Conformational Analysis of Bicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylic Acid Derivatives and Related Compounds[1)]

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The stereoselective synthesis of esters **5a**, **6**, **7**, **8**, **12b**, **12c**, and **13** and dicarboxylic acids **5**, **12**, and **12a** by $KMnO_4$ oxidation, and, in the case of esters, diazomethane esterification, of the known tricyclic ketones **1**, **2**, **3**, and **4** or their derivatives **9**, **9a**, **9b**, **10**, **10a**, **11**, and **11a**, is described. Conformational analyses of these compounds have been carried out by 200-MHz ^{1}H-NMR and ^{13}C-NMR spectroscopy at room temperature with the aid of theoretical calculations (MM2 program). Also, a ^{1}H-NMR study of compound **5a** at temperatures between 21 and 119°C is presented. In general, a good agreement has been found among experimental and calculated average *vicinal* proton/proton coupling constant values. Compounds **5** and **5a**, in [D_6]DMSO and $CDCl_3$ solutions, respectively, exist mainly as *boat-chair* conformers, while compounds **6**, **7**, **8**, and **13** exist mainly as *chair* conformers with respect to the bis(methoxycarbonyl)-substituted cyclohexane or oxane ring. Compounds **12**, **12a**, **12b**, and **12c** show similar proportions for *boat-chair* and *chair-chair* conformers.

Konformationsanalyse von Bicyclo[3.3.1]nonan-*exo*-2,*exo*-4-dicarbonsäure-Derivaten und strukturell verwandten Verbindungen

Die stereoselektive Synthese der Ester **5a**, **6**, **7**, **8**, **12b**, **12c** und **13** sowie der Dicarbonsäuren **5**, **12** und **12a**, durch Oxidation mit $KMnO_4$ und, im Fall der Ester, durch Veresterung mit Diazomethan, ausgehend von den bekannten tricyclischen Ketonen **1**, **2**, **3** und **4** oder ihren tricyclischen Derivaten **9**, **9a**, **9b**, **10**, **10a**, **11** und **11a** wird beschrieben. Konformationsanalysen dieser Verbindungen wurden mittels 200-MHz-^{1}H-NMR- und ^{13}C-NMR-Spektroskopie bei Raumtemperatur und mit Hilfe theoretischer Berechnungen (MM2-Programm) durchgeführt. Zusätzliche ^{1}H-NMR-Studien an Verbindung **5a** zwischen 21 und 119°C werden ebenso beschrieben. In der Regel wurde eine gute Übereinstimmung zwischen experimentellen und berechneten Mittelwerten der *vicinalen* Proton/Proton-Kopplungskonstanten gefunden. Verbindungen **5** und **5a** in [D_6]DMSO bzw. $CDCl_3$ befinden sich bevorzugt in der Wannen-Sessel-Konformation, während Verbindungen **6**, **7**, **8** und **13** bevorzugt in der Sessel-Form relativ zum Bis(methoxycarbonyl)-substituierten Cyclohexan- oder Oxan-Ring existieren. Verbindungen **12**, **12a**, **12b** und **12c** nehmen sowohl die Wannen-Sessel- als auch die Sessel-Sessel-Konformation ein.

The conformational analysis of bicyclo[3.3.1]nonane derivatives has been the subject of many publications[2-16]. Unsubstituted bicyclo[3.3.1]nonane (Figure 1) and bicyclo[3.3.1]nonan-9-one exist preferentially in a *chair-chair* conformation, in which both *chairs* are flattened due to the *endo*-3-H/*endo*-7-H interaction. The absence of the *exo*-3-H/*syn*-9-H interaction in the *boat-chair* conformation of bicyclo[3.3.1]nonan-9-one is responsible for the greater population of this conformation in this compound (22%)[10] with respect to the bicyclo[3.3.1]nonane (5 ± 4%)[9]. An *exo*-2 substituent such as Cl or OH does not change the preference of the system for the *chair-chair* conformation[4]. However, one *endo*-3 substituent makes the *boat-chair* conformation, in which this substituent is *equatorial*, the preferred one[2-8,12].

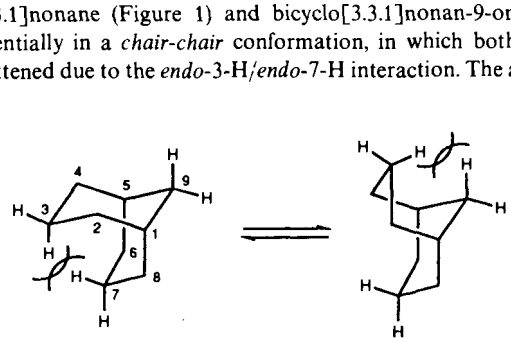


Figure 1. *Chair-chair* and *boat-chair* conformations of bicyclo[3.3.1]nonane

Much attention has been paid also to the conformational analysis of 3-heterobicylo[3.3.1]nonane derivatives (3-oxa derivatives[17] and specially 3-aza derivatives[18-25]) in which the *chair-chair* conformation lacks the *endo*-3-H/*endo*-7-H interaction. Less attention has received the conformational analysis of bicyclo[3.2.1]octane derivatives[26,27], in which the preferred conformation with a *chair* cyclohexane ring does not show severe destabilizing H/H interactions.

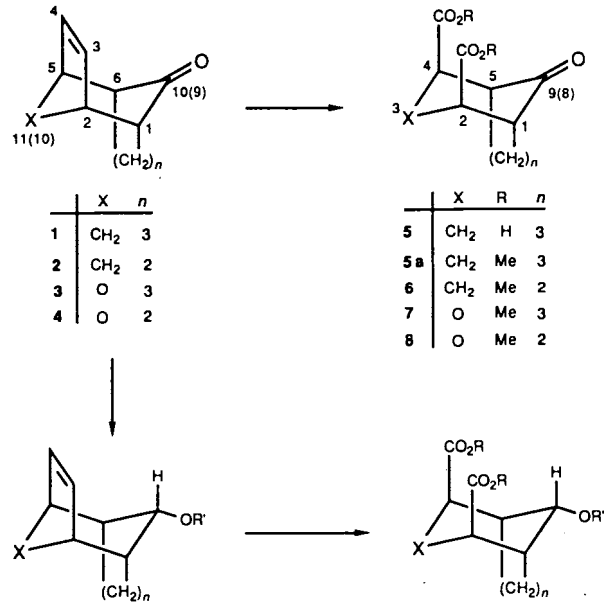
Some time ago, we established[13] that *exo*-2,*exo*-4-dimethoxybicyclo[3.3.1]nonan-9-one exists preferentially in a *chair-chair* con-

formation with *axial* methoxy groups. Later, Baker and Frazer[14] observed the same preferred conformation for *exo*-2-acetoxy-*exo*-4,5-dimethylbicyclo[3.3.1]nonan-9-one. Nearly simultaneously we found[15] that 9-oxobicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylic acid (**5**) exists preferentially in a *boat-chair* conformation, and later, Ravishankar et al.[16] observed the same preference for *exo*-2,*exo*-4-diphenylbicyclo[3.3.1]nonan-9-one.

In this publication, we describe the synthesis and conformational analysis of several compounds related to the diacid **5** prepared from the readily available ketones **1**[28,29], **2**[30,31], **3**[32], and **4**[31,32] by 200-MHz ^{1}H-NMR and ^{13}C-NMR spectroscopy with the aid of molecular mechanics calculations (MM2 program).

Ketones **1**, **2**, and **3** were stereoselectively reduced to the corresponding *anti*-alcohols **9**, **10**, and **11**, in 89, 80, and 89% yield, respectively, by refluxing a solution of the ketone in xylene with an excess of aluminum triisopropoxide. Ketone **4** could not be reduced under these conditions due to its thermal instability[31]. It is known that $LiAlH_4$ reduction of some of these ketones (**1**[29], **2**[31], **4**[31]) leads stereoselectively, as expected, to the corresponding *syn*-alcohols, while Na/2-propanol reduction of ketone **2**[33] gives a mixture of alcohol **10** (43% yield) and its C-9 epimer (6% yield) among other reduction products. Acetylation of these alcohols with acetic anhydride gave the corresponding acetates **9a**, **10a**[33], and **11a**, respectively. Alcohol **9** was also treated with benzoyl chloride in pyridine to give the corresponding benzoate **9b** (Scheme 1).

Scheme 1



	X	n
1	CH_2	3
2	CH_2	2
3	O	3
4	O	2

	X	R	n
5	CH_2	H	3
5a	CH_2	Me	3
6	CH_2	Me	2
7	O	Me	3
8	O	Me	2

	X	R'	n
9	CH_2	H	3
9a	CH_2	COMe	3
9b	CH_2	COPh	3
10	CH_2	H	2
10a	CH_2	COMe	2
11	O	H	3
11a	O	COMe	3

	X	R	R'	n
12	CH_2	H	COMe	3
12a	CH_2	H	COPh	3
12b	CH_2	Me	COMe	3
12c	CH_2	Me	COPh	3
13	CH_2	Me	COMe	2
14	O	Me	COMe	3

The ^{1}H-NMR and ^{13}C-NMR data of these tricyclic alcohols and esters have been collected in Tables 1 and 2, respectively. Assignment of the ^{1}H-NMR spectra of these compounds has been carried out on the basis of the chemical shift for the different protons and double-resonance experiments, and that of the ^{13}C-NMR spectra on the basis of the chemical shift for the different carbon atoms, absorption intensiy, type of carbon atom using the DEPT pulse sequence, as well as by comparison of the spectra of related compounds (pairs ketone/corresponding alcohol, alcohol/corresponding ester, alcohol **9**/alcohol **11**, etc.).

The configuration of C-10 in alcohol **9** was easily established by comparison of its ^{13}C-NMR spectrum with that of the previously described C-10-epimeric alcohol[29]. The most salient feature of the ^{13}C-NMR spectrum of alcohol **9** is the chemical shift of C-7(9) (δ = 20.1), 8.5 ppm upfield with respect to the corresponding value of its C-10 epimer. The hydroxyl group of **9** is *axial* to the *chair* cyclohexane ring determined by C-1, C-10, C-6, C-7, C-8, and C-9, and thus, a great γ effect must be expected for C-7(9) as it is the case in cyclohexane[34] and bicyclo[3.2.1]octane[35] derivatives. Also, the signal of C-3(4) is shifted upfield by 2.5 ppm in passing from ketone **1** to alcohol **9**, while it is shifted downfield by 3.0 ppm in going from ketone **1** to the C-10 epimer of **9**.

The ^{1}H-NMR spectra of alcohol **9** and its C-10 epimer show also significant differences. Thus, the signal for the 3(4)-H of **9** is shifted upfield by 0.09 ppm while for the C-10 epimer of **9** it is shifted downfield by 0.33 ppm with respect to the corresponding value in ketone **1**. Also, the chemical shift for 10-H of **9** is 0.31 ppm downfield with respect to the value in its C-10 epimer. Both differences in chemical shifts are easily correlated with the configuration of C-10 in these alcohols. The coupling constant $J_{1\text{-H},10\text{-H}}$ is not significant in relation to the C-10 configuration of these alcohols.

A similar situation has been found in comparing the ^{1}H-NMR and ^{13}C-NMR spectra of alcohol **10**[33], its C-9 epimer[31], and ketone **2**, thus confirming the *anti* configuration of alcohol **10**. In this case, however, the effect of the configuration of C-9 on the ^{13}C chemical shift of C-7(8) is small.

Since the C-10 epimer of alcohol **11** is not known, we compared the changes experienced by the ^{13}C chemical shifts of ketone **3** in passing to alcohol **11** that showed a very similar pattern to that found in going from ketone **1** to alcohol **9**, thus pointing to the *anti* configuration of C-10 for alcohol **11**. The validity of this comparison lies in the similar geometries of both ketones and alcohols. Moreover, in going from ketone **3** to alcohol **11**, the chemical shift for the ethylenic protons is shifted upfield by 0.12 ppm, a very similar shift to that observed in passing from ketone **1** to alcohol **9** (0.09 ppm).

Consequently, as expected, aluminum triisopropoxide reduction of ketones **1**, **2**, and **3** gives the corresponding thermodynamically more stable *anti*-alcohols, in contrast with the described kinetically controlled $LiAlH_4$ reduction of ketones **1**, **2**, and **4** that gives the corresponding *syn*-alcohols.

The ^{1}H-NMR and ^{13}C-NMR spectra of esters **9a**, **9b**, **10a**, and **11a** do not show significant changes with respect to the

Table 1. ^{1}H-NMR data (200 MHz) of tricyclo[4.3.1.1^{2,5}]undecane, tricyclo[4.2.1.1^{2,5}]decane, 11-oxatricyclo[4.3.1.1^{2,5}]undecane, and 10-oxatricyclo[4.2.1.1^{2,5}]decane derivatives ($CDCl_3$, 25°C). The chemical shift is given only for the lowest numbered proton among equivalent ones. Absolute values for coupling constants are given

	Compound						
	9	**9a**	**9b**	**11**	**11a**	**10**	**10a**
δ(ppm)							
1-H	1.70	1.90	1.90	1.60	1.65	1.73	1.99
2-H	2.61	2.61	2.67	4.78	4.71	2.50	2.52
3-H	6.01	6.08	6.14	6.26	6.28	5.83	5.93
10-H (9-H)[a]	3.95	5.02	5.30	4.02	5.00	3.84	4.80
exo-11-H (*exo*-10-H)[a]	1.40	1.44	1.50			1.15	1.17
endo-11-H (*endo*-10-H)[a]	2.36	2.38	2.43			1.69	1.74
7,8-H (7-H)[a]	1.3–2.1	1.3–2.0	1.4–2.0	1.4–2.5	1.3–2.5	1.5–1.9	1.5–1.8
OH	1.40			1.4–2.5		1.08	
CH_3O		2.05			2.01		1.97
C_6H_5CO			7.48 8.58				
J [Hz]							
1-H,2-H	4.0	4.0		2.5	2.0		
1-H,10-H (1-H,9-H)[a]	4.8	4.0	4.0	4.3	4.0		
2-H,*exo*-11-H (2-H,*exo*-10-H)[a]	4.0	4.0	4.0			4.0	4.0
2-H,*endo*-11-H (2-H,*endo*-10-H)[a]		0.9	0.9				
exo-11-H,*endo*-11-H (*exo*-10-H,*endo*-10-H)[a]	10.7	10.8	10.9			10.5	10.0
ortho-H,*meta*-H			6.8				

[a] Corresponding number for tricyclo[4.2.1.1^{2,5}]decane and 10-oxatricyclo[4.2.1.1^{2,5}]decane derivatives in parentheses.

Table 2. ^{13}C-NMR data of tricyclo[4.3.1.1^{2,5}]undecane, tricyclo[4.2.1.1^{2,5}]decane, 11-oxatricyclo[4.3.1.1^{2,5}]undecane, and 10-oxatricyclo-[4.2.1.1^{2,5}]decane derivatives ($CDCl_3$, 25°C). The chemical shift is given only for the lowest numbered carbon atom among equivalent ones

Compound	C-1	C-2	C-3	C-7	C-8	C-10 (C-9)[a]	C-11 (C-10)[a]	CH_3CO_2	CO_2
9	30.9	45.7	135.1	20.1	16.8	69.7	36.5		
9a	28.5	45.8	135.3	20.9	16.9	74.3	36.6	21.5	170.6
9b[b]	28.7	45.8	135.3	21.1	17.0	74.8	36.6		165.9
11	34.2	83.8	132.6	21.1	19.7	62.2			
11a	32.0	83.7	132.9	21.9	19.8	70.5		21.3	170.4
10	37.9	43.6	131.7	26.5		77.1	37.9		
10a	35.0	42.6	131.0	26.0		80.2	37.2	20.4	169.5

[a] Corresponding number for tricyclo[4.2.1.1^{2,5}]decane and 10-oxatricyclo[4.2.1.1^{2,5}]decane derivatives in parentheses. – [b] *C-ipso:* 131.1, *C-ortho:* 129.5, *C-meta:* 128.3, *C-para:* 132.7.

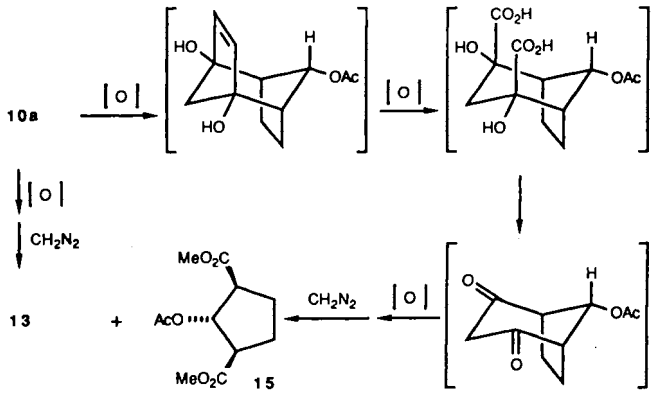
spectra of the corresponding alcohols, except for 10-H (or 9-H) and C-10 (or C-9), in accord with expectations.

Ketone **1** and esters **9a** and **9b** were oxidized with $KMnO_4$ under phase-transfer conditions to give the corresponding dicarboxylic acids **5**, **12**, and **12a**, in 95, 76, and 57% yield, respectively. These acids were esterified in high yield with ethereal solution of diazomethane to the corresponding dimethyl esters **5a**, **12b**, and **12c**, respectively. Ketones **2**, **3**, and **4** were similarly oxidized, and the ethereal solution of the diacid was treated with diazomethane, isolating directly the corresponding dimethyl esters **6**, **7**[36], and **8**, in 56, 34, and 26% yield, respectively.

By similar treatment (oxidation followed by diazomethane esterification), ester **10a** gave a mixture of compounds **13** and **15** in the approximate ratio 2:1 (by GLC) (Scheme 2). Although this mixture could not be separated neither by column chromatography nor by semipreparative HPLC, a pure sample of the major component (**13**) could be obtained since it crystallized from its mixture with **15** after standing at room temperature. Significant ^{1}H-NMR and ^{13}C-NMR

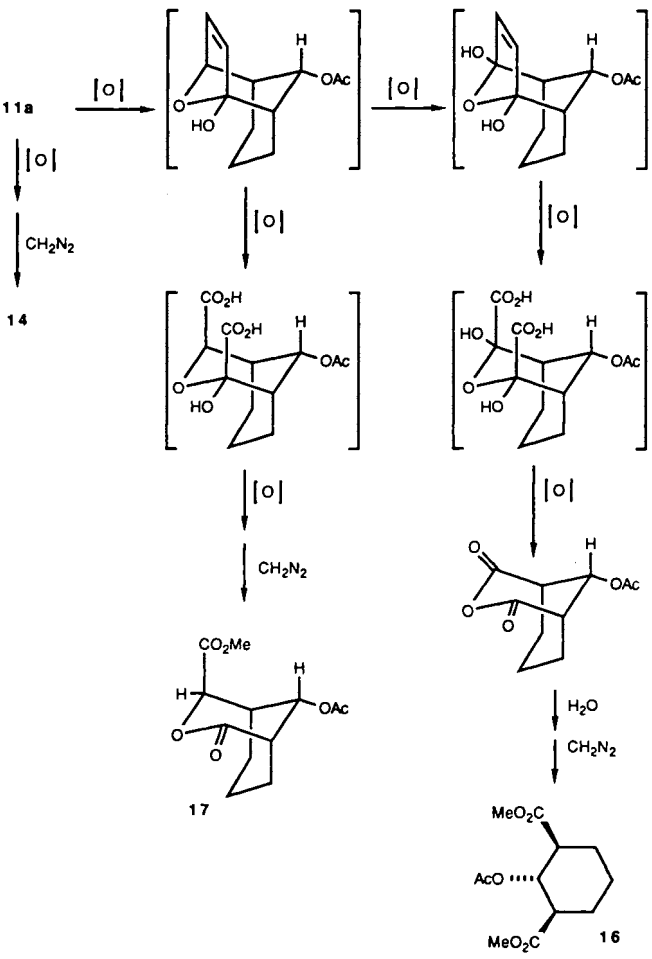
data of the minor component (**15**) were obtained from the spectra of mixtures with **13**, which together with its mass spectrum obtained by using the GLC/MS technique allowed the characterization. These spectra (see Experimental) are fully in accord with the proposed structure for **15**, which is also supported by mechanistic considerations (Scheme 2).

Scheme 2



Similarly, ester **11a** gave, in low yield, a complex mixture that was partially resolved by column chromatography (Scheme 3). A fraction containing nearly pure **16** was isolated, purified by crystallization from 2-propanol, and fully characterized by its spectral data (see Experimental), and elemental analysis. Although the molecular ion was not observed in the mass spectrum of **16**, the principal ions show *m/z* values easy to correlate with **16**. Its 50-MHz ^{13}C-NMR spectrum reveals the symmetry of the compound, i.e., the relative *cis* position of the methoxycarbonyl groups. The 200-MHz ^{1}H-NMR spectrum of **16** clearly shows its (*r*-1,*t*-2,*c*-3) relative configuration and its preferred *chair* conformation with *equatorial* acetoxy and methoxycarbonyl substituents. The value of $J_{1(3)\text{-H},2\text{-H}} = 10.6$ Hz is significant in this respect. The configuration of C-2 in **16** confirms the assigned *anti* configuration of alcohol **11**.

Scheme 3



Another fraction seemed to contain mainly (^{1}H-NMR and ^{13}C-NMR spectra) a compound for which we propose structure **17** on the basis of spectral data (see Experimental) and on mechanistic grounds (Scheme 3).

GLC/MS showed that this fraction contained other minor components, among them probably ester **14**. The formation of **15** from **10a** and of **16** and **17** from **11a** under these reaction conditions ($KMnO_4$ oxidation/diazomethane esterification) may be explained by competitive oxidation of the tertiary C-2(5) carbon atoms, probably through a radical mechanism (Schemes 2 and 3). This competitive oxidation must be favoured by the presence of an oxygen adjacent to C-2 and C-5 (oxatricyclic derivatives **3**, **4**, and **11a**) and by the sp^3 hybridization of C-10(9) making the carbon–carbon double bond oxidation (tricyclic esters **9a**, **9b**, **10a**, and **11a**) more difficult. Also, this competitive bridgehead oxidation seems to be comparatively favoured in the case of tricyclo-[4.2.1.1^{2,5}]decane derivatives (**2**, **4**, and **10a**).

The ^{1}H-NMR and ^{13}C-NMR data of the bicyclic compounds prepared in this work have been collected in Tables 3 and 4, respectively. Assignment of the ^{1}H-NMR spectra has been carried out as described above.

In connection with the conformational analysis of these compounds we carried out molecular mechanics calculations (MM2 program)[37] on compounds **5a**, **6**, **7**, **8**, **12b**, and **13** in order to obtain for each compound the relative energies, populations, and significant dihedral angles for the different conformers, taking into account not only the conformation of the bicyclic system but also the different situations obtained by rotation around the C-2–COOMe and C-4–COOMe bonds. In all cases, the preferred *syn*-coplanar conformation for the methoxycarbonyl groups[38] was assumed, and in the case of bicylo[3.3.1]nonane derivatives only the most populated *chair-chair* and *boat-chair* conformations [bis(methoxycarbonyl)-substituted cyclohexane ring in *boat* conformation] were considered.

Moreover, by using Altona's equation[39] we calculated for each conformer of a given compound the value of significant *vicinal* coupling constants. By combining the relative population of the different *chair-chair*, *boat-chair*, and *chair-chair* plus *boat-chair* conformers (*chair*, *boat*, and *chair* plus *boat*, respectively, in the case of bicyclo[3.2.1]octane and 3-oxabicyclo[3.2.1]octane derivatives) with the corresponding calculated coupling constant values, we obtained for each compound significant average coupling constants. Table 5

Table 3. ^{1}H-NMR data of bicyclo[3.3.1]nonane, bicyclo[3.2.1]octane, 3-oxabicyclo[3.3.1]nonane, and 3-oxabicyclo[3.2.1]octane derivatives[a]. The chemical shift is given only for the lowest numbered proton among equivalent ones. Italic values can be interchanged. Absolute values for coupling constants are given

	Compound									
	5	**5a**	**7**	**12**	**12a**	**12b**	**12c**	**6**	**8**	**13**
δ(ppm)										
1-H	2.57	2.84	2.90	2.22	2.40	2.34	2.59	2.64	2.70	2.63
2-H	2.96	2.96	4.81	2.58	2.70	2.60	2.74	2.96	4.67	2.60
exo-3-H	1.23	1.70		1.92	2.00	*2.05*	2.30	2.50		2.33
endo-3-H	2.17	2.38		1.92	2.00	*2.10*	2.30	2.32		1.85
6,8-H (6-H)[b]	1.4–2.0	1.6–2.2	1.6–2.7	1.2–2.0	1.3–2.1	1.5–2.0	1.4–2.2	1.7–2.1	2.0–2.2	1.4–2.1
9-H (8-H)[b]				4.89	5.19	5.00	5.35			5.16
CO_2H	12.46			12.24	–					
CO_2CH_3		3.70	3.73			3.63	3.72	3.69	3.76	3.72
CH_3CO_2				2.02		2.00				2.01
$C_6H_5CO_2$					7.50		7.50			
					8.02		8.06			
J[Hz]										
1-H,2-H	4.3	3.5	0.8	2.4	–	2.7	2.3	3.6	2.5	
1-H,*exo*-3-H								0.8		
1-H,4-H			0.8							
1-H,9-H (1-H,8-H)[b]				4.0	4.2	3.5	4.0			
2-H,*exo*-3-H	13.0	11.8		8.0	7.5	8.0	7.5	1.6		1.3
2-H,*endo*-3-H	4.3	4.9		8.0	7.5	8.0	7.5	7.3		7.5
exo-3-H,*endo*-3-H	13.0	14.2		–	–	14.2	–	15.3		15.0
ortho-H,*meta*-H					8.2		8.4			

[a] The spectra have been taken at 200 MHz in $CDCl_3$ (esters **5a**, **6**, **7**, **8**, **12b**, **12c**, and **13**) or [D_6]DMSO (acids **5**, **12**, and **12a**) solution at 25°C. – [b] Corresponding number for bicyclo[3.2.1]octane and 3-oxabicyclo[3.2.1]octane derivatives in parentheses.

Table 4. ^{13}C-NMR data of bicyclo[3.3.1]nonane, bicyclo[3.2.1]octane, 3-oxabicyclo[3.3.1]nonane, and 3-oxabicyclo[3.2.1]octane derivatives[a]. The chemical shift is given only for the lowest numbered carbon atom among equivalent ones

Compound	C-1	C-2	C-3	C-6	C-7	C-9 (C-8)[b]	CO_2H (CO_2Me)	CO_2CH_3	CH_3CO_2	CH_3CO_2	$PhCO_2$
5	47.3	43.8	27.0	35.0	15.9	215.7	175.2				
5a	47.4	44.8	26.6	35.1	16.5	215.2	173.7	52.3			
7	48.3	81.4		36.0	19.4	209.5	170.0	52.3			
12	31.7	42.9	23.7	25.2	16.3	68.6	176.3		21.2	169.6	
12a[c]	31.7	43.1	23.8	25.5	16.5	69.6	176.2				164.9
12b	31.8	43.8	23.9	25.2	16.9	68.7	175.1	51.9	21.2	169.8	
12c[d]	32.1	43.9	24.0	25.6	17.1	69.4	175.2	52.1			165.5
6	43.8	50.3	21.5	21.7		213.3	172.9	51.9			
8	45.7	85.1		21.1		208.3	169.6	52.3			
13	40.8	45.8	20.7	26.2		78.1	174.3	51.8	21.3	170.1	

[a] The spectra have been taken at 50 MHz in $CDCl_3$ (esters **5a**, **6**, **7**, **8**, **12b**, **12c**, and **13**) or [D_6]DMSO (acids **5**, **12**, and **12a**) solution at 25°C. – [b] Corresponding number for bicyclo[3.2.1]octane and 3-oxabicyclo[3.2.1]octane derivatives in parentheses. – [c] C-*ipso*: 130.2, C-*ortho*: 129.3, C-*meta*: 129.0, C-*para*: 133.4. – [d] C-*ipso*: 130.6, C-*ortho*: 129.6, C-*meta*: 128.5, C-*para*: 132.9.

collects the global percentage of the *chair* and *boat* conformers [relative to the bis(methoxycarbonyl)-substituted cyclohexane or oxane ring] together with the coupling constant values calculated for an average among *chair*, *boat*, and *chair* plus *boat* conformers, and the corresponding experimental values for compounds **5a**, **6**, **7**, **8**, **12b**, and **13**.

Calculations show that the bicyclic skeleton of the *chair-chair* conformers of **5a** is slightly twisted but substantially flattened, especially the substituted cyclohexane ring. However, in the *boat-chair* conformers, the bicyclic skeleton is essentially untwisted, and only the unsubstituted cyclohexane ring is slightly flattened. As can be seen from Table 5, calculations predict a 15.5% global population for the *chair-chair* conformers of **5a** and 84.5% for the *boat-chair* ones (Figure 2). The experimental coupling constants $J_{1\text{-H},2\text{-H}}$, $J_{2\text{-H},exo\text{-3-H}}$, and $J_{2\text{-H},endo\text{-3-H}}$ show values closer to those calculated for the average of *boat-chair* conformers than for the average of *chair-chair* ones. In fact, the agreement between the experimental values and those calculated for the average of *boat-chair* plus *chair-chair* conformers is better.

Table 5. Global percentage of *chair* (C) and *boat* (B) conformers and coupling constant values [Hz] (calculated for an average among *chair*, *boat*, and *chair* plus *boat* conformers and experimental) for the bicyclic compounds **5a**, **6**, **7**, **8**, **12b**, and **13**

	Compound					
	5a	**6**	**7**	**8**	**12b**	**13**
%						
C[a]	15.5	99.5	99.3	99.9	44.5	99.9
B[a]	84.5	0.5	0.7	0.1	55.5	0.1
J(1-H,2-H)						
C	0.82	2.38	0.64	1.66	0.91	2.40
B	4.18	1.76	4.67	2.30	3.43	1.20
C + B	3.66	2.38	0.67	1.66	2.31	2.40
Exp.[b]	3.5	3.6	0.8	2.5	2.7	2.3
J(2-H,*exo*-3-H)						
C	1.08	1.16			1.05	1.06
B	12.31	11.84			12.10	11.38
C + B	10.57	1.21			7.19	1.08
Exp.[b]	11.8	1.6			7.5	1.3
J(2-H,*endo*-3-H)						
C	6.72	6.35			6.91	6.73
B	3.65	4.91			4.42	5.78
C + B	4.13	6.34			5.53	6.72
Exp.[b]	4.9	7.3			7.5	7.5

[a] *Chair* (C) and *boat* (B) refer to the conformation of the bis(methoxycarbonyl)-substituted cyclohexane or oxane ring, thus meaning *chair-chair* and *boat-chair*, respectively, in the case of bicyclo[3.3.1]nonane and 3-oxabicyclo[3.3.1]nonane derivatives. — [b] For other experimental (Exp.) ^{1}H-NMR data, see Table 3.

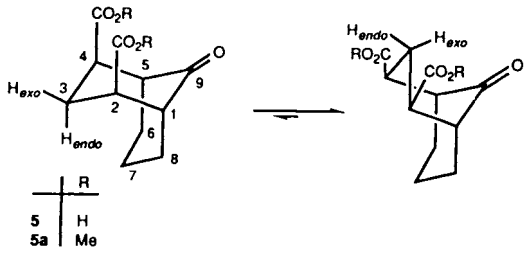


Figure 2. *Chair-chair* and *boat-chair* conformations of *exo*-2,*exo*-4-dicarboxylic acid **5** and its dimethyl ester **5a**

Especially significant is $J_{2\text{-H},exo\text{-3-H}}$, since the calculated values for the average of *boat-chair* and *chair-chair* conformers are very different (1.08 and 12.31 Hz, respectively).

If we assume that the calculated coupling constants for diacid **5** and ester **5a** are similar, it is worthy to note that the experimental values $J_{1\text{-H},2\text{-H}}$ = 4.3 Hz and $J_{2\text{-H},exo\text{-3-H}}$ = 13.0 Hz for diacid **5** (Table 3) are indicative of its nearly exclusive existence as *boat-chair* conformers. This fact must be related to the solvation of the carboxylic groups in [D$_6$]DMSO that must increase their steric effects, thus favouring the *boat-chair* conformers in which both carboxyl groups are farther away.

Also, we had observed[15] that *exo*-3-H of diacid **5** shows a resonance at very high field (δ = 1.23) due to the proximity of this proton to the ketone function in the *boat-chair* conformers. The chemical shift for this proton of **5a** (δ = 1.70) is indicative of a lower population of the *boat-chair* conformers in this case.

The ^{13}C-NMR spectra of ester **5a** and diacid **5** are also in accord with the above conclusion. Peters et al.[40] have calculated the average values for the chemical shifts of the different carbon atoms of bicyclo[3.3.1]nonan-9-one in *chair-chair*, *boat-chair*, and *twist boat-boat* conformations. Since the introduction of methoxycarbonyl substituents at C-2 and C-4 must not affect essentially the chemical shift of C-7 (small δ effect), the expected $\delta_{C\text{-}7}$ value will be around 21.0 ppm in *chair-chair*-**5a** and around 15.7 ppm in *boat-chair*-**5a**. The experimental value (δ = 16.5) might correspond to a rapid equilibrium among *boat-chair* (84.5%) and *chair-chair* (15.5%) conformers, in accord with calculations and ^{1}H-NMR data. Moreover, $\delta_{C\text{-}7}$ in diacid **5** (δ = 15.7) is concordant with its nearly exclusive existence as *boat-chair* conformers in [D$_6$]DMSO.

In the case of diester **6**, calculations predict a clear preference of the *chair* conformers, and a good agreement between significant experimental and calculated *vicinal* coupling constant values is observed. Also, a W coupling constant between 1(5)-H and *exo*-3-H is observed in this case ($J_{1(5)\text{-H},exo\text{-3-H}}$ = 0.8 Hz). This type of coupling is only possible in the *chair* conformation of the bicyclic system of **6**. It had been observed in *exo*-2,*exo*-4-dimethoxybicyclo[3.3.1]nonan-9-one[13] that exists mainly as *chair-chair* conformers but it is not observed in the cases of **5** and **5a**. Also indicative of the nearly exclusive existence of ester **6** as *chair* conformers, is the chemical shift of *exo*-3-H (δ = 2.50), since it is not shifted upfield by the ketone function as it is the case in **5** and **5a**.

Thus, the ^{1}H-NMR data of **6** are fully concordant with calculations, confirming the high preference of the *chair* conformers. The ^{13}C-NMR data of diester **6** (Table 4) are difficult to correlate with its conformation due to the absence of average values for the unsubstituted *boat*-bicyclo[3.2.1]-octan-8-one and for the effect of *exo*-2-methoxycarbonyl substituents.

For diester **7**, calculations predict a clear preference of the *chair-chair* conformers. In this case, we have only one significant coupling constant, $J_{1\text{-H},2\text{-H}}$, whose experimental value (0.8 Hz) is much closer to the calculated average value for the *chair-chair* conformers (0.64 Hz) than that for the *boat-chair* ones (4.67 Hz), in accord with the calculated preference of the *chair-chair* conformers of **7**.

A coupling constant $J_{1\text{-H},4\text{-H}}$ = 0.8 Hz is observed also in the ^{1}H-NMR spectrum of ester **7**. This type of coupling through five bonds has been observed in related systems[41] and implies an *equatorial* arrangement of the 1-H and 4-H protons and, consequently, a *chair-chair* conformation for the bicyclic skeleton of **7**.

By combining the average chemical shifts calculated by Peters et al. for the different carbon atoms of 3-oxabicyclo-[3.3.1]nonane[17] in *chair-chair* and *boat-chair* conformation (cyclohexane ring in *boat* conformation) with those for the bicyclo[3.3.1]nonane and bicyclo[3.3.1]nonan-9-one[40] in *chair-chair*, *boat-chair*, and *twist boat-boat* conformations, and assuming that the introduction of *exo*-2 substituents does not affect the chemical shift of C-7 (null δ effect), we estimated for diester **7** values of $\delta_{C\text{-}7}$ = 20.7 and 15.4 for the

average of *chair-chair* and *boat-chair* conformers, respectively. The experimental value ($\delta_{C\text{-}7}$ = 19.4) is also indicative of the existence of **7** preferentially as *chair-chair* conformers in $CDCl_3$ solution.

For diester **8**, calculations predict a high preference of the *chair* conformers. However, in this case, the experimental and calculated values for $J_{1\text{-}H,2\text{-}H}$ are not conclusive.

The ^{13}C-NMR data of **8** are also not very significant in connection with its conformation. However, a comparison of the ^{13}C-NMR spectra of the pairs of compounds ketone **2**/diester **6** and ketone **4**/diester **8** show a similar trend for the resonance lines of corresponding carbon atoms in passing from ketone **2** to diester **6** and from ketone **4** to diester **8**, what might be indicative of the same preferred conformation of diesters **6** and **8**, i.e., preference of the *chair* conformers of **8**.

For diester **12b**, calculations predict a 44.5% global population for the *chair-chair* conformers and 55.5% for the *boat-chair* ones. A good agreement is found among the experimental $J_{1\text{-}H,2\text{-}H}$ and $J_{2\text{-}H,exo\text{-}3\text{-}H}$ coupling constants and the corresponding values calculated for the average among *chair-chair* plus *boat-chair* conformers. The experimental value for $J_{2\text{-}H,endo\text{-}3\text{-}H}$ (7.5 Hz) is larger than that calculated for an average among *chair-chair* plus *boat-chair* conformers (5.53 Hz). However, in general, we have observed that the calculated *vicinal* coupling constants are underestimated when the carbon atoms bearing the protons under consideration also bear carbonyl substituents.

Similar experimental values for these coupling constants have been observed in the case of ester **12c** and diacids **12** and **12a** (Table 3), which is indicative of an important population of both *chair-chair* and *boat-chair* conformers in the conformational equilibria of these compounds in solution ($CDCl_3$ or [D_6]DMSO).

The ^{13}C-NMR data of ester **12b** (Table 4) is also indicative of the preference of the *boat-chair* conformers in $CDCl_3$ solution. By using the average values calculated by Peters et al.[40] for the chemical shifts of the different carbon atoms of bicyclo[3.3.1]nonane in *chair-chair*, *boat-chair*, and *twist boat-boat* conformations, we estimated roughly the chemical shift for C-7 in *chair-chair*-**12b** and *boat-chair*-**12b** [bis-(methoxycarbonyl)-substituted ring in *boat* conformation] to be ca. 22.3 and 16.4 ppm, respectively. As in the case of ester **5a**, a null δ effect of the C-2(4) methoxycarbonyl substituents was assumed, and the δ effect of the *anti*-9-acetoxy substituent on C-7 was considered to be equivalent to the δ effect of an *axial*-acetoxy substituent in a cyclohexane ring[42]. The experimental value of $\delta_{C\text{-}7}$ in **12b** (16.9 ppm) suggests a preference of the *boat-chair* conformers, in accord with calculations; in this case it is difficult to obtain an accurate estimate of the conformational population due to the approximate character of the calculated values.

A similar situation is found in ester **12c** ($\delta_{C\text{-}7}$ = 17.1). Worthy to note is the upfield chemical shift of C-7 in diacids **12** ($\delta_{C\text{-}7}$ = 16.3) and **12a** ($\delta_{C\text{-}7}$ = 16.5), what might suggest a greater population of the *boat-chair* conformers in the equilibria of these acids in [D_6]DMSO solution with respect to the corresponding esters, as it was observed for diacid **5** as compared with ester **5a**. Solvation of the carboxylic groups by [D_6]DMSO might be responsible for these changes in the population of conformers, as it was pointed out for diacid **5**.

For ester **13**, calculations predict a very high preference of the *chair* conformers, and a good agreement between significant experimental and calculated coupling constant values is observed.

The ^{13}C-NMR data of ester **13** (Table 4) are difficult to correlate with its conformation due to the absence of average values for the chemical shift of the different carbon atoms of the unsubstituted *boat*-bicyclo[3.2.1]octane and for the effect of *exo*-2-methoxycarbonyl substituents, as it was the case for diester **6**.

An equilibrium such as that found for **5a** must be clearly dependent on the temperature. An increase in the temperature must tend to equalize the population of the different conformers, i.e., in this case, to shift the equilibrium towards the *chair-chair* conformers. Combined molecular mechanics calculations and Altona's equation gave us the coupling constant values ($J_{1\text{-}H,2\text{-}H}$, $J_{2\text{-}H,exo\text{-}3\text{-}H}$, and $J_{2\text{-}H,endo\text{-}3\text{-}H}$) for an average of *chair-chair* plus *boat-chair* conformers of **5a** at dif-

Table 6. Experimental 200-MHz ^{1}H-NMR chemical shifts and coupling constants [Hz] of ester **5a** in $C_6D_5NO_2$ at different temperatures. Calculated *vicinal* coupling constants values for an average among *chair-chair* plus *boat-chair* conformers of **5a** are shown in parentheses under the corresponding experimental values. Absolute values for the coupling constants are given

	Temperature [°C]					
	21	39.5	59	79	99	119
δ(1-H)	2.95	2.93	2.92	2.90	2.88	2.87
δ(2-H)	3.06	3.05	3.04	3.03	3.02	3.02
δ(*endo*-3-H)	2.41	2.40	2.40	2.39	2.39	2.39
δ(*exo*-3-H)	1.74	1.75	1.75	1.75	1.76	1.76
δ(OCH_3)	3.71	3.70	3.69	3.69	3.68	3.67
J(2-H,*exo*-3-H)	11.79	11.68	11.66	11.56	11.48	11.38
	(10.57)	(10.41)	(10.22)	(10.04)	(9.87)	(9.71)
J(2-H,*endo*-3-H)	4.84	4.85	4.90	4.96	4.97	4.98
	(4.13)	(4.17)	(4.22)	(4.28)	(4.32)	(4.37)
J(*exo*-3-H,*endo*-3-H)	13.97	13.98	14.05	14.08	14.10	14.11
J(1-H,2-H)	3.52	3.62	3.55	3.55	3.52	–
	(3.66)	(3.62)	(3.56)	(3.51)	(3.46)	(3.41)

ferent temperatures (values in parentheses of Table 6). It can be seen that as the temperature increases a diminuation of $J_{1\text{-H},2\text{-H}}$ and specially of $J_{2\text{-H},exo\text{-3-H}}$ and an increase of $J_{2\text{-H},endo\text{-3-H}}$ is calculated, in accord with the expected higher population of the *chair-chair* conformers. Significant ^{1}H-NMR data of ester **5a** in $C_6D_5NO_2$, at different temperatures, have been collected also in Table 6.

From these data it is clear that the value of $J_{2\text{-H},exo\text{-3-H}}$ diminishes while the value of $J_{2\text{-H},endo\text{-3-H}}$ increases with increasing temperature. The value of $J_{1\text{-H},2\text{-H}}$ does not seem to be essentially affected. Also significant is the fact that the value $\delta_{exo\text{-3-H}}$ increases (although only by 0.02 ppm) while the values of $\delta_{1\text{-H}}$, $\delta_{2\text{-H}}$, and $\delta_{endo\text{-3-H}}$, all diminish (by 0.08, 0.04, and 0.02 ppm, respectively) in passing from 21 to 119°C. All these facts can be easily correlated with an increase in the population of the *chair-chair* conformers of **5a**.

The 200-MHz ^{1}H-NMR spectra of esters **6**, **7**, **8**, and **12b** in $C_6D_5NO_2$ do not show significant chemical shift or coupling constant changes in passing from 21 to 119°C that could be associated with a modification of the conformational population. This was to be expected for esters **6**, **7**, and **8** due to the great preference of the *chair-chair* (or *chair*) conformers and also for ester **12b** where the population of the *chair-chair* and *boat-chair* conformers is very similar.

Conclusion

In general, good agreement between experimental and calculated average *vicinal* proton/proton coupling constant values has been observed for the compounds studied in this work. The *exo*-2,*exo*-4-bis(methoxycarbonyl) derivatives of 3-oxabicyclo[3.3.1]nonane (diester **7**), bicyclo[3.2.1]octane (esters **6** and **13**), and 3-oxabicyclo[3.2.1]octane (diester **8**), all seem to exist preferentially as *chair-chair* or *chair* conformers, while the corresponding derivatives of bicyclo-[3.3.1]nonane (esters **5a**, **12b**, and **12c**) and the related dicarboxylic acids (**5**, **12**, and **12a**, respectively) seem to exist more or less preferentially as *boat-chair* conformers. The absence of the *endo*-3-H/*endo*-7-H interaction in those cases, present in the bicyclo[3.3.1]nonane derivatives, must stabilize the conformers in which the bis(methoxycarbonyl)-substituted cyclohexane or oxane ring has *chair* conformation. Also, as expected, the sp^2 hybridization of C-9 in **5** and **5a** stabilizes the *boat-chair* conformers versus the *chair-chair* ones as compared with **12**, **12a**, **12b**, and **12c** where C-9 presents an sp^3 hybridization.

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Experimental

IR: Perkin-Elmer 843 or 1310 spectrometers. – 200-MHz ^{1}H NMR and 50-MHz ^{13}C NMR: Varian XL 200 spectrometer, internal TMS (δ scale). – GLC: Perkin-Elmer model Sigma 3B chromatograph. – GLC/MS: Hewlett-Packard model 5988A spectrometer connected to a Hewlett-Packard model 5890 chromatograph, 12.5 m × 0.2 mm cross-linked methylsilicone column. – HPLC: Waters HPLC chromatograph, model 6000A. – Column chromatography: Merck 60 (0.063–0.200 mm) silica gel. – Melting points, uncorrected: Kofler hot-stage. – Microanalyses: Microanalysis Service of the Centro de Investigación y Desarrollo, C.S.I.C., Barcelona, Spain. – Calculations were carried out on a VAX-8800 computer at the Computing Center of the Universidad Autónoma, Barcelona, Spain.

Starting Compounds: Ketones **1**[28,29], **2**[30,31], **3**[32], and **4**[31,32] were obtained by published methods.

Typical Procedure for the Aluminum Triisopropoxide Reduction of Ketones **1**, **2**, *and* **3**: A mixture of the ketone (25 mmol), aluminum triisopropoxide (12.24 g, 60 mmol), and 200 ml of anhydrous xylene was heated to reflux in a moisture-free atmosphere. A few drops of acetone was added and heating to reflux continued for 12 h. Aqueous NaOH (100 ml, 10%) was added and the mixture stirred for 30 min. The organic phase was separated and the aqueous one extracted with xylene (100 ml). The combined organic phases were dried (anhydrous $MgSO_4$), and the solvent was evaporated under reduced pressure (10 Torr) to give the crude product that was crystallized from hexane.

anti-Tricyclo[4.3.1.1^{2,5}]undec-3-en-anti-10-ol (**9**): 89% yield, m.p. 112–114°C. – IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (m), 3220 (m).

$C_{11}H_{16}O$ (164.25) Calcd. C 80.44 H 9.82
Found C 80.48 H 10.04

anti-Tricyclo[4.2.1.1^{2,5}]dec-3-en-anti-9-ol (**10**): 80% yield, m.p. 89–92°C (ref.[33] 149–150°C).

$C_{10}H_{14}O$ (150.22) Calcd. C 79.96 H 9.39
Found C 79.78 H 9.51

anti-11-Oxatricyclo[4.3.1.1^{2,5}]undec-3-en-anti-10-ol (**11**): 89% yield, m.p. 97–99°C. – IR (KBr): $\tilde{\nu}$ = 3460 cm^{-1} (s).

$C_{10}H_{14}O_2$ (166.22) Calcd. C 72.26 H 8.49
Found C 72.38 H 8.39

Typical Procedure for the Acetylation of Alcohols **9**, **10**, *and* **11**: A mixture of the alcohol (20 mmol), acetic anhydride (50 ml), and pyridine (2 ml) was stirred at room temp. for 24 h. The excess acetic anhydride and the volatile materials were evaporated under reduced pressure (30 Torr). CH_2Cl_2 (50 ml) and aqueous $NaHCO_3$ (200 ml, 3%) were added to the residue, and, after stirring for 15 min, the organic phase was separated and the aqueous one extracted with CH_2Cl_2 (25 ml). The combined organic phases were dried (anhydrous $MgSO_4$) and the solvent evaporated at reduced pressure (30 Torr) to give the crude product that was crystallized from 2-propanol or chromatographed on silica gel.

anti-Tricyclo[4.3.1.1^{2,5}]undec-3-en-anti-10-yl Acetate (**9a**): 77% yield of product chromatographed on silica gel (mixtures of hexane/ether as eluent), m.p. near 20°C. – IR (CCl_4): $\tilde{\nu}$ = 1725 cm^{-1} (s).

$C_{13}H_{18}O_2$ (206.29) Calcd. C 75.69 H 8.80
Found C 75.52 H 8.72

anti-Tricyclo[4.2.1.1^{2,5}]dec-3-en-anti-9-yl Acetate[33] (**10a**): 79% yield of product chromatographed on silica gel (mixtures of hexane/ether as eluent), colorless liquid.

$C_{12}H_{16}O_2$ (192.26) Calcd. C 74.97 H 8.39
Found C 74.78 H 8.72

anti-11-Oxatricyclo[4.3.1.1^{2,5}]undec-3-en-anti-10-yl Acetate (**11a**): 89% yield, m.p. 89–91°C (2-propanol). – IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1} (s).

$C_{12}H_{16}O_3$ (208.26) Calcd. C 69.21 H 7.74
Found C 68.73 H 7.96

anti-Tricyclo[4.3.1.1^{2,5}]undec-3-en-anti-10-yl Benzoate (**9b**): Benzoyl chloride (7.00 g, 49.8 mmol) was added to a stirred solution of alcohol **9** (4.92 g, 30.0 mmol) in anhydrous pyridine (25 ml) at room

temp. After stirring for 24 h, CH_2Cl_2 (50 ml) was added and the solution washed with aqueous HCl (3 × 100 ml, 5%) and water (100 ml). The organic phase was dried (anhydrous Na_2SO_4) and the solvent removed under reduced pressure (30 Torr) to give a crude product that was crystallized from 2-propanol (25 ml); 5.96 g, (74% yield), colorless prismatic crystals, m.p. 82–84°C. – IR (KBr): ν = 1710 cm^{-1} (s).

$C_{18}H_{20}O_2$ (268.36) Calcd. C 80.56 H 7.51
Found C 80.69 H 7.48

Typical Procedure for the Oxidation of Ketones **1**, **2**, **3**, *and* **4**, *and Esters* **9a** *and* **9b**: A solution of the compound to be oxidized (50.0 mmol) and tetrabutylammonium bromide (618 mg, 1.9 mmol) in benzene (200 ml) was slowly added (60 min) to a stirred solution of $KMnO_4$ (40 g, 253.0 mmol) in water (400 ml) keeping the temp. of the reaction mixture at 5°C. After stirring for 12 h at room temp., the mixture was filtered and the residue washed with water (200 ml). The combined filtrate and washing was treated with $NaHSO_3$ (10 g) and acidified to pH = 2 with concd. HCl (20 ml). The organic phase was separated and the aqueous one concentrated at reduced pressure (30 Torr) to a final volume of about 200 ml.

Workup Procedure (a): The diacid was crystallized from this solution.

Workup Procedure (b): The aqueous solution of the diacid was extracted with ether (5 × 250 ml), and the combined ether extracts were dried with anhydrous $MgSO_4$. Evaporation of the solvent gave the diacid that was crystallized from 2-propanol.

Workup Procedure (c): The dried ethereal solution of the diacid was treated with excess of an ethereal solution of diazomethane (no more nitrogen evolution). Evaporation of the volatile materials yielded the crude ester that was crystallized from the appropriate solvent.

Typical Procedure for the Esterification of Diacids **5**, **12**, *and* **12a** *with an Ethereal Solution of Diazomethane:* An ethereal solution of diazomethane was added to a solution of the diacid (10 mmol) in ether (50 ml) at 0°C until no more nitrogen evolution was observed. Evaporation of the volatile materials gave the crude ester which was crystallized from the appropriate solvent.

9-Oxobicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylic Acid[15] (**5**): Workup procedure (a), 95% yield, m.p. 220–222°C (H_2O) (ref.[15] 209–211°C). – IR (KBr): $\tilde{\nu}$ = 3600–2300 cm^{-1} (s), 1720 (s), 1700 (s).

$C_{11}H_{14}O_5$ (226.23) Calcd. C 58.40 H 6.24
Found C 58.42 H 6.07

Dimethyl 9-Oxobicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylate (**5a**): 91% yield from diacid **5**, m.p. 89–90°C (2-propanol). – IR (KBr): $\tilde{\nu}$ = 1730 cm^{-1} (s), 1710 (s).

$C_{13}H_{18}O_5$ (254.29) Calcd. C 61.41 H 7.14
Found C 61.49 H 7.38

Dimethyl 8-Oxobicyclo[3.2.1]octane-exo-2,exo-4-dicarboxylate (**6**): Workup procedure (c), 56% yield, m.p. 88–90°C [ether/hexane (5:2)]. – IR (KBr): $\tilde{\nu}$ = 1745 cm^{-1} (s), 1725 (s).

$C_{12}H_{16}O_5$ (240.26) Calcd. C 59.99 H 6.71
Found C 59.81 H 6.69

Dimethyl 9-Oxo-3-oxabicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylate (**7**): Workup procedure (c), 34% yield, m.p. 95–97°C (ether) (ref.[34] 93.6–94.6°C).

Dimethyl 8-Oxo-3-oxabicyclo[3.2.1]octane-exo-2,exo-4-dicarboxylate (**8**): Workup procedure (c), 26% yield, m.p. 87–89°C [ether/hexane (2:1)]. – IR (KBr): = 1750 cm^{-1} (s), 1730 (s).

$C_{11}H_{14}O_6$ (242.23) Calcd. C 54.54 H 5.83
Found C 54.41 H 5.79

anti-9-Acetoxybicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylic Acid (**12**): Workup procedure (b), 76% yield, m.p. 174–177°C (2-propanol). – IR (KBr): $\tilde{\nu}$ = 3600–2400 cm^{-1} (s), 1735 (s), 1700 (s).

$C_{13}H_{18}O_6$ (270.29) Calcd. C 57.77 H 6.71
Found C 57.56 H 6.74

Dimethyl anti-9-Acetoxybicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylate (**12b**): 96% yield from **12**, m.p. 80–81°C (2-propanol). – IR (KBr): $\tilde{\nu}$ = 1740 cm^{-1} (s), 1725 (s).

$C_{15}H_{22}O_6$ (298.34) Calcd. C 60.39 H 7.43
Found C 60.41 H 7.49

anti-9-Benzoyloxybicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylic Acid (**12a**): Workup procedure (b), 57% yield, m.p. 214–217°C (2-propanol). – IR (KBr): $\tilde{\nu}$ = 3600–2400 cm^{-1} (s), 1710 (s), 1700 (s).

$C_{18}H_{20}O_6$ (318.33) Calcd. C 65.05 H 6.07
Found C 65.01 H 5.92

Dimethyl anti-9-Benzoyloxybicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylate (**12c**): 93% yield from **12a**, m.p. 124–126°C (ether). – IR (KBr): $\tilde{\nu}$ = 1730 cm^{-1} (s), 1715 (s).

$C_{20}H_{24}O_6$ (360.41) Calcd. C 66.65 H 6.71
Found C 66.60 H 6.71

Oxidation of Acetate **10a**, *Isolation of Dimethyl anti-8-Acetoxybicyclo[3.2.1]octane-exo-2,exo-4-dicarboxylate* (**13**), *and Detection of Dimethyl t-2-Acetoxycyclopentane-r-1,c-3-dicarboxylate* (**15**): From acetate **10a** (4.82 g, 25.1 mmol), after workup procedure (c), 3.60 g of a mixture of **13** and **15** was obtained, relative area by GLC [2 m OV-1 column; 25 ml N_2/min; I and D 250°C, C 1 min at 70°C, 70–175°C (15°C/min), 7 min at 175°C; **13**: t_r = 13.47 min, **15**: t_r = 8.79 min], **13**:**15** = 2:1. Neither column chromatography nor semipreparative HPLC (30-cm μ-porasil semipreparative column, mixtures of hexane/ethyl acetate as eluent) led to separation of this mixture. The major component (**13**) crystallized on standing after several weeks. Filtration and recrystallization gave an analytical sample, m.p. 80–81°C (2-propanol). – IR ($CHCl_3$): ν = 1720 cm^{-1} (s). – MS (EI): *m/z* (%) = 253 (8) [M^+ – MeO], 224 (18) [M^+ – HCOOMe], 192 (6) [M^+ – HCOOMe – MeOH], 165 (22) [M^+ – HCOOMe – COOMe], 164 (100) [M^+ – 2HCOOMe], 150 (5), 133 (7), 124 (5), 123 (5), 106 (5), 105 (37) [M^+ – 2HCOOMe – CH_3COO], 104 (7), 100 (6), 95 (6), 93 (10), 91 (5), 79 (13), 77 (7), 67 (6), 59 (8), 55 (8), 43 (47, CH_3CO), 41 (5).

$C_{14}H_{20}O_6$ (284.31) Calcd. C 59.13 H 7.10
Found C 58.79 H 7.03

15: 200-MHz ^1H NMR ($CDCl_3$) (obtained from the spectrum of a mixture with **13**): δ = 2.0–2.1 [m, 4(5)-H], 2.05 (s, CH_3CO), 2.85 [m, 1(3)-H], 3.72 (s, OCH_3), 5.57 (t, *J* = 6.2 Hz, 2-H). On irradiation at δ = 2.85, the absorption at δ = 5.57 became a singlet. – 50-MHz ^{13}C NMR ($CDCl_3$) (obtained from the spectrum of a mixture with **13**): δ = 20.9 (CH_3, CH_3COO), 27.4 [CH_2, C-4(5)], 50.0 [CH, C-1(3)], 52.1 (CH_3, CH_3O), 79.5 (CH, C-2), 170.2 (C, CH_3COO), 173.5 (C, $COOCH_3$). – MS (EI): *m/z* (%) = 213 (1.5) [M^+ – MeO], 201 (8) [M^+ – CH_3CO], 184 (3) [M^+ – HCOOMe], 174 (16) [M^+ – CH_2CO – CO], 169 (6) [M^+ – CH_3CO – MeOH], 158 (7), 153 (31) [M^+ – HCOOMe – MeO], 152 (15), 142 (14), 116 (13), 114 (16), 110 (6), 93 (7), 87 (19), 68 (21), 59 (13), 55 (18), 43 (100) [CH_3CO^+].

Oxidation of Acetate **11a**, *Isolation of Dimethyl t-2-Acetoxycyclohexane-r-1,c-3-dicarboxylate* (**16**), *and Detection of Dimethyl anti-9-Acetoxy-3-oxabicyclo[3.3.1]nonane-exo-2,exo-4-dicarboxylate* (**14**) *and Methyl anti-9-Acetoxy-2-oxo-3-oxabicyclo[3.3.1]nonane-exo-4-carboxylate* (**17**): From acetate **11a** (4.16 g, 20.0 mmol), after workup procedure (c), 1.40 g of crude product was obtained. By column chromatography using mixtures of hexane/ether as eluent,

two fractions were separated, fraction A 150 mg of nearly pure **16** and fraction B 172 mg of a mixture of several components.

16: M. p. 60–61 °C (2-propanol). – IR ($CHCl_3$): $\tilde{\nu}$ = 1730 cm^{-1} (s). – 200-MHz ^1H NMR ($CDCl_3$): δ = 1.30 (tq, J = 3.6 Hz, J' = 12.8 Hz, 5-H_{ax}), 1.63 [dq, J = 3.4 Hz, J' = 12.8 Hz, 4(6)-H_{ax}], 1.84 (dquint, J = 12.8 Hz, J' = 3.4 Hz, 5-H_{eq}), 1.99 (s, CH_3CO), 2.0 [dm, J = 12.8 Hz, 4(6)-H_{eq}], 2.50 [ddd, J = 3.9 Hz, J' = 10.6 Hz, J'' = 12.8 Hz, 1(3)-H], 3.66 (s, CH_3O), 5.28 (t, J = 10.6 Hz, 2-H). – 50-MHz ^{13}C NMR ($CDCl_3$): δ = 20.7 (CH_3, CH_3COO), 23.7 (CH_2, C-5), 27.9 [CH_2, C-4(6)], 48.6 [CH, C-1(3)], 52.1 (CH_3, CH_3O), 72.6 (CH, C-2), 169.8 (C, CH_3COO), 173.1 (C, $COOCH_3$). – MS (EI): m/z (%) = 227 (1.4) [M^+ – MeO], 226 (0.5), 215 (10) [M^+ – MeCO], 198 (5) [M^+ – HCOOMe], 183 (6) [M^+ – MeCO – MeOH], 167 (18) [M^+ – HCOOMe – MeO], 166 (20), 156 (7) [M^+ – COOMe – MeCO], 138 (9) [M^+ – 2HCOOMe], 128 (6), 124 (6), 107 (6), 87 (11), 79 (20) [M^+ – 2HCOOMe – MeCOO], 68 (7), 59 (13), 55 (16), 43 (100) [$MeCO^+$], 41 (11).

$C_{12}H_{18}O_6$ (258.27) Calcd. C 55.79 H 7.04
Found C 55.79 H 7.14

Fraction B seemed to be mainly **17** by ^1H-NMR and ^{13}C-NMR spectroscopy. – IR ($CHCl_3$): $\tilde{\nu}$ = 1730 cm^{-1} (vs), 1720 (vs). – 200-MHz ^1H NMR ($CDCl_3$): δ = 1.6–2.2 (m, 6-H, 7-H, and 8-H), 2.12 (s, CH_3CO), 2.58 (br. s, 5-H), 3.08 (br. s, 1-H), 3.83 (s, CH_3O), 4.90 (br. s, 4-H), 5.15 (m, 9-H). On irradiation at δ = 5.15, the absorption at δ = 4.90 was transformed into a d (J = 1.6 Hz), and the absorptions at δ = 2.58 and 3.08 were affected. On irradiation at δ = 3.08, the absorption at δ = 4.90 became a d (J = 1.6 Hz), and the absorptions at δ = 2.58 and 5.15 were affected. On irradiation at δ = 2.58, the absorption at δ = 4.90 became an s, the absorption at δ = 3.08 became a q (J = 3.5 Hz), and the absorption at δ = 5.15 became a d (J = 4 Hz). – 50-MHz ^{13}C NMR ($CDCl_3$): δ = 18.6 (CH_2, C-7), 20.9 (CH_3, CH_3COO), 23.6 (CH_2, C-6 or C-8), 25.4 (CH_2, C-8 or C-6), 33.6 (CH, C-5), 41.4 (CH, C-1), 53.1 (CH_3, $COOCH_3$), 64.9 (CH, C-9), 80.0 (CH, C-4), 169.6 (C, COO), 169.9 (C, COO), 170.9 (C, COO).

GLC/MS analysis of fraction B [4 ml He/min; I 250 °C, C 100–250 °C (20 °C/min)] showed to contain several components, among them **17** and **14**.

17: t_r = 6.49 min. – MS (EI): m/z (%) = 197 (2) [M^+ – COOMe], 168 (3) [M^+ – HCOOMe – CO], 155 (19) [M^+ – COOMe – CH_2CO], 137 (11) [M^+ – COOMe – MeCOOH], 109 (7) [M^+ – COOMe – CO – MeCOOH], 108 (6), 81 (29), 80 (6), 79 (14), 69 (5), 67 (7), 61 (7), 59 (7), 57 (8), 55 (12), 53 (7), 45 (6), 44 (8), 43 (100), 42 (5), 41 (17).

14: t_r = 5.94 min. – MS (EI): m/z (%) = 257 (1) [M^+ – MeCO], 229 (9) [M^+ – MeCO – CO], 197 (8) [M^+ – MeCO – HCOOMe], 169 (42) [M^+ – MeCO – HCOOMe – CO], 168 (8), 140 (10), 137 (30) [M^+ – MeCO – 2HCOOMe], 136 (5), 109 (15) [M^+ – MeCO – 2HCOOMe – CO], 108 (12), 97 (5), 93 (5), 90 (5), 87 (5), 81 (39), 80 (11), 79 (21), 77 (5), 70 (5), 67 (10), 65 (5), 59 (15), 57 (8), 55 (23), 53 (8), 44 (11), 43 (100), 41 (14).

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1: 54585-23-8 / **2**: 66953-28-4 / **3**: 42768-72-9 / **4**: 84525-43-9 / **5**: 101558-81-0 / **5a**: 120853-95-4 / **6**: 120853-83-0 / **7**: 72550-53-9 / **8**: 120853-84-1 / / **9**: 120925-94-2 / **9a**: 120853-92-1 / **9b**: 120853-94-3 / **10**: 119478-28-3 / **10a**: 119478-29-4 / **11**: 120853-85-2 / **11a**: 120853-93-2 / **12**: 120853-86-3 / **12a**: 120854-00-4 / **12b**: 120853-99-8 / **12c**: 120854-01-5 / **13**: 120853-87-4 / **14**: 120853-88-5 / **15**: 120853-89-6 / **16**: 120853-90-9 / **17**: 120853-91-0 / 8-oxobicyclo[3.2.1]octane-*exo*-2,*exo*-4-dicarboxylic acid: 120853-96-5 / 9-oxo-3-oxabicyclo[3.3.1]nonane-*exo*-2,*exo*-4-dicarboxylic acid: 120853-97-6 / 8-oxo-3-oxabicyclo[3.2.1]octane-*exo*-2,*exo*-4-dicarboxylic acid: 120853-98-7

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