The Pagodane → Dodecahedrane Concept—Shorter Routes, Higher Yields

Martin Bertau, Jürgen Leonhardt, Andreas Weiler, Klaus Weber, and Horst Prinzbach*

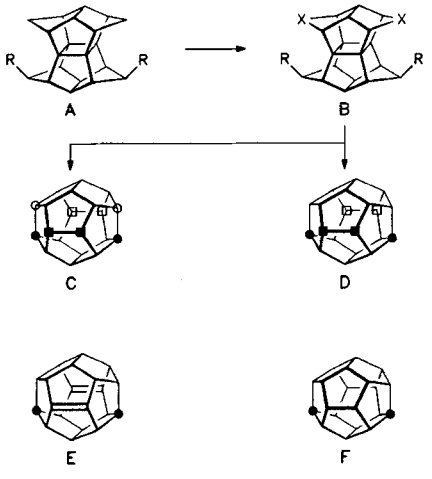
Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday

Abstract: Two variants of the "S_N2 route" from pagodanes (**A**, **B**) to functionalized dodecahedranes (**D**, **F**) and particularly dodecahedradienes (**E**) offer considerable improvements in the number of operations (from nine to five to three) and yields (e.g., for diester **F** from 55–65 to 70–75 to 85–91%). Key steps are the regio- and stereospecific introduction of four to six bromine substituents into dimethyl pagodane-4-*syn*,9-*syn*-dicarboxylate (**1b**) and a highly complex (thirteen bond-breaking/bond-forming events in four participating structures), yet very convenient (one-pot operation) and extremely efficient (nearly quantitative) transformation of secopagodane to bissecododecahedradiene with complete stereocontrol in transannular CH_2 functionalizations. The prohibitively low kinetic acidity of "caged" hydrogens has so far only been overcome with the recently reported P_2F reagent (Schwesinger). Further improvement of the overall economy of the pagodane → dodecahedrane scheme has been achieved by efficiently channeling a by-product of the pagodane synthesis (ca. 10%) back into the S_N2 track.

Keywords
cage effects · dodecahedranes · organic synthesis · pagodanes

Introduction

Pentagonal dodecahedranes with broadly variable functionalization patterns are accessible ultimately from isodrin[1] along the "aldol route" and "S_N2 route" (**C**,[2] **D**[3]) via the 4,9-di- and 4,9,14,19-tetrasubstituted pagodanes **A** and **B**.[4] Prominent members of the **D** family are the disubstituted 1,16-dodecahedradienes **E** and their saturated analogues **F**, which we have used as the starting points of synthetically as well as theoretically intriguing projects, such as preparatively superior access to the parent $C_{20}H_{20}$ hydrocarbon, to totally substituted $C_{20}X_{20}$ derivatives,[5] to nonpentagonal dodecahedranes,[6] to novel C_{40} and C_{60} cage structures,[7] to caged radical cations[8] and dications[9] with unusual properties and novel electronic configurations, and potentially to the C_{20} fullerene.[5] Interest in the last has resulted in expanding demand for basic dodecahedral compounds, which has heightened the pressure for more preparative economy and for the improvement of synthetic processes not long ago hailed as nearly optimal.



In this paper we describe successful efforts in this direction and present two variations of the S_N2 route, which are not only much less time-consuming, but also significantly more efficient.[10, 11]

Results and Discussion

New S_N2 route (1): The first variant consists, in principle, of a novel access to an intermediate of the original S_N2 sequence.[3] To ease the comparison and the assessment of the progress achieved, the original route is shown in Scheme 1 as the sequence **1a** → **2** → **3** → **4** → **5(6)** → 7 → **8**. In this route, the 13-*anti*,18-*anti* leaving groups (Br) needed for the final cyclization steps (7 → **8**) are introduced into the 4-*syn*,9-*syn*-pagodane dicarboxamide **1a**, prepared by a slightly modified standard pagodane synthesis,[12] via the diketodinitrile **2** and bislactone **3**. Though the multitude of bond-forming and bond-breaking steps involved in the transformation of **1a** into **8** is accomplished in only nine one-pot operations with a total yield of about 50%, the sheer amount of time needed for the preparation of gram quantities of material remained a limiting factor. The new version, juxtaposed in Scheme 1, starts from 4-*syn*,9-*syn*-pagodane diester **1b**, a direct offspring of the standard synthetic procedure,[12] and reenters the original track at the stage of the secotetrabromide **5**, after addition of bromine to the four-membered ring (to give **9**), four hydrogen-substituting

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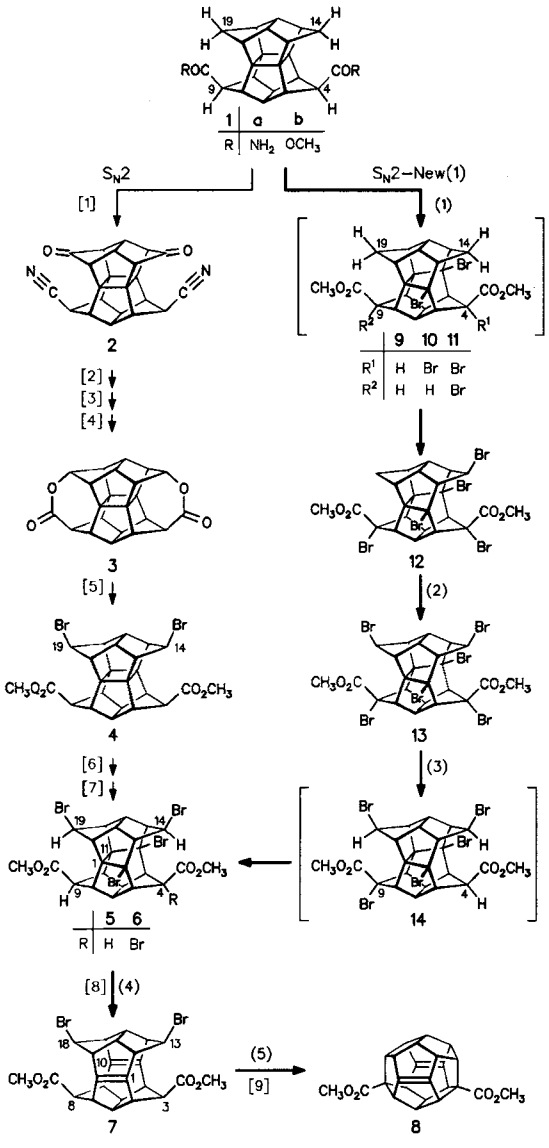


Scheme 1.

brominations (to give **10**, **11**, **12**, **13**) and two bromine-substituting hydrogenations (**14**, **5**). The functionalization of the two nonactivated methylene positions, which for pagodane dicarboxamide **1a** is effected by means of the astonishingly productive Barton-type oxidation (→ **2**) and here furnishes the crucial 2,4,9,12,14,19-hexabromide **13**, is now brought about in the secopagodane skeleton (**11**, **12**) by radical bromination.

There were some early hints with respect to the selectivities involved in the introduction of the six bromine atoms of **13**. From exploratory photobromination experiments with diester **1b**,[13] we knew that under controlled conditions seco-2,4,12-tribromide **10** can be obtained with at least 90% selectivity together with trace amounts of 2,4,9,12-tetrabromide **11** and 2,4,9,12,14-pentabromide **12**, and that under more vigorous conditions up to 85% of **12** together with 5% of a hexabromide are formed. Later, when working on the S_N2 route, particularly on the generation of 2,12,14,19-tetrabromide **5**, it was realized that addition of bromine to **4** (to give **5**) cannot be separated from substitution (to give **6**) and, a decisive feature, that the component isolated in about 5% yield together with 92% of 2,4,12,14,19-pentabromide **12** is indeed the desired hexabromide **13**. This latter discovery, together with the team's growing impatience, was sufficient incentive to resume the search for, ideally, a onepot transformation of **1b** →**13**; this would have meant a short cut to **5** and hence to **8** by four operations.

To cut a long story of trial and error short, there was no way for an efficient one-pot hexabromination **1b** →**13**; in a series of photobromination experiments, the latter never resulted as a dominant component in the rather complex mixtures of higher bromides obtained. Still, the access to pentabromide **12** described above could be optimized to a reproducible yield of 93–95% along with 3–5% of tetrabromide **11**, easily separable on silica gel. As a more mechanistic hint, after longer irradiation times **11** was still present in a comparable percentage. It is essential in this context of analyzing and separating the bromide mixtures that for these higher substituted bromides the hydrolysis of the tertiary C–Br bonds does not pose a problem as previously experienced, for example, with **9**.[10] With pure pentabromide **12** as starting material, the use of still higher concentrations of bromine, higher fluxes of light, higher reaction temperatures, and longer reaction times could not bring about a nearly total conversion to **13**. A high stationary concentration of HBr and trace amounts of water[14] were found to make the difference: in the final protocol, the refluxing solution of **12** and about one hundred equivalents of Br_2 in distilled but not dried CH_2Cl_2 saturated with HBr was irradiated with a 300 W daylight lamp (Pyrex vessel) until the composition of the reaction mixture remained constant (48 h, 2.0 mmolar scale); 90–92% of pure **13** were separated from 4–5% of **12**, traces of other components,[15] and polymers by filtration through silica gel (CH_2Cl_2/CCl_4 1:1); again, the fact that conversion of **12** was incomplete had to be accepted, since longer irradiation led only to more polymers.

These polybromination reactions deserve some comment. According to calculations (MM2, MM3[16]),[17] substitution at any of the bridgeheads[18] in the pagodane **1b** and the secopagodane skeleton of bromides **9**–**13** is energetically unfavorable (cf. the findings with, e.g., norbornane[19]); the total absence of higher bromides in the increasingly "brutal" photobrominations **11** →**12** and **12** →**13** is nevertheless a happy coincidence. In fact, in the [2.2.1.1] and the iso[1.1.1.1]/[2.2.1.1] pagodanes the preferences are totally different.[13, 20] Several pieces of evidence point to the mechanistic complexity of the formation of **12** and **13**; besides the failure to bring about total conversions, these include the identification of the dibromopagodane **4**, the tetrabromide **5**, and the 2,4,9,12,19-pentabromo isomer of **12** ("iso-**12**") as the trace components (<1%) observed in the combined residues of several runs, with halodehalogenations as potential complications.[21] With respect to the CH_2 brominations **11** →**12** →**13**, recent studies with the parent pagodane[17] (cf. Scheme 12) demonstrate that the *syn*-ester groups in **10** and **11** do not necessarily provide anchimeric assistance.[3] At this point it is worth mentioning the influence of added iodine upon the outcome of the bromination of diester **1b**. 4-*anti*(9-*anti*)-Iododebromination was presumably involved when, in a typical run with 1.0 mmol of **1b** in the presence of 0.1 mmol of iodine, dibromide **9** was produced cleanly; in the presence of 0.01 mmol of iodine the tetrabromide **11** was the exclusive product (no CH_2 functionalization).

For the hydrodebrominations **13** →**14** →**5** the crowding of the eight functional groups around the molecular periphery and particularly the layout of the six bromine atoms in **13** as visualized with the Schakal plot[22] in Figure 1

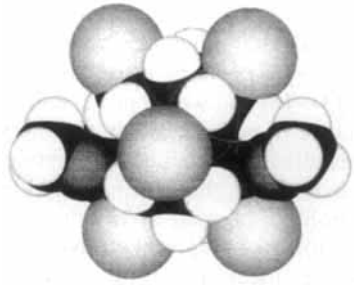
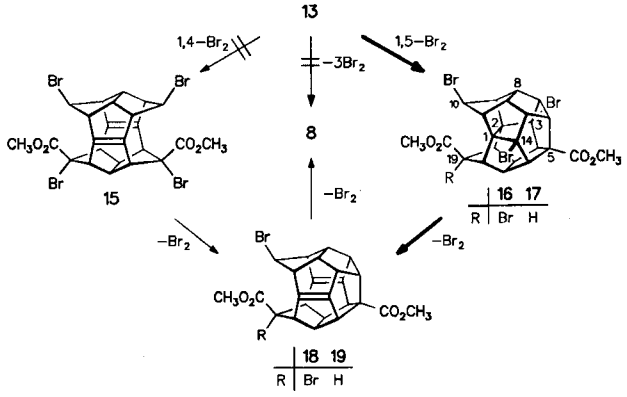


Fig. 1. Schakal plot of hexabromide **13**.

caused doubts about the implied selectivity. Both these reactions profit from strain release, the one at C4 more than at C9; for angular as well as electronic reasons the reduction at C4 should be faster. In the experiment, exposure of **13** to the catalytic hydrogenation conditions previously applied to the reductions **6** → **5** and **10** → **9** (Pt/CH_2Cl_2; most of the HBr generated is expelled with the H_2 stream) rapidly und exclusively produced the 2,9,12,14,19-pentabromide **14** (isomer of **6** and **12**); under more forcing conditions, however, C–Br bonds other than C9–Br were also involved (the 12,14-*anti*,19-*anti*-tribromide was characterized, see Experimental Section). Yet this hurdle was overcome when the addition of small, defined amounts of methanol (activation of the catalyst?) induced the smooth twofold reduction **13** → **14** → **5**; when larger amounts of methanol were added, the reduction of the tertiary C–Br bonds became competitive (the 2,14,19-tribromo analogue of **10** has been identified).

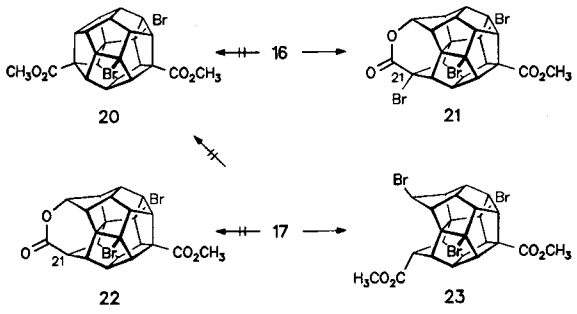
With tetrabromide **5**, reentry into the original S_N2 route was accomplished; the new version accounts for a cut from nine to five operations (**1b** → **12** → **13** → **5** → **7** → **8**) and for an increase of the total yield based on the last common precursor ([2.2.1.1]pagodanediones[12]) from 55–65% to 70–75%, now reproducibly achieved on a 1–2 g scale.

At this point, we had to ask whether full advantage had been taken of the synthetic potential offered by hexabromide **13**. Given the positioning of the six bromine substituents, what about combining metal-mediated radicaloid 1,4- and ionic 1,5-bromine eliminations, as illustrated in Scheme 2, with the reaction sequences **13** → **15** (or **16**) → **18** → **8**? After all, the best possible outcome, direct execution (**13** → **8**), would mean a further shortening by two operations. A certain analogy to these pathways had been seen in the mass spectrum of hexabromide **13**; the fragmentation pattern demonstrated the sequential loss of $3\,Br_2$ and $2\,CH_3OCOH$, and intense signals at $m/1 = 252$ and $m/2 = 126$ that were ascribed to $C_{20}H_{12}$ dodecahedratetraene(s).[2, 3, 23] With the better accessibility of **13** our exploratory efforts[2, 3] were reactivated in the hope that, under one or another set of proven conditions (Zn; Fe; $Fe/NaI/Na_2SO_3$; DMF, ≥150 °C), either the fragmenting 1,4-bromine elimination (**13** → **15**) could be made faster than the lateral 1,5-cyclization (**13** → **16**) and would proceed directly to **18** and **8**, or the reluctance of isododecahedranes of type **16** (**17**) to undergo fragmenting 1,4-bromine elimination could be overcome. It was understood, though, that any kinetic discrimination would be problematic, that in **13** other modes for bromine elimination (Grob-type fragmentations) do exist, and that in addition all dienes involved are, for different reasons, sensitive to radicals and electrophiles.



Scheme 2.

In practice, the threefold Br_2 elimination **13** → **8** could not be achieved. Unlike pentabromide **6**,[3] hexabromide **13** was not transformed into **15** upon treatment with Zn (Fe) at 120 °C, but nearly quantitatively into isododecahedrane **16**; at 153 °C the latter was only reduced to **17**, which yielded only traces of **19** or none at all. Even though this hurdle could be overcome with a change in the reducing agent (n-Bu_3SnH), yields no better than 40–50% of **19** did not look promising. Remarkably, exposure of **16** to KI in refluxing DMF again provided neither **18** (cf. the straightforward elimination **28** → **30** in Scheme 6) nor didehydrododecahedrane **20**, but instead the two-atom-bridged isododecahedrane **21** (Scheme 3) in high yield (92%); lactonization after attack of iodide ion at the α-brominated and hence particularly compressed *syn*-ester group of **16** profits from a considerable gain in strain energy. Structure **21**, derived from the spectral data (Fig. 2), was unequivocally established by its reductive conversion (n-Bu_3SnH) into the known O–CO-bridged homododecahedradiene.[6] Treatment of **17** with NaH/THF again did not yield either **20** or **22** but the epimerized **23**.[3]



Scheme 3.

In Figure 2 the ^1H and ^{13}C NMR data are presented for the secopagodane polybromides **11**, **12**, **13**, and the bridged isododecahedrane **21**; for completeness the previously unreported data of dibromide **9** and the tribromides **10** and *iso*-**10** are included. As pointed out before,[2, 3, 13] with α-bromination the rotation of the ester groups is hindered to such an extent as to make rotamers observable at room temperature; in order not to overload the illustrations, the double (and triple...) ^{13}C shifts of rotamers are not given.

New S_N2 route (2): In essence, the second variant of the S_N2 route shares the starting material **1b** and the formation of the two lateral C–C bonds by S_N2 substitutions on a 3,8,13,18-tetrafunctionalized bissecododecahedradiene with the first route, but differs in the way **1b** is transformed into the bissecodiene intermediate.

The background for the strategy followed here is found in classical work by Prelog and Schenker on transannular reactivity in medium-sized rings,[24] particularly on the functionalization through 1,5-transannular hydride (hydrogen) transfer in eight-membered rings which are embedded in rigid polycyclic molecular skeletons **G** (Scheme 4).[25] Proper orientation of the bonds involved and 1,5-C–C distances not much more than twice the van der Waals carbon radius are prerequisites for the degree of cooperativity postulated with the nonclassical, "symmetrical" transition states **H** and hence for the strict inversion at both ends in the products **I**.

In the pagodanes (e.g., **24**), the secopagodanes (e.g., **10**), and the bissecodienes (e.g., **29**), the lateral half-cages can be viewed as being made of such conformationally frozen eight-membered

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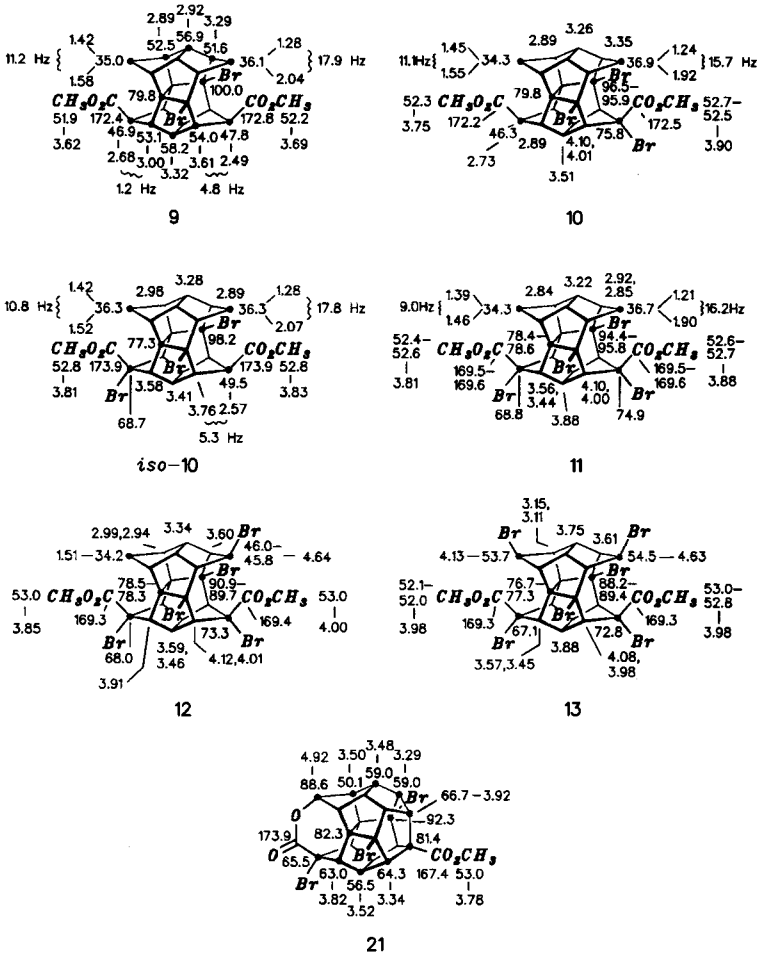
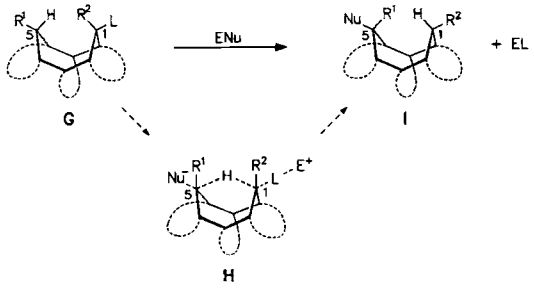
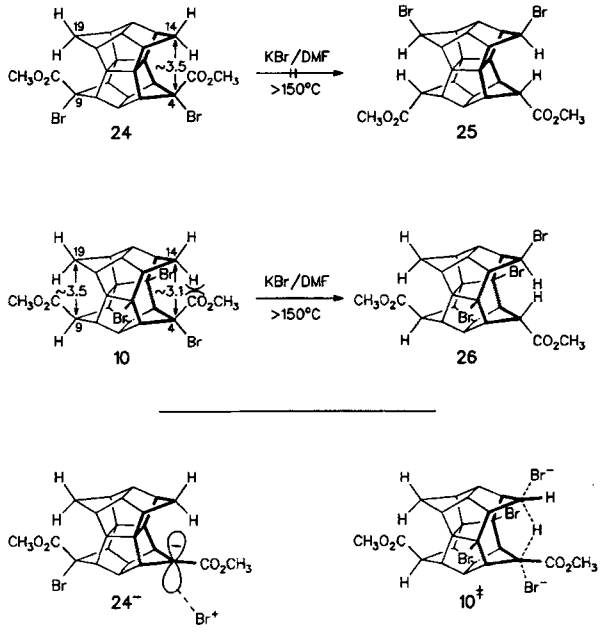


Fig. 2. ^1H, ^{13}C NMR ($CDCl_3$, δ, J (Hz)) data for the brominated secopagodanes **9**, **10**, *iso*-**10**, **11**, **12**, **13**, and homoisododecahedrane **21**.



Scheme 4.

rings with 1,5-distances ranging from about 3.5 to about 3.0 Å.[12, 26] At least in the latter situations, it should be possible to use transannular reactions of the type **G** → **I** for specific *anti*-functionalization; the bromines at the ester-carrying carbons would function as nucleofuges L. The adverse influence of the α-ester groups, weakened but still operative even in highly concerted transition states (**H**), should at least partly be offset by the gain in strain energy when this large group is shifted from the *syn*- to the *anti*-side of the half-cages. After all, even for the relatively "distant" situation in diester **1b** the strain increment for one H/CO_2CH_3 pair is of the order of 7 kcal mol^{-1};[27] on the "open" side of **11** (no free rotation any more for the ester group), this increment is estimated to be significantly larger. As the experiments with pagodane **24** and secopagodane **10** (Scheme 5) revealed, the loosening of the ester-deactivated

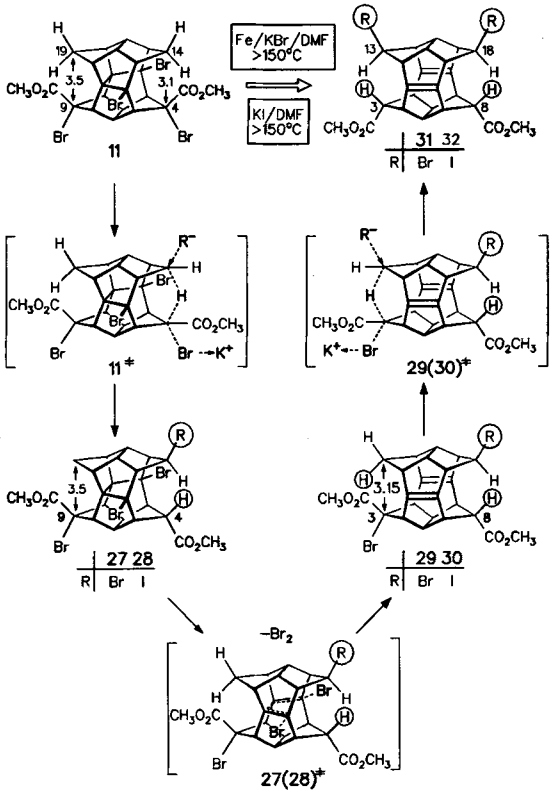


Scheme 5.

C–Br bonds as initiating step needed rather forcing conditions, with the distinction between "closed" (3.5 Å) and "open" (3.0–3.1 Å) sides becoming clear: after boiling a solution of **24** in DMF (this solvent providing high ionizing power and a broad temperature range) for hours, no change at all had occurred. In contrast, under the same conditions a good part of **10** (ca. 50%) had been transformed after only minutes into the 4-*anti*-,14-*anti*-isomer **26**. Addition of increasing amounts of KBr (as the source of electrophile E^+ and nucleophile Nu^- in **H**) had no effect on the outcome with **24**, but speeded up the reaction **10** → **26**. The latter, however, was not stable under the given conditions, the C9–H bond presumably being the weak point.

Scheme 6 illustrates how we envisaged a breakthrough in the form of a highly economical access to all-*anti*-3,8,13,18-tetrasubstituted bissecodiene **31** (**32**) with the tetrabromide **11** as starting material and with the insights gained from models **24** and **10**: transannular functionalization on the "open" side of **11** (→**11**‡ → **27**), fragmenting 1,4-bromine elimination in **27** (→ **27**‡ → **29**; the other side is now "open"), and transannular functionalization in the diene **29** (→ **29**‡ → **31**), ideally executed as a one-pot operation. Selectivity hardly seemed a problem: in **11** and **26** with C9/C19 distances of approximately 3.5 Å, similar to C4/C14 in **24**, the "closed" sides should not interfere; only in the elimination **27** → **29** was competitive cleavage of the C9–Br bond in **27** and of the C3–Br bond in **29** (cf. **16** → **17**) judged to be a potential complication.

The basis for the experiment was provided in a most satisfying manner when, by means of modifying the photobromination procedure **1b** → pentabromide **12** (primarily in temperature and reaction time), we developed a protocol for the nearly exclusive formation of tetrabromide **11** (93–95% besides traces of **12**). Treatment of **11** with KBr/DMF, as elaborated for **24**, furnished a nearly quantitative yield of **27**; nothing had happened to the "closed" sides of **11**/**27**, and the latter, unlike **26**, proved to be insensitive to the reaction conditions. When control experiments had shown that addition of **27** to a boiling suspension of Fe powder in DMF yielded no C_s-diene **29** but only C_{2v}-diene **31**, and that the functionalization **11** → **27** was much faster than



Scheme 6.

the elimination **27** → **29**, a "direct" conversion **11** → **31** could be designed. To this end, **11** was added to the boiling suspension of KBr/Fe/DMF: the deep red color changed into yellow after three minutes, and the crystalline material collected after aqueous workup was practically pure **31** (99%, mmolar scale).

When it was necessary to replace the bromines in **31** by better leaving groups (vide infra), the diiodide **32** was prepared from **11**, with the modification that with the reduction potential of iodide ion being high enough to bring about the elimination **28** → **30**, the protocol was simplified to boiling the suspension of **11** and a large excess of KI in DMF. From a standardized run with **11** (1.0 g, 1.44 mmol) and KI (3.0 g, 18.0 mmol), 900 mg of colorless, crystalline, high-melting **32** (99%, m.p. >297–300 °C, decomp.) was isolated. Clearly, the liberated bromide ions do not compete in the transition states **11*** and **30***.

The NMR data for the bissecodiene **31** (Fig. 3), and similarly for **32**, manifest discrepancies compared with those of isomer **7** which are typical for the change in stereochemistry at C-3(8) such as a significant paramagnetic shift for the 3*syn*(8*syn*)-H and 13*syn*(18*syn*)-H signals ($\Delta\delta = 0.79$ and 1.19 ppm, respectively), primarily as expression of the absence of an anisotropic influence by the *syn*-ester groups and of strong H/H compression. In the MS spectrum of **31** once again the high intensity of the signals with $m/z = 252-256$ ($m/2z = 126$) is noteworthy; the UV spectrum features a shoulder at 279 nm ($\varepsilon = 280$) as expression of the π,π-homoconjugation.[13]

Chemically, there are the expected analogies with **7**:[3,4,27] clean [2+2] photocycloaddition (**31** → **33**, Scheme 7), homoconjugate addition, for example, of Br_2 (**31** → **34**) to the proximate C=C double bonds, resistance to acting as π_2 component in cycloaddition reactions, saturation by N_2H_2 of only one of the hyperstable C=C double bonds (**35**, **36**). Epoxidation (*m*-chloroperbenzoic acid) was unproblematic for **31** (giving **37**, **41**) and **35** (**39**) but complicated for **32** at the stage of **38** and for **36** (oxidation of iodine substituents, no **40**, **42**).

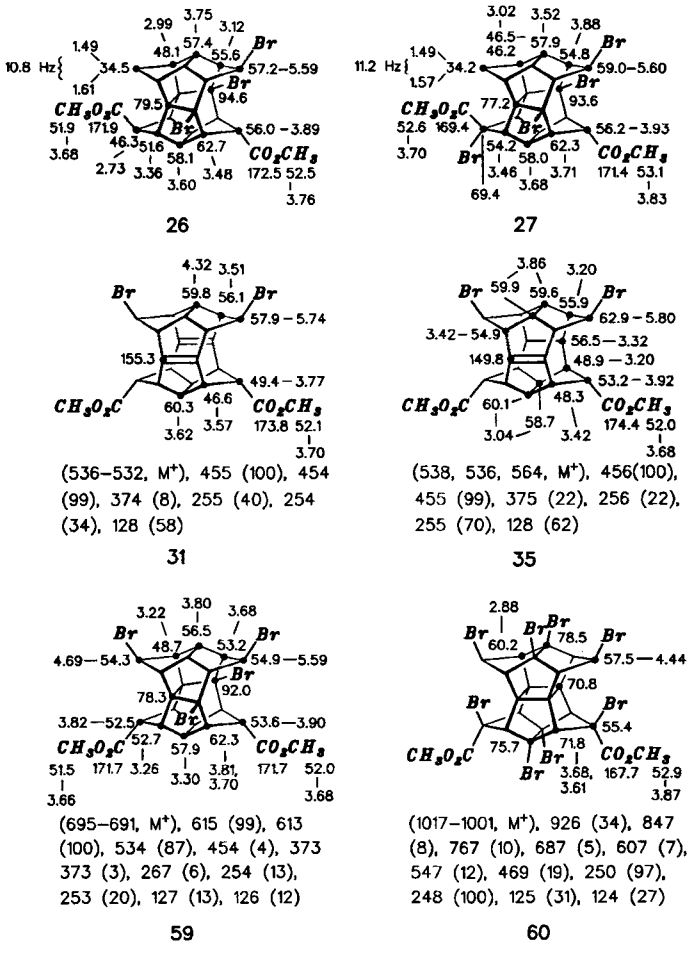
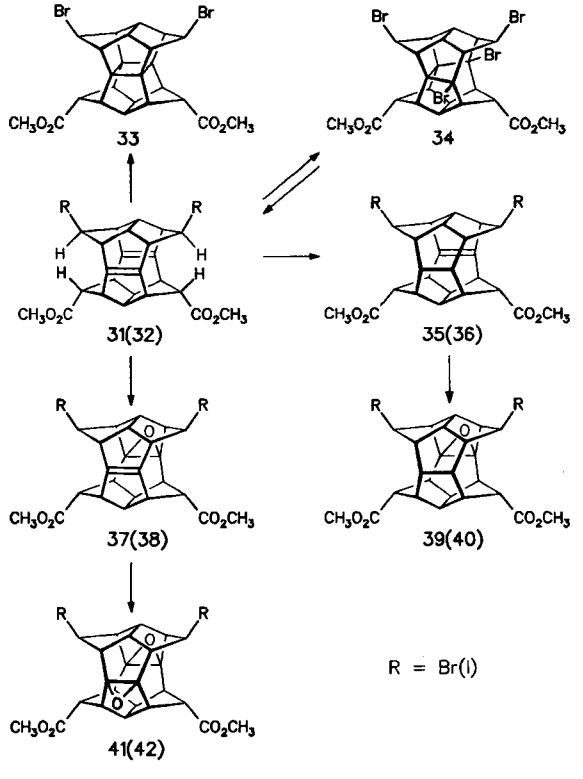


Fig. 3. ^1H, ^{13}C NMR ($CDCl_3$, δ, J (Hz)) and MS data (m/z (%)) for the brominated secopagodanes **26**, **27**, **59**, the bissecoolefins **31**, **35**, and pagodane **60**.



Scheme 7.

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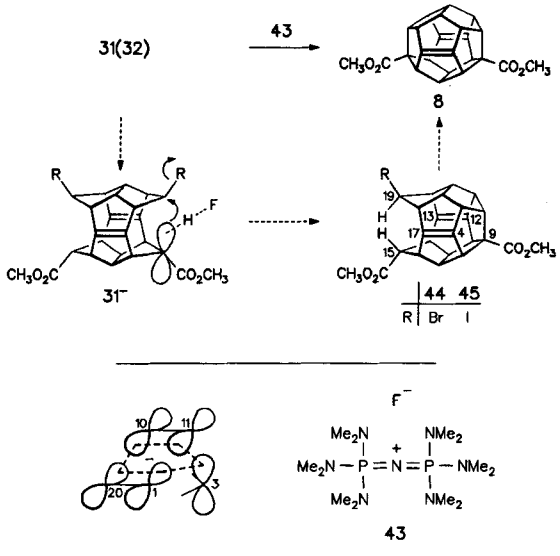
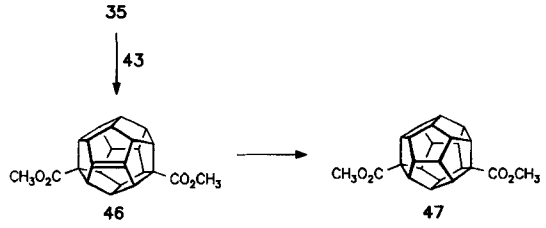
Because of its highly pyramidalized olefinic carbons ($\Phi = 43°$), the dodecahedradiene **8** is extremely sensitive to oxygen and strong nucleophiles. For the high yields achieved in its generation from **7**[3] it was necessary to work under careful exclusion of air and to utilize base systems (inter alia *tert*-Bu-P_4 base[29]) that were compatible with the functionalities present and allowed a rapid isolation procedure (by filtration and concentration, no aqueous workup). With these restrictions and with the kinetic acidity of the 3*syn*(8*syn*)-hydrogens in bissecodiene **31** and similarly of the 15*syn*(19*syn*)-hydrogens in the secodiene intermediate **44** being reduced by an estimated 5 pK_a units as a consequence of smaller steric strain and lessened accessibility, problems were anticipated for the generation of **8**. On the other hand the latter's rather high thermal stability was expected to allow conditions sufficiently forcing to overcome this barrier. It therefore came as a shock when no base, not even those successfully utilized for the cyclizations **7** → **8**, effected any deprotonation of **31**, even under conditions coming close to the destruction of substrate and base, until the P_2F reagent **43**, reported recently by Schwesinger,[30] could be tried. The "naked" fluoride ion, a small, weak nucleophile yet very strong base, readily soluble in benzene as the solvent of choice, did the job if provided with an absolutely dry and oxygen-free environment (glovebox). However, even when this base was added in at least twofold excess (the liberated HF "neutralizes" one equivalent by F–H–F bonding) up to 50% of material was lost, presumably by polymerization. When control experiments proved **8** to be stable under the given conditions, there was speculation that if S_N2 substitution by the incipient *syn*-anions was not fast enough (**31**$^-$ → **44**; **44**$^-$ → **8**, Scheme 8), competitive interactions with the proximate C=C double bonds (potentially in the sense of the 5c/6e trishomoaromatic ions[31] or intermolecularly) would start polymerization. In this situation, we resorted to the diiodide **32**; and indeed, under otherwise analogous conditions, polymer formation was largely avoided—so far, however, only on a small scale (100 mg, >95%); on the mmolar scale the yield of isolated (purified) diene **8** drops to as low as 80%. Up to 10% of the missing material has been found as the monoacid derivative of **8** which was retained on the silica gel column together with the P_2 salts; after elution with polar solvents they are utilized for the generation of **47**. This partial saponification is caused by the (so far unavoidable) admixture of P_2OH (5–10%) with the P_2F reagent.



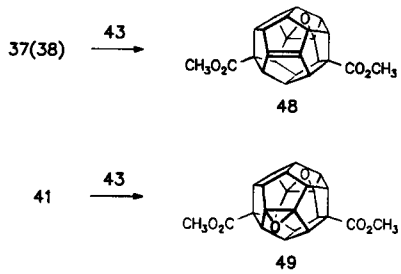
Scheme 8.

Remarkably, and in line with the above speculation about the involvement of both C=C double bonds in the polymerization of **31**$^-$ (**44**$^-$), in the analogously performed small-scale cyclization of monoene **35** to dodecahedrene **46**, polymerization did not interfere (Scheme 9). For the saturated dodecahedrane-1,6-diester **47** the one-pot "hydrogenating cyclization" described for **7** → **47** could be applied; after cyclization of **32** (cf. **8**) the reaction mixture was directly subjected to catalytic hydrogenation and aqueous workup, which allows the convenient isolation of **47** in 90–92% yield on the g scale. The 5–8% of monoacid isolated in addition brings the total yield close to quantitative.



Scheme 9.

In contrast, with the ene epoxide **37** as well as with the diepoxide **41**, the amount of polymerization accompanying the formation of the epoxydodecahedranes **48** and **49** increased again to 40–50% (Scheme 10). With diiodide **38** polymerization could only partially be circumvented (ca. 70% **48**). Backside epoxide opening by the incipient *syn*-α-ester anion is suspected of initiating the polymerization, once more marking a mechanistically interesting difference between the fate of the α-anions (enolates) derived from the *syn*- and *anti*-(bis)secopagodane esters. Another potential complication is the suspected homoconjugative attack by F–H–F$^-$ on the ene epoxide.



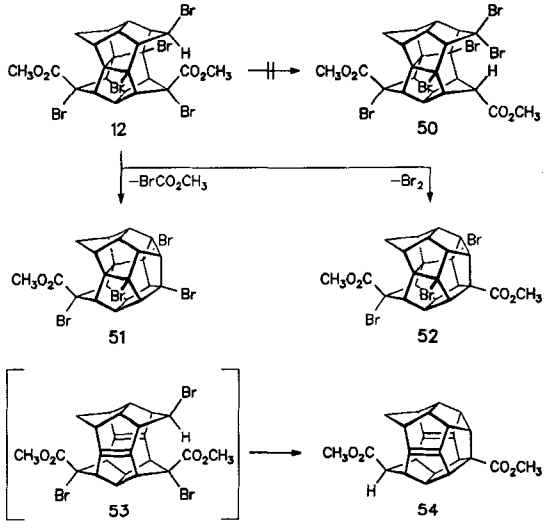
Scheme 10.

Conclusion

A search for alternatives to a proven synthetic procedure is not necessarily a popular endeavor; for the pagodane → dodecahedrane scheme, however, the quest for more economical routes led to some intriguing developments. And indeed, the reward for intensive experiment and repeated frustrations lived up to the highest expectations: the two variants of the original S_N2 route make for significant savings in time—from months to weeks to days—and for substantial increases in total yields, for example, for saturated diester **47** as prominent dodecahedrane of type **F** from originally 55–65% to 70–75% to 85–91%; this can be extrapolated to approximately 75% based on **1b** for the recently presented route to parent $C_{20}H_{20}$ dodecahedrane.[5, 32] The complications met in the cyclizations of **31** and **41**, so far not understood, represent some limitations in the application of the P_2F base. With regard to this second variation, it is also appro-

priate to comment that the acquisition of the P_2F reagent of the necessary quality is demanding[33] and its proper handling needs experience (it is commercially available but rather expensive).[34] More mechanistically, there are compelling demonstrations of "selectivity", such as in the introduction of four to six bromine substituents into the pagodane diester **1b**, or in the combination of $2\sigma \rightarrow 2\pi$ isomerizations with C,H-activation in the one-pot transformations **11** → **31** (**32**).

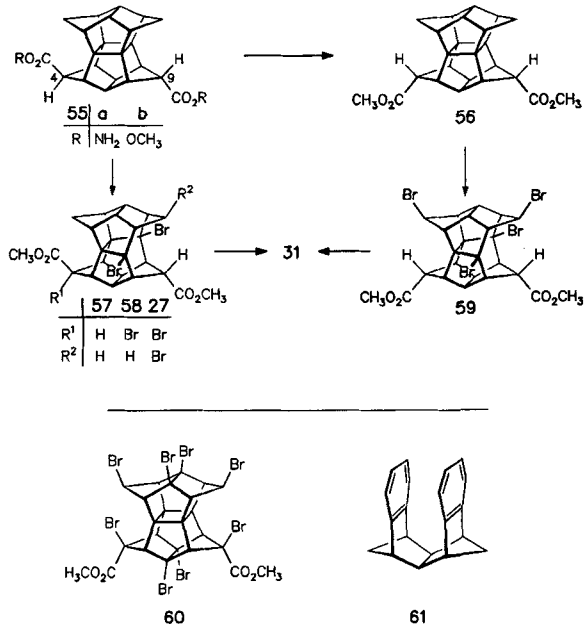
Can the strategy for CH_2-functionalization, so marvellously successful in the second new route (e.g., **11** → **31**),[35] be put to further synthetic use to permit the introduction of other functional groups? A notable limitation has already been met: unlike tetrabromide **11**, pentabromide **12** under analogous conditions did not undergo transannular H-transfer to give **50** with its sterically highly demanding CBr_2 unit. Instead, depending on the reagent used, after far from uniform reaction courses the *iso*-dodecahedrane **51** (KBr/DMF, 150 °C; ca. 50%, and 5% **52**) and the secododecahedradiene **54** (KI/DMF, 150 °C; ca. 50%, most probably arising from diene **53**) were obtained (Scheme 11). When considered alongside the behavior of pago-



Scheme 11.

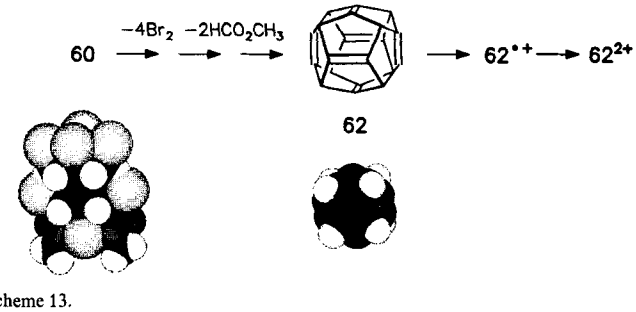
dane **23** and secotribromide **10**, this outcome with **12**, suggestive of S_N2 cyclization after attack of Br^- at either C3–CO_2CH_3 or C3–Br, convincingly emphazises the fortuitous aspect in the uniformity of the sequence **11** → **31**. Clearly, differences in the substituents and the steric impact of the respective secopagodane half-cages are crucial for the selectivities, the degree of anchimeric assistance, the cooperativity in and timing of individual transformations.

In this context it is appropriate to address a recent improvement of the overall economy of the pagodane → dodecahedrane scheme. There was a weak point: because of incomplete stereocontrol in the photo-Wolff rearrangement leading to 4-*syn*,9-*syn*-diamide **1a** and diester **1b**,[12] up to 10% of their *syn*,*anti*-isomers **55a,b** were produced and had amassed over the time in multigram quantities. Scheme 12 shows how advantage was taken of the reactivity differences for the two secopagodane half-cages and particularly of the selectivities involved in the polybromination of *syn*,*syn*-diester **1b** in order to channel **55a,b** back into the new S_N2 track (2). In short, when subjected to the bromination procedure *syn*,*syn*-diester **1b** → pentabromide **12** (Scheme 1), diester **55b** yielded tetrabromide **27** nearly quanti-



Scheme 12.

tatively (95%; >90% **31**)—in line with strain considerations, the initial addition of bromine to the four-membered ring occurred regiospecifically from the side of the "*anti*" ester group (the *syn*-ester group stays with the wider "closed" side),[36] dibromide **57** was exclusively brominated at C-9, tribromide **58** at C-14, and tetrabromide **27** resisted further substitution. Diamide **55a** was first transformed into the *anti*,*anti*-diester **56** (85–92%) whose bromination under forcing conditions (cf. **12**, **27**) only marginally involved the α-ester positions and led nearly uniformly to the tetrabromide **59** (90–95%; two trace components identified as the unusually densely functionalized octabromopagodane diester **60** and the totally defunctionalized pagodane precursor **61** indicate the mechanistic intricacies inherent in these polybromination reactions); standard fragmenting bromine elimination provided 90% of bissecodiene **31** (overall 65–70%).[10] The essential data proving the structures of **59** and **60** are listed for comparison in Figure 3. As a glimpse into the future, the MS fragmentation pattern of **60** again nourishes speculation about the nature of the ions $m/z = 248$ (100%) and $m/2z = 124$—signs of the existence of $C_{20}H_8$ dodecahedrahexaene **62** (T_d symmetrical with all double bonds nonconjugated and "protected" by four allylic hydrogens), of the 12c/11e radical cation $\mathbf{62}^{\bullet+}$ and (hexahomoaromatic) 12c/10e dication $\mathbf{62}^{2+}$ (Scheme 13)? To summarize, the base for further activities in the dodecahedrane area has been broadened. Dodecahedranes for everybody? The route from isodrin to the pagodanes **1a,b** (**55a,b**) remains long and strenuous.



Scheme 13.

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Experimental Section

Experimental data were recorded as follows: melting points (m.p.), Bock Monoscop M; analytical TLC, Merck silica gel plates with F_{254} indicator; IR, Perkin–Elmer 457 and Philips PU 9706; UV, Perkin–Elmer Lambda 15; ^{1}H NMR, Bruker WM 250, AM 400 (if not specified otherwise, the 250 MHz spectra are given); ^{13}C NMR, AM 400 (100.6 MHz); MS, Finnigan MAT 445 (if not specified otherwise, the spectra were taken at 70 eV). Chemical shifts were recorded relative to TMS ($\delta = 0$), and coupling constants are in Hz. For signal assignment, standard techniques such as homo- and hetereonuclear decoupling experiments, 2D FT COSY or heterocorrelation spectra were employed; assignments indicated with * (+) can be interchanged. Generally, the H,H and C,H connectivities were established by two-dimensional homo- and hetereonuclear correlated spectra. Whenever necessary, NOE measurements were performed to elucidate stereochemical (transannular) relationships.

Bromine was distilled before use. The cyclization experiments with P_2F were performed with best possible exclusion of air and moisture (glovebox). For the yields given, the base must be of perfect quality.

Dimethyl 2,4-*anti*,9-*anti*,12-tetrabromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*syn*,9-*syn*-dicarboxylate (rotamers) (11): A solution of **1b** (1.50 g, 4.00 mmol) and bromine (25 mL, 490 mmol) in dry CH_2Cl_2 (225 mL), purged with argon, was irradiated at 0 °C with a 150 W Hg low-pressure lamp (solidex tubes) until TLC (cyclohexane/ethyl acetate = 4:1) showed total conversion of **1b** and of intermediate bromides (R_f (*iso*-**10**) = 0.26, R_f (**11**) = 0.32) and the presence of only **11** besides traces of **12** (R_f (**11**) = 0.32, R_f (**12**) = 0.40) (60–90 min; irradiation up to 8 h did not significantly alter the composition). After concentration in vacuo, the solid residue was chromatographed on silica gel (15/5 cm, CH_2Cl_2/CCl_4 1:1, R_f(**11**) = 0.30, R_f(**12**) = 0.42) to provide **11** (2.58–2.64 g, 93–95%) besides pentabromide **12** (93–155 mg, 3–5%); ^{13}C NMR ($CDCl_3$): δ = 169.6, 169.5, 169.5, (C=O), 95.9, 95.2, 94.4, (C-2, -12), 78.6, 78.4, (C-1, -11), 74.9 (C-4), 68.8 (C-9), 60.6, 60.6, 60.6, 60.5, (C-3, -5), 59.5, 59.2, 58.3, (C-6, -7), 58.1, 58.1, 58.0, 57.9 (C-16, -17), 53.4, 53.3 (C-13, -15), 53.2, 53.1 (C-8, -10), 52.7, 52.6 (OCH_3/4), 52.6, 52.4 (OCH_3/9), 46.5, 46.4, 46.2, 46.2 (C-18, -20), 36.7 (C-14), 34.3 (C-19); MS (EI): *m/z* (%) = inter alia (695 (10), 693 (15), 691 (10)) [M^+], 615 (100), 613 (99), 534 (25), 373 (9); $C_{24}H_{22}O_4Br_4$ (694.0).

Dimethyl 2,4-*anti*,9-*anti*,12,14-*anti*-pentabromodecacyclo-[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*syn*,9-*syn*-dicarboxylate (rotamers) (12): A solution of **1b** (750 mg, 2.0 mmol) and of bromine (25 mL, 490 mmol) in dry CH_2Cl_2 (225 mL) was irradiated at 0 °C until TLC (cyclohexane/ethyl acetate = 4:1) showed total conversion of the intermediate **10** into **11** (ca. 1 h) and then without cooling (temperature rises to ca. 35 °C) until TLC showed no further conversion of **11** to **12** (ca. 3 h, R_f(**11**) = 0.32, R_f(**12**) = 0.40). After concentration in vacuo, the solid residue was chromatographed on silica gel (15/5 cm, CH_2Cl_2/CCl_4 = 1:1), to give first **12** (1.47–1.50 g, 95–97%, R_f = 0.42), then **11** (42–69 mg, 3–5%, R_f = 0.30).

Dimethyl 2,4-*anti*,9-*anti*,12,14-*anti*,19-*anti*-hexabromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*syn*,9-*syn*-dicarboxylate (rotamers) (13): A solution of **12** (1.55 g, 2.0 mmol) and bromine (30 mL, 589 mmol) in CH_2Cl_2 (20 mL) saturated with gaseous HBr was irradiated under reflux (300 W daylight lamp, Pyrex tubes) until TLC (cyclohexane/ethyl acetate = 4:1) revealed only **12** (R_f(**12**) = 0.40) and **13** (R_f(**13**) = 0.47) (ca. 48 h). After concentration in vacuo, chromatography on silica gel (15/5 cm, CH_2Cl_2/CCl_4 = 1:1) yielded first **13** (1.50–1.60 g, 89–92%) then **12** (62–93 mg, 4–6%). When later fractions of several runs were collected and analyzed by chromatography on silica gel (CH_2Cl_2/CCl_4 = 1:1) trace amounts of **14**, *iso*-**12**, **6**, **5**, and **4** (in this sequence, < 1% in total) were eluted and identified by ^{1}H NMR comparison.

Hydrogenolysis 13 → 5. A solution of **13** (1.50 g, 1.76 mmol) in CH_2Cl_2 (150 mL) and methanol (1.5 mL) was saturated with H_2 and stirred over PtO_2 (3.0 g) for 30 min (total conversion, TLC (CH_2Cl_2), R_f (**13**) = 0.73, R_f (**5**) = 0.42). Filtration through silica gel (2/5 cm, CH_2Cl_2) gave 1.19–1.2 g (97–98%) of pure **5**. If methanol was added in larger amounts (> 15 mL), **5** was further reduced to give, inter alia:

Dimethyl 12,14-*anti*,19-*anti*-tribromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*syn*,9-*syn*-dicarboxylate (2-debromo-**5**): Colorless crystals (CH_2Cl_2/ethyl acetate); m.p. 231–232 °C; IR (KBr): $\tilde{\nu}$ = 2978, 2854 (C–H), 1724 (C=O), 1188 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (s, 14*syn*-H), 4.24 (s, 19*s*-H), 3.87 (s, OCH_3/4), 3.78 (s, OCH_3/9), 3.75 (m, 6-H*), 3.74 (m, 3-, 5-H), 3.62 (m, 7-H*), 3.18 (d, 13-H*), 3.01 (d, 15-H*), 2.97 (m, 17-H$^+$), 2.84 (m, 16-H$^+$), 2.77 (m, 8-, 10-H), 2.69 (m, 18-, 20-H), 2.64 (t, 4*anti*-H), 2.58 (d, 9*a*-H), 2.40 (d, 2-H); ^{13}C NMR ($CDCl_3$): δ = 172.8 (C=O/4), 172.7 (C=O/9), 95.4 (C-12), 76.7 (C-11), 69.0 (C-1), 61.5 (C-13), 58.9 (C-15), 58.2 (C-17), 57.6 (C-16), 57.0 (C-6), 56.8 (C-7), 56.1 (C-14), 55.6 (C-19), 53.2 (C-4), 52.6 (OCH_3/4), 52.5 (C-18, -20), 52.2 (OCH_3/9), 51.8 (C-5), 51.6 (C-3), 50.6 (C-9), 47.6 (C-2), 46.3 (C-10), 45.6 (C-8); MS (EI): *m/z* (%) = inter alia (617 (1), 615 (4), 613 (4), 611 (1)) [M^+], 537 (51), 535 (100), 533 (52), 455 (5), 375 (3), 255 (14); $C_{24}H_{23}Br_3$ (615.0): calcd C 46.83 H 3.74, found C 46.58 H 3.68.

Dimethyl 2-,6-,21-*anti*-tribromo-20-oxo-19-oxadodecacyclo [11.9.0.0^{1,17}.0^{2,9}.0^{3,16}.0^{4,8}.0^{5,15}.0^{6,13}.0^{7,11}.0^{10,22}.0^{12,21}.0^{14,18}]docosane-8-dicarboxylate (21):

From tetrabromide 16: To a boiling solution of anhydrous KI (100 mg, 0.60 mmol) in DMF (5 mL), **16** (30 mg, 0.04 mmol) was added (N_2 atm.) while the mixture was stirred. After total conversion (30 min), the reaction solution was concentrated in vacuo and the solid residue dissolved in CH_2Cl_2 (20 mL). After washing with 10% aqueous $Na_2S_2O_3$ (25 mL), the aqueous phase was extracted three times with CH_2Cl_2 (15 mL each). The combined CH_2Cl_2 phase was dried ($MgSO_4$) and concentrated in vacuo, and the solid residue chromatographed on silica gel (18/1 cm, CH_2Cl_2); first **21** (24 mg, 92%), then **17** (1 mg, 5%) were eluted. Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 252–253 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2960 (C–H), 1720 (C=O), 1266, 1093 (C–O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 4.92 (t, 18*a*-H), 3.92 (t, 4-H), 3.82 (m, 12-, 22-H), 3.78 (s, OCH_3), 3.52 (m, 10-, 11-H), 3.50 (m, 14-, 17-H), 3.48 (m, 15-, 16-H), 3.34 (m, 7-, 9-, 14-, 17-H), 3.29 (m, 3-, 5-H); ^{13}C NMR ($CDCl_3$): δ = 173.9 (C-20), 167.4 (C=O/8), 92.3 (C-2, -6), 88.6 (C-18), 82.3 (C-1, -13), 81.4 (C-8), 66.7 (C-4), 65.5 (C-21), 64.3 (C-7, -9), 63.0 (C-12, -22), 59.0 (C-3, -5, -15, -16), 56.5 (C-10, -11), 53.0 (OCH_3), 50.1 (C-14, -17); MS (EI): *m/z* (%) = inter alia (M^+ not detectable), 566 (16), 565 (15), 519 (62), 517 (100), 517 (61), 475 (4), 473 (6), 471 (4), 439 (3), 437 (5), 435 (3), 377 (5), 253 (20); $C_{23}H_{17}O_4Br_3$ (597.0): calcd C 46.23 H 2.85, found C 46.40 H 2.89.

From hexabromide 13: KI (400 mg, 2.40 mmol), DMF (5 mL), **13** (100 mg, 0.12 mmol), 30 min. After workup and chromatographic separation (20/2 cm, SiO_2, CH_2Cl_2, R_f (**21**) = 0.12, R_f (**17**) = 0.45) **21** (49 mg, 69%), **17** (2 mg, 4%), traces of (probably) 21-debromo-**21** and other nonidentified components.

Dimethyl 4-*anti*,9-*anti*-dibromoundecacyclo[9.9.0.0^{1,5}.0^{2,12}.0^{2,18}.0^{3,7}.0^{6,10}.0^{8,12}.0^{11,15}.0^{13,17}.0^{16,20}]icosane-4-*syn*,9-*syn*-dicarboxylate (24): A suspension of **1b** (100 mg, 0.27 mmol), *N*-bromosuccinimide (NBS) (570 mg, 2.71 mmol) and azobisisobutyronitrile (AIBN) (10 mg) in anhydrous CCl_4 (10 mL) was refluxed until total conversion (ca. 60 min, TLC, R_f (**1b**) = 0.43; CH_2Cl_2). After concentration the residue was chromatographed (SiO_2, 25/1.5 cm, CH_2Cl_2); inter alia, first **24** (53 mg, 37%) and then the monobromide (22 mg, 18%) were eluted. Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 263 °C; ^{1}H NMR ($CDCl_3$): δ = 3.70 (s, OCH_3), 3.69 (m, 6-, 7-H), 3.02 (m, 3-, 5-H*), 2.90 (m, 8-, 10-H*), 2.61 (m, 16-, 17-H), 2.37 (m, 13-, 15-H$^+$), 2.29 (m, 18-, 20-H$^+$), 1.58 (d, 14*s*-, 19*s*-H), 1.11 (d, 14*a*-, 19*a*-H), $J_{14a,14s}$ = 11.6 Hz; ^{13}C NMR ($CDCl_3$): δ = 169.9 (C=O), 73.8 (C-4, -9), 60.6 (C-1, -2, -11, -12), 59.3 (C-6, -7), 59.2 (C-16, -17), 52.7 (OCH_3), 50.1 (C-3, -5, -8, -10), 42.0 (C-13, -15, -18, -20), 40.5 (C-14, -19); MS (CI, isobutane): *m/z* (%) = inter alia (536 (52), 534 (100), 532 (52)) [M^+], 455 (12), 453 (11), 373 (8), 255 (12), 253 (20); $C_{24}H_{22}O_4Br_2$ (534.0): calcd C 53.33 H 4.12, found C 52.90 H 4.08.

Dimethyl 2,12,14-*anti*-tribromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*anti*,9-*syn*-dicarboxylate (rotamers) **(26)**: To a boiling solution of anhydrous KBr (150 mg, 1.26 mmol) in DMF (5 mL, N_2 atm.), **10** (50 mg, 0.08 mmol) was added. After being stirred for 3 min (ca. 50% conversion, TLC, R_f (**10**) = 0.41, R_f (**26**) = 0.36) and concentrated in vacuo the residue was dissolved in CH_2Cl_2 (40 mL) and washed with 10% aq NH_4Cl (50 mL), and the combined organic phases were extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 phase was dried ($MgSO_4$) and concentrated in vacuo. Chromatography (SiO_2, 18/1 cm, CH_2Cl_2) gave pure **26** (24 mg, 48%) besides educt **10** (25 mg, 50%). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 241 °C; IR (KBr): $\tilde{\nu}$ = 2971 (C–H), 1716 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 5.59 (s, 14*s*-H), 3.89 (s, 4*s*-H), 3.76 (s, OCH_3/4), 3.75 (m, 16-, 17-H), 3.68 (s, OCH_3), 3.60 (m, 6-, 7-H), 3.48 (m, 3-, 5-H), 3.36 (m, 8-, 10-H), 3.12 (m, 13-, 15-H), 2.99 (m, 18-, 20-H), 2.73 (t, 9*a*-H), 1.61 (d, 19*s*-H), 1.49 (dt, 19*a*-H), $J_{19a,19s}$ = 10.8 Hz; ^{13}C NMR ($CDCl_3$): δ = 172.5 (C=O/4), 171.9 (C=O/9), 94.6 (C-2, -12), 79.5 (C-1, -11), 62.7 (C-3, -5), 58.1 (C-6, -7), 57.4 (C-16, -17), 57.2 (C-14), 55.6 (C-13, -15), 52.5 (OCH_3/4), 51.9 (OCH_3/9), 51.8, 51.6 (C-8, -10), 48.1 (C-18, -20), 46.3 (C-9), 34.5 (C-19); MS (EI): *m/z* (%) = inter alia (617 (4), 615 (12), 613 (12), 611 (4)) [M^+], 537 (52), 535 (100), 533 (52), 456 (52), 454 (52), 378 (2), 255 (19); $C_{24}H_{23}O_4Br_3$ (615.0): calcd C 46.83 H 3.74, found C 46.14 H 3.71.

Dimethyl 2,9-*anti*-12,14-*anti*-tetrabromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*anti*,9-*syn*-dicarboxylate (27, rotamers) (cf. **26)**: To a solution of anhydrous KBr (75 mg, 0.63 mmol) in abs. DMF (3 mL) kept at 120 °C (N_2 atm.), **11** (25 mg, 0.04 mmol) was added. After total conversion (TLC, cyclohexane/ethyl acetate = 4:1 (R_f = 0.51), ca. 10 min stirring) and workup, filtration through silica gel (1/2 cm, CH_2Cl_2) gave **27** (74 mg, 99%). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 261 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2978, 2946, 2884 (C–H), 1734 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60 (s, 14*s*-H), 3.93 (s, 4*s*-H), 3.83 (s, OCH_3/4), 3.71 (m, 3-, 5-H), 3.70 (s, OCH_3/9), 3.68 (m, 6-, 7-H), 3.52 (m, 16-, 17-H), 3.58, 3.46 (m, 8-, 10-H), 3.38 (m, 13-, 15-H), 3.02, 2.98 (m, 18-, 20-H), 1.57 (dt, 19*s*-H), 1.49 (dt, 19*a*-H), $J_{19a,19s}$ = 13.8 Hz; ^{13}C NMR ($CDCl_3$): δ = 171.4 (C=O/4), 169.4 (C=O/9), 93.6 (C-2, -12), 77.2 (C-1, -11), 69.3 (C-9), 62.3, 62.2 (C-3, -5), 59.0 (C-14), 58.0, 59.7 (C-6, -7)*, 57.9 (C-16, -17)*, 56.2 (C-4), 54.8 (C-13, -15), 54.2, 54.2 (C-8, -10), 53.1 (OCH_3/4), 52.6 (OCH_3/9), 46.5, 46.2(C-18, -20), 34.3 (C-19); MS (EI): *m/z* (%) = inter alia (696 (8), 694 (10), 692 (7)) [M^+], 614 (99), 613 (100), 534 (46), 454 (8), 373 (5),267 (6), 253 (24); $C_{24}H_{22}O_4Br_4$ (694.0): calcd C 41.49 H 3.17, found C 41.18 H 3.12.

Dimethyl 13-*anti*,18-*anti*-dibromononacyclo[12.6.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]icosa-1(20),10-diene-3-*anti*,8-*anti*-dicarboxylate (31): To a vigorously boiling suspension of anhydrous KBr (3.0 g, 25 mmol) and Fe powder (1.0 g) in DMF (20 mL), **11** (1.0 g, 1.44 mmol) was rapidly added (N_2 atm.). After stirring for approximately 4 min (the color changed from deep red to yellowish) DMF was distilled off in vacuo. After addition of CH_2Cl_2 (50 mL) the suspension was washed with 10% aqueous NH_4Cl (25 mL), the aqueous phase extracted with CH_2Cl_2 (3 × 25 mL), and the combined CH_2Cl_2-phase dried ($MgSO_4$). After concentration in vacuo and filtration through silica gel (0.5/2 cm, CH_2Cl_2), 760 mg (99%) **31** was obtained as colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 223 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2964 (C–H), 1712 (C=O), 1283, 1031 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (s, 13*s*-, 18*s*-H), 4.32 (m, 15-, 16-H), 3.77 (s, 3*s*-, 8*s*-H), 3.70 (s, OCH_3), 3.62 (m, 5-, 6-H), 3.56 (m, 2-, 4-, 7-, 9-H), 3.51 (m, 12-, 14-, 17-, 19-H); ^{13}C NMR ($CDCl_3$): δ = 173.8 (C=O), 155.3 (C-1, -11, -12, -20), 60.3 (C-5, -6), 59.8 (C-15, -16), 57.9 (C-13, -18), 56.1 (C-12, -14, -17, -19), 52.1 (OCH_3), 49.4 (C-3, -8), 46.6 (C-2, -4, -7, -9); MS (EI): *m*/*z* (%) = i.a. 536 (41), 534 (95), 532 (42) [M^+], 455 (100), 454 inter alia (99), 374 (8), 255 (40) 254 (34), 128 (58); $C_{24}H_{22}O_4Br_2$(534.0): calcd C 53.33 H 4.12, found C 53.52 H 4.17.

Dimethyl 13-*anti*,18-*anti*-diiodononacyclo[12.6.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]icosa-1(20),10-diene-3-*anti*,8-*anti*-dicarboxylate (32) (cf. **31**): Anhydrous KI (3.0 g, 18.0 mmol), **11** (1.0 g, 1.44 mmol), DMF (20 mL), 153 °C, 15 min, 900 mg (98%) **32**. Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 297–300 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2945 (C–H), 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (s, 13*s*-, 18*s*-H), 4.49 (m, 15-, 16-H), 3.85 (s, 3*s*-, 8*s*-H), 3.69 (s, OCH_3), 3.6 (m, 2-, 4-, 5-, 6-, 7-, 9-H), 3.51 (m, 12-, 14-, 17-, 19-H); ^{13}C NMR ($CDCl_3$): δ = 173.9 (C=O), 155.5 (C-1, -11, -12, -20), 62.4 (C-5, -6), 59.7 (C-15, -16), 57.7 (C-13, -18), 52.1 (OCH_3), 49.5 (C-12, -14, -17, -19), 46.5 (C-3, -8), 36.4 (C-2, -4, -7, -9); MS (EI): *m*/*z* (%) = inter alia 628 (M^+, 100), 501 (7), 374 (33), 255 (56), 253 (59), 128 (57); $C_{24}H_{22}O_4I_2$ (628.0): calcd C 45.89 H 3.53, found C 46.64 H 3.57.

Dimethyl 13-*anti*,18-*anti*-dibromononacyclo[12.6.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]icosa-1(20)-ene-3-*anti*,8-*anti*-dicarboxylate (35): To an ice-cooled solution of **31** (1.0 g, 1.87 mmol) in CH_2Cl_2 (dist.; 90 mL) and CH_3OH (dist., 45 mL), $N_2(CO_2K)_2$ (10.0 g, 61.0 mmol) was added. While the solution was intensively stirred, glacial acetic acid (3 mL) was added over 5 min. Stirring was continued for 12 h while the solution was allowed to warm up slowly to room temperature until total conversion (ca. 12 h, TLC, **31** changes $KMnO_4$ color to yellow, **35** to colorless). Workup (10% aq. NH_4Cl; CH_2Cl_2) and filtration through silica gel (1/2 cm, CH_2Cl_2) gave pure **35** (970 mg, 97%). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 217–219 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2944 (C–H), 1723 (C=O), 1269 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80 (s, 13*s*-, 18*s*-H), 3.92 (s, 3*s*-, 8*s*-H), 3.86 (m, 15-, 16-H), 3.68 (s, OCH_3), 3.42 (m, 2-, 7-, 14-, 19-H), 3.32 (m, 10-, 11-H), 3.20 (m, 4-, 9-, 12-, 17-H), 3.04 (m, 5-, 6-H); ^{13}C NMR ($CDCl_3$): δ = 174.4 (C=O), 149.8 (C-1, -20), 62.9 (C-13, -18), 60.1 (C-6), 59.9 (C-15), 59.6 (C-16), 58.7 (C-5), 56.5 (C-10, -11), 55.9 (C-12, -17), 54.9 (C-14, -19), 53.2 (C-3, -8), 52.0 (OCH_3), 48.9 (C-4, -9), 48.3 (C-2, -7); MS (EI): *m*/*z* (%) = inter alia 538 (32), 536 (64), 534 (40)) [M^+], 456 (100), 455 (99), 375 (22), 256 (22), 255 (70); $C_{24}H_{24}O_4Br_2$ (536.2): calcd C 53.73 H 4.47, found C 53.22 H 4.36.

Dimethyl 13-*anti*,18-*anti*-diiodononacyclo[12.6.0.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]icosa-1(20)-ene-3-*anti*,8-*anti*-dicarboxylate (36) (cf. **35**): **32** (250 mg, 0.40 mmol), $N_2(CO_2K)_2$ (3.0 g, 18.0 mmol) gave **36** 242 mg (97%). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 258 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2982, 2946 (C–H), 1720 (C=O), 1269, 1159 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (s, 13*s*-, 18*s*-H), 4.08 (s, 3*s*-, 8*s*-H), 3.98 (m, 15-, 16-H), 3.68 (s, OCH_3), 3.49 (m, 2-, 7-H), 3.39 (m, 10-, 11-H), 3.30 (m, 4-, 9-, 14-, 19-H), 3.18 (m, 12-, 17-H), 3.04 (m, 5-, 6-H); ^{13}C NMR ($CDCl_3$): δ = 174.4 (C=O), 149.9 (C-1, -20), 63.1 (C-13, -18), 60.2 (C-6), 60.0 (C-15), 59.6 (C-16), 58.6 (C-5), 56.5 (C-10, -11), 55.9 (C-12, -17), 54.9 (C-14, -19), 53.2 (C-3, -8), 52.2 (OCH_3), 49.2 (C-4, -9), 48.3 (C-2, -7); MS (CI, isobutane): *m*/*z* (%) = inter alia 631 [M^+], 503 (38), 377 (100); $C_{24}H_{24}O_4I_2$ (630.0): calcd C 45.74 H 3.81, found C 46.04 H 3.76.

Dimethyl 13-*anti*-18-*anti*-dibromo-21-oxadecacyclo[12.7.0.0^{1,20}.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]henicosa-10-ene-3-*anti*,8-*anti*-dicarboxylate (37): To an anhydrous solution of mCPA (*m*-chloroperbenzoic acid) (100 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) at 0 °C, NaH_2PO_4 (100 mg, 700 mmol) and **31** (40 mg, 0.08 mmol) were added. After being stirred for 20 min (TLC, R_f(**37**) = 0.82, R_f(**31**) = 0.90, CH_2Cl_2/ethyl acetate = 9:1) and standard workup (15% aqueous K_2CO_3; CH_2Cl_2), **37** (38 mg, 94%) was chromatographically (SiO_2, 15/1 cm, CH_2Cl_2/ethyl acetate = 9:1) separated from **41** (2 mg, 5–6%, R_f = 0.75). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 271 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2944 (C–H), 1719 (C=O), 1257, 1070 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (s, 13*s*-, 18*s*-H), 3.99 (s, 3*s*-, 8*s*-H), 3.98 (m, 15-H*), 3.79 (m, 16-H*), 3.69 (s, OCH_3), 3.50 (m, 4-, 9-, 12-, 17-H), 3.31 (m, 6-H$^+$), 3.20 (m, 5-H$^+$), 2.99 (m, 2-, 7-H), 2.90 (m, 14-, 19-H); ^{13}C NMR ($CDCl_3$): δ = 172.7 (C=O), 153.8 (C-10, -11), 84.8 (C-1, -20), 62.7 (C-15), 62.6 (C-6), 58.9 (C-16), 58.2 (C-5), 55.0 (C-2, -7), 54.7 (C-14, -19), 48.8 (C-3, -8), 52.3 (OCH_3), 48.8 (C-4, -9), 47.9 (C-12, -17); MS (CI, NH_3): *m*/*z* (%) = inter alia 551 (3, M^+), 471 (20), 469 (20), 389 (18), 376 (7), 256 (11), 59 (100); $C_{24}H_{22}O_5Br_2$ (550.2): calcd C 52.36 H 4.36, found C 52.07 H 4.33.

Dimethyl 13-*anti*-18-*anti*-diiodo-21-oxadecacyclo[12.7.0.0^{1,20}.0^{2,6}.0^{4,11}.0^{5,9}.0^{7,20}.0^{10,17}.0^{12,16}.0^{15,19}]henicosa-10-ene-3-*anti*,8-*anti*-dicarboxylate (38) (cf. **37**): mCPA (100 mg, 0.58 mmol), NaH_2PO_4 (100 mg), CH_2Cl_2 (5 mL), **32** (40 mg, 0.06 mmol), 38 mg (94%) **38**. The reaction has to be carefully controlled (0 °C); it is stopped as soon as a violet color develops. 30 °C should not be surpassed during workup procedure to avoid partial decomposition by oxidation of the iodine substituents. Colorless crystals (CH_2Cl_2/ethyl acetate); m.p. 231 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2944 (C–H), 1720 (C=O), 1258 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74 (s, 13*s*-, 18*s*-H), 4.10 (s, 3*s*-, 8*s*-H), 4.07 (m, 15-H*), 3.92 (m, 16-H*), 3.69 (s, OCH_3), 3.57 (m, 4-, 9-H), 3.49 (m, 12-, 17-H), 3.30 (m, 6-H$^+$), 3.19 (m, 5-H$^+$), 3.09 (m, 2-, 7-H), 2.90 (m, 14-, 19-H); ^{13}C NMR ($CDCl_3$): δ = 172.7 (C=O), 154.0 (C-10, -11), 84.5 (C-1, -20), 64.1 (C-15), 62.6 (C-6), 61.1 (C-16), 57.8 (C-5), 56.4 (C-2, -7), 56.2 (C-14, -19), 52.9 (C-3, -8), 52.3 (OCH_3), 48.8 (C-4, -9), 48.0 (C-12, -17); MS (EI): *m*/*z* (%) = inter alia 644 (6) [M^+], 628 (5), 532 (3), 517 (100), 390 (23), 374 (1), 255(5); $C_{24}H_{22}O_5I_2$ (644.0).

Dimethyl 14-*anti*,19-*anti*-dibromo-11,22-dioxaundecacyclo[13.7.0.0^{1,21}.0^{2,6}.0^{4,12}.0^{5,9}.0^{7,21}.0^{10,12}.0^{10,18}.0^{13,17}.0^{16,20}]docosane-3-*anti*,8-*anti*-dicarboxylate (41) (cf. **37**): mCPA (100 mg), CH_2Cl_2 (5 mL), NaH_2PO_4 (100 mg), **31** (40 mg, 0.08 mmol), 24 h at 0 °C (total conversion, TLC, R_f = 0.75, CH_2Cl_2/ethyl acetate = 9:1). After standard workup 39 mg (92%). Colorless crystals (CH_2Cl_2/ethyl acetate): m.p. 309–312 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2946 (C–H), 1785 (C=O), 1138 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (s 14*s*-, 19*s*-H), 4.00 (s, 3*s*-, 8*s*-H), 3.88 (m, 16-, 17-H), 3.68 (s, OCH_3), 3.21 (m, 5-, 6-H), 3.10 (dd, 2-, 4-, 7-, 9-H), 3.00 (dd, 13-, 15-, 18-, 20-H), $J_{2,6}$ = 6.9 Hz, $J_{15,16}$ = 6.8 Hz; ^{13}C NMR ($CDCl_3$): δ = 172.2 (C=O), 83.1 (C-1, -10, -12, -21), 63.5 (C-16, -17), 63.1 (C-5, -6), 54.5 (C-14, -19), 54.2 (C-13, -15, -18, -20), 52.4 (OCH_3), 49.0 (C-3, -8), 47.7 (C-2, -4, -7, -9); MS (EI): *m*/*z* (%) = inter alia 568 (19), 566 (37), 564 (19)) [M^+], 534 (2), 507 (5), 487 (38), 485 (38), 455 (17), 453 (17), 425 (10), 405 (23), 373 (1), 257 (16); $C_{24}H_{22}O_6Br_2$ (566.2): calcd C 50.91 H 3.52, found C 51.87 H 3.55.

Dimethyl undecacyclo[9.9.0.0^{2,9}.0^{3,7}.0^{4,20}.0^{5,18}.0^{6,16}.0^{8,15}.0^{10,14}.0^{12,19}.0^{13,17}]-icosa-8,18-diene-1,6-dicarboxylate (8): To a stirred solution of **32** (314 mg, 0.5 mmol) in anhydrous benzene (25 mL), **43** (1.66 g, 5.0 mmol) was added in small portions (all operations were performed with air and moisture excluded as well as possible). After 15 min (total consumption of **8**, TLC, cyclohexane/ethyl acetate = 4:1, *Rf* (**32**) = 0.15, *Rf* (**8**) = 0.40), anhydrous MeOH (5 mL, 123.5 mmol) was added, the solution was concentrated in vacuo, the solid residue containing **8** and the P_2 salts was dissolved in cyclohexane/ethyl acetate (4:1, 25 mL), the solution filtered through a silica gel column (10/2 cm; the silica gel had been deoxygenated by heating to 550 °C in vacuo, following which it was washed with anhydrous MeOH (20 mL) and thoroughly dried in vacuo). After washing the column once more with cyclohexane/ethyl acetate (4:1, 10 mL), the combined solutions of **8** were evaporated in vacuo. In order to remove the last traces of P_2 salts, the solid residue, dissolved in cyclohexane/ethyl acetate (4:1, 10 mL), was filtered once more through silica gel (5/2 cm; deoxygenated as above); after washing the column (10 mL) and evaporation, the residue consisted of pure **8** (149–154 mg, 79–82%) [3]. Up to 10% of the missing material is made up by the monoacid derivative of **8**, which had remained on the silica gel together with the P_2 salts. Since aqueous workup was not applicable, this 10% is used for the generation of **47**; for this purpose, the mixture of monoacid and P_2 salts was eluted with ethyl acetate/methanol 1:1 (cf. **47**).

Dimethyl undecacyclo[9.9.0.0^{2,9}.0^{3,7}.0^{4,20}.0^{5,18}.0^{6,16}.0^{8,15}.0^{10,14}.0^{12,19}.0^{13,17}]-icosane-1,6-dicarboxylate (47): To a stirred solution of **35** (1.05 g, 2.0 mmol) in anhydrous benzene (100 mL) **43** (6.6 g, 20.0 mmol) was added. After 15 min (total consumption of **35**, TLC, cyclohexane/ethyl acetate = 4:1, R_f (**35**) = 0.15, R_f (**46**) = 0.40) anhydrous MeOH (5 mL, 123.5 mmol) and Pd/C (5%, 160 mg) were added. Hydrogen gas was bubbled through the stirred solution until total consumption of **46** (5–10 min, TLC, **47** does not change the color of $KMnO_4$). The suspension was washed with water (100 mL), the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$). The solution was concentrated in vacuo and filtered through silica gel (1.5/2 cm, CH_2Cl_2/ethyl acetate 10:1, R_f = 0.89). After evaporation the solid residue consisted of pure **47** (665–680 mg, 90–92%). Elution of the silica gel with ethyl acetate (50 mL) gave the monoacid derivative of **47** (36–58 mg, 5–8%; R_f = 0.08, CH_2Cl_2/ethyl acetate 10:1). 95–98% total yield.

Cyclization 37 → 48 (cf. **8**): **37** (25 mg, 0.05 mmol), anhydrous benzene (10 mL), **43** (83 mg, 0.25 mmol), 15 min stirring (total consumption of **37**, TLC, cyclohexane/ethyl acetate = 4:1, R_f (**37**) = 0.15, R_f (**48**) = 0.28), anhydrous MeOH (3 mL, 74.1 mmol; deoxygenated). After workup as for **8**, yielded 7 mg (31%) of pure **48** [3].

Cyclization 38 → 48: **38** (25 mg, 0.04 mmol), **43** (132 mg, 0.40 mmol), anhydrous benzene (10 mL), anhydrous MeOH (3 mL, 74.1 mmol; deoxygenated); yielded 10 mg (63%) of pure **48**.

Cyclization 41 → 49 (cf. **47**): **41** (50 mg, 0.09 mmol), anhydrous benzene (10 mL), **43** (150 mg, 0.45 mmol), 15 min stirring (total consumption of **41**, TLC, CH_2Cl_2/ethyl acetate = 9:1, R_f (**41**) = 0.75, R_f (**49**) = 0.69), anhydrous MeOH (3 mL, 74.1 mmol). After workup as for **47** (here without special treatment of the silica gel) the final residue of 24 mg (65%) was pure **49** [3].

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Dimethyl 2-,12-,14-*anti*,19-*anti*-tetrabromodecacyclo[9.9.0.0^{1,8}.0^{2,15}.0^{3,7}.0^{5,12}.0^{6,10}.0^{11,18}.0^{13,17}.0^{16,20}]icosane-4-*anti*,9-*anti*-dicarboxylate (rotamers) (59): A solution of **56** (750 mg, 2.0 mmol) and of bromine (25 mL, 490 mmol) in dry CH_2Cl_2 (225 mL), kept at 25 °C (reflux condenser) was irradiated until total consumption (TLC, cyclohexane/ethyl acetate = 9:1). After concentration in vacuo, the solid residue was chromatographed on silica gel (15/5 cm, CH_2Cl_2) to give **59** (1.25–1.32 g, 90–95%, $R_f = 0.48$) with some **60** (21–29 mg, 1–2%, $R_f = 0.61$) and **61** (3–5 mg, 1–2%, $R_f = 0.80$). Colorless crystals (CH_2Cl_2): m.p. 304 °C (decomp.); IR (KBr): $\tilde{\nu}$ = 2982, 2942 (C–H), 1717 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (s, 14*s*-H), 4.69 (s, 19*s*-H), 3.90 (s, 4*s*-H), 3.82 (s, 9*s*-H), 3.81 (m, 3*-H), 3.80 (m, 16-, 17-H), 3.70 (m, 5*-H), 3.68 (s, OCH_3/4), 3.66 (s, OCH_3/9), 3.30 (m, 6-, 7-H), 3.26 (m, 8-, 10-H), 3.22 (m, 18-, 20-H); ^{13}C NMR ($CDCl_3$): δ = 171.7 (C=O), 92.0 (C-2, -12), 78.3 (C-1, -11), 62.3 (C-3, -5), 57.9 (C-6, -7), 56.5 (C-16, -17), 56.1 (C-13, -15), 54.9 (C-14), 54.3 (C-19), 53.6 (C-4), 53.2 (C-13, -15), 52.6 (C-8, -10), 52.5 (C-9), 52.0 (OCH_3/4), 51.5 (OCH_3/9), 48.7 (C-18, -20); MS (EI): *m*/*z* (%) = inter alia (695–691 (>1)) [M^+], 615 (99), 613 (100), 534 (87), 454 (4), 373 (3), 267 (6), 254 (13), 253 (20), 127 (13), 126 (12); $C_{24}H_{22}O_4Br_4$ (694.0): calcd C 41.50 H 3.17, found C 41.40 H 3.15.

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[33] P_2F: 1,1,1,3,3,3-Hexakis(dimethylamino)diphosphazenium fluoride, Fluka 52585.

[34] This was not the first time for us that the P_2F reagent saved a project that was stranded just in sight of the goal after a long journey. For further examples see: M. Wollenweber, R. Pinkos, H. Prinzbach, *Angew. Chem.* **1994**, *106*, 84; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 117; T. Mathews, M. Keller, H. Prinzbach, unpublished.

[35] A similar concerted H-transfer mechanism has been invoked for the conversion of the 14,19-dimethoxy analogue of **6** into the 14-oxo-4-*anti*-ester in ref. [2] (**26** → **27**).

[36] Another example of such a side-selective bromine addition was reported in ref. [6] (**11** → **12**).