138. Tandem *Diels-Alder* Reactivity Controlled by Remote Substituents. Regioselective Synthesis of Linearly Annellated Six-Membered Ring Systems from (1*RS*,5*SR*,6*RS*,7*SR*)-6,7-Bis(chloromethyl)-8,9-dimethylidene-2-oxabicyclo[3.2.2]nonan-3-one. Crystal Structure of (1*RS*,5*RS*,6*SR*,11*RS*)-6,7-Bis(chloromethyl)-3-oxo-2-oxatricyclo[7.4.0.0^{1,5}]tridec-8-en-11-yl Methyl Ketone[1][2])

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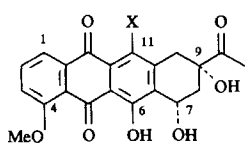
Syntheses of 6,7,8,9-tetramethylidene-2-oxabicyclo[3.2.2]nonan-3-one (**12**), 6,7,8,9-tetramethylidene-2-azatricyclo[3.2.2]nonan-3-one (**13**), and (1*RS*,5*SR*,6*RS*,7*SR*)-6,7-bis(chloromethyl)-8,9-dimethylidene-2-oxabicyclo-[3.2.2]nonan-3-one (**14**) are presented. The rate constants of the two successive *Diels-Alder* additions of a given dienophile to **12** and **13** were nearly the same. *Lewis*-acid-catalyzed *Diels-Alder* additions of methyl vinyl ketone to **14** gave adduct **39** with high regio- and stereoselectivity. *Lewis* acids isomerized **39** into (1*RS*,5*RS*,6*SR*,7*SR*,11*RS*)-6,7-bis(chloromethyl)-3-oxo-2-oxatricyclo[7.4.0.0^{1,5}]tridec-8-en-11-yl methyl ketone (**40**) whose structure was determined by single-crystal X-ray crystallography. Heating **39** with CsF/Cs_2CO_3 in DMF/HMPT gave (1*RS*,5*RS*,11*RS*)-6,7-dimethylidene-3-oxo-2-oxatricyclo[7.4.0.0^{1,5}]tridec-8-en-11-yl methyl ketone (**42**). The exocyclic butadiene moiety of triene **42** added to methyl propynoate and 2,3-didehydroanisole with good regioselectivity giving polysubstituted anthracenyl and naphthacenyl derivatives, respectively.

Introduction. – The anthracyclines constitute a group of natural antibiotics [2] certain members of which possess significant antineoplastic activity. Among these, daunorubicin [3] and 11-deoxydaunomycin [4] whose aglycone parts, daunomycinone (**1**) and 11-deoxydaunomycinone (**2**), respectively, are examples of polysubstituted linearly annellated six-membered ring systems. Total synthesis of **1** and **2** and related anthracyclinones have



1 X = OH
2 X = H

[1]) For a preliminary communication, see [1].

[2]) Part of the planned Ph. D. thesis of *Bernard Demarchi*, University of Lausanne.

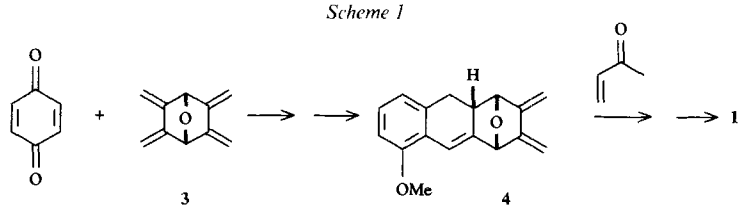
been the subject of intense study in the last twenty years [5], due to the lack of an efficient biosynthetic process [6], as well as a search for more active analogs with reduced cardiotoxicity [7].

In 1979, we proposed [8] a general, doubly convergent approach to the total synthesis of anthracyclinones based on the tandem *Diels-Alder* additions of 2,3,5,6-tetramethylidene-7-oxabicyclo[2.2.1]heptane (**3**), a compound readily obtained from the inexpensive furan and maleic anhydride [9]. The principle of our strategy rests upon the fact that the rate constant of the *Diels-Alder* addition of **3** to a first equiv. of a given dienophile is significantly larger than that of the reaction of the second equiv. of dienophile [10]. In order to control the regioselectivity of the two successive cycloadditions, a number of stratagems have been proposed *(Schemes 1–3)*. In our synthesis of daunomycinone (**1**) [11], the adduct resulting from the addition of benzoquinone to tetraene **3** was transformed selectively into the non-symmetrical triene **4**. Because of homoconjugative interactions between the exocyclic diene moiety and the styryl double bond [12], **4** added to methyl vinyl ketone with high stereo- and regioselectivity in the presence of $BF_3 \cdot Et_2O$ in CH_2Cl_2 *(Scheme 1)* [11].

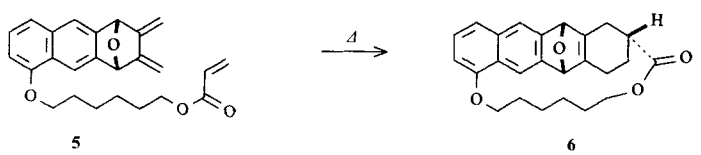
Another way to control the stereo- and regioselectivity of the addition of the second dienophile to a monoadduct of **3** was to link the two reagents by a spacer of appropriate length as illustrated with the thermal intramolecular *Diels-Alder* addition **5**→**6** *(Scheme 2)* [13].

A more general and more selective method was realized with the C_2 disubstituted tetraene **8** readily derived from **3** by addition of 2 equiv. of 2-nitrobenzenesulfenyl

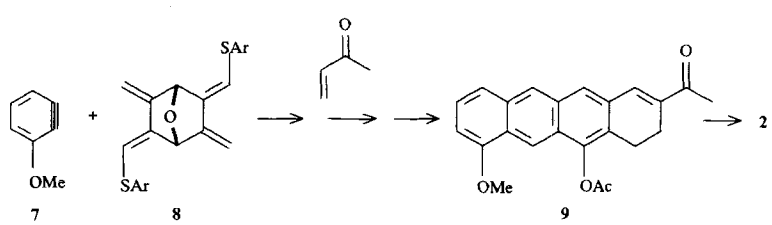
Scheme 1



Scheme 2

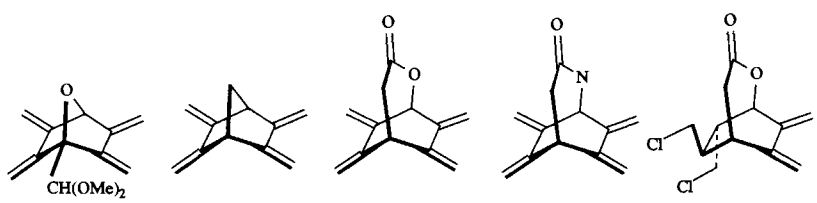


Scheme 3



chloride, followed by the double elimination of HCl [14]. Because of the electron-donating arenesulfenyl substituents, the tandem *Diels-Alder* additions of **8** were highly regioselective even in absence of strong *Lewis* acids. Using 2,3-didehydroanisole (**7**) as the first dienophile and methyl vinyl ketone as the second dienophile, a simple and short synthesis of 11-deoxydaunomycinone (**2**) was realized *(Scheme 3)* [15].

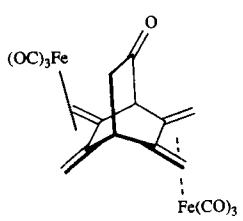
We have also reported that a dimethyl-acetal moiety substituting one of the bridgehead centres of tetraene **3**, as in **10**, can render the tandem *Diels-Alder* addition of the tetraene regio- and stereoselective [16]. The *Diels-Alder* reactivity of 2,3,5,6-tetramethylidenebicyclo[2.2.*n*]alkanes depends on the nature of the bridge. For instance, the 7-oxanorbornane derivative **3** reacts 170 times more slowly than 2,3,5,6-tetramethylidenebicyclo[2.2.1]heptane (**11**) towards ethylenetetracarbonitrile (TCNE) in toluene at 25° [10]. This was attributed to the inductive effect of the O(7) bridge which increases the ionization potential of **3** compared with that of **11** [17]. These two types of results suggested to us that a lactone or a lactam bridge as in **12** and **13**, respectively, could make the two successive cycloadditions of these exocyclic tetraenes regioselective and, thus, would make **12** and **13** potential starting materials for the preparation of polysubstituted, linearly-condensed six-membered ring systems, including unusual anthracyclinone ana-



10 **11** **12** **13** **14**

logs. We report here on the synthesis of 6,7,8,9-tetramethylidene-2-oxa- and -2-azabicyclo[3.2.2]nonan-3-ones (**12** and **13** resp.) and on their *Diels-Alder* reactivity. As we shall see, the rate constants of the two successive additions of a given dienophile to **12** and **13** were nearly the same, thus these tetraenes have only a limited synthetic potential. We have found, however, that the mono-diene **14** could be prepared readily from a precursor of **12**. Compound **14** was found to add to strong dienophiles with good regio- and stereoselectivity. Further transformations of the monoadducts gave useful synthetic intermediates for the preparation of polysubstituted anthracenyl and naphthacenyl derivatives.

Results and Discussion. – Our initial approach to the synthesis of lactone **12** and lactam **13** was to exploit the readily available dinuclear iron complex **15** of 5,6,7,8-tetramethylidenebicyclo[2.2.2]octan-2-one [18]. Unfortunately, all our attempts to induce a *Baeyer-Villiger* rearrangement [19] on **15** with a large variety of peracids under various conditions failed. This was attributed to the difficulty of quaternizing centre C(2) of **15** due to steric hindrance arising from the *syn*-$Fe(CO)_3$ moiety. This hypothesis was confirmed by the complete lack of reactivity of ketone **15** toward hydroxylamine. As expected, though, the monocomplex **16** [18] reacted with $NH_2OH \cdot HCl$ [20] and afforded the corresponding oxime **17** (74%). Unfortunately, our attempts to induce a *Beckmann*



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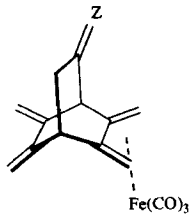
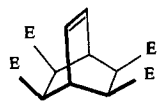


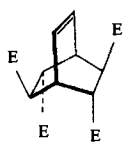
16 Z = O
17 Z = NHOH



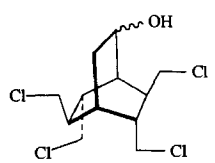
18 E = COOEt
18′ E = COOMe

rearrangement [21] of **17** failed too. In the presence of peracids, **16** gave mixtures of unstable compounds.

The tetraene complexes **15** and **16** were derived from tetraester **18** [18]. Base-induced isomerization of **18** in MeOH gave the all-*trans* derivative **19** as major product [22]. It was then transformed to alcohols **20** [18a] which were oxidized (CrO_3/pyridine, CH_2Cl_2, 0°) to the corresponding ketone **21** in 70% yield. Treatment with *O*-(mesitylenesulfonyl)-hydroxylamine in CH_2Cl_2 [23] afforded **22** in 85% yield (one unique stereoisomer). Heating in boiling EtOH (2 h) led to the product of *Beckmann* rearrangement **23** (69%). The same lactam **23** was obtained in a lower overall yield (18%), by first generating the oxime **24** (67%) from ketone **21**, followed by esterification with TsCl in pyridine to give **25** (37%), and heating of **25** in EtOH (75°, 4 h). Quadruple elimination of HCl (THF, *t*-BuOK, 60°) from the tetrachloride **23** gave tetraene-lactam **13** in 73% yield. The



19 E = COOMe



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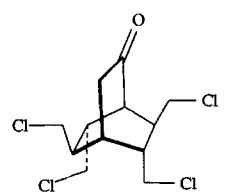

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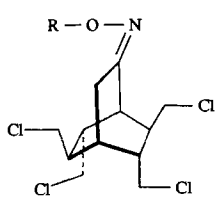
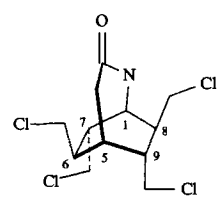


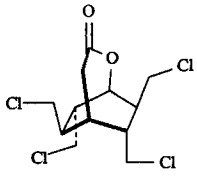
22 R = 2,4,6-$Me_3C_6H_2SO_2$
24 R = H
25 R = 4-$MeC_6H_4SO_2$



23

structure of **13** was deduced from its spectral data and elemental analysis (see *Exper. Part*); it confirmed that the *Beckmann* rearrangements **22**→**23** and **25**→**23** implied the migration of the secondary alkyl group, rather than that of the primary alkyl group.

The high chemoselectivity of the above rearrangements suggested to us that the analogous *Baeyer-Villiger* oxidation of ketone **21** should lead to the desired lactone **26** resulting from the migration of the secondary alkyl group. To our surprise, all our attempts using various peracids and oxidants [24] gave only the unexpected isomer **27**.



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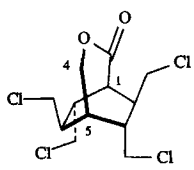

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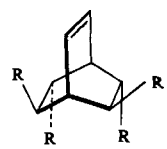
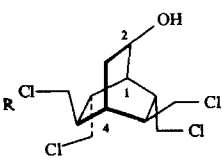


28 R = COOMe
29 R = CH_2OH
30 R = CH_2Cl



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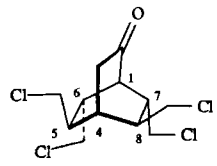

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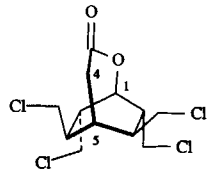

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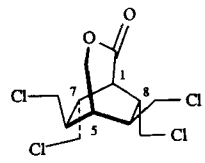

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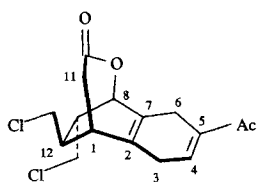
Since the conformation of the intermediates in the *Baeyer-Villiger* rearrangement can influence the stereoselectivity of the reaction [25], we looked for an isomer of ketone **21** in which the CH_2Cl substituents would not perturb the neighborhood of the carbonyl group as much as in **21**. We found that an equilibrated mixture of the methyl tetraesters obtained by treatment of **18'** with MeONa in abs. MeOH at 65° yielded a precipitate of isomer **28** (20%) on addition to ice. The other isomers (mostly the all-*trans* tetraester **19**) were reequilibrated with MeONa/MeOH. Reduction of **28** with $LiAlH_4$ in boiling THF afforded tetrol **29** (75%). Treatment with an excess of $SOCl_2$/pyridine at 80° gave the corresponding tetrachloride **30** (76%). Hydroboration ($NaBH_4 + BF_3 \cdot Et_2O$ in THF) followed by oxidative workup ($H_2O_2/KOH/H_2O$) furnished alcohol **31** in 97.5% yield. Oxidation with CrO_3/pyridine in CH_2Cl_2 gave the corresponding ketone **32** (66% based on **30**).

The *Baeyer-Villiger* oxidation of ketone **32** was studied under a large variety of conditions. With 20% AcOOH in $CHCl_3$ or dioxane at 50°, a slow oxidation was observed giving, after 4 days, a mediocre yield of a 1:5 to 1:4 mixture of lactones **33** and **34**. The proportion of **33** and **34** did not change in a significant fashion in the presence of AcONa. When using 5 equiv. of a 1:1 mixture of propionic anhydride and 90% H_2O_2 in CH_2Cl_2 only the undesired lactone **34** was formed after 5 days at 20°. Addition of K_2CO_3 (0.05 equiv.) led to a 1:5 mixture **33/34** in low yield (20°, 5 d). In contrast, on addition of a small amount of TsOH, the desired lactone **33** became the major product (CH_2Cl_2, 20°, 5 d), but with an isolated yield lower than 20%. With *m*-chloroperbenzoic acid, the *Baeyer-Villiger* oxidation of **32** was somewhat faster (CH_2Cl_2, 20°, 20 h) and led to a 1:3 mixture **33/34**. Addition of KF retarded the reaction (CH_2Cl_2, 20°, 60 h for completion) and gave a 1:11 mixture **33/34**. With a two-fold excess of $(CF_3CO)_2O$/90% H_2O_2 1:1, oxidation of **32** was complete after 7 h at 20° (CH_2Cl_2) and afforded a 67% yield of a 1:5 mixture **33/34**. Again, addition of a buffer such as Na_2HPO_4 led to an increase of the proportion of the undesired lactone **34** (**33/34** 1:10, 88% isolated yield). Finally, we found that the best yield of **33** was obtained by treating **32** with a large excess of citraconic anhydride, 90% H_2O_2, and a trace amount of TsOH in CH_2Cl_2 (20°, 8 d; see *Exper. Part*). The relatively low isolated yield (38%) was due to the instability of **33** and its decom-

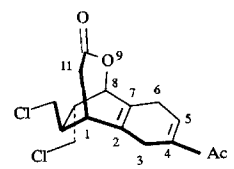
position under the conditions used for its purification. The 360-MHz ^{1}H-NMR spectra of the crude reaction solutions indicated that only a trace of **34** was formed under the latter conditions. On heating to 60° in CH_2ClCH_2Cl, the reaction time was significantly reduced (1 d), but **33** and **34** were formed in similar proportions and led to a poorer isolated yield of **33**.

Heating lactone **33** in anh. DMF/hexamethylphosphoric triamide (HMPA) 15:2 with 5 mol-equiv. of anh. CsF and 1 mol-equiv. of Cs_2CO_3 (80°, 75 min) gave an oily mixture containing mostly diene **14** and small amounts of tetraene-lactone **12**. Prolonged heating (80°, 12 h) under the same conditions afforded **12** in 62% isolated yield. Both the diene **14** and tetraene **12** are unstable compounds and must be stored in solutions at low temperature or used directly in *Diels-Alder* reactions. The selective formation of conjugated diene **14** has a parallel with the selective double elimination of HCl from 2,3,5,6-tetrakis(chloromethyl)-7-oxabicyclo[2.2.1]heptane [26]. The structures of **12–14**, **21–27**, and **31–34** were deduced from their mode of formation, reactivity, and their spectral data (see *Exper. Part*). For this, the 360-MHz ^{1}H-NMR spectra and double-irradiation experiments were very useful. The structural assignments were confirmed by the X-ray structure of one derivative (see below).

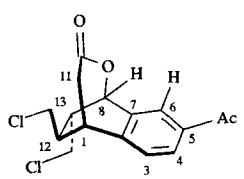
The thermal *Diels-Alder* additions of tetraenes **12** and **13** toward methyl propynoate, 3-butyn-2-one, and methyl vinyl ketone were not highly regioselective (by 360-MHz ^{1}H-NMR). Furthermore, it was found that the reactions forming the bisadducts had rate constants similar to those giving the corresponding monoadducts, thus making difficult the isolation of monoadducts of **12** and **13** in reasonable yields. Moreover, **12** and **13** and their corresponding adducts had a strong tendency to polymerize. These observations thus demonstrated the limited synthetic potential of these new tetraenes. The thermal *Diels-Alder* additions of diene **14** toward methyl propynoate and methyl vinyl ketone were not regioselective (by 360-MHz ^{1}H-NMR). With 3-butyn-2-one, a 3:2 mixture **35**/**36** was obtained (C_6H_6, 50°, 6 h). The slight *'meta'* regioselectivity was consistent with the expected electron-withdrawing effect of the O(2) atom (inductive effect) [27] [28]. The



35 (*'meta'*)



36 (*'para'*)



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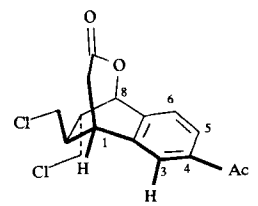

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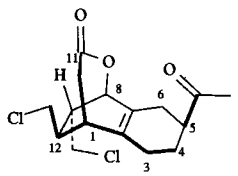
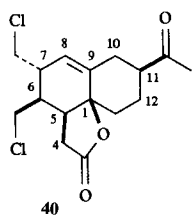
structures of **35** and **36** were deduced from those of the corresponding acetophenones **37** and **38** obtained in 95% yield on treatment with dichlorodicyanobenzoquinone (= DDQ; C_6H_6, 70°, 3.5 h). Nuclear *Overhauser* effect (NOE) measurements between the aromatic and bridgehead protons in their 360-MHz ^{1}H-NMR spectra established the structures of **37** and **38**.

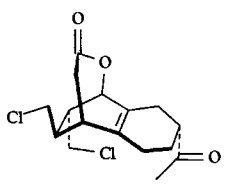
In the presence of methyl vinyl ketone precomplexed with $BF_3 \cdot Et_2O$ [29], diene **14** reacted at −78° (CH_2Cl_2, 3 h) to give one unique adduct **39** (69%, isolated yield), after quenching the reaction mixture with Et_3N at −78°. When the quenching was done at higher temperature or when the reaction mixture was allowed to warm up to −40°, **39** was quickly isomerized to **40** due to a facile allylic rearrangement induced by the *Lewis* acid. The structure of **39** was deduced from its elemental analysis and its spectral data. It was confirmed by X-ray crystallography of derivative **40** (see *Exper. Part*). On treatment of **39** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 (20°, 15 h), a 1:1 mixture of **39** and **41** was obtained. Isomers **39** and **41** could be separated by column chromatography on silica gel.



39



40



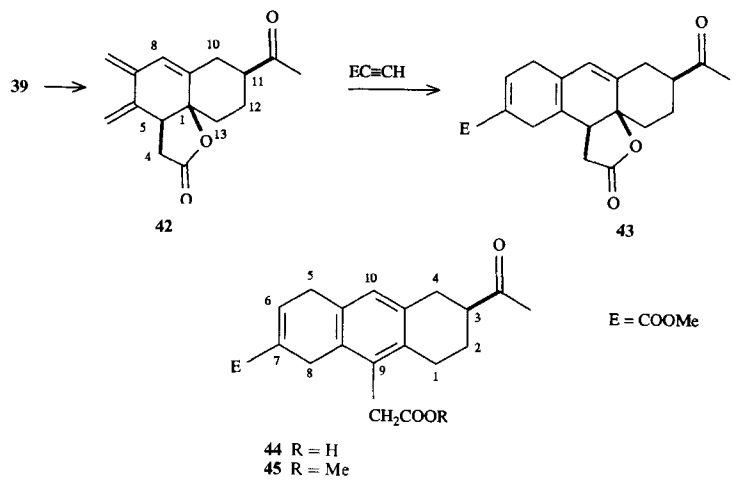
41

The *'meta'* regioselectivity of the *Lewis*-acid-catalyzed *Diels-Alder* addition of methyl vinyl ketone to **14** was parallel to that observed for the thermal addition of 3-butyn-2-one to **14**. $BF_3 \cdot Et_2O$ also catalyzed the latter cycloaddition but led to concurrent decomposition of adducts **35** and **36**. The higher regioselectivity of the *Lewis*-acid-catalyzed *Diels-Alder* additions compared with that observed under thermal conditions was expected [28–30]. The relatively high stereoselectivity of reaction **14** + methyl vinyl ketone + $BF_3 \cdot Et_2O \rightarrow$ **39** was not expected. It suggested an eventual double coordination [31] of the *Lewis* acid to O(2) of **14** and to the carbonyl group of the dienophile. The same adduct **39** was also obtained when using methyl vinyl ketone precomplexed with $EtAlCl_2$. In the latter case, the allylic rearrangement **39** → **40** was competitive with the formation of **39**. The same results were obtained when **14** was first precomplexed with the *Lewis* acids.

Treatment of adduct **39** with an excess of CsF and 1 mol-equiv. of Cs_2CO_3 in anh. DMF/HMPA 15:2 (80°, 7 h) gave triene **42** (48%, isolated). The double elimination of HCl was accompanied by an anionotropic, allylic rearrangement. The electron-donating ability of the endocyclic double bond in **42** renders its exocyclic s-*cis*-butadiene moiety highly *'para'*-regioselective [28] (95% by ^{1}H-NMR of the crude reaction mixture) in its cycloaddition to methyl propynoate (C_6H_6, 50°, 10 h) to give the tetracyclic adduct **43**. Purification on silica gel led to the formation of acid **44**, whose methyl ester **45** was isolated (76%) after treatment with CH_2N_2/Et_2O.

The *Diels-Alder* addition of 2,3-didehydroanisole, generated by deamination of 2-amino-6-methoxybenzoic acid [32] (pentyl nitrite, dioxane, 70°), to triene **42** afforded a

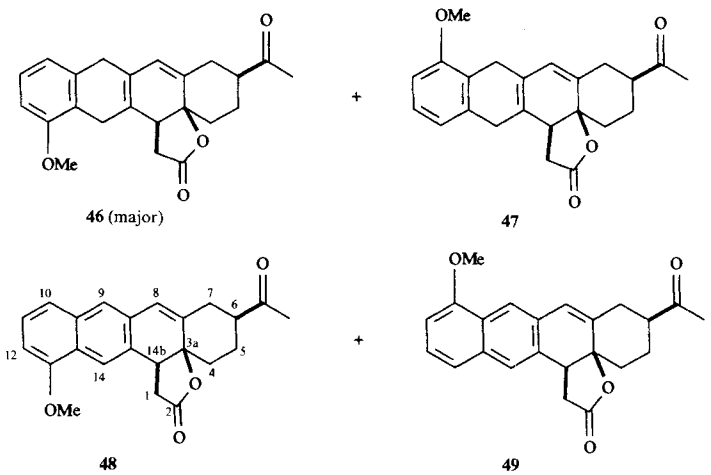
Scheme 4



42 43

44 R = H
45 R = Me

4:1 mixture **46**/**47** which was oxidized to a 4:1 mixture **48**/**49** (34%, isolated) under our reaction conditions. The structures of **45** and **48** were given by their spectral data and with the help of NOE measurements in their ^{1}H-NMR spectra. The relatively good regioselectivity of the cycloaddition of **42** to 2,3-didehydroanisole is noteworthy [15]. It is not yet excluded that the observed selectivity gives an image of the structure of a precomplex between **42** and 2-diazonio-6-methoxybenzenecarboxylate, the precursor of 2,3-didehydroanisole, rather than the 'unbiased' regioselectivity of the *Diels-Alder* addition of this dienophile [33].



46 (major) 47

48 49

Conclusion. – Contrary to 2,3,5,6-tetramethylidenebicyclo[2.2.1]heptane (**11**) and derivatives [10] (*e.g.* **3**, **10**), the new tetraenes **12** (6,7,8,9-tetramethylidene-2-oxabicyclo[3.2.2]nonan-3-one) and **13** (6,7,8,9-tetramethylidene-2-azabicyclo[3.2.2]nonan-2-one) have rate constants for their two successive *Diels-Alder* additions to a given

dienophile that are nearly the same. Thus, **12** and **13** with a three-membered bridge ressemble 2,3,5,6-tetramethylidenebicyclo[2.2.2]octane and [2.2.2]hericene [10] in their tandem *Diels-Alder* reactivity, a property which limits their synthetic potential. As in the case of 2-*exo*,3-*exo*,5-*exo*,6-*exo*-tetrakis(chloromethyl)-7-oxabicyclo[2.2.1]heptane, (1*r*,4*r*,6*R*,7*S*,8*R*,9*S*)-6,7,8,9-tetrakis(chloromethyl)-2-oxabicyclo[3.2.2]nonan-3-one (**33**), the synthetic precursor of tetraene-lactone **12**, eliminated 2 equiv. of HCl in the presence of CsF/Cs_2CO_3 to give selectively (1*RS*,5*SR*,6*RS*,7*SR*)-6,7-bis(chloromethyl)-8,9-dimethylidene-2-oxabicyclo[3.2.2]nonan-3-one (**14**). This exocyclic conjugated diene is a useful synthetic intermediate for the preparation of complicated, linearly annellated six-membered ring systems. The *Lewis*-acid-catalyzed *Diels-Alder* additions of **14** to non-symmetrical dienophiles such as methyl vinyl ketone are highly stereo- and regioselective. Under basic conditions, the adducts (*e.g.* **39**) eliminate 2 equiv. of HCl and undergo an allylic rearrangement giving a tricyclic compound (*e.g.* **42**) with an exocyclic butadiene moiety which adds to non-symmetrical dienophiles such as methyl propynoate or 2,3-didehydroanisole with good regioselectivity. The latter is controlled by the endocyclic double bond cross-conjugated with the exocyclic diene unit. The results demonstrate a new possibility for tandem *Diels-Alder* additions whose regioselectivity is controlled by remote substituents. This technology (tandem *Diels-Alder* addition/allylic rearrangement/*Diels-Alder* addition) might be useful for the preparation of anthracyclinone analogs, including those with C-substituents at C(6).

We thank *F. Hoffmann-La Roche & Co. AG*, Basel, the *Swiss National Science Foundation*, the *Fonds Herbette*, Lausanne, and the *College of Arts and Science of the University of Toledo* for financial support.

Experimental Part

General. See [34].

(E)/(Z)-Mixture of Tricarbonyl[(1RS,4RS,5RS,6SR)-C,5,6,C-η-(5,6,7,8-tetramethylidenebicyclo[2.2.2]-octan-2-one oxime)]iron (**17**). To a soln. of $NH_2OH \cdot HCl$ (440 mg, 6.33 mmol) in H_2O (2 ml), 1.5 N aq. K_2CO_3 soln. was added until pH 3–4. A soln. of **16** [18a] (195 mg, 0.62 mmol) in dioxane (10 ml) and then EtOH (3 ml) were added. After stirring at 20° for 15 h, CH_2Cl_2 (40 ml) was added and the mixture washed with sat. aq. NaCl soln. (100 ml, twice). After drying ($MgSO_4$), the soln. was evaporated and the residue purified by column chromatography on silica gel (9 g, CH_2Cl_2/AcOEt 6:1) yielding 80 mg (74%, based on recovered **16**) of **17** and 92 mg of **16**. Data of **17**: Yellow oil. IR (KBr): 3580, 3100, 3000, 2980, 2920, 2050, 1985, 1355, 1230, 1220, 1165, 960, 940, 910, 900. ^{1}H-NMR (80 MHz, $CDCl_3$): 9.2 (br. *s*, NOH); 5.28, 4.9 (2 *d*, *J* = 3, 4 olef. H); 3.9 (*s*, H–C(1)); 3.4 (*t*, *J* = 3, H–C(4)); 2.85 (*d*, *J* = 3, CH_2(3)); 1.9 (*m*, 2 H); 0.27, 0.20 (2 *d*, *J* = 3, 2 H–C(sp^2)-Fe). MS (70 eV): 327 (0.6), 299 (22), 271 (82), 243 (100).

(1RS,4SR,5SR,6SR,7SR,8SR)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-one (**21**). CrO_3 (3.22 g, 32.2 mmol) was added portionwise to a stirred mixture of anh. pyridine (5.2 ml, 65 mmol) and anh. CH_2Cl_2 (50 ml) at 0° under N_2. The mixture was warmed to 20° and **20** (1.1 g, 3.4 mmol) [18a] dissolved in a minimum of anh. CH_2Cl_2 added dropwise. After stirring at 20° for 1.5 h, the mixture was filtered through silica gel and the precipitate washed with CH_2Cl_2 (150 ml). The soln. was washed with 1N HCl (40 ml, 3 times), then with H_2O (40 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue filtered on silica gel (CH_2Cl_2) and recrystallized from $CHCl_3$/hexane, yielding 775 mg (70%), colourless crystals. M.p. 94–94.5°. IR (KBr): 2965, 2920, 2875, 1735, 1445, 1405, 1305, 1220, 1175, 1140. ^{1}H-NMR (80 MHz, $CDCl_3$): 3.95–3.17 (*m*, 4 CH_2Cl); 2.7–2.4 (*m*, CH_2(3), H–C(1)); 2.2 (*m*, H–C(4)); 2.1–1.65 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)). ^{13}C-NMR (15.08 MHz, $CDCl_3$): 210.7 (C(2)); 48.1, 46.7 (C(1), C(3)); 45.5, 44.7, 43.9 (4 CH_2Cl); 40.8, 39.5, 37.9, 37.7 (C(5), C(6), C(7), C(8)); 32.4 (C(4)). MS (70 eV): 322 (1), 320 (3.3), 318 (6), 285 (8), 283 (20), 281 (21), 269 (11), 267 (13), 240 (24), 238 (27), 202 (23), 189 (40), 167 (44), 153 (36), 115 (33), 105 (42), 103 (42), 91 (100), 77 (94). Anal. calc. for $C_{12}H_{16}Cl_4O$ (318.07): C 45.31, H 5.07, Cl 42.51; found: C 45.24, H 5.02, Cl 42.58.

(1RS,4SR,5SR,6SR,7SR,8SR)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-one [O-(2',4',6'-Trimethylbenzenesulfonyl)oxime] (**22**). A mixture of **21** (2.1 g, 7 mmol) and freshly purified *O*-(mesitylenesulfonyl)hydroxylamine [23] (1.6 g, 7.5 mmol) in CH_2Cl_2 (15 ml) was prepared at 0°. After stirring at 20° for 3 h, CH_2Cl_2 (30 ml) was added and the mixture dried ($MgSO_4$). The solvent was evaporated and the residue recrystallized from CH_2Cl_2/hexane yielding 3.1 g (85%), colourless crystals. IR (KBr): 3060, 3040, 3000, 2960, 2920, 2900, 2880, 1605, 1445, 1355, 1310, 1190, 1175, 1090, 1055, 1030, 1020, 860. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.0 (*s*, 2 arom. H); 3.8–2.7 (*m*, 4 CH_2Cl, H–C(1)); 2.7 (*s*, 2 Me); 2.6–2.4 (*m*, CH_2(3), H–C(4)); 2.3 (*s*, Me); 1.9–1.5 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 168.4 (*s*, C(2)); 143.7, 140.6 (2 *s*, arom. C); 131.6 (*d*, ^1J(C,H) = 160, 2 arom C); 44.9 (*d*, ^1J(C,H) = 132, C(1)); 45.7 (*t*, ^1J(C,H) = 154); 45.3 (*t*, ^1J(C,H) = 153); 44.5 (*t*, ^1J(C,H) = 152); 44.2 (*t*, ^1J(C,H) = 150, 4 CH_2Cl); 41.8, 38.1, 37.9, 37.8 (4 *d*, ^1J(C,H) = 135 ± 5, C(5), C(6), C(7), C(8)); 30.5 (*d*, ^1J(C,H) = 142, C(4)); 27.9 (*t*, ^1J(C,H) = 136, C(3)); 22.7 (*q*, ^1J(C,H) = 132, 2 Me); 20.9 (*q*, ^1J(C,H) = 130, Me). MS (70 eV): 455 (0.7), 453 (3), 451 (7), 449 (5), 440 (2), 438 (10), 436 (20), 434 (17), 418 (5), 416 (14), 414 (15), 333 (1), 300 (2), 298 (7), 296 (8), 282 (4), 280 (3), 178 (6), 136 (47), 119 (100).

(E)/(Z)-Mixture of (1RS,4SR,5SR,6SR,7SR,8SR)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-one Oxime (**24**). $NH_2OH \cdot HCl$ (1.1 g, 15.7 mmol) was dissolved in H_2O (5 ml) and 1.5N K_2CO_3 added until pH 3–4, followed by EtOH (5 ml) and then **21** (2 g, 6.28 mmol) in dioxane (50 ml). After staying at 20° for 15 h, CH_2Cl_2 (100 ml) was added and the soln. washed with sat. aq. NaCl soln. (100 ml, twice). The solvent was evaporated and the residue recrystallized from $CHCl_3$/hexane yielding 1.4 g (67%), colourless crystals. M.p. 137–138°, then 169–170°. IR (KBr): 3320, 2960, 2900, 1725, 1440, 1300, 1280, 940, 740, 720. ^{1}H-NMR (80 MHz, $CDCl_3$): 8.5 (*s*, NOH); 3.9–3.2 (*m*, 4 CH_2Cl); 2.9–2.2 (*m*, CH_2(3), H–C(1), H–C(4)); 2.05–1.5 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)). MS (70 eV): 335 (2), 333 (2.5), 331 (2.5), 300 (27), 298 (91), 296 (100), 282 (28), 260 (15), 192 (8), 158 (15), 107 (77). Anal. calc. for $C_{12}H_{17}Cl_4NO$ (333.09): C 43.27, H 5.14; found: C 43.55, H 5.13.

(1RS,4SR,5SR,6SR,7SR,8SR)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-one O-(p-*Toluenesulfonyl)oxime* (**25**). A soln. of TsCl (0.54 g, 3 mmol) in anh. pyridine (0.9 ml) cooled to 0° was added to a stirred soln. of **24** (500 mg, 1.5 mmol) in anh. pyridine (0.9 ml) at 0°. After stirring at 0° for 8 h, CH_2Cl_2 (20 ml) was added and the soln. washed with sat. aq. $CuSO_4$ soln. (20 ml, 3 times), then with H_2O (20 ml, twice). After drying ($MgSO_4$), the solvent was evaporated and the residue purified by column chromatography on silica gel (CH_2Cl_2) and recrystallization from $CHCl_3$/hexane, yielding 255 mg (37%), colourless crystals. M.p. 152–152.5°. IR (KBr): 3080, 3060, 3040, 2960, 2930, 2920, 2880, 1725, 1655, 1600, 1495, 1450, 1375, 1195, 1180, 1095, 815, 800. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.85, 7.35 (2 *d*, *J* = 8, 4 arom. H); 3.8–3.0 (*m*, 4 CH_2Cl); 2.75–2.2 (*m*, H–C(1), H–C(4)); 2.45 (*s*, Me); 2.1–1.4 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)). ^{13}C-NMR (15.08 MHz, CD_3COCD_3): 169.4 (C(2)); 146.1, 134.0, 130.8, 130.6, 129.5, 128.5 (6 arom. C); 46.4, 45,9, 45.1, 44.7, 41.5, 38.9, 38.5, 34.5, 31.2, 29.1. CI-MS (isobutane): 492 (16), 491 (28), 490 (51), 489 (66), 488 (96), 487 (100), 486 (73), 485 (65). Anal. calc. for $C_{19}H_{23}Cl_4NO_3S$ (487.27): C 46.83, H 4.76; found: C 46.87, H 4.70.

(1RS,5SR,6SR,7RS,8RS,9SR)-6,7,8,9-Tetrakis(chloromethyl)-2-azabicyclo[3.2.2]nonan-3-one (**23**). *A.* A mixture of **25** (40 mg, 0.082 mmol) and anh. EtOH (0.5 ml) was heated to 75° for 4 h. After cooling to 20°, CH_2Cl_2 (5 ml) was added and the soln. washed with sat. aq. NaCl soln. (10 ml, twice). The solvent was evaporated and the residue filtered through silica gel (AcOEt/petroleum ether 4:1) and recrystallized from $CHCl_3$/hexane yielding 20 mg (73%), colourless crystals.

B. A mixture of **22** (3.1 g, 6 mmol) in anh. EtOH (30 ml) was heated to reflux for 2 h. The solvent was evaporated and the residue taken with CH_2Cl_2 (50 ml). The soln. was washed with sat. aq. $NaHCO_3$ soln. (50 ml), then with H_2O (50 ml). After drying ($MgSO_4$), the solvent was evaporated and the residue recrystallized from CH_2Cl_2/hexane yielding 1.38 g (69%), colourless crystals. M.p. 146–146.5°. IR (KBr): 3220, 2970, 2940, 2915, 2900, 2880, 1645, 1485, 1445, 1410, 1390, 1360, 1350, 1310, 1280, 1170, 1090, 790, 760, 750. ^{1}H-NMR (360 MHz, $CDCl_3$): 6.84 (*d*, *J* = 7.5, NH); 3.76–3.32 (*m*, 4 CH_2Cl); 3.75 (*m*, H–C(1)); 2.78 (*dd*, *J* = 18.7, 2.6), 2.57 (*dd*, *J* = 18.7, 5.6, CH_2(4)); 2.50 (*m*, H–C(5)); 2.22 (*td*, *J* = 9.7, 3.7), 1.90 (*td*, *J* = 9.7, 3.7), 1.84 (*m*, 2 H; H–C(6), H–C(7), H–C(8), H–C(9)). MS (70 eV): 337 (3), 335 (10), 333 (19), 331 (14), 300 (28), 298 (95), 296 (100), 286 (5), 284 (12), 282 (12), 272 (5), 270 (14), 268 (14), 240 (8), 180 (16), 178 (22), 167 (9), 154 (11), 152 (15), 149 (22), 91 (18), 83 (14), 77 (14).

6,7,8,9-Tetramethylidene-2-azabicyclo[3.2.2]nonan-3-one (**13**). *t*-BuOK (8.8 g, 78.4 mmol) was added portionwise to a stirred soln. of **23** (2.9 g, 8.7 mmol) in anh. THF (35 ml). After heating to 60° for 7.5 h, the mixture was poured onto ice. The mixture was extracted with CH_2Cl_2 (50 ml), the org. extract washed with sat. aq. NaCl soln. (50 ml) and H_2O (50 ml), dried ($MgSO_4$), and evaporated, and the residue recrystallized from CH_2Cl_2/hexane yielding 1.2 g (73%), unstable white crystals. M.p. 50–70° (dec.). UV (95% EtOH): 247 (8950), 237 (10000), 231 (10100). IR (KBr): 3600–3000, 3230, 3100, 2940, 2910, 1645, 1610, 1460, 1410, 1385, 1285, 1225, 1080, 1025, 905, 845. ^{1}H-NMR (80 MHz, $CDCl_3$): 8.1 (br. *d*, *J* = 7, NH); 5.43 (*s*), 5.03 (br. *s*, 8 olef. H); 4.15 (*d*, *J* = 7, H–C(1));

3.33 (*t*, J = 4, H–C(5)); 2.73 (*d*, J = 4, CH_2(4)). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 173.0 (*s*, C(3)); 144.0, 143.9 (2 *s*, C(6), C(7), C(8), C(9)); 109.9, 109.4 (2 *td*, ^1J(C,H) = 162, ^3J(C,H) = 4, 4 CH_2=C); 60.4 (*d*, ^1J(C,H) = 146, C(1)); 46.7 (*d*, ^1J(C,H) = 136, C(5)); 44.9 (*t*, ^1J(C,H) = 133, C(4)). MS (70 eV): 187 (36), 159 (78), 158 (100), 144 (69), 130 (26), 128 (30), 117 (35), 115 (39), 106 (24), 91 (28), 80 (25), 77 (28), 72 (16), 65 (20), 51 (25). Anal. calc. for $C_{12}H_{13}NO$ (187.24): C 76.98, H 6.99; found: C 76.85, H 6.86.

*(1*RS,*5*SR,*6*SR,*7*SR,*8*SR,*9*SR*)-6,7,8,9-Tetrakis(chloromethyl)-3-oxabicyclo[3.2.2]nonan-2-one* (**27**). At 0°, 90% H_2O_2 soln. (1.5 ml, 53 mmol) and $(CF_3CO)_2O$ (8.4 ml, 60 mmol) were added dropwise to CH_2Cl_2 (50 ml). After stirring at 0° for 15 min, a soln. of **21** (3 g, 9.4 mmol) in CH_2Cl_2 (5–7 ml) was added. After staying at 20° for 15 h, the soln. was washed with sat. aq. $NaHCO_3$ soln. until neutralization, then with H_2O (30 ml). After drying ($MgSO_4$), the solvent was evaporated and the residue filtered through silica gel (CH_2Cl_2/AcOEt 9:1) and recrystallized from $CHCl_3$/hexane, yielding 1.88 g (60%), colourless crystals. M.p. 129–129.5°. IR (KBr): 3040, 3000, 2980, 2960, 2920, 2870, 1710, 1475, 1465, 1450, 1440, 1420, 1380, 1360, 1350, 1340, 1310, 1305, 1260, 1220, 1180, 1070, 1060, 1035, 980, 770, 740, 730. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.48 (*d*, J = 13, H–C(4)); 4.13 (*dd*, J = 13, 5, H–C(4)); 3.9–3.2 (*m*, 4 CH_2Cl, H–C(1)); 2.75 (*m*, H–C(5)); 2.3–1.8 (*m*, H–C(6), H–C(7), H–C(8), H–C(9)). ^{13}C-NMR (15.08 MHz, CD_2Cl_2): 171.1 (C(2)); 69.1 (C(4)); 46.5, 45.5, 44.6, 43.7, 42.0, 39.2, 38.9, 37.1, 35.3. MS (70 eV): 336 (0.6), 334 (1.5), 332 (1), 299 (4), 297 (4), 271 (3), 269 (8), 267 (8), 255 (16), 253 (17), 243 (23), 241 (65), 239 (67), 227 (12), 225 (13), 219 (8), 217 (12), 205 (32), 203 (50), 193 (8), 191 (17), 189 (11), 181 (6), 177 (11), 167 (22), 153 (27), 126 (52), 102 (100), 92 (73). Anal. calc. for $C_{12}H_{16}Cl_4O_2$ (334.07): C 43.14, H 4.83, Cl 42.45; found: C 42.98, H 4.80, Cl 42.55.

*(1*r,*2*R,*3*S,*4*r,*5*R,*6*S*)-Tetramethyl Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylate* (**18**). Under a *Soxhlet* extractor containing 3-Å molecular sieves, (1*r*,2*R*,3*S*,4*r*,5*R*,6*S*)-bicyclo[2.2.2]oct-2-ene-2,3,5,6-tetracarboxylic bisanhydride [22] (250 g, 1 mol), TsOH (2.5 g), MeOH (1.5 l), and $CHCl_3$ (0.75 l) were heated under reflux for 7 d. The wet molecular sieves were replaced by dry molecular sieves every 2 d. The solvent was evaporated, the residue dissolved in CH_2Cl_2 (800 ml), the soln. washed with sat. aq. $NaHCO_3$ soln. (200 ml), H_2O (200 ml, twice), and sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$) and evaporated, and the residue dried over P_4O_{10} *in vacuo*, yielding 340 g (100%), white solid with same data as reported [22].

*(1*r,*2*R,*3*R,*4*s,*5*S,*6*S*)-Tetramethyl Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylate* (**28**). Metallic Na (6.2 g, 270 mmol) was dissolved in anh. MeOH (600 ml). After addition of **18'** (100 g, 294 mmol), the mixture was heated under reflux for 30 min. The hot soln. was poured at once onto ice (400 g). The precipitate was dissolved in CH_2Cl_2 (500 ml), the soln. washed with H_2O (300 ml, 3 times), dried ($MgSO_4$), and evaporated, and the residue recrystallized from MeOH (280 ml), yielding 20 g (20%), colourless crystals. M.p. 149–149.5°. ^{1}H-NMR (80 MHz, $CDCl_3$): 6.55, 6.1 (2 *dd*, J = 7, 8, H–C(7), H–C(8)); 3.65, 3.62 (2 *s*, 4 MeO); 3.55 (*m*, H–C(1), H–C(4)); 3.28, 2.85 (2 *dd*, J = 6, 2, H–C(2), H–C(3), H–C(5), H–C(6)). ^{13}C-NMR (15.08 MHz, $CDCl_3$): 173.3, 172.8 (2 *s*); 136.3, 130.2 (2 *d*, ^1J(C,H) = 169); 52.1, 52.0 (2 *q*, ^1J(C,H) = 148); 44.7, 43.4 (2 *d*, ^1J(C,H) = 132); 35.1, 34.9 (2 *d*, ^1J(C,H) = 146).

The soln. (after precipitation) containing the isomers of **28** was neutralized with conc. HCl soln. and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (1 l), the soln. washed with H_2O (200 ml, 3 times) and sat. aq. NaCl soln. (200 ml) and evaporated and the residue dried over P_4O_{10} *in vacuo*. It was then esterified as above with MeOH/TsOH/molecular sieves (see **18'**) and equilibrated with MeONa/MeOH as above to give more **28**.

*(1*r,*2*R,*3*R,*4*s,*5*S,*6*S*)-Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetramethanol* (**29**). To a stirred suspension of $LiAlH_4$ (10 g, 264 mmol) in anh. THF (260 ml), **28** (28.5 g, 84 mmol) was added portionwise as a solid. When the mixture became too viscous, the remaining of **28** was added together with anh. THF (280 ml). After boiling under reflux for 3 d, the mixture was cooled to 20° and H_2O/EtOH 10:1 added dropwise. Then, the mixture was heated under reflux until a white suspension was obtained. It was filtered through hot silica gel. The precipitate and the silica gel were extracted (2 h) with boiling EtOH (250 ml, twice). The filtrates were combined and the solvent evaporated. The residue was triturated with EtOH (13 ml) at 60° for 15 h. The solid was dried *in vacuo*, yielding 14.4 g (75%), white solid. M.p. 131.5–132°. UV (95% EtOH): final absorption $\varepsilon_{216} < 200$. IR (KBr): 3280, 3050, 2970, 2930, 2900, 2870, 1475, 1380, 1110, 1100, 1040, 1010, 715. ^{1}H-NMR (80 MHz, D_2O): 6.5, 5.95 (2 *dd*, H–C(7), H–C(8)); 4.6 (OH, H_2O); 3.6, 3.2 (2 *m*, 4 CH_2OH); 2.65 (*m*, H–C(1), H–C(4)); 1.4 (*m*, H–C(2), H–C(3), H–C(5), H–C(6)). ^{13}C-NMR (15.08 MHz, D_2O): 138.7, 129.7 (2 *d*, ^1J(C,H) = 168 ± 2, C(7), C(8)); 66.4, 66.1 (2 *t*, ^1J(C,H) = 141, 4 CH_2OH); 46.4, 44.1 (2 *d*, ^1J(C,H) = 127, C(2), C(3), C(5), C(6)); 34.1, 33.8 (2 *d*, ^1J(C,H) = 134, C(1), C(4)). MS (70 eV): 210 (1), 192 (2), 179 (4), 162 (4), 156 (3), 143 (7), 131 (24), 117 (18), 105 (33), 92 (90), 91 (82), 79 (100). Anal. calc. for $C_{12}H_{20}O_4$ (228.29): C 63.13, H 8.83; found: C 62.95, H 8.70.

*(1*r,*4*s,*5*R,*6*R,*7*S,*8*S*)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]oct-2-ene* (**30**). Anh. pyridine (32.5 g, 411 mmol) was added dropwise to freshly distilled $SOCl_2$ (60.9 g, 512 mmol). Then, **29** (30 g, 131 mmol) was added portionwise at 20°. After boiling at 80° for 2 h, the mixture was cooled to 0° and cold CH_2Cl_2 (500 ml) added. H_2O (200 ml) was added dropwise at 0° under stirring. The aq. phase was extracted with CH_2Cl_2 (*150 ml, twice*), the combined org. phase washed successively with sat. aq. $NaHCO_3$ soln. (300 ml, twice), 3N HCl (180 ml, twice) and

H_2O (200 ml, twice), dried ($MgSO_4$), and evaporated, and the residue filtered on silica gel (CH_2Cl_2), yielding 30.3 g (76%), colourless crystals. M.p. 60–60.5°. UV (95% EtOH): final absorption $\varepsilon_{216} < 100$. IR (KBr): 3080, 3060, 2980, 2910, 1440, 1310, 710. ^{1}H-NMR (80 MHz, $CDCl_3$): 6.6 (*t*, *J* = 7.5), 6.0 (*dd*, *J* = 8, 7.5, H–C(2), H–C(3)); 4.0–3.1 (*m*, 4 CH_2Cl); 3.05 (*m*, H–C(1), H–C(4)); 1.9–1.3 (*m*, H–C(5), H–C(6), H–C(7), H–C(8)). ^{13}C-NMR (15.08 MHz, $CDCl_3$): 138.1, 128.7 (2 *d*, ^1J(C,H) = 168, C(2), C(3)); 48.2, 47.6 (2 *t*, ^1J(C,H) = 150, 4 CH_2Cl); 47.3, 45.4 (2 *d*, ^1J(C,H) = 132, C(5), C(6), C(7), C(8)); 35.6 (*d*, ^1J(C,H) = 140, C(1), C(4)). MS (70 eV): 306 (0.3), 304 (1), 302 (1.7), 300 (1), 267 (1), 265 (2), 255 (2), 253 (6), 251 (6), 231 (1), 229 (1), 217 (2), 215 (2), 178 (15), 176 (24), 164 (3), 162 (5), 149 (7), 141 (9), 139 (8), 127 (39), 105 (9), 91 (100). Anal. calc. for $C_{12}H_{16}Cl_4$ (302.07): C 47.71, H 5.34; found: C 47.68, H 5.43.

*(1*RS,*2*SR,*4*SR,*5*SR,*6*SR,*7*RS,*8*RS*)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-ol* (**31**). A soln. of **30** (31 g, 103 mmol) and $NaBH_4$ (10.3 g, 272 mmol) in anh. THF (310 ml) was cooled to 0° and freshly distilled $BF_3 \cdot Et_2O$ (44 ml, 350 mmol) added dropwise. After stirring at 20° for 1 d, the mixture was cooled to 0°, and H_2O (20.6 g), 3N KOH (30 ml), and 30% H_2O_2 soln. (30.6 ml) were added successively dropwise. After stirring at 20° for 3 d, CH_2Cl_2 (1 l) was added and the mixture filtered through silica gel. The solvent was evaporated, the residue dissolved in CH_2Cl_2 (500 ml), the soln. washed with H_2O (200 ml, 3 times) and sat. aq. NaCl soln. (100 ml), dried ($MgSO_4$), and evaporated, and the residue dried over P_4O_{10} *in vacuo* and paraffin. The oily residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone 9:1), yielding 32 g (97.5%), colourless oil. UV (95% EtOH): final abs. $\varepsilon_{220} < 100$. IR (CH_2Cl_2): 3610, 2960, 2900, 1460, 1440, 1320, 1110, 1040, 980. ^{1}H-NMR (360 MHz, CD_2Cl_2): 3.86 (*dt*, *J* = 9.5, 3, H–C(2)); 3.84–3.58 (*m*); 3.39 (*dd*, *J* = 11, 9, CH_2Cl); 2.25 (*m*, H–C(4)); 2.19 (*m*, H–C(8)); 2.18 (*m*, H–C(1)); 2.0 (br. *s*, OH); 1.90 (*dddd*, *J* = 15, 9.5, 3.0, 1.7, H–C(3) *cis* to OH); 1.58 (*m*, H–C(5), H–C(6)); 1.49 (*m*, H–C(7)); 1.33 (*m*, H–C(3) *trans* to OH). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 68.6 (*d*, ^1J(C,H) = 146, C(2)); 48.0, 47.7, 46.4, 45.7 (4*t*, ^1J(C,H) = 150, 4 CH_2Cl); 46.2, 45.5, 43.8, 36.6 (4 *d*, ^1J(C,H) = 130–132, C(5), C(6), C(7), C(8)); 37.8, 30.0 (2 *d*, ^1J(C,H) = 136, C(1), C(4)); 25.1 (*t*, ^1J(C,H) = 129, C(3)). MS (70 eV): 322 (0.5), 320 (1), 318 (1), 304 (1), 302 (1), 300 (1), 282 (2), 270 (4), 269 (2), 267 (3), 265 (3), 253 (12), 251 (13), 246 (6), 204 (35), 202 (49), 168 (46), 153 (57), 139 (31), 105 (40), 91 (100). Anal. calc. for $C_{12}H_{18}Cl_4O$ (320.09): C 45.03, H 5.67; found: C 45.11, H 5.72.

*(1*s,*4*r,*5*R,*6*R,*7*S,*8*S*)-5,6,7,8-Tetrakis(chloromethyl)bicyclo[2.2.2]octan-2-one* (**32**). Under stirring, CrO_3 (96 g, 960 mmol) was added portionwise to a soln. of anh. pyridine (155 ml, 1.92 mol) in anh. CH_2Cl_2 (1.65 l), cooled to 0°. The mixture was allowed to reach 20° and **31** (32.85 g, 103 mmol) in CH_2Cl_2 (50 ml) added slowly. After stirring at 20° for 4 h, the mixture was filtered through silica gel with CH_2Cl_2 (800 ml). After concentration to 500 ml *in vacuo*, the soln. was washed with 2N HCl (330 ml, 3 times) and H_2O (300 ml, twice), dried ($MgSO_4$), and evaporated and the residue recrystallized from CH_2Cl_2, yielding 21.6 g (66%), colourless crystals. M.p. 109–109.5°. UV (95% EtOH): 291 (50). UV (dioxane): 294 (50). IR (KBr): 2980, 2955, 2900, 1740, 1455, 1440, 1315, 1200, 750, 705. ^{1}H-NMR (360 MHz, $CDCl_3$): 3.80 (*dd*, *J* = 11, 7), 3.57 (*dd*, *J* = 11, 7.5, CH_2Cl–C(6), CH_2Cl–C(7)); 3.76 (*dd*, *J* = 11.5), 3.44 (*dd*, *J* = 11, 9.5, CH_2Cl–C(5), CH_2Cl–C(8)); 2.87 (br. *t*, *J* = 1.5, H–C(1)); 2.75 (br. *tt*, *J* = 3, 2, H–C(4)); 2.33 (*d*, *J* = 3, CH_2(3)); 1.93 (*m*, H–C(6), H–C(7)); 1.89 (*m*, H–C(5), H–C(8)). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 209.7 (*s*, C(2)); 47.7 (*d*, ^1J(C,H) = 150, C(1)); 46.9, 45.5 (2 *t*, ^1J(C,H) = 150, 4 CH_2Cl); 45.9 (*d*, ^1J(C,H) = 129, C(6), C(7)); 41.7 (*d*, ^1J(C,H) = 132, C(5), C(8)). 33.0 (*t*, ^1J(C,H) = 129, C(3)); 32.6 (*d*, ^1J(C,H) = 139, C(4)). MS (70 eV): 322 (0.5), 320 (8), 318 (25), 316 (22), 285 (12), 283 (31), 281 (35), 268 (6), 267 (5), 247 (20), 245 (36), 240 (26), 217 (12), 209 (24), 202 (62), 189 (49), 181 (18), 167 (72), 153 (100), 139 (35), 131 (53), 115 (37), 105 (55), 91 (94), 77 (97). Anal. calc. for $C_{12}H_{16}Cl_4O$ (318.07): C 45.31, H 5.07; found: C 45.29, H 5.06.

*(1*r,*4*r,*6*R,*7*S,*8*R,*9*S*)-6,7,8,9-Tetrakis(chloromethyl)-2-oxabicyclo[3.2.2]nonan-3-one* (**33**). Citraconic anhydride (22.3 g, 199 mmol), 90% H_2O_2 soln. (6.12 ml), and TsOH (0.35 g, 1.8 mmol) were dissolved successively in anh. CH_2Cl_2 (80 ml) at 0°. Then, **32** (9 g, 28.3 mmol) in anh. CH_2Cl_2 (80 ml) was added dropwise. After 8 d at 20°, the soln. was washed with sat. aq. $NaHCO_3$ soln. (500 ml, 3 times) and H_2O (500 ml, 3 times), dried ($MgSO_4$), and evaporated and the residue purified by column chromatography on silica gel (CH_2Cl_2). A 1st fraction gave 1.5 g (17%) of **32**. The 2nd fraction afforded 3 g (38%, taken into account recovered **32**) of **33**, colourless crystals. M.p. 138–139°. UV (95% EtOH): 219 (80). IR (KBr): 3020, 2975, 2940, 2900, 1710, 1410, 1450, 1350, 1330, 1245, 1210, 1035, 810, 720. ^{1}H-NMR (360 MHz, CD_2Cl_2): 4.87 (br. *t*, *J* = 1.3, H–C(1)); 3.79 (*dd*, *J* = 11.5, 5.4), 3.56 (*dd*, *J* = 11.5, 9.7, CH_2Cl–C(6), CH_2Cl–C(9)); 3.73 (*dd*, *J* = 11.7, 5.8); 3.46 (*dd*, *J* = 11.7, 10.3, CH_2Cl–C(7), CH_2Cl–C(8)); 2.90 (*d*, *J* = 4, CH_2(4)); 2.67 (*tt*, *J* = 4, 3.5, H–C(5)); 2.45 (*ddddd*, *J* = 10.3, 8, 5.8, 1.5, 1.3, H–C(7), H–C(8)); 1.92 (*dddd*, *J* = 9.7, 8, 5.4, 3.5, H–C(6), H–C(7)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 169.8 (*s*, C(3)); 74.6 (*d*, ^1J(C,H) = 152, C(1)); 45.7 (*d*, ^1J(C,H) = 124, C(7), C(8)); 45.1, 44.8 (2*t*, ^1J(C,H) = 148, 4 CH_2Cl); 43.8 (*d*, ^1J(C,H) = 125, C(6), C(9)); 30.6 (*t*, ^1J(C,H) = 128, C(4)); 30.4 (*d*, ^1J(C,H) = 134, C(5)). MS (70 eV): 336 (0.4), 334 (0.7), 332 (0.6), 301 (1), 299 (83), 297 (4), 270 (9), 268 (5), 252 (6), 245 (35), 243 (96), 241 (100), 207 (11), 205 (27), 181 (32), 179 (53), 153 (10), 143 (16), 117 (23), 115 (28), 105 (28), 92 (37), 91 (74), 89 (49). Anal. calc. for $C_{12}H_{16}Cl_4O_2$ (334.07): C 43.14, H 4.83; found: C 43.29, H 5.01.

(1r,4r,6R,7S,8R,9S)-6,7,8,9-Tetrakis(chloromethyl)-3-oxabicyclo[3.2.2]nonan-2-one (**34**). Same procedure as for the preparation of **33**, using 1 equiv. of potassium citraconate per equiv. of citraconic anhydride. ^{1}H-NMR of the crude mixture: **33**/**34** 1:10. ^{1}H-NMR (360 MHz, CD_2Cl_2) of **34**: 4.40 (*d*, J = 3, CH_2(4)); 3.87–3.43 (*m*, 4 CH_2Cl); 3.37 (br. *s*, H–C(1)); 2.87 (*q*, J = 3.2, H–C(5)); 2.18 (*q*, J = 7.5, H–C(7), H–C(8)); 2.03–1.9 (*m*, H–C(6), H–C(9)).

(1RS,5SR,6RS,7SR)-6,7-Bis(chloromethyl)-8,9-dimethylidene-2-oxabicyclo[3.2.2]nonan-3-one (**14**). A mixture of anh. CsF (2.35 g, 15.5 mmol), Cs_2CO_3 (980 mg, 3 mmol), **33** (1 g, 3 mmol), anh. DMF (45 ml), and anh. HMPA (5.9 ml) was stirred at 80° for 75 min in a flame-dried flask. After cooling to 20°, CH_2Cl_2 (150 ml) was added, the soln. washed with H_2O (200 ml, 6 times) and sat. aq. NaCl soln. (100 ml) and evaporated, and the residue purified by filtration on *Florisil* (15 g, 100–200 mesh, CH_2Cl_2), yielding 485 mg (62%), unstable oil. Must be stored as soln. in CH_2Cl_2 at −30°. ^{1}H-NMR (360 MHz, CD_2Cl_2): 5.78, 5.54, 5.34, 5.12 (4 *s*, 4 olef. H); 4.85 (*d*, J = 1.5, H–C(1)); 3.75 (*dd*, J = 12, 6, 1 H of CH_2Cl–C(6)); 3.56 (*m*, 1 H of CH_2Cl–C(6), 1 H of CH_2Cl–C(7)); 3.25 (*dd*, J = 12, 10, 1 H of CH_2Cl–C(7)); 3.02 (*dd*, J = 19, 4), 2.79 (*ddd*, J = 19, 4, 1, CH_2(4)); 2.93 (*q*, J = 4, H–C(5)); 2.38, 1.88 (2 *m*, H–C(6), H–C(7)). ^{1}H-NMR (360 MHz, $CDCl_3$): 5.76, 5.50, 5.32, 5.08 (4 *s*, 4 olef. H); 4.84 (*d*, J = 1.5, H–C(1)); 3.71 (*dd*, J = 12, 6, 1 H of CH_2Cl–C(6)); 3.49 (*m*, 1 H of CH_2Cl–C(6), 1 H of CH_2Cl–C(7)); 3.20 (*dd*, J = 12, 10, 1 H of CH_2Cl–C(7)); 3.02 (*dd*, J = 19, 4), 2.80 (*ddd*, J = 19, 4, 1, CH_2(4)); 2.91 (*q*, J = 4, H–C(5)); 2.34, 1.88 (2 *m*, H–C(6), H–C(7)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 169.7 (*s*, C(3)); 143.7, 138.9 (2 *s*); 116.7 (*t*, ^1J(C,H) = 160); 110.5 (*t*, ^1J(C,H) = 158); 79.6 (*d*, ^1J(C,H) = 156, C(5)); 45.9, 43.1 (2 *d*, ^1J(C,H) = 130, C(6), C(7)); 45.1, 44.7 (2 *t*, ^1J(C,H) = 150, 2 CH_2Cl); 37.7 (*d*, ^1J(C,H) = 132, C(5)); 36.8 (*t*, ^1J(C,H) = 128, C(4)).

6,7,8,9-Tetramethylidene-2-oxabicylo[3.2.2]nonan-3-one (**12**). A mixture of anh. CsF (820 mg, 5.4 mmol), anh. Cs_2CO_3 (343 mg, 1.05 mmol), **33** (0.33 g, 0.99 mmol), anh. DMF (16 ml), and anh. HMPA (2.1 ml) was heated to 80° for 12 h under stirring. After cooling to 20°, CH_2Cl_2 (100 ml) was added, the soln. washed with H_2O (150 ml, 6 times) and sat. aq. NaCl soln. (50 ml) and evaporated, and the residue filtered through *Florisil* (15 g, 100–200 mesh, CH_2Cl_2), yielding 116 mg (62%), colourless oil. Unstable at 20° in the condensed state; must be stored as diluted soln. in CH_2Cl_2 at −30°. ^{1}H-NMR (360 MHz, CD_2Cl_2): 5.71, 5.47, 5.35, 5.08 (4 *s*, 8 olef. H); 5.08 (*s*, H–C(1)); 3.32 (*t*, J = 4, H–C(5)); 2.92 (*d*, J = 4, CH_2(4)). ^{1}H-NMR (360 MHz, $CDCl_3$): 5.68, 5.43, 5.32, 5.05 (4 *s*, 8 H); 5.07 (*s*, H–C(1)); 3.28 (*t*, J = 4); 2.92 (*d*, J = 4). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 169.7 (*s*, C(3)); 143.1, 141.1, (2 *s*, C(6), C(7), C(8), C(9)); 114.6, 109.2 (2 *t*, ^1J(C,H) = 160, 4 CH_2=C); 83.1 (*d*, ^1J(C,H) = 154, C(1)); 46.2 (*d*, ^1J(C,H) = 136, C(5)); 44.2 (*t*, ^1J(C,H) = 131, C(4)).

(1RS,8SR,12SR,13RS)-12,13-Bis(chloromethyl)-10-oxo-9-oxatricyclo[6.3.2.0^{2,7}]trideca-2(7),4-dien-5-yl and -4-yl Methyl Ketones (**35**/**36**). The crude **14** resulting from the treatment of 50 mg (0.15 mmol) of **33** was dissolved immediately in 3-butyn-2-one (0.3 ml, 3.8 mmol) and C_6H_6 (0.2 ml). Hydroquinone (0.5 mg) was added and the mixture heated to 50° for 6 h. The solvent was evaporated, the residue taken with toluene (2 ml) and the solvent evaporated to dryness. The residue was purified by chromatography on silica gel (10 g, CH_2Cl_2/acetone 95:5) yielding a 1st fraction containing 20 mg of **33** and a 2nd fraction yielding 17 mg (57% based on **33**, taking into account recovered **33**) of a 3:2 mixture **35**/**36**, colourless oil. ^{1}H-NMR (360 MHz, CD_2Cl_2): 6.89 (*m*, H–C(5) of **36**); 6.86 (*m*, H–C(4) of **35**); 4.66 (*m*, H–C(8)); 3.81 (*m*, 2 H); 3.75 (*m*, 4 H); 3.27 (*dd*, 2 H, 2 CH_2Cl); 3.3–2.9 (*m*, CH_2(3), CH_2(6)); 2.92, 2.71 (2 *m*, CH_2(11)); 2.62 (*m*, H–C(1)); 2.46 (*m*, H–C(13)); 2.32, 2.31 (2 *s*, MeCO); 1.92 (*m*, H–C(12)).

(1RS,8SR,12SR,13RS)-12,13-Bis(chloromethyl)-10-oxo-9-oxatricyclo[6.3.2.0^{2,7}]trideca-2,4,6-trien-5-yl and -4-yl Methyl Ketones (**37**/**36**). A 3:2 mixture **35**/**36** (17 mg, 0.051 mmol) and DDQ (30 mg, 0.13 mmol) in C_6H_6 (0.4 ml) were heated to 70° for 3.5 h. The mixture was filtered through silica gel (1 g, CH_2Cl_2/acetone 95:5), the solvent evaporated, the residue dissolved in CH_2Cl_2 (10 ml), the soln. washed with sat. aq. $NaHCO_3$ soln. (30 ml, 3 times), H_2O (30 ml, twice), and sat. aq. NaCl soln. (30 ml) and evaporated, and the residue filtered through silica gel (10 g, CH_2Cl_2/acetone 95:5) yielding 16 mg (95%), viscous, colourless oil. ^{1}H-NMR (360 MHz, CD_2Cl_2): 8.03 (*dd*, J = 8, 2, H–C(4) of **37**); 8.0 (*d*, J = 2, H–C(6) of **37**, NOE with H–C(8) at 5.43); 7.94 (*dd*, J = 8, 2, H–C(5) of **38**); 7.9 (*d*, J = 2, H–C(3) of **38**, NOE with H–C(1) at 2.83); 7.54 (*d*, J = 8, H–C(6) of **38**, NOE with H–C(8) at 5.40); 7.45 (*d*, J = 8, H–C(3) of **37**, NOE with H–C(1) at 2.83); 5.43 (*d*, J = 1.5, H–C(8) of **37**); 5.40 (*d*, J = 1.5, H–C(8) of **38**); 3.92 (*m*, CH_2Cl); 3.72 (*m*, CH_2Cl); 3.45 (*m*, 2 CH_2Cl); 3.12 (*m*, CH_2(11) of **37**, **38**); 2.83 (*m*, H–C(1) of **37**, **38**); 2.69, 1.97 (2 *m*, H–C(12), H–C(13)); 2.6 (*s*, MeCO of **37**, **38**). MS (70 eV): 334 (0.7), 332 (5), 330 (6), 289 (13), 277 (0.5), 272 (12), 270 (17), 261 (14), 259 (12), 251 (23), 235 (19), 227 (46), 215 (24), 191 (33), 179 (32), 169 (38), 159 (13), 155 (100), 145 (24), 143 (55), 141 (51), 129 (64), 128 (56), 115 (49), 105 (31), 91 (77).

(1RS,5RS,8SR,12SR,13RS)-12,13-Bis(chloromethyl)-10-oxo-9-oxatricyclo[6.3.2.0^{2,7}]tridec-2(7)-en-5-yl Methyl Ketone (**39**). The crude **14** resulting from double elimination of HCl of 1 g (3 mmol) of **33** was dissolved in anh. CH_2Cl_2 (18 ml). Methyl vinyl ketone (0.95 ml, 11.6 mmol) was added and the mixture cooled to −78°. Under

stirring, $BF_3 \cdot Et_2O$ (1.4 ml, 11.2 mmol) was added dropwise. After stirring at −78° for 3 h, Et_3N (3.2 ml, 23 mmol) was added and the mixture poured onto sat. aq. $NaHCO_3$ soln. (100 ml). The org. phase was collected and washed with sat. aq. $NaHCO_3$ soln. (100 ml, 3 times), 0.5N HCl (50 ml, twice), H_2O (100 ml, twice), and sat. aq. NaCl soln. (30 ml). The solvent was evaporated and toluene (10 ml) added. The solvent was again evaporated and the residue purified by column chromatography on silica gel (130 g, CH_2Cl_2/acetone 95:5) yielding 370 mg (1.1 mmol) of unreacted **33**, then 26 mg (4%) of **40** (see below) and finally 432 mg (69% based on reacted **33**) of **39**, colourless oil. ^{1}H-NMR (360 MHz, CD_2Cl_2): 4.58 (*d*, *J* = 1.6, H–C(8)); 3.79 (*dd*, *J* = 5.8, 11.5), 3.58 (*dd*, *J* = 11.5, 5), 3.55 (*dd*, *J* = 11.5, 9.8), 3.34 (*dd*, *J* = 11.5, 8, 2 CH_2Cl); 2.84 (*dd*, *J* = 19.5, 3), 2.63 (*dd*, *J* = 19.5, 4, 1.3, CH_2(11)); 2.6 (*m*, H–C(5)); 2.51 (*m*, H–C(6), H–C(1)); 2.44 (*m*, H–C(13)); 2.24 (*m*, CH_2(3), H–C(6)); 2.16 (*s*, MeCO); 2.04 (*m*, H–C(4)); 1.91 (*m*, H–C(12)); 1.58 (*m*, H–C(4)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 209.3 (*s*, CO); 169.9 (*s*, C(10)); 142.4 (*s*, C(7)); 130.6 (*s*, C(2)); 77.7 (*d*, ^1J(C,H) = 144, C(8)); 47.2 (*d*, ^1J(C,H) = 124, C(13)); 46.7 (*d*, ^1J(C,H) = 128, C(5)); 46.0, 45.0 (2 *t*, ^1J(C,H) = 143, 2 CH_2Cl); 42.0 (*d*, ^1J(C,H) = 126, C(12)); 35.0 (*d*, ^1J(C,H) = 128, C(1)); 33.3 (*t*, ^1J(C,H) = 123, C(11)); 29.4, 26.8, 24.1 (3 *t*, ^1J(C,H) = 120–123, CH_2(3), CH_2(4), CH_2(6)); 27.4 (*q*, ^1J(C,H) = 127, *Me*CO). CI-MS (CH_4): 333 (14, *M* + 1), 331 (18), 315 (62), 313 (100), 297 (10), 295 (26), 287 (8), 285 (8), 277 (16), 271 (57), 259 (14), 253 (14), 249 (14), 235 (22). Anal. calc. for $C_{16}H_{20}Cl_2O_3$ (331.24): C 58.02, H 6.09; found: C 57.91, H 5.98.

*(1*RS,*5*RS,*6*SR,*7*SR,*11*RS*)-6,7-Bis(chloromethyl)-3-oxo-2-oxatricyclo[7.4.0.0^{1,5}]tridec-8-en-11-yl Methyl Ketone* (**40**). Same procedure as for the preparation of **39**, the quenching with Et_3N being carried out at 0°. Yield 70%, colourless crystals. M.p. 146–146.5° (CH_2Cl_2/hexane). IR (CH_2Cl_2): 2980, 2950, 2920, 2860, 1760, 1710, 1460, 1370, 1350, 1310, 1260, 1240, 1200, 1170, 940, 850. ^{1}H-NMR (360 MHz, CD_2Cl_2): 5.48 (*s*, H–C(8)); 3.77 (*m*, CH_2Cl); 3.67 (*dd*, *J* = 11.5, 5, 1 H); 3.51 (*dd*, *J* = 11.5, 8, 1 H, CH_2Cl); 2.78 (*ddd*, *J* = 12, 8, 3.8, H–C(5)); 2.65 (*m*, 1 H); 2.58 (*dd*, *J* = 17.5, 8), 2.47 (*dd*, *J* = 17.5, 12, CH_2(4)); 2.45–2.30 (*m*, 4 H); 2.13 (*s* MeCO); 2.03–1.79 (*m*, 4 H). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 208.7 (*s*, CO); 173.7 (*s*, C(3)); 138.0 (*s*, C(9)); 123.7 (*d*, ^1J(C,H) = 156, C(8)); 84.2 (*s*, C(1)); 51.8 (*d*, ^1J(C,H) = 130, C(11)); 46.4 (*t*, ^1J(C,H) = 152, CH_2Cl); 44.9 (*t*, ^1J(C,H) = 149, CH_2Cl); 42.0 (*d*, ^1J(C,H) = 130, C(5)); 36.9, 36.0 (2 *d*, ^1J(C,H) = 128, C(6), C(7)); 36.5, 24.5 (2 *t*, ^1J(C,H) = 130), 32.9, 29.8 (2 *t*, ^1J(C,H) = 132, C(4), C(10), C(12), C(13)); 27.3 (*q*, ^1J(C,H) = 127, *Me*CO). CI-MS (CH_4): 333 (19, *M* + 1), 331 (27), 315 (60), 313 (100), 295 (27), 287 (9), 285 (9), 277 (12), 273 (27), 271 (37), 259 (9), 253 (11), 249 (11), 235 (13), 229 (12), 227 (18). Anal. calc. for $C_{16}H_{20}Cl_2O_3$ (331.24): C 58.02, H 6.09; found: C 58.07, H 6.05.

*(1*RS,*5*SR,*8*SR,*12*SR,*13*RS*)-12,13-Bis(chloromethyl)-10-oxo-9-oxatricyclo[6.3.2.0^{2,7}]tridec-2(7)-en-5-yl Methyl Ketone* (**41**). A soln. of **39** (200 mg, 0.6 mmol) and DBU (0.5 ml, 0.33 mmol) in CH_2Cl_2 (10 ml) was stirred at 20° for 15 h. The soln. was washed with 0.01N HCl (4 ml) and then with H_2O (20 ml) at 0° and evaporated and the residue purified by column chromatography on silica gel (CH_2Cl_2/acetone 95:5). The 1:1 mixture **39**/**41** was separated by HPLC (*Dupont-Instruments-830* liquid chromatograph, SiO_2 1 × 25 cm, CH_2Cl_2/acetone 95:5) yielding first 90 mg (45%) of **41** and a 2nd fraction containing 85 mg (42.4%) of **39**. Data of **41**: oil. ^{1}H-NMR (360 MHz, CD_2Cl_2): 4.62 (*d*, *J* = 1.5, H–C(8)); 3.81 (*dd*, *J* = 11, 6.5), 3.54 (*m*, 2 H); 3.42 (*dd*, *J* = 11.5, 9, 2 CH_2Cl); 2.86 (*dd*, *J* = 18, 4), 2.66 (*ddd*, *J* = 18, 4, 1.3, CH_2(11)); 2.74 (*m*, H–C(5)); 2.49 (*q*, *J* = 4, H–C(1)); 2.4 (*m*, H–C(13), H–C(6)); 2.28 (*m*, H–C(6), H–C(3)); 2.17 (*s*, CH_3CO); 2.16 (*m*, H–C(3)); 2.02 (*m*, H–C(4)); 1.83 (*m*, H–C(12)); 1.75 (*m*, H–C(4)). ^{13}C-NMR (90.55 MHz, C_6H_6/CD_2Cl_2 1:3): 209.4 (*s*, CO); 170.4 (*s*, C(10)); 142.7, 130.8 (2 *s*, C(2), C(7)); 77.8 (*d*, ^1J(C,H) = 135, C(8)); 47.7 (*d*, ^1J(C,H) = 134, C(12)); 46.8 (*d*, ^1J(C,H) = 128, C(5)); 46.1, 45.8 (2 *t*, ^1J(C,H) = 150, 2 CH_2Cl); 43.0 (*d*, ^1J(C,H) = 132, C(13)); 35.7 (*d*, ^1J(C,H) = 134, C(1)); 34.4 (*t*, ^1J(C,H) = 129, C(11)); 29.3 (*t*, ^1J(C,H) = 129), 26.9 (*t*, ^1J(C,H) = 127), 24.3 (*t*, ^1J(C,H) = 130, C(3), C(4), C(6)); 27.7 (*q*, ^1J(C,H) = 126, *Me*CO).

*(1*RS,*5*RS,*11*RS*)-6,7-Dimethylidene-3-oxo-2-oxatricyclo[7.4.0.0^{1,5}]tridec-8-en-11-yl Methyl Ketone* (**42**). A mixture of anh. CsF (3 g, 19.7 mmol), anh. Cs_2CO_3 (1.3 g, 4 mmol), crude **39** (1.67 g, 5.04 mmol; contains 4–20% of **40**, before separation by chromatography), anh. DMF (60 ml), and anh. HMPA (8 ml) was heated to 80° for 6.5 h in a flame-dried vessel. After cooling to 20°, CH_2Cl_2 (200 ml) was added, the soln. washed with H_2O (600 ml, 6 times), dried ($MgSO_4$), and evaporated, and the residue purified by column chromatography on *Florisil* (CH_2Cl_2) yielding 620 mg (2.4 mmol, 48%), colourless oil. Polymerizes quickly in the condensed phase. UV (dioxane): 216 (10100), 223 (12900), 230 (12600), 243 (9600). IR (CH_2Cl_2): 3080, 3010, 2960, 2880, 1780, 1720, 1370, 1230, 1170, 945. ^{1}H-NMR (360 MHz, CD_2Cl_2): 6.1, 5.35, 5.30, 5.05, 5.01 (5 *d*, *J* = 1.5, olef. H); 3.12 (*dd*, *J* = 11.5, 9.5, H–C(5)); 2.545 (*d*, *J* = 9.5), 2.54 (*d*, *J* = 11.5, CH_2(4)); 2.52, 2.44, 2.34 (3 *m*, 3 H); 2.15 (*s*, Me); 2.04–1.75 (*m*, CH_2(12), CH_2(13)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 208.9 (*s*, CO); 173.9 (*s* C(3)); 141.6, 138.9, 137.1 (3 *s*); 124.7 (*d*, ^1J(C,H) = 158, C(8)); 113.3, 112.3 (2 *t*, ^1J(C,H) = 159, CH_2 = C(6), CH_2 = C(7)); 85.3 (*s*, C(1)); 52.0 (*d*, ^1J(C,H) = 130, C(5)); 48.2 (*d*, ^1J(C,H) = 132, C(11)); 36.3 (*t*, ^1J(C,H) = 130), 34.9 (*t*, ^1J(C,H) = 135), 32.8 (*t*, ^1J(C,H) = 132), 24.4 (*t*, ^1J(C,H) = 130, C(4), C(10), C(12), C(13)); 27.4 (*q*, ^1J(C,H) = 127, CH_3CO). MS (70 eV): 258 (9), 215 (19), 198 (26), 169 (100), 155 (78), 141 (25), 128 (14), 115 (18), 91 (14), 84 (7), 52 (9). CI-MS (CH_4): 259 (61, *M* + 1), 241 (39), 229 (9), 213 (100), 199 (90), 197 (53), 181 (29), 171 (87), 169 (100), 157 (80).

3-Acetyl-1,2,3,4,5,8-hexahydro-7-(methoxycarbonyl)anthracene-9-acetic Acid (**44**). A soln. of **42** (100 mg, 0.387 mmol) in methyl propynoate (0.8 ml, 9.5 mmol) and C_6H_6 (0.4 ml) was heated to 50° for 10 h. The solvent was evaporated, toluene (10 ml) added, the solvent evaporated, and the residue dissolved in $CHCl_3$ (3 ml) and stirred with silica gel (0.2 g) at 20° for 24 h. The silica gel was filtered off and washed with acetone (10 ml). The solvent was evaporated, the residue dissolved in CH_2Cl_2 (10 ml), the soln. extracted with sat. aq. soln. of $NaHCO_3$ (20 ml, 3 times), and combined aq. layer acidified with 2N HCl and extracted with CH_2Cl_2 (50 ml, 3 times). After drying ($MgSO_4$) and evaporation, the residue was purified by prep. TLC on silica gel (CH_2Cl_2/acetone 95:5) yielding 31 mg (23%), amorphous solid. ^{1}H-NMR (360 MHz, CD_2Cl_2): 7.12 (*m*, H–C(10)); 6.89 (*s*, H–C(6)); 3.75 (*s*, MeO, $CH_2(\alpha)$); 3.57 (*m*, CH_2(5)); 3.50 (*m*, CH_2(8)); 2.86 (*d*, J = 8, CH_2(4)); 2.89–2.61 (*m*, H–C(3), CH_2(1)); 2.20 (*s*, *Me*CO); 2.18, 1.70 (*m*, CH_2(2)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 210.2 (*s*, Me*C*O); 174.4, 166.8 (2 *s*, COO); 136.0 (*d*, ^1J(C,H) = 162, C(6)); 133.8, 133.1, 130.3, 130.0, 129.6 (5 *s*, arom. C); 128.0 (*d*, ^1J(C,H) = 154, C(10)); 127.6 (*s*, C(7)); 51.2 (*q*, ^1J(C,H) = 148, MeO); 48.9 (*d*, ^1J(C,H) = 130, C(3)); 33.2 (*t*, ^1J(C,H) = 128, C(α)); 3.10, 30.8 (2 *t*, ^1J(C,H) = 130, C(5), C(8)); 27.5 (*q*, ^1J(C,H) = 127, *Me*CO); 26.6, 26.0, 25.3 (3 *t*, ^1J(C,H) = 129, C(1), C(2), C(4)). MS (70 eV): 342 (11), 324 (16), 310 (100), 296 (95), 282 (10), 265 (15), 252 (51), 237 (59), 219 (25), 207 (19), 193 (43), 179 (75), 165 (39), 152 (16), 115 (12), 71 (10), 59 (33).

Methyl 3-Acetyl-1,2,3,4,5,8-hexahydro-7-(methoxycarbonyl)anthracene-9-yl Acetate (**45**). Crude **44** (50 mg, 0.146 mmol; before purification by prep. TLC) was dissolved in a minimum of CH_2Cl_2. A soln. of CH_2N_2 in Et_2O was added dropwise until persistence of the yellow colour. The excess of CH_2N_2 was destroyed by addition of AcOH. The solvent was evaporated and the residue purified by HPLC (*Dupont-Instruments-830* liquid chromatograph, silica gel 25 × 1 cm, CH_2Cl_2/AcOEt 95:5) and recrystallization from CH_2Cl_2/hexane, yielding 40 mg (76%), colourless crystals. M.p. 107.5–108°. UV (95% EtOH): 247 (12700), 285 (2000), 296 (1880). UV (dioxane): 247 (12800), 252 (1300), 285 (1800), 296 (1600). IR (KBr): 2990, 2930, 2900, 2860, 1710, 1700, 1685, 1440, 1420, 1360, 1340, 1245, 1225, 1210, 1160, 990, 930, 905, 865, 830, 780, 750, 710, 655, 605. ^{1}H-NMR (360 MHz, CD_2Cl_2): 7.12 (*m*, J = 2, H–C(10)); 6.89 (br. *s*, H–C(6)); 3.76, 3.67 (2 *s*, 2 MeO); 3.71 (*s*, CH_2(2)); 3.58, 3.5 (2 *m*, CH_2(5), CH_2(8)); 2.87 (*d*, J = 8, CH_2(4)); 2.87–2.59 (*m*, H–C(3), CH_2(1)); 2.2 (*s*, MeCO); 2.18, 1.71 (2 *m*, CH_2(2)). ^{13}C-NMR (90.55 MHz, CD_2Cl_2): 210.2 (*s*, Me*C*O); 171.2, 166.7 (2 *s*, 2 *C*OOMe); 135.9 (*d*, ^1J(C,H) = 160, C(6)); 135.6, 133.0, 130.9, 129.9, 129.4, 127.6 (6 *s*, 5 arom. C, C(7)); 127.7 (*d*, ^1J(C,H) = 144, C(10)); 51.6, 51.2 (2 *q*, ^1J(C,H) = 148, 2 MeO); 46.8, (*d*, ^1J(C,H) = 128, C(3)); 33.7, 31.0, 30.8 (3 *t*, ^1J(C,H) = 128, C(α), C(5), C(8)); 27.5 (*q*, ^1J(C,H) = 132, *Me*CO); 26.5, 26.0, 25.3 (3 *t*, ^1J(C,H) = 128, C(1), C(2), C(4)). MS (70 eV): 356 (20), 325 (75), 296 (25), 279 (23), 251 (23), 237 (38), 219 (13), 207 (15), 193 (35), 179 (100), 165 (29), 152 (15), 141 (8), 115 (12), 103 (5), 91 (6), 59 (33). Anal. calc. for $C_{21}H_{24}O_5$ (356.41): C 70.77, H 6.79; found: C 70.70, H 6.78.

*(3a*RS,*6*RS,*14b*RS)*-6-Acetyl-5,6,7,14b-tetrahydro-13-methoxynaphthaceno[4a,5-*b*]furan-2(1*H*)-one* (**48**). A soln. of isopentyl nitrite (0.27 ml, 2 mmol) and 2-amino-6-methoxybenzoic acid (210 mg, 1.26 mmol) in anh. dioxane (1 ml) was added dropwise to a soln. of **42** (400 mg, 1.55 mmol) in anh. dioxane (2 ml) heated to 70°. The same addition was repeated after 15, 45, and 90 min. The mixture was allowed to stand at 70° for another h, then cooled to 20°, and poured into 5% aq. NaOH soln. (100 ml). The mixture was extracted with CH_2Cl_2 (80 ml, 3 times), the combined extract evaporated, and the residue purified by column chromatography on silica gel (CH_2Cl_2/acetone 95:5) yielding 194 mg (34%) of a 4:1 mixture **48**/**49**, colourless oil. IR (CH_2Cl_2): 3070, 3010, 2940, 2840, 1770, 1715, 1600, 1580, 1460, 1380, 1220, 1160, 1085, 950. ^{1}H-NMR (360 MHz, CD_2Cl_2) of **48**: 7.96 (*s*, H–C(14)); 7.50 (*s*, H–C(9), NOE with H–C(10) at 7.35 and H–C(8), at 6.47); 7.35 (*d*, J = 4, H–C(12)); 7.35 (*d*, J = 5, H–C(10), NOE with H–C(9)); 6.82 (*dd*, J = 5, 4, H–C(11)); 6.47 (*d*, J = 2, H–C(8), NOE with H–C(9)); 3.98 (*s*, MeO); 3.68 (*dd*, J = 11, 9, H–C(14b)); 2.92 (*dd*, J = 11, 9, H–C(14b)); 2.92 (*dd*, J = 17.5, 9, 1 H–C(1)); 2.71 (*m*, H–C(6)); 2.68 (*dd*, J = 17.5, 11, 1 H–C(1)); 2.54 (*m*, CH_2(7)); 2.16 (*s*, MeCO); 2.15–1.83 (*m*, CH_2(4), CH_2(5)). ^{13}C-NMR (360 MHz, CD_2Cl_2): 208.6 (Me*C*O); 173.8 (*s*, C(2)); 154.9 (*s*, C(13)); 137.4, 134.0, 131.1, 128.9 (3 arom. C, C(7a)); 126.2 (*d*, ^1J(C,H) = 160), 125.4 (*d*, ^1J(C,H) = 160), 125.4 (*d*, ^1J(C,H) = 156), 123.1 (*d*, ^1J(C,H) = 158), 120.9 (*d*, ^1J(C,H) = 160), 119.7 (*d*, ^1J(C,H) = 162, 5 arom. C, C(8)); 86.8 (*s*, C(3a)); 55.2 (*q*, ^1J(C,H) = 142, MeO); 53.2, 44.3 (2 *d*, ^1J(C,H) = 134, C(6), C(14b)); 38.6 (*dd*, ^1J(C,H) = 139, 129, CH_2(1)); 38.1 (*t*, ^1J(C,H) = 128, C(7)); 27.3 (*q*, ^1J(C,H) = 126, *Me*CO); 33.0, 24.4 (2 *t*, ^1J(C,H) = 130, C(4), C(5)). MS (70 eV): 362 (100), 319 (14), 302 (14), 273 (39), 260 (46), 259 (64), 252 (18), 250 (11), 235 (10), 217 (11), 215 (13), 202 (10), 189 (7), 178 (5), 165 (7).

Crystal-Structure Determination of **40**. Compound **40** crystallized as colourless rods. X-Ray intensity data collection was carried out with an *Enraf-Nonius-CAD4* automatic diffractometer. The crystal data, intensity collection, structure solution, and refinement methods are summarized in the *Table*. The structure was solved by *direct methods*. Positions of H-atoms were calculated and, in the final least-squares refinement, non-H-atom anisotropic temperature factors were included and the H-atoms constrained to have ideal geometry with isotropic

Table. *Crystal Data for (±)-***40**, $C_{16}H_{20}Cl_2O_3$, *Intensity Measurements, Structure Solution, and Refinement*

A. Crystal data			
Mol. wt.	331.24	Monoclinic space group $P2_1/n$	
$F(000)$	696	$a = 8.395\ (1)$, $b = 13.257\ (2)$, $c = 14.790\ (2)$ Å	
Crystal dimensions	0.28 × 0.16 × 0.10 mm	$\beta = 94.95\ (1)°$	
Peak width at half-height	0.16°	$V = 1639.8$ Å^3	
MoK_α radiation	($\lambda = 0.71073$ Å)	$Z = 4$	
Temperature	21 ± 1°	$\rho = 1.34$ g/cm^3	
		$\mu = 4.0$ cm^{-1}	
B. Intensity measurements			
Monochromator	graphite crystal, incident beam	Scan rate	1–7°/min (in ω)
Attenuator	Zr foil, factor 19.5	Scan width, deg	$0.7 + 0.344 \tan\theta$
Take-off	2.8°	Maximum 2θ	52.0°
Detector aperture	1.8 to 1.9 mm horizontal, 4.0 mm vertical	No. of reflexions measured	4443 total, 3376 unique
Crystal-detector distance	21 cm	Corrections	*Lorentz*-polarization
Scan type	ω-2θ		linear decay (from 0.958 to 1.056 on I)
			reflection averaging (agreement on $I = 1.8\%$)
			extinction (coefficient = 0.0000007)
C. Structure solution and refinement			
Solution	direct methods	Weighted agreement factor	0.065
Refinement	full-matrix least-squares	Factor including unobserved data	0.082
Minimization function	$\Sigma\omega(\|F_o\| - \|F_c\|)^2$	E.s.d. of obs. of unit weight	1.85
Least-squares weights	$4F_o^2/\sigma^2(F_o^2)$	Convergence, largest shift	0.01 σ
Anomalous dispersion	all non-H-atoms	High peak in final diff. map	0.29 (4) e/Å^3
Reflections included	1830 with $F_o^2 > 3.0\ \sigma(F_o^2)$	Low peak in final diff. map	−0.36(4) e/Å^3
Parameters refined	191	Computer hardware	*VAX11/750*
Unweighted agreement factor	0.048	Computer software	SDP/VAX (*Enraf-Nonius & B. A. Frenz & Associates, Inc.*)

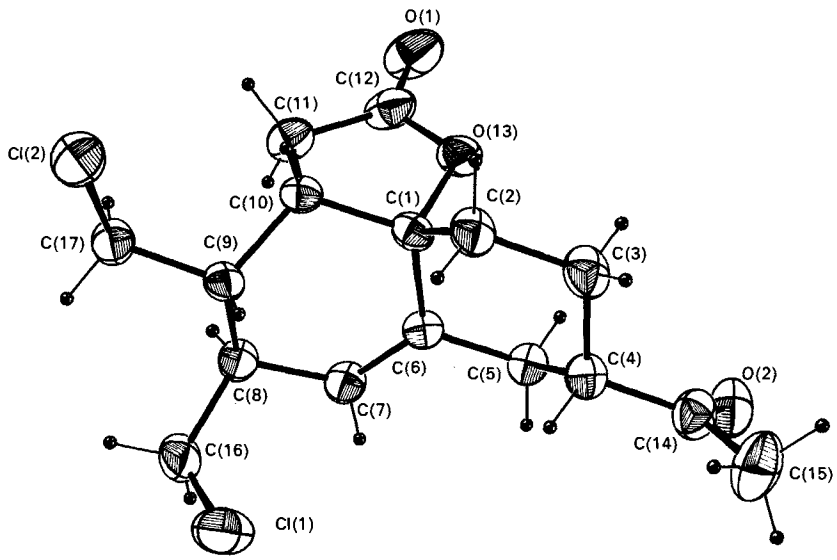


Figure. *ORTEP representation* [37] *of (±)-***40**. For reason of simplicity, the atom numbering does not follow the IUPAC rules. Heavy atoms are reproduced with 50% thermal elipsoids, the size of H-atoms is arbitrary for clarity.

temperature factors 1.3 times U(equiv.) of the bonding atom. All calculations were carried out on a *VAX-11/750*, using VAXSDP [35]. Scattering factors for the neutral atoms and anomalous dispersion coefficients were taken from [36]. A perspective drawing of the molecule is shown in the *Figure*. Tables of final atomic coordinates, calculated bond lengths and angles, observed and calculated structure factors, H-atom coordinates, temperature factors, and a detailed description of data collection, structure solution, and refinement are available as supplementary material.

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