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Conformationally Controlled Transannular Reactions of a 12-Membered Macrocyclic Trienol

Juan I. Padrón, Jesús T. Vázquez, Ezequiel Q. Morales, Miguel Zárraga, and Julio D. Martín*

Centro de Productos Naturales Orgánicos Antonio González, Universidad de La Laguna-C.S.I.C., Carretera de La Esperanza 2, 38206 La Laguna, Tenerife, Spain

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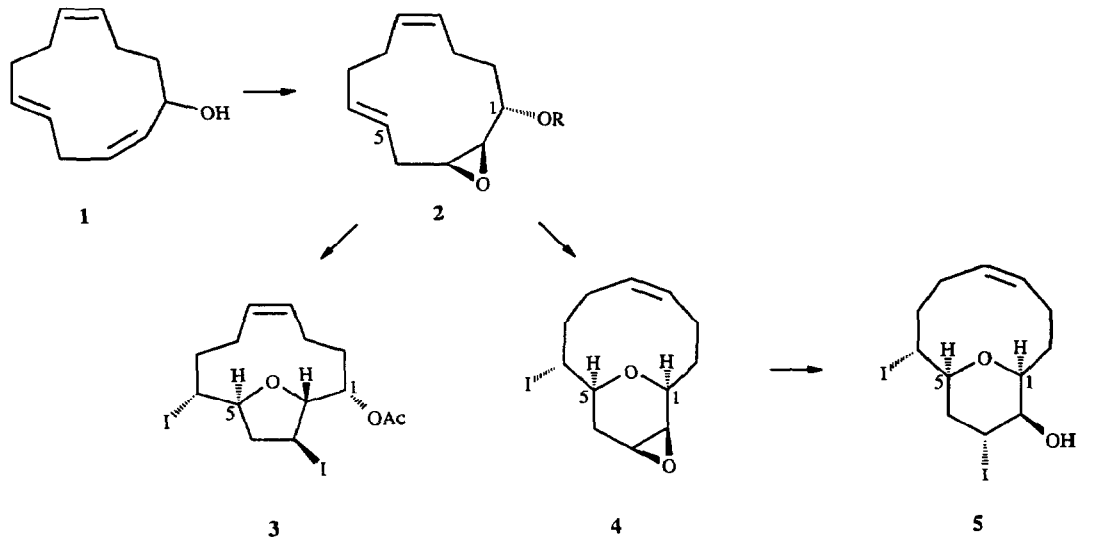
Abstract: Iodine-induced transannular ring enlargements of several epoxide derivatives of the cyclotrienol (Z,E,Z)-1-hydroxy-cyclododeca-2,5,9-triene (**1**) are presented. The diastereoselection exhibited by both the inter- and intramolecular reactions studied, appears to be associated with the conformational preferences of the macrocycle since simple molecular mechanics calculations allowed semiquantitative predictions in the product distributions. An absolute configurational study based on CD exciton chirality methodology is also included.

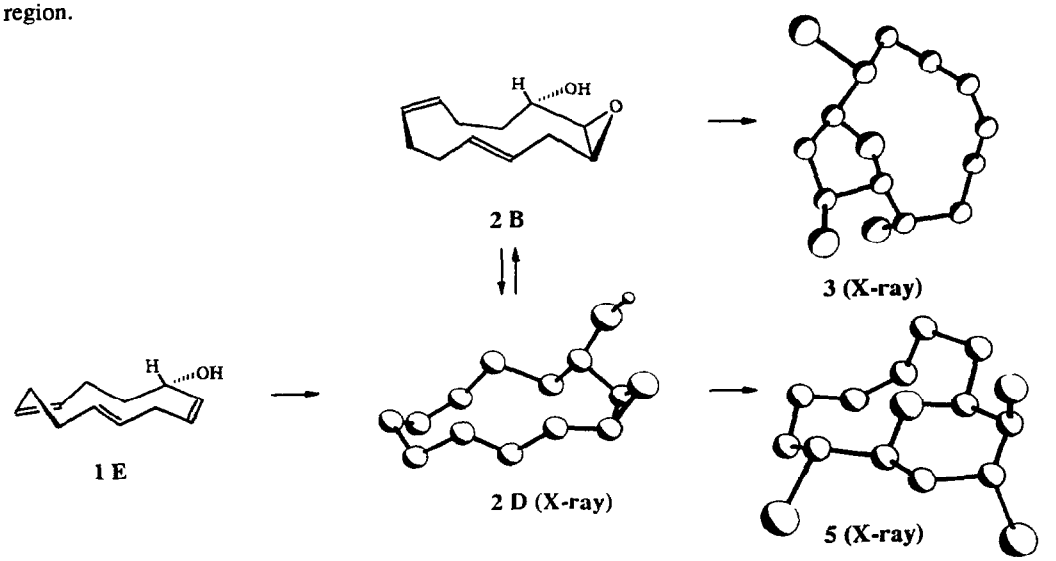
Macrocyclic compounds have conformational properties which are quite useful for chemo-, regio- and stereochemical control in synthetic intermolecular reactions.[1] Transannular reactions on macrocycles can also take place with great ease[2] but have rarely been used as a cornerstone in specific syntheses.[3] Recently, we have pointed out[4] that transannular epoxide-ring enlargements on epoxy-cycloalkenes represent a powerful approach for the development of totally new strategies for the construction of complex oxocyclic molecules. In this respect, we have studied the reactivity of the *cis-trans-cis* 12-membered macrocyclic trienol **1** to give **3** or **5** according to the sequence outlined in Scheme 1.[5] A conformational study of compound **1**, based on the X-ray crystallographic analyses of compounds **2**, **3** and **5** (Scheme 2), would lead to the conformation **1E** (Table I) as that preferred for the triene precursor. Beyond the genetic relations **1E - 2D - 2B - 3** and **1E - 2D - 5**, we searched for direct evidence for the conformations of **1** and **2** in solution in order to improve the understanding of conformational factors controlling inter- and intramolecular oxidative addition reactions in cycloalkene systems.

Stereochemical predictions (or analyses) in macrocyclic systems present the difficulty of their various possible conformations. Much of the most detailed information at this level has been provided by molecular mechanics calculations[6] and MM2 transition structure models[7] which have proved useful in predictions of the stereoselectivities in macrocyclic reactions. Thus, molecular mechanics calculations[8] of (Z,E,Z)-1-hydroxy-cyclododeca-2,5,9-triene (**1**) revealed eleven energy minima conformers, **1A-K, R=H**, Table I, the structure of the three lowest conformers **1A-C** being represented in Figure 1. The conformational biasing observed for these conformers is based on a general property of cycloalkenes, which arises from the pronounced tendency of these molecules to minimize transannular non-bonded repulsions in conformations in which sp^2 centers tend to stand



Scheme 1

perpendicular to the plane of the ring.[1a] These calculations also showed that a "*jump rope rotation*"[9] of the trans-5,6-double bond occurs for each conformer. Thus, the following pair of conformers **1A/1B, 1D/1G, 1H/1E, 1J/1C,** and **1K/1I** (conformers with the hydrogen at five position in beta disposition/conformers with the same hydrogen in the alfa configuration) presents an almost identical conformation except in the *trans*-5,6-double bond region.

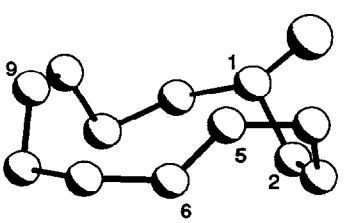


Scheme 2

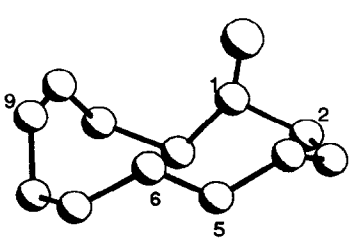
Table I. Molecular Mechanics Data for Compound **1**, **R = H**

Hydrogen at C5 beta			Hydrogen at C5 alfa		
Conformer	Strain energy kcal/mol	Distribution %	Conformer	Strain energy kcal/mol	Distribution %
1A	0.00	38.0	1B	0.16	29.0
1D	1.06	6.4	1G	1.77	1.9
1H	1.81	1.8	1E	1.30	4.2
1J	2.90	0.3	1C	0.57	14.5
1K	2.95	0.3	1I	2.84	0.3
			1F	1.44	3.3

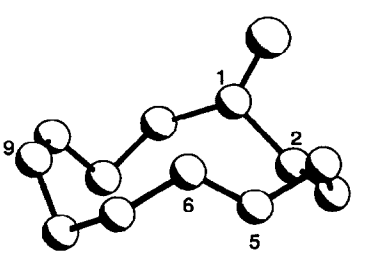
It is clear from these views that the two faces of the olefinic π systems in **1** are sterically very different, the addition reactions being likely to occur largely, or perhaps exclusively, from the less hindered peripheral face of the olefinic linkage. Thus, the allylic epoxidation of **1** to give **2** can satisfactorily be explained by the peripheral oxygen approach to any of the lowest energy conformers **1A-1C**, (Figure 1). The stereostructure of these stable conformers representing 82 % of the conformational population, adequately explains the *threo* stereostructure of **2**, showing that the stereochemistry of the allylic epoxidation is *conformationally controlled.*



1 A



1 C



1 B

Figure 1. Three Lowest Energy Conformations of Compound **1**, **R = H**

This conformational expectation derived by molecular mechanics calculations is in agreement with the ^{1}H NMR studies of compound **1** (**R=H, Ac, Bz**). The spectral data, δ 4.34 (dt, J = 3.6 and 9.8, H1), 5.80 (br q, J = 9.6, H3), 2.88 (dt, J = 15.4 and 8.5, H4β) and 2.59 (ddd, J = 2.0, 7.5 and 15.4, H4α) for compound **1, R=H**, and the almost identical multiplicities when **R=Ac** or **R=BrBz**, are in agreement with the stereostructures of conformers **1A-1C** obtained by MM calculations. Besides, a ROESY study of compound **1, R=BrBz**, showed clear NOE enhancements for protons H12β and H4β when H1 was irradiated, for protons H5, H1 and H4α, and H5, H3 and H4β when protons H4β and H4α were irradiated, respectively. The observed NOE over H5 is much higher from H4β than from H4α, in agreement with a higher stability of conformer **1A**, which possesses the H5 in a *beta* disposition.

All attempts at the kinetic resolution of the racemic allylic alcohol **1** by means of the enantioselective Sharpless epoxidation[10] were unsuccessful, as well as by using different chiral derivatizing reagents.[11] The racemic mixture of **1** was analytically resolved by treatment with α-naphthyl isocyanate in toluene at 90 °C, and the resulting carbamate derivatives were separated by liquid chromatography on a chiral stationary phase.[12] On a preparative scale, the racemic alcohol **1** was converted into its acid phthalate ester, and resolved in good yield by means of the alkaloid (-)-brucine.[13]

The absolute configuration of the (Z,E,Z)-1-hydroxy-cyclododeca-2,5,9-triene (**1**) was determined by applying the allylic benzoate method in circular dichroism.[14] Thus, compound **(+)-1, R=BrBz**, was prepared in the usual way with *p*-bromobenzoyl chloride in pyridine, and analysed. The conformation of this 12-membered macrocyclic derivative has not been altered with respect to the underivatized compound **1, R=H**, since both compounds possess almost identical coupling constants in their ^{1}H NMR spectra. The UV spectrum of **(+)-1, R=BrBz**, shows a *p*-bromobenzoate $\pi \rightarrow \pi^*$ transition at 242.0 nm (21300), in which region the CD spectrum shows a positive Cotton effect, λ_{ext} 239.5 nm, $\Delta\varepsilon$ +9.9 (CH_3CN), indicating a clockwise relationship between the allylic double bond and the *p*-bromobenzoate chromophores. The absolute configuration of **(+)-1** was thus found to be *1S*.[15]

To study the influence of the solvent in the conformation of the 12-membered macrocyclic trienol **1**, the CD spectrum of compound **(+)-1, R=BrBz**, was measured in polar (protic and aprotic) and in apolar solvents. The almost identical intensities of the Cotton effects in the *p*-bromobenzoate region, 9.4 in MeOH, 9.9 in acetonitrile and 10.4 in methylcyclohexane, indicate the non-solvent dependence of the conformational population of this compound.

Molecular mechanics calculations of the *threo* 2,3-epoxy-alcohol **2** reveal five energy minima conformers, **2A-E, R=H**, Table II, the structure of the three lowest conformers **2A-C** being represented in Figure 2, where the existence of a "*jump rope rotation*"[9] of the trans-5,6-double bond can be observed between conformers **2A** and **2C** for this compound also.

The transannular epoxide ring expansion described in Scheme 2 involves an initial *exo* reversible addition of iodine to the *trans*-5,6-double bond in **2** followed by an irreversible *endo* attack of the C1-hydroxyl group, or of the C2,C3 epoxide oxygen, to yield **5** or **3**, respectively. In these endocyclic cyclizations, the inner side of the π orbitals oriented horizontally to the plane of the ring is used for the carbon-oxygen bond formation.

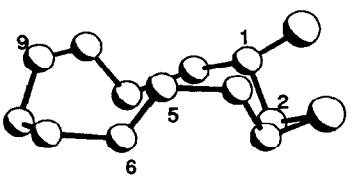
Based on the assumption of the early reactant-like transition state for the ring closure, it was clear that the lowest energy conformer **2A** should yield undetected oxobicyclic stereoisomers of **3** and **5**. Therefore a "*jump rope*

rotation" of the *trans*-5,6-double bond from the less energy conformer **2A** to reach the conformer precursors **2B** and **2D** (Scheme 2) must be involved in order to explain the reaction compounds **3** and **5**.

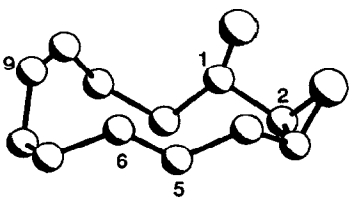
Table II. Molecular Mechanics Data for Compound **2**, **R = H**

Hydrogen at C5 beta			Hydrogen at C5 alfa		
Conformer	Strain energy kcal/mol	Distribution %	Conformer	Strain energy kcal/mol	Distribution %
2A	0.00	63.3	2C	1.08	10.2
			2B	0.70	19.4
			2D	1.42	5.8
			2E	2.30	1.3

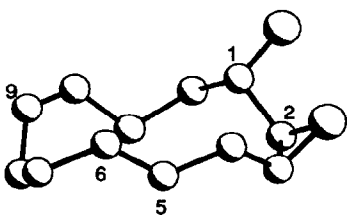
These results indicate that the election of least motion reactions connecting a starting material conformation with a closely related product conformation ignoring those reaction pathways starting from more highly strained conformations, which is a rule generally applied in "*exocyclic*" reactions of macrocyclic compounds, is not always of general use in "*endocyclic*" processes.



2 A



2 B



2 C

Figure 2. Three Lowest Energy Conformations of Compound **2**, **R = H**

The conformational nature of **1** and **2**, especially the horizontal π-orbital orientation of the *trans*-5,6-double bond to the plane of the ring, should give a different direction and degree of regio- and stereoselectivity as described in the epoxidation reactions on the *trans*-5,6-double bond of compounds **1** and **2** shown in Scheme 3.

It was hoped that the introduction of an oxirane ring would impart some of the conformational rigidity present in the olefinic systems, such that the anticipated oxiranyl intermediates would react in a stereoselective manner. Treatment of compound **1, R=BrBz**, with mCPBA in methylene chloride at 0°C proceeded with high regio- and stereoselectivity to give a 6:3:1 mixture of the epoxy-derivatives **6**, **7** and **8**, **R=BrBz**,[16] which were isolated by HPLC.

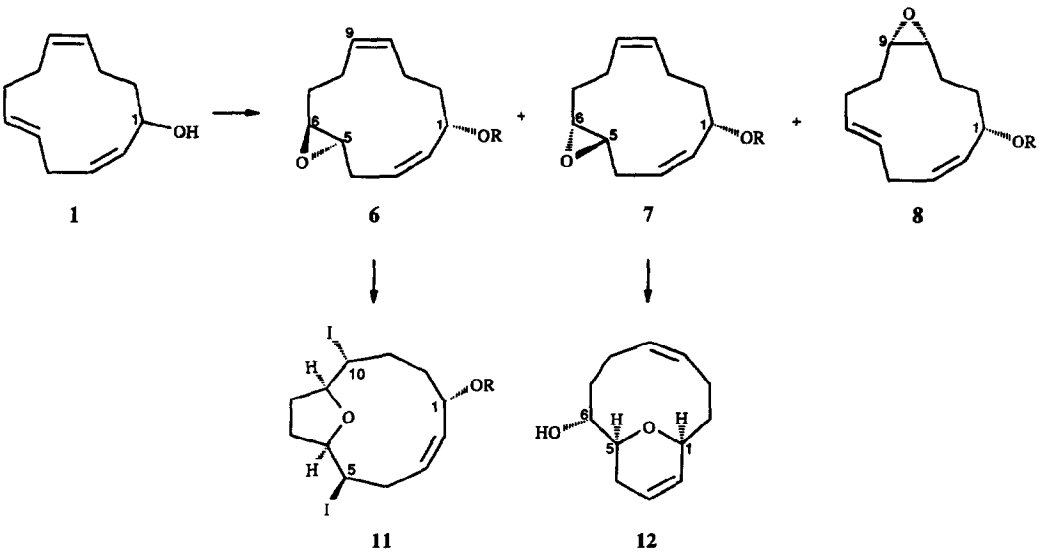
The stereostructures of the resulting compounds **6-8** were determined by careful analysis of their ^{1}H NMR spectra. The multiplicities and coupling constants observed for protons 5 and 6 in the ^{1}H NMR spectrum of compound **6, R=BrBz**, δ 2.85 (br s, H5) and 2.75 (dt, J = 10.5 and 2.2, H6), and those for compound **7, R=BrBz**, δ 2.56 (dd, J = 2.3 and 10.0, H5) and 2.89 (dt, J = 10.2 and 2.3, H6) led straightforwardly to the 1*S*,5*S*,6*S* and to the 1*S*,5*R*,6*R* configuration for compounds **6** and **7**, respectively. The assigned stereochemistries were confirmed by ROESY experiments, while compound **6, R=BrBz**, exhibited NOE enhancements for protons H4α, H5 and H1 when H4β was irradiated, and for protons H4α, H4β and H7β, and protons H3, H7α and H8α, when protons 5 and 6 were irradiated respectively, compound **7, R=BrBz**, showed NOE enhancements for protons H1, H4β and H7β when H6 was irradiated, and for protons H3 and H7α when proton 5 was irradiated. NMR studies of compound **8** showed that the peripheral epoxidation occurred over the *cis*-9,10-double bond and since this reaction is conformationally controlled the stereochemistry of this epoxide should be, as shown, 1*S*,9*S*,10*R*.

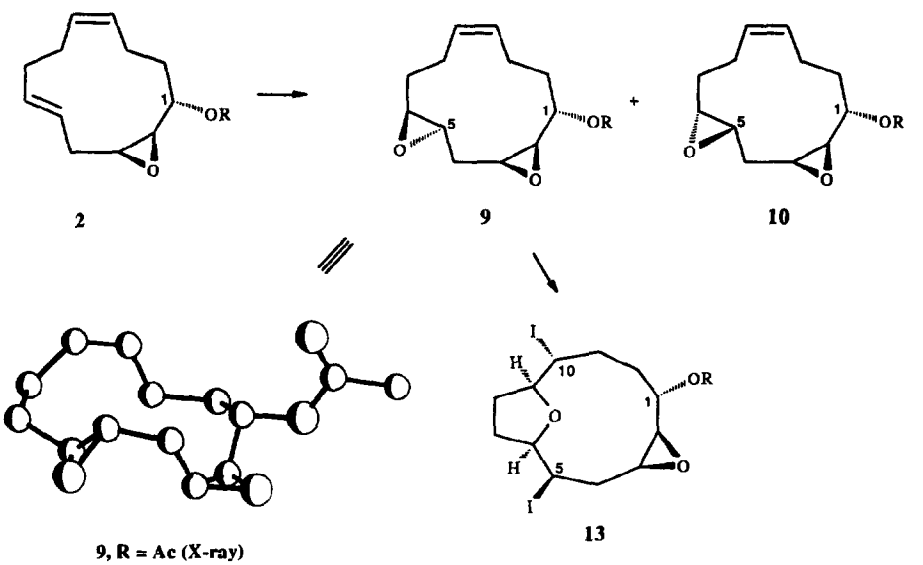
Similarly, epoxidation of **2, R=Ac**, under the above described conditions gave a 2:1 mixture of the diepoxide derivatives **9** and **10, R=Ac**. The peripheral addition of oxygen proceeded preferentially through the lowest energy conformers **2A**, representing 63 % of the conformational population. The stereostructure of the diepoxides **9** and **10, R=Ac**, were in accordance with their spectroscopic data, the former being independently confirmed by single-crystal X-ray diffraction analysis.[17]

Hydrolysis of compound **6, R=BrBz**, led to the expected hydrolysed compound **6, R=H**. However, under the same reaction conditions compound **7, R=BrBz**, gave the oxabicyclo **12** as a single compound, supporting the assigned stereochemistry for compound **7**, as will be seen below.

Although several low energy conformations were obtained by means of molecular mechanics calculations for compounds **6** and **7** (Table III), and **9** and **10** (Table IV), the lowest conformer **6A** and the two more stable conformers **7A** and **7B** were under 0.99, 1.53 and 1.00 kcal/mol in steric energy with respect to the following more stable conformers **6B** and **7C**, respectively, and those obtained for compound **9** and **10**,(**9A**[18] and **10A**), were under 1.93 and 1.04 kcal/mol with respect to conformers **9B** and **10B**, respectively (Figure 3). In accord with these expectations, compounds **11, R=Ac** and **13, R=Ac**, were obtained when **6, R=Ac** and **9, R=Ac**, were respectively subjected to reaction with iodine in dichloromethane (Scheme 3).

The stereostructures of the reaction products **11-13** are predictable, based on the *cis* geometric relationship of the alkyl substituents at position α and α' of the resulting oxabicyclic compounds (**11-13**), and on the conformational properties of their precursors, compounds **6**, **7** and **9**. Of these last compounds, only the C1-hydroxyl group of compound **7** can participate in the C5,C6-oxirane ring opening reaction, by simple rotation of the carbon supporting it (C12) (conformers **7A** and **7B**), and lead to an oxabicyclo with a *cis* configuration. The





Scheme 3

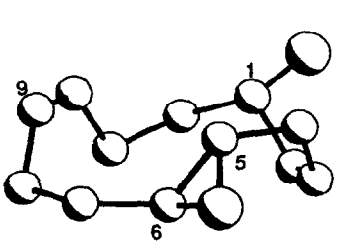
Table III. Molecular Mechanics Data for Compounds **6** and **7**, **R = H**

Conformer	**Compound 6** Strain energy kcal/mol	Distribution %	Conformer	**Compound 7** Strain energy kcal/mol	Distribution %
6A	0.00	78.7	7A	0.00	64.3
6B	0.99	14.8	7B	0.53	26.3
6C	1.82	3.6	7C	1.53	4.9
6D	2.24	1.8	7D	1.96	2.4
6E	2.52	1.1	7E	2.39	1.1
			7F	2.84	0.5
			7G	2.87	0.5

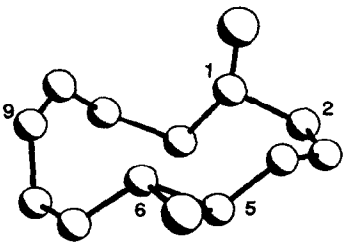
C1-hydroxyl group, the C2,C3-double bond or the C2,C3-epoxide participation in the C5,C6-oxirane ring opening reactions in compounds **6** or **9**, according to the conformer **6A** or **9A**, should give an unfavorable *trans* relationship of the resulting oxabicyclic compounds. The regio- and stereoselectivity of the iodonium-assisted C5-C6 oxirane ring expansion in compounds **6** and **9**, to give the oxabicyclos **11** and **13**, respectively, is totally predictable based on conformers **6A** or **9A**.

Table IV. Molecular Mechanics Data for Compounds **9** and **10**, **R = H**

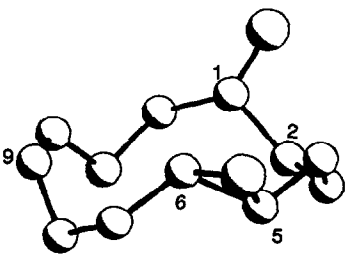
Conformer	**Compound 9** Strain energy kcal/mol	Distribution %	Conformer	**Compound 10** Strain energy kcal/mol	Distribution %
9A	0.00	96.3	10A	0.00	80.0
9B	1.93	3.7	10B	1.04	13.8
			10C	1.74	4.2
			10D	2.22	2.0



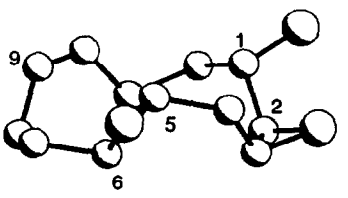
6 A



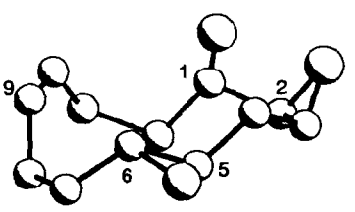
7 A



7 B



9 A



10 A

Figure 3. Lowest Energy Conformation of Compound **6**, **9** and **10**, **R** = **H**, and the Two Lowest Energy Conformations of Compound **7**, **R** = **H**

Thus, conformational analysis is important to predict the regio- and stereoselectivity in macrocyclic reactions, and these considerations of stereochemical control based on MM calculations might be predictably valuable in projected several steps synthetic schemes.

Experimental Section

General. NMR spectra were recorded on a Bruker Model AMX400 spectrometer (δ scale). MMX force field was used for molecular mechanics calculations (Ref. 8). MS data were obtained with a VG Micromass Model ZAB-2F. UV spectra were performed on a Perkin Elmer Model 550D. CD spectra were recorded on a JASCO J-600 spectropolarimeter. Optical rotations were determined with a Perkin Elmer Model 241 polarimeter. GLC was performed on a HP Model 5790A gas chromatograph, SGE capillary column, OV-1, 25 m x 0.22 mm ID. HPLC was performed on a Waters 6000A LC with a μ-Porasil column, 30 cm x 7.8 mm ID, EtOAc/n-hexane solvent systems.

Compound 1, R=H. This compound was prepared in two steps from (E,E,Z)-cyclododeca-1,5,9-triene. 1) Epoxidation of the latter (1.0 g, 6.16 mmol) in EtOAc (4 mL) was carried out by addition of a solution of mCPBA (75% purity) (1.42 g, 6.17 mmol) in EtOAc (2 mL), under N_2 and at 0°C. The reaction was monitored by GLC (t_R triene 3.54 min, t_R epoxide 6.61 min, T=150°C), quenched with sodium bisulfite and extracted with ether in the usual way. The combined organic layers were concentrated and the residue obtained chromatographed on silica gel 60G, with n-hexane/ EtOAc (95:5) as eluent, to give 924.8 mg (5.19 mmol) of the 1,2-epoxy derivative. 2) To a solution of phenyllithium (32 mL, 1M) under N_2 at room temperature was slowly added a solution of the 1,2-epoxy derivative (924.8 mg, 5.18 mmol) in anhydrous ether (4 mL). The reaction was monitored by TLC, quenched, at 0°C, by adding EtOH (2 mL), and extracted with ether in the usual way. The combined organic layers were concentrated and the resulting residue chromatographed on silica gel 60G with n-hexane/ EtOAc (90:10) as eluent, affording a mixture of two compounds (908 mg, 5.09 mmol), of which the desired compound (Z,E,Z)-1-hydroxy-cyclododeca-2,5,9-triene (**1**) was the major product (90 %). Further purification of this compound was performed by crystallization in cold n-hexane and/or by acetylation, using the standard procedure with acetic anhydride/Py, and chromatographic purification on silica gel with n-hexane/ EtOAc (95:5) as eluent. Compound **1, R=H**: solid, mp 75°C; ^{1}H-NMR ($CDCl_3$) δ 5.80 (br q, J = 9.6 Hz, H3), 5.34 (m, 5H), 4.34 (dt, J = 3.6 & 9.8 Hz, H1), 2.88 (dt, J = 15.4 & 8.5 Hz, H4β), 2.59 (ddd, J = 2.0, 7.5 & 15.4 Hz, H4α), 2.16-1.69 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 135.0 (d), 131.6 (d), 130.8 (d), 130.4 (d), 129.5 (d), 128.4 (d), 65.6 (d), 37.2 (t), 30.9 (t), 29.7 (t), 28.2 (t), 22.7 (t); MS (EI) *m / z* (relative intensity) 178 (M^+, 3), 160 (M^+-H_2O, 6), 149 (23), 109 (35), 95 (90), 79 (94), 67 (100).

Compound **1, R=Ac**, ^{1}H-NMR ($CDCl_3$) δ 5.88 (q, J = 8.9 Hz, H3), 5.36 (m, 6H), 3.15 (dt, J = 15.3 & 7.6 Hz, H4β), 2.57 (ddd, J = 1.9, 7.4 & 15.3 Hz, H4α), 2.00 (s, 3H), 2.19-1.68 (m, 8H).

Resolution of the racemic mixture (±)-1, R=H. A solution of the racemic mixture **(±)-1** (500 mg, 2.80 mmol) in dry pyridine (5 mL) was treated with phthalic anhydride (414.4 mg, 2.80 mmol), and the resulting solution heated at 80°C until TLC indicated the disappearance of the starting material. The reaction mixture was diluted with CH_2Cl_2 and extracted with dilute HCl, and the combined organic layers were concentrated. The resulting residue was chromatographed on silica gel 60G, with n-hexane/ EtOAc (70:30) as eluent, to give the corresponding acid phthalate derivative of compound **1** (894.5 mg, 2.74 mmol). To this last compound, acetone (5 mL) and (-)-brucine (1.08 g, 2.74 mmol) were added, and the reaction was heated at 60°C until clear in colour and then

cooled. A precipitate of the corresponding diasteromeric salts was obtained, which after repeated recrystallization in methanol afforded a pure diasteromeric salt,[13] mp 130.7-132.2. This salt was saponified by treatment with sodium hydroxide (3 pellets) in methanol (10 mL) to give, after usual work up, compound (+)-**1** (180 mg), showing an enantiomeric excess ≥ 99% and a positive optical activity, $[\alpha]_D$ = +143.1° (1.01, $CHCl_3$).

The allylic epoxidation of compound 1, R=H, to yield 2, R=H.[5] This epoxide was obtained as a single product by asymmetric epoxidation of (±)-**1**, **R=H**, as described in the literature,[10] using (±)-DET. mp 54°C; ^{1}H-NMR ($CDCl_3$) δ 5.32 (m, 4H), 3.45 (dt, J = 4.8 & 8.4 Hz, H1), 3.36 (dt, J = 9.8 & 4.2 Hz, H3), 2.91 (dd, J = 8.4 & 4.2 Hz, H2), 2.87 (br d, J = 14.1 Hz, H4), 2.11 (m, 5H), 1.83 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 131.6 (d), 130.8 (d), 128.8 (d), 124.5 (d), 66.1 (d), 60.9 (d), 58.1 (d), 35.1 (t), 32.0 (t), 31.2 (t), 27.9 (t), 22.1 (t); MS (EI) *m/z* (relative intensity) 194 (M^+, 1), 192 (3), 176 (M^+-H_2O, 7), 148 (12), 147 (13), 119 (24), 117 (22), 91 (55), 79 (88), 67 (100).

Acetylation of compound 2, R=H. To a solution of **2** (196 mg, 1.01 mmol) in pyridine (3 mL) at room temperature was added an excess of acetic anhydride (3 mL). The reaction was quenched with MeOH, and the excess solvent removed under reduced pressure in the presence of heptane. The residue was chromatographed on a silica gel column (n-hexane/EtOAc, 95:5) to give compound **2, R=Ac** (233 mg, 0.99 mmol). ^{1}H-NMR ($CDCl_3$) δ 5.47 (m, 1H), 5.32 (m, 3H), 4.77 (dt, J = 5.2 & 8.4 Hz, H1), 3.24 (dt, J = 9.9 & 4.2 Hz, H3), 2.92 (dd, J = 4.2 & 8.4 Hz, H2), 2.83 (br d, J = 15.8 Hz, H4), 2.06 (s, 3H), 2.17-1.90 (m, 8H), 1.80 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 170.1 (s), 131.3 (d), 130.0 (d), 129.3 (d), 124.9 (d), 69.4 (d), 58.1 (d), 56.5 (d), 33.5 (t), 31.5 (t), 31.1 (t), 27.8 (t), 22.0 (t), 21.1 (q).

Benzoylation of compound 1, R=H. A solution of **1, R=H**, (505 mg, 2.83 mmol) in dry pyridine (10 mL) with DMAP as catalyst was treated with *p*-bromobenzoyl chloride (925 mg, 4.22 mmol). The resulting solution was heated at 60°C and stirred overnight. The reaction was quenched with MeOH, and the excess solvent was removed under reduced pressure in the presence of n-heptane. The residue obtained was chromatographed on silica gel, with n-hexane/ EtOAc (95:5) as eluent, to give 892 mg (2.47 mmol) of compound **1, R=BrBz**. ^{1}H-NMR ($CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 5.93 (br q, J = 8.1 Hz, H3), 5.61 (dt, J = 3.7 & 9.9 Hz, H1), 5.43 (m, 3H), 5.32 (m, 2H), 3.24 (dt, J = 15.6 & 7.7 Hz, H4β), 2.62 (ddd, J = 2.0, 7.0 & 15.6 Hz, H4α), 2.21-1.86 (m, 8H).

Benzoylation of compound (+)-1, R=H. This reaction was performed as described above for the benzoylation of (±)-**1**. Thus, compound (+)-**1, R=H**, (5.3 mg, 0.030 mmol) led, after purification by preparative TLC (n-hexane/EtOAc, 95:5), to the benzoate derivative (+)-**1, R=BrBz** (8.9 mg, 0.025 mmol). Prior to measurement of UV and CD spectra this compound was further purified by HPLC. UV (CH_3CN) λ_{max} 242 nm (ε 21300), CD (CH_3CN) λ_{ext} 239.5 nm (Δε +9.9); UV (methyl cyclohexane) λ_{max} 243 nm, CD (methyl cyclohexane) λ_{ext} 242.3 (Δε +10.4); UV (MeOH) λ_{max} 243 nm, CD (MeOH) λ_{ext} 242.1 nm (Δε +9.4).

Epoxidation of compound 1, R=BrBz, to give compounds 6-8, R=BrBz. To a solution of **1, R=BrBz** (743.7 mg, 2.06 mmol) in dry CH_2Cl_2 (15 mL) was added mCPBA (75% purity) (474.0 mg, 2.06 mmol) under

N_2 at 0°C. After 3 h, the reaction was quenched with KF and left with stirring for 1 h. The mixture was filtered and purified on a silica gel column (n-hexane/EtOAc, 90:10) to afford a mixture of the epoxides **6-8, R=BrBz** (730.8 mg, 1.94 mmol). Most of the epoxide **6** (367.7 mg, 0.98 mmol) was obtained by crystallization on n-hexane/EtOAc (95:5), the mother liquor affording, after HPLC (n-hexane/EtOAc, 95:5; flow rate 1 mL/min), the epoxides **6** (80.7 mg, 0.21 mmol, R_t 44.6), **7** (212.3 mg, 0.56 mmol, R_t 38.5) and **8** (70.1 mg, 0.19 mmol, R_t 42.0).

Compound **6, R=BrBz**: ^{1}H-NMR ($CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.6 Hz, 2H), 5.79 (dt, J = 3.9 & 10.7 Hz, H1), 5.62 (dt, J = 5.7 & 11.2 Hz, H3), 5.43 (m, 3H), 3.08 (ddd, J = 3.7, 11.3 & 15.2 Hz, H4β), 2.85 (br s, H5), 2.75 (dt, J = 10.5 & 2.2 Hz, H6), 2.51 (dd, J = 5.7 & 15.2 Hz, H4α), 2.34 (m, H8α), 2.18 (m, H7α, H11's), 2.06 (m, H12β, H8β), 1.93 (m, H12α), 1.10 (ddt, J = 3.2, 10.5 & 13.1 Hz, H7β). ^{13}C-NMR ($CDCl_3$) δ 165.0 (s), 131.6 (d), 131.1 (d), 131.0 (d), 130.0 (d), 129.9 (d), 129.5 (d), 128.0 (s), 69.2 (d), 60.6 (d), 57.2 (d), 33.2 (t), 30.9 (t), 27.3 (t), 24.5 (t), 22.5 (t); MS (EI) *m / z* (relative intensity) 378, 376 (M^+, 2, 2), 193 (M^+-C_7H_4OBr, 3), 185, 183 (C_7H_4OBr, 100, 100), 176 (M^+-BrBzOH, 12), 157, 155 (C_6H_4Br, 43, 39), 117 (22), 91 (31), 79 (38), 65 (48).

Compound **7, R=BrBz**: ^{1}H-NMR ($CDCl_3$) δ 7.85 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 5.84 (dt, J = 6.6 & 10.6 Hz, H3), 5.53 (m, H1, H2), 5.40 (m, H9, H10), 2.89 (dt, J = 10.2 & 2.3 Hz, H6), 2.58 (dd, J = 6.3 & 12.8 Hz, H4α), 2.56 (dd, J = 2.3 & 10.0 Hz, H5), 2.36 (m, H4β), 2.28 (m, H11's), 2.17 (m, H7β, H8's), 1.96 (m, H12's), 1.06 (m, H7α); ^{13}C-NMR ($CDCl_3$) δ 165.0 (s), 131.6 (d), 131.1 (d), 131.0 (d), 130.0 (d), 129.9 (d), 129.5 (d), 128.0 (s), 69.2 (d), 60.6 (d), 57.2 (d), 33.2 (t), 30.9 (t), 27.3 (t), 24.5 (t), 22.5 (t).

Compound **8, R=BrBz**: ^{1}H-NMR ($CDCl_3$) δ 7.88 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 5.92 (br q, J = 7.7 Hz, H3), 5.55 (m, 4H), 3.22 (dt, J = 15.5 & 8.1 Hz, H4β), 2.92 (m, H9, H10), 2.68 (m, H4α), 2.15 (m, 6H), 1.75 (m, 1H), 1.15 (m, 1H).

Hydrolysis of compound 6, R=BrBz. An excess of K_2CO_3 was added to a solution of **6** (154.5 mg, 0.41 mmol) in MeOH (15 mL) at room temperature and stirred overnight. The reaction was diluted with water and extracted with ether in the usual way. The residue obtained was submitted to chromatography (n-hexane/EtOAc, 80:20) to give the epoxy-alcohol **6, R=H** (76.5 mg, 0.39 mmol). ^{1}H-NMR ($CDCl_3$) δ 5.49 (dt, J = 6.0 & 11.0 Hz, H3), 5.35 (m, 3H), 4.52 (dt, J = 3.8 & 10.7 Hz, H1), 2.77 (br s, H5), 2.76 (br d, J = 9.2 Hz, H6), 2.74 (ddd, J = 3.6, 9.2 & 12.5 Hz, H4β), 2.44 (dd, J = 4.5 & 12.5 Hz, H4α), 2.31 (m, H8α), 2.10 (m, H7α, H8β, H11's), 1.93 (m, H12β), 1.78 (br s, OH), 1.66 (m, H12α), 1.06 (ddt, J = 3.3, 10.3 & 13.2, H7β). ^{13}C-NMR ($CDCl_3$) δ 135.2 (d), 130.7 (d), 129.6 (d), 128.1 (d), 65.9 (d), 61.0 (d), 57.6 (d), 36.4 (t), 31.3 (t), 27,4 (t), 24.8 (t), 23.5 (t); MS (EI) *m / z* (relative intensity) 194 (M^+, 0.3), 177 (1), 159 (3), 147 (4), 133 (10), 117 (13), 95 (40), 91 (33), 79 (68), 67 (93), 55 (100).

Acetylation of compound 6, R=H. This compound (24.1 mg, 0.124 mmol) dissolved in pyridine (1 mL) was acetylated by treatment with an excess of acetic anhydride (1 mL) at room temperature. After 4 h, the reaction was quenched with MeOH, and the excess solvent removed under reduced pressure in the presence of heptane. The residue was chromatographed on a silica gel column (n-hexane/EtOAc, 90:10) to give the acetate (23.8 mg, 0.10 mmol). ^{1}H-NMR ($CDCl_3$) δ 5.55 (m, H1,H3), 5.32 (m, 3H), 2.97 (ddd, J = 3.7, 11.4 & 15.0 Hz, H4β), 2.79 (br s, H5), 2.70 (br d, J = 10.2 Hz, H6), 2.43 (dd, J = 5.6 & 15.0 Hz, H4α), 2.32 (m, H8α), 2.13 (m, H7α, H11's),

2.01 (s, 3H), 1.80 (m, H8β, H12's), 1.06 (ddt, J = 3.0, 7.3 & 13.1 Hz, H7β).

Hydrolysis of compound 7, R=BrBz, to yield 12, R=H. To a solution of **7, R=BrBz** (48.8 mg, 0.129 mmol) in MeOH (5 mL) was added an excess of K_2CO_3 at room temperature. After 3 h, water was added to the reaction mixture and extracted with ether in the usual way. Removal of the solvent and chromatography on silica gel with a mixture of n-hexane/EtOAc (90:10) as eluent afforded the oxabicyclo **12** (18.2 mg, 0.09 mmol). Yield 72%. ^{1}H-NMR ($CDCl_3$) δ 5.74 (m, H2, H3), 5.47 (dt, J = 4.7 & 10.8 Hz, H9), 5.34 (ddt, J = 1.4, 5.4 & 11.0 Hz, H10), 3.88 (m, H1), 3.60 (m, H6), 3.32 (dt, J = 6.0 & 8.4 Hz, H5), 2.60 (dq, J = 2.3 & 10.1 Hz, H8), 2.51 (dq, J = 5.8 & 12.6 Hz, H11), 2.09 (m, 4H), 1.87 (m, H11), 1.67 (m, 1H), 1.61 (br s, OH), 1.50 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 133.3 (d), 130.7 (d), 126.5 (d), 124.5 (d), 79.2 (d), 74.2 (d), 73.2 (d), 37.1 (t), 30.8 (t), 28.6 (t), 23.6 (t), 22.5 (t); MS (EI) *m / z* (relative intensity) 194 (M^+, 10), 176 (M^+-H_2O, 8), 165 (11), 147 (11), 135 (15), 107 (20), 96 (37), 91 (36), 79 (75), 67 (100).

Acetylation of compound 12, R=H. A solution of compound **12, R=H** (2.4 mg, 0.012 mmol) in dry pyridine (0.5 mL) was treated with an excess of acetic anhydride (0.5 mL), leaving the solution with stirring at room temperature for 2 h. The mixture was quenched with MeOH and the excess solvent removed under reduced pressure in the presence of heptane. The residue was chromatographied on silica gel column (n-hexane/EtOAc, 90:10) to give the acetate (2.5 mg, 0.010 mmol). ^{1}H-NMR ($CDCl_3$) δ 5.72 (br s, H2, H3), 5.46 (dt, J = 4.6 & 10.9 Hz, H9), 5.34 (ddt, J = 1.5, 5.2 & 11.2 Hz, H10), 4.79 (dt, J = 3.7 & 9.6 Hz, H6), 3.83 (m, H1), 3.44 (dt, J = 4.7 & 9.6 Hz, H5), 2.65 (m, H8), 2.56 (dq, J = 6.2 & 12.4 Hz, H11), 2.13 (m, 1H), 2.03 (s, 3H), 2.02 (m, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.52 (m, 1H), 1.42 (m, 1H); MS (EI) *m / z* (relative intensity) 236 (M^+, 11), 194 (M^+-CH_2CO, 15), 193 (M^+-CH_3CO, 8), 177 (M^+-AcO, 39), 176 (M^+-AcOH, 88), 147 (32), 133 (32), 107 (56), 79 (71), 67 (54), 43 (100).

Diepoxides 9 and 10, R=Ac. The epoxidation of **2, R=Ac** (221 mg, 0.94 mmol) to give the diepoxides **9, R=Ac** (149.9 mg, 0.594 mmol) and **10, R=Ac** (68.4 mg, 0.271 mmol) was performed as described above for the epoxidation of compound **1.** The residue was chromatographed on a silica gel column with n-hexane/EtOAc (90:10) as eluent.

Compound **9, R=Ac,** ^{1}H-NMR ($CDCl_3$) δ 5.42 (m, H9, H10), 4.88 (dt, J = 5.6 & 8.8 Hz, H1), 2.88 (m, H2, H5, H6), 2.74 (br s, H3), 2.57 (d, J = 16.1 Hz, H4), 2.26 (m, 4H), 2.13 (s, 3H), 1.92 (m, 4H), 1.12 (m, H7β); ^{13}C-NMR ($CDCl_3$) δ 130.5 (d), 129.2 (d), 68.9 (d), 57.9 (d), 57.2 (d), 56.2 (d), 53.7 (d), 32.5 (t), 31.4 (t), 27.3 (t), 24.3 (t), 22.1 (t), 21.0 (q).

Compound **10, R=Ac,** ^{1}H-NMR ($CDCl_3$) δ 5.45 (m, H9, H10), 4.76 (dt, J = 3.0 & 8.8 Hz, H1), 3.15 (dt, J = 8.5 & 4.7 Hz, H3), 2.98 (dd, J = 4.7 & 8.8 Hz, H2), 2.88 (dt, J = 10.3 & 3.4 Hz, H5), 2.78 (ddd, J = 2.4, 3.4 & 10.2 Hz, H6), 2.15 (s, 3H), 1.30 (m, 2H); ^{13}C-NMR ($CDCl_3$) 133.7 (d), 124.5 (d), 74.0 (d), 57.8 (d), 57.3 (d), 56.7 (d), 54.1 (d), 33.4 (t), 28.9 (t), 27.4 (t), 27.2 (t), 23.5 (t), 21.0 (q).

Oxabicyclo 11. To a solution of the epoxy-acetate **6, R=Ac** (22.4 mg, 0.095 mmol) in dry methylene chloride (1.5 mL), iodine (48.2 mg, 0.190 mmol) was added at room temperature. After 6 h, the reaction mixture

was diluted with ether and extracted with sodium bisulphite. The combined organic layers were concentrated and the residue obtained chromatographed on preparative TLC (n-hexane/ EtOAc, 80:20) to give the oxabicyclo **11, R=Ac** (22.3 mg, 0.046 mmol). ^{1}H-NMR ($CDCl_3$) δ 5.91 (dt, J = 5.6 & 11.0 Hz, H3), 5.61 (dt, J = 3.0 & 11.0 Hz, H1), 5.29 (t, J = 11.0 Hz, H2), 4.48 (m, H6, H9), 4.16 (m, H10), 3.72 (dt, J = 3.1 & 15.0 Hz, H4), 3.61 (m, H5), 2.47 (dt, J = 15.0 & 6.0 Hz, H4'), 2.10 (m, 4H), 2.03 (s, 3H), 1.79 (m, 3H), 1.62 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 170.1 (s), 131.6 (d), 129.7 (d), 86.4 (d), 85.2 (d), 68.9 (d), 35.5 (t), 33.6 (d), 32.5 (t), 30.9 (t), 30.8 (t), 29.9 (d), 24.9 (t), 21.3 (q); MS (EI) *m / z* (relative intensity) 490 (M^+, 0.6), 448 (M^+-CH_2CO, 8), 447 (M^+-CH_3CO, 4), 430 (M^+-AcOH, 3), 363 (M^+-I, 24), 321 (41), 303 (40), 254 (100), 175 (73), 127 (69), 105 (50), 93 (44), 91 (94), 79 (90), 67 (76), 43 (75).

Oxabicyclo 13. This compound was obtained by using the same procedure as described above for compound **11**. Thus, compound **9, R=Ac** (60.3 mg, 0.239 mmol) led to the oxabicyclo **13, R=Ac** (65.3 mg, 0.129 mmol). ^{1}H-NMR (C_6D_6) δ 5.03 (dt, J = 9.1 & 6.5 Hz, H1), 4.48 (ddd, J = 3.2, 6.1 & 9.5 Hz, H10), 4.05 (m, H9), 3.91 (m, H6), 3.12 (m, H5), 2.88 (m, H3), 2.61 (dd, J = 3.8 & 9.1 Hz, H2), 2.42 (m, H4's), 1.62 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.2 (s), 86.8 (d), 83.3 (d), 70.5 (d), 58.4 (d), 54.7 (d), 36.2 (t), 31.8 (t), 31.6 (t), 30.8 (t), 28.7 (d), 27.3 (d), 24.3 (t), 21.0 (q); MS (EI) *m / z* (relative intensity) 463 (M^+-CH_3CO, 1), 447 (M^+-CH_3CO_2, 7), 379 (M^+-I, 16), 337 (6), 319 (M^+-AcOH-I, 78), 301 (9), 192 (22), 191 (35), 173 (39), 145 (34), 95 (44), 91 (44), 79 (77), 67 (100), 55 (98).

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