H), 1.23 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.9, 83.1, 78.0, 72.2, 69.6, 68.0, 53.4, 47.6, 45.6, 41.3, 38.6, 32.4, 27.2, 22.6, 12.7, 11.0. MS (EI) m/z (rel intensity) 361 ($M^+$+1, 1), 343 (2 ), 247 (3); HRMS (CI) calcd. for $C_{16}H_{20}O_5S$ ($M^+$ - $2H_2O$) 324.10315, found 324.10155

*Preparation of 27*

To a solution of **26** (28 mg, 0.07 mmol) in 1 mL of THF at -55°C was added a cold (-55°C) solution of THF (0.06 mL), pyridine (0.06 mL), and thionyl chloride (0.03 mL). The reaction mixture was stirred for 15 min, and then cold water and ether were added. The reaction mixture was thoroughly extracted with ether, the organic layer was dried and concentrated. Chromatography over silica gel (40% EtOAc in hexane) yielded 17

mg (65%) of **27** as an oil; $R_f$= 0.28 (silica, 40% EtOAc in hexane); $[\alpha]_D^{25}$ + 132.5 (*c* 1.41, $CHCl_3$); IR ($CHCl_3$) 2950, 1780, 1370; $^1H$ NMR ($CDCl_3$) δ 5.17 ( s, 1H), 5.11 (s, 1H), 5.09 (d, *J*= 6.7 Hz, 1H), 4.40 (d, *J*= 10.0 Hz, 1H), 3.08 (s, 3H), 2.96 (d, *J*= 8.1 Hz, 1H), 2.62 (m, 1H), 2.45-2.04 (m, 6H), 1.60 (s, 3H), 1.47-1.37 (m, 1H), 1.27 (d, *J*= 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 177.1, 146.5, 115.0, 83.5, 77.8, 72.8, 68.3, 47.6, 47.3, 41.3, 39.3, 38.5, 36.8, 33.1, 13.2, 11.2; MS (EI) m/z (rel intensity) 343 ($M^+$+1, 1); 263 (2); HRMS (CI) calcd for $C_{15}H_{19}O_4$ ($M^+$ -$CH_3SO_2$) 263.12833, found 263.13228.

*Preparation of 25*

To a solution of **27** (17 mg, 0.05 mmol) in glyme (0.075 mL) powdered zinc (32.5 mg, 0.5 mmol) and sodium iodide (37.2 mg, 0.25 mmol) were added. The reaction mixture was refluxed for 4 h, cooled and diluted with $CH_2Cl_2$-water. After extraction ($CH_2Cl_2$), the organic layer was washed successively with saturated $NaHCO_3$, water, 5% $NaHSO_3$, water and brine, dried and concentrated. Chromatography over silica gel (25% EtOAc in hexane) yielded 9.8 mg (80%) of **25**, as a crystalline solid; $R_f$= 0.47 (silica, 30% EtOAc in hexane); m.p. 102-104°C; $[\alpha]_D^{25}$ + 27.9 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3590, 2950, 1780, 1300 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.69 (d, *J*=1.5 Hz, 1H), 4.89 (s, 1H), 4.82 (s, 1H), 4.12 (d, *J*= 9.7 Hz, 1H), 2.87 (dd, *J*= 7.6, 3.8 Hz, 1H), 2.70-2.63 (m, 1H), 2.56-2.39 (m, 2H), 2.33-2.10 (m, 5H), 1.79 (d, *J*= 1.5 Hz, 3H), 1.39-1.29 (m, 1H), 1.25 (d, *J*= 7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 178.6, 148.0, 141.4, 129.5, 113.1, 85.9, 85.3, 55.4, 44.0, 41.7, 36.6, 35.6, 32.8, 13.7, 13.2; MS (EI) m/z (rel intensity) 248 ($M^+$, 13), 230 (9) 215 (2); HRMS (CI) calcd. for $C_{15}H_{20}O_3$ ($M^+$) 248.14124 found 248.14134.

*Acid cyclization of 28*

A solution of **28** (120 mg, 0.48 mmol) in 15 mL (0.03 M) of $CHCl_3$ saturated with HCl gas was stirred at room temperature for 2 days. The reaction mixture was diluted with $CHCl_3$, washed with a saturated solution of $NaHCO_3$, water and brine, dried and concentrated. HPLC separation (25% EtOAc in hexane) afforded 26 mg (19%, $r_t$= 21.0 min) of **29**, 25 mg (21%, $r_t$= 24.0) of **30**, 33 mg (28%, $r_t$= 25.0 min) of **31** and 16 mg (12%, $r_t$= 30.0 min) of **32**.

**29**: $^1H$ NMR ($CDCl_3$) δ 5.52 (s, 1H), 5.16 (s, 1H), 3.78 (d, *J*= 10.4 Hz, 1H), 2.57-1.85 (m, 7H), 1.79 (s, 3H), 1.68-1.59 (m, 2H), 1.24 (d, *J*= 6.7 Hz, 3H).

**30**: IR ($CHCl_3$) 3580, 1770 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.80 (bs, 1H), 5.70 (s, 1H), 5.15 (s, 1H), 3.95 (d, *J*= 10.1 Hz, 1H), 2.58 (dd, *J*= 15.2, 7.4 Hz, 2H), 2.37-2.13 (m, 3H), 2.10-1.85 (m, 4H), 1.80 (s, 3H), 1.66 (s, 1H), 1.22 (d, *J*= 6.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 178.2, 154.8, 137.3, 124.8, 112.2, 90.3, 75.5, 49.5, 43.8, 40.6, 32.0, 26.4, 25.9, 23.4, 12.2; MS (EI) m/z (rel intensity) 248 ($M^+$, 5), 230 (2), 202(7); HRMS (CI) calcd. for $C_{15}H_{20}O_3$ ($M^+$) 248.14124, found 248.1401

**31**: IR ($CHCl_3$) 3600, 2900, 1770, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 5.64 (s, 1H), 5.15 (s, 1H), 5.08 (s, 1H), 5.06 (s, 1H), 3.97 (d, *J*= 10.1 Hz, 1H), 2.64-2.40 (m, 3H), 2.38-2.30 (m, 2H), 2.28-2.08 (m, 3H), 2.01-1.52 (m, 4H), 1.22 (d, *J*= 6.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 178.4, 154.4, 143.2, 115.3, 111.2, 89.2, 75.4, 50.3, 43.4, 41.0, 35.0, 30.3, 26.4, 24.5, 12.3.

**32**: IR ($CHCl_3$) 3550, 2800, 1770, 1450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.22 (s, 1H), 5.03 (s, 1H), 4.21 (d, *J*= 10.30 Hz, 1H), 2.64-2.58 (m, 2H), 2.57-2.50 (m, 1H), 2.46-2.08 (m, 6H), 1.95-1.87 (m, 1H), 1.55 (s, 3H), 1.49-1.43 (m, 2H), 1.27 (d, *J*=7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 177.9, 153.2, 109.1, 82.7, 80.2, 76.3, 60.7,

42.7, 42.6, 41.8, 29.4, 28.9, 27.4, 26.5, 13.0; MS (EI) m/z (rel intensity) 284.5 ($M^+$, 1.6), 283.5 ($M^+$, 3.5), 248 (6), 230 (10), 202 (11).

*Acid cyclization of 34*

The same procedure described for the cyclization of **28** was used. 80 mg (0.32 mmol) of **34** afforded, after HPLC separation (15% EtOAc in hexane), 4 mg (4.6%, $r_t$= 9 min) of **39**, 17 mg (20.9%, $r_t$= 11 min) of **36**, 3 mg (4.1%, $r_t$= 12 min) of **38**, 11 mg (13.6%, $r_t$= 13 min) of **37**, 35 mg (33.4%, $r_t$= 14 min) of **40**, and 1 mg (1.1%, $r_t$= 15 min) of **41**.

**39**: $^1$H NMR ($CDCl_3$) δ 3.86 (d, *J*=10.4 Hz, 1H), 2.44 (dd, *J*= 9.1, 3.2 Hz, 1H), 2.35-1.79 (m, 8H), 1.72 (s, 3H), 1.65-1.57 (m, 2H), 1.47-1.33 (m, 1H), 1.24 (d, *J*=6.8 Hz, 3H), 1.07 (d, *J*=6.8 Hz, 3H).

**36**: $[\alpha]_D^{25}$ -67.85 (*c* 0.84, $CHCl_3$); IR ($CHCl_3$) 3600, 2900, 1770, 1500, 1380 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.80-5.77 (m, 1H), 3.84 (d, *J*=10.1 Hz, 1H), 2.63 (dd, *J*=10.1, 9.3 Hz, 1H), 2.27-2.20 (m, 3H), 2.19-1.80 (m, 6H), 1.79 (s, 3H), 1.54-1.32 (m, 1H), 1.21 (d, *J*= 6.7 Hz, 3H), 1.13 (d, *J*= 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 178.5, 137.8, 124.6, 93.4, 77.7, 49.5, 43.5, 43.4, 40.7, 31.4, 26.5, 26.2, 24.4, 15.1, 12.3; MS (EI) m/z (rel intensity) 250 ($M^+$, 2 ), 217 ( 3 ), 204 ( 4 ).

**38**: $^1$H NMR ($CDCl_3$) δ 4.94 (s, 1H), 4.88 (s, 1H), 3.94 (d, *J*= 9.8 Hz, 1H), 2.61 (dd, *J*= 7.9, 7.6 Hz, 1H), 2.55 (m, 1H), 2.39-2.35 (m, 1H), 2.21-1.92 (m, 5H), 1.87-1.82 (m, 1H), 1.71-1.62 (m, 1H), 1.33-1.28 (m, 2H), 1.23 (d, *J*=6.9 Hz, 3H), 1.07 (d, *J*=6.7 Hz, 3H).

**37**: m.p. 120-122°C; $[\alpha]_D^{25}$ -21.4 (c O.2, $CHCl_3$); IR ($CHCl_3$) 3565, 2950, 1765 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.15 (s, 1H), 5.05 (s, 1H), 3.77 (d, *J*= 10.1 Hz, 1H), 2.47 (m, 3H), 2.22-2.11 (m, 2H), 2.03-1.60 (m, 7H), 1.20 (d, *J*=6.9 Hz, 3H), 1.16 (d, *J*=6.8 Hz, 3H); MS (EI) m/z (rel intensity) 250 ($M^+$, 1), 232 ( 3 ).

**40**: m.p. 132-135 °C; $[\alpha]_D^{25}$ - 23.69 (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 3570, 2900, 1770, 1500, 1380 cm$^{-1}$; $^1$H NMR ($CHCl_3$) δ 4.06 (d, *J*= 10.0 Hz, 1H), 2.66 (dd, *J*= 8.6, 8.4 Hz, 1H), 2.46-2.42 (m, 1H), 2.34-2.24 (m, 1H), 2.23-2.16 (m, 3H), 1.99-1.95 (m, 1H), 1.89-1.72 (m, 3H), 1.56 (s, 3H), 1.55-1.43 (m, 3H), 1.24 (d, *J*=6.8Hz, 3H), 1.06 (d, *J*= 6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 178.0, 87.3, 81.2, 77.2, 62.3, 45.9, 45.8, 44.4, 41.5, 31.4, 28.8, 27.4, 26.4, 13.5, 12.8; MS (EI) m/z (rel intensity) 285.9 ($M^+$-1, 16.3 ), 287.8 ($M^+$ -1, 6.4), 286.9 ($M^+$, 3.5), 251(100).

**41**: IR ($CHCl_3$) 3250, 2900, 1770, 1550 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 3.91 (d, *J*=10.3 Hz, 1H), 2.58-2.46 (m, 3H), 2.24-1.99 (m, 4H), 1.89-1.77 (m, 3H), 1.74 (s, 3H), 1.63-1.36 (m, 3H), 1.23 (d, *J*= 6.8 Hz, 3H), 1.16 (d, *J*= 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 178.6, 139.0, 134.8, 90.2, 79.5, 47.3, 45.7, 41.6, 33.3, 31.9, 31.1, 28.6, 24.7, 13.9, 12.4.

*Acid cyclization of 35*

The same procedure described for the cyclization of **28** was used. 15 mg (0.06 mmol) of **35** afforded, after HPLC separation (15% EtOAc in hexane), 1 mg (6%, $r_t$= 11 min) of **44**, 7 mg (46%, $r_t$= 14 min) of **42**, 4 mg (26%, $r_t$= 16 min) of **43**, and 1 mg (6% $r_t$= 17 min) of **45**.

**44**: IR ($CHCl_3$) 3590, 2900, 1770 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.13 (d, *J*=10.6 Hz, 1H), 2.52-2.41 (m, 1H), 2.37-2.04 (m, 9H), 1.73 (s, 3H), 1.34-1.26 (m, 2H), 1.24 (d, *J*= 6.8 Hz, 3H), 1.05 (d, *J*=7.0 Hz, 3H);

**42**: IR ($CHCl_3$) 3590, 2950, 1770, 1300 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.78 (bs, 1H), 4.0 (d, *J*=10.3 Hz, 1H), 2.67 (dd, *J*= 9.7, 9.4 Hz, 1H), 2.31-1.89 (m, 8H), 1.80 (s, 3H), 1.46 (s, 1H), 1.23 (d, *J*= 6.8 Hz, 3H), 1.06

(d, *J*=6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 178.6, 137.4, 124.3, 88.3, 80.1, 45.8, 44.9, 43.0, 41.0, 31.0, 26.6, 26.4, 24.9, 18.9, 12.3.

**43**: m.p. 140-142°C; $[\alpha]_D^{25}$ = +31.6 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3550, 2950, 1770, cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.14 (s, 1H), 5.05 (s, 1H), 3.95 (d, *J*=10.1 Hz, 1H), 2.51-2.44 (m, 3H), 2.35-2.23 (m, 2H), 2.05-1.81 (m, 3H), 1.80-1.72 (m, 2H), 1.56-1.49 (m, 2H), 1.26-1.23 (m, 1H), 1.22 (d, *J*= 6.9 Hz, 3H), 1.05 (d, *J*= 7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 178.5, 144.4, 114.7, 86.6, 78.7, 48.2, 43.5, 41.8, 41.5, 35.2, 31.0, 26.8, 25.3, 18.8, 12.4.

**45**: IR ($CHCl_3$) 3590, 2950, 1770 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.21 (d, *J*= 10.0 Hz, 1H), 2.68 (dd, *J*= 10.0, 8.5 Hz, 1H), 2.51-2.48 (m, 2H), 2.46-2.09 (m, 5H), 1.98-1.92 (m, 2H), 1.66 (s, 3H), 1.48-1.43 (m, 2H), 1.26 (d, *J*= 6.8 Hz, 3H), 0.97 (d, *J*= 7.1 Hz, 3H).

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