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Insights into the Formation of Symmetrical Trimers of Dialkylated Ketenes Starting from Acid Chloride Precursors

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Summary. Application of known dialkyl ketene di- and trimerization to more complex precursors could readily open the route to highly functionalized symmetrical cyclobuta-1,3-diones and cyclohexa-1,3,5-triones. We report herein the results on three substrates containing either a C=C double bond or a protected glycol moiety as illustrative functionalized groups. The nature of the substituents is found to be crucial: while cyclopentenyl and more constrained dioxolanocyclopentenyl precursors efficiently dimerize, a diallylic derivative fails. At the millimolar scale, methoxide-catalyzed trimerization shows limited reproducibility, even for the reported substrate tetramethylcyclobuta-1,3-dione. However, systematic studies, including the use of microwaves, demonstrate that formation of symmetrical trimers is favored under solvent-free conditions and conventional heating, which allowed us to isolate and characterize trispiro[4.1.4.1.4.1]octadeca-2,9,15-triene-6,12,18-trione.

Keywords. Microwave-assisted synthesis; Ketenes; Cycloadditions; Strained molecules; Spiro compounds.

Introduction

In our quest to create new, highly functionalized, tridentate concave ligands for a variety of applications in coordination, supramolecular, and bio-organic chemistry, we focussed our attention on C_3-symmetric *cis*,*cis*-configured tri-functionalized cyclohexane derivatives [1]. One way to simultaneously or even selectively introducing three functional groups on a cyclohexane system can be envisaged *via* a 1,3,5-triketone precursor. However, it is well-established that such species do only exist if no α protons are present, thus avoiding enolization and thus the establishment of extended π systems or even aromatic systems [2]. By contrast, in the absence of such protons, cyclohexane-1,3,5-triones can be quite stable and are in a number of cases synthetically accessible (Scheme 1). Compounds **2** and **5** can be formally regarded as the symmetric homo-trimerization products of the corresponding ketenes.

Yet isolation of ketenes [3, 4] is a thoroughly distinct science from that of the preparation of diones and triones as depicted in Scheme 1. In effect, trimeric dimethylketene **2** can be made by treatment at 100°C of the dimer **1** or its polymer with bases in a solvent free manner [5]; sodium methoxide has proved most efficient [6]. A more extensive investigation, conducted by *Clark* [7], led to the conclusion that, starting from the unsymmetrical dimer **12**, the most vigorous basic conditions always favor the symmetric trimer **2** over all other oligomerization products. Compound **2** also forms unexpectedly during attempts to polymerize dimethylketene. Under specific conditions it forms considerable amounts of the trimer **2** (up to 42% in $AlBr_3$/toluene) [8]. However, using *Lewis* or protic acids and letting the mixture reach room temperature leads reliably to dimer **1** formation.

The most systematic study of symmetric ketene trimer formation appears to be the study by *Erickson*

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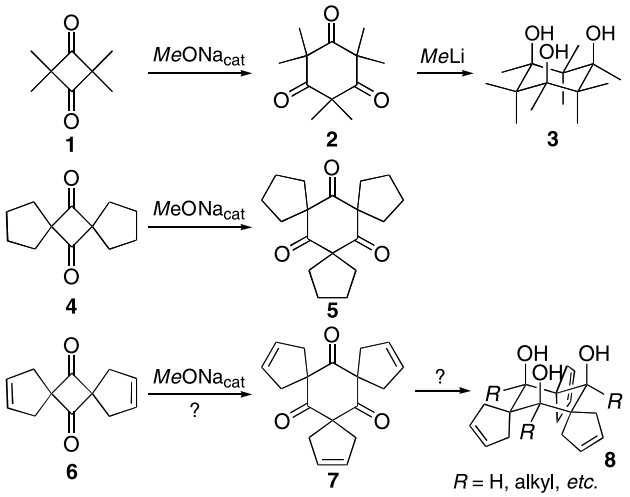


Scheme 1

et al. [9]. They succeeded in preparing **5** and several other saturated cyclic compounds in a manner comparable to that of **2**. Their work expanded on the observation that dimethylketene dimer **1** could be transformed into its trimer **2** very efficiently by sodium methoxide catalysis (97% yield) [6]. Literature indicates that this method is sufficiently reproducible to be of service as a reliable source of symmetric ketene trimers [10–12], provided that the spiro unit does not contain a too strained ring system, *i.e*., a cyclopropane unit [6, 9, 13].

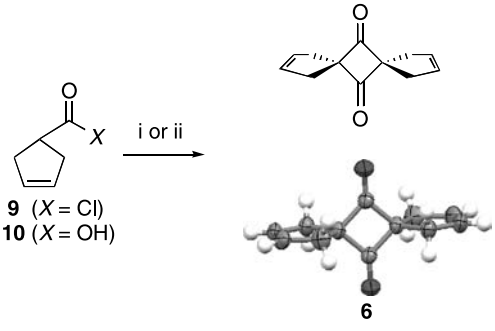
We therefore decided to explore the preparation of trimer **7** from dimer **6** that shows enhanced analogy to **4** in that it does not carry any heteroatoms on its substituents, displays the same ring size, while only differing in the presence of two isolated double bonds. The latter may serve later on to efficiently functionalize any tridentate concave system, such as **8** that may be obtained in the same manner as **3** from **2** [14].

Results and Discussions

In order to obtain ketene dimers like **1** and **4**, one usually prepares the corresponding acid chlorides and dehydrochlorinates them in ether solution with a nitrogen base leading directly to the dimerized product. Literature mentions in several instances the isolation of an acylated quaternary ammonium species as the initial intermediate (see Ref. [9] and references therein). In following this synthesis scheme, we set out to prepare 3-cyclopentene-1-carboxylic acid chloride (**9**) according to well-known literature procedures [15] starting from dimethyl malonate.

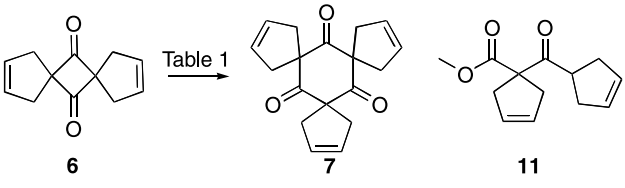
Several related conditions were explored to optimize the conversion of **9** to dimer **6**. Although there exists a more recent protocol [16], we opted for the one originally described by *Erickson et al.* [9] as a guide in optimizing yields of **6**. While working under "diluted" concentrations of **9** ($<0.3\,\mathrm{mol}\cdot\mathrm{dm}^{-3}$) gives poorly reproducible yields ranging from 16 to 52%, highly concentrated acid chloride in *THF* using *TEA* is the method of choice (70% yield). Even a one-pot procedure starting from carboxylic acid **10** and using oxalyl chloride followed by *TEA* gave a very satisfactory yield of 55% (Scheme 2).

The attempt to obtain yields of target trimer **7** comparable to those observed in the literature [9] for **5** proved disappointing (Table 1, Scheme 3). Short periods of heating of **6** either in neat form or dissolved in *DMF* in the presence of catalytic amounts



(i) *X* = Cl, 1.45 eq. *TEA* in *THF* (70%); (ii) *X* = OH, $(COCl)_2$ in *DCM* then 1.45 eq. *TEA* in *THF* (55%)

Scheme 2



Scheme 3

Table 1. Trimerization attempts of **6**

Entry[a]	Conditions[b]	**6**	**7**	**11**
1	30 min, 170°C	26.3%	3.3%	–
2	10 min, reflux *DMF*	–	2.5%	1.8%
3	5 min, reflux *DMF*	–	2.4%	5.8%

[a] Isolated yields except entry 1; [b] 0.2 eq. *Me*ONa

of sodium methoxide as described by *Erickson et al*., did not lead to appreciable amounts of **7** (Table 1). On the other hand, simple nucleophilic opening of the strained cyclobutadione ring by methoxide attack, postulated for the trimerization mechanism [6], led to the formation of β-ketoester **11**. Large amounts of the starting material **6** were left unaccounted for with the applied work-up procedure, and presumably polymerized. In view of the high similarity and thus the impossibility to separate trimer **7** from dimer **6** by silica gel chromatography, it was crucial for the identification and characterization of trimer **7** that the conditions in entries 2 and 3 led to complete consumption of **6**. To give one an appreciation of the similarity of the NMR spectra of both compounds **6** and **7**, they are depicted in Fig. 1. While ^{1}H spectra in $CDCl_3$ are virtually identical, the ^{13}C spectra differ in all signals except that for the olefinic carbons.

With an authentic sample of **7** in hand, we were able to conduct a more thorough search for conditions favoring trimerization by using gas chromatographic analysis (Table 2). While neither long nor short reaction times appeared to favor formation of **7**, change of the solvent or even working without one did not improve the results. We thus turned to the application of microwaves as the source of energy for its known capacity to stem side reactions or even wholly altering reaction paths [17]. Use of a monomodal research instrument that allowed for the execution of test reactions in sealed vials gave the results as listed in Table 2 (entries 4–6). Base catalysis appears to be essential, while either neat conditions or working in *DMF* equally favor formation of **7**. Also, reaction times should be as short as possible, a feat that is scarcely possible with classical heating devices. However, in no case did we observe a reversion of the dimer/trimer ratio.

We thus decided to elucidate the factors favoring trimerization by exploring varying conditions in the conversion of dimer **1**, since its efficient trimerization is well established [5–7], and also because **1** is commercially available. The simpler NMR spectra of the dimethyl system allowed us to analyze a number of conditions employing conventional or MW heating. It was thus possible to assess the ensemble of all products formed from dimer **1**, basically consisting of four compounds: unreacted starting material **1**, trimer **2**, unsymmetrical dimer **12** [18], and unsymmetrical trimer **13** [19] (Scheme 4). Reactions conducted in a classical oil bath (Table 3, entries 1–3) pointed to the habitual conditions favoring trimer formation, *i.e*., methoxide catalysis with dimer **1** either introduced in neat form or dissolved in *DMF*. Curiously, in the case of **1**, formation of any methyl ester was not detected. Use of *DMF* which allows complete consumption of **1** leads to higher amounts of lactone derivatives **12** and **13** compared to solvent-free conditions. Entries 1 and 2 illustrate how poorly reproducible this base-catalyzed transformation really is. In fact, the reaction has to take off in a violent fashion to give excellent results which is unfortunately not reliably observed during repeated attempts using apparently identical conditions.

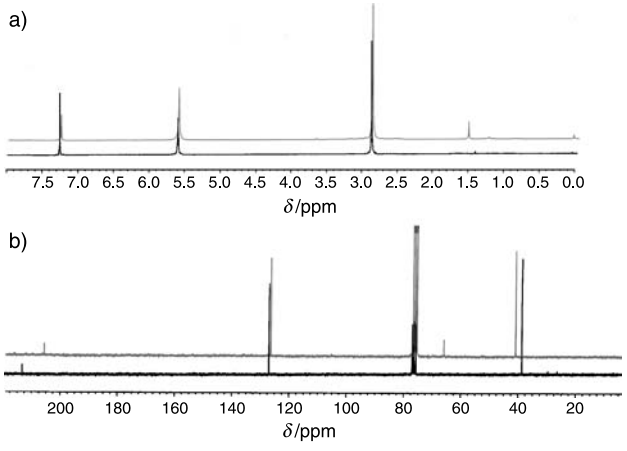
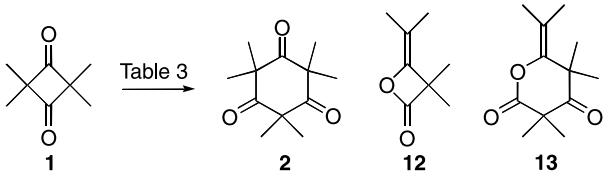


Fig. 1. ^{1}H (a) and ^{13}C (b) NMR spectra of **6** (down) and **7** (up) in $CDCl_3$

Table 2. Trimerization of **6**: selective conditions, analyzed by GC

Entry	Conditions (*Me*ONa catalytic)	**6**:**7**
1	Oil-bath heating, 5 min, 130°C, *DMF*	5000:1
2	Oil-bath heating, 80 min, reflux toluene	1200:1
3	Oil-bath heating, 3 min, 115°C, *DMSO*	1000:1
4	MW heating, 5 min, 180°C, neat	760:1
5	MW heating, 1 min 15 sec, 220°C, neat	175:1
6	MW heating, 45 sec, 180°C, *DMF*	15:1



Scheme 4

Table 3. Trimerization of **1**, analyzed by ^{1}H NMR

Entry	Conditions (*Me*ONa catalytic)	**2**[a]	**12**[a]	**13**[a]
1[b]	Oil-bath heating, 30 min, 170°C	35%	1%	5%
2[b]	Oil-bath heating, 5 min, reflux *DMF*	76%	9%	15%
3	Oil-bath heating, 2 h, reflux toluene	40%	–	48%
4[c]	MW heating, 1–5 min, 180°C	28%	1%	4%
5[d]	MW heating, 1–3 min, 180°C *DMF*	trace	61%	21%

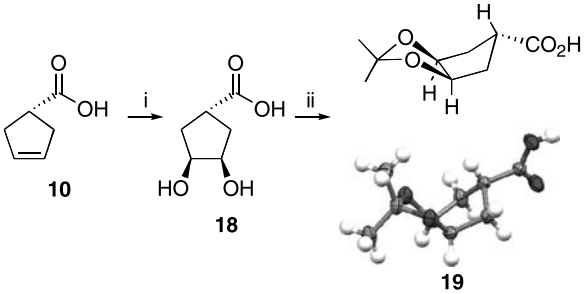
[a] Remaining starting material **1** represents the only other species detected otherwise mentioned; [b] average results over 3 runs; best yield in **2**: 98%; [c] average results over 3 runs; best yield in **2**: 84%; [d] average results over 3 runs; presence of an acyclic trimer

This impression is not significantly altered when switching to microwave-enhanced experimentation (Table 3, entries 4–5). Base catalysis is still essential, while working in *DMF* is actually favoring unsymmetrical dimerization and trimerization products (**12** and **13**). This confirms the notion that microwaves effectively alter reaction paths, but unfortunately, in this case, not in favor of formation of the trimer **2**. Again, working with **1** in neat form is not reproducible in our hands. This behavior finds its parallel in the observation of *Egret et al.*, that cationic polymerization of dimethylketene gives ''disperse yields . . . , even if similar conditions of polymerization are used'' [8].

In spite of the poor reproducibility of the conversion of **1** into **2**, we then decided to test whether extension of the ''open-chain'' substituents in **1** could lead us to highly functionalized cyclohexatriones. We thus prepared 2-allylpent-4-enoic acid (**15**) according to a literature procedure [20], and subjected it to the conditions previously employed for the synthesis of cyclobutadione **6**. Surprisingly, no dimerization product **16** [21] could be detected at all. Instead, carboxylic acid **15** and anhydride **17** were obtained after aqueous work-up (Scheme 5). Since strictly anhydrous conditions were maintained during the reaction, we assume that the reaction was put on hold at the initial stage of the acylated ammonium intermediate; this apparently does not continue to react either towards proton abstraction, thus initiating ketene formation, or attack by any enolate as proposed by *Erickson et al.* [9].

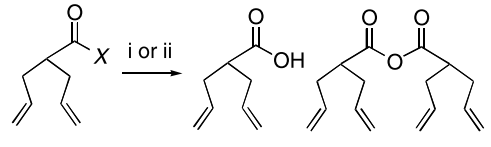
We made one more attempt to benefit from our stock in **10** to test whether the internal C=C bond present in dimer **6**, representing the only difference compared to published compound **4**, is responsible for poor conversion to the trimeric form. A dihydroxylated analogue of **6** would still be a very attractive entry into functionalized cyclohexatriones. In order to form dioxolane **19** starting from **10**, the 2-step procedure developed by *David et al.*, was applied [22]. Unfortunately, dihydroxylation using $KMnO_4$ under basic conditions furnished glycol **18** in poor yields. We thus turned to asymmetric dihydroxylation [23] which gave rise to diastereoisomer **18** in a satisfactory 65% yield. Its relative stereochemistry (*trans*) was determined by X-ray crystal structure analysis of the corresponding dioxolane derivative **19** (Scheme 6).

The one-pot procedure previously employed for the synthesis of **6** allowed us to convert **19** into the cyclobutadione **20** (Scheme 7). Surprisingly, only



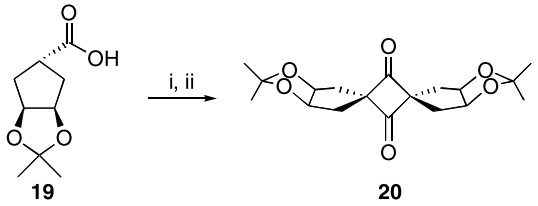
(i) AD-mix α, rt, 3 d (65%); (ii) acetone dimethyl acetal (98%)

Scheme 6



(i) X = Cl, *TEA* in *THF*; (ii) X = OH, $(COCl)_2$ in *DCM* then *TEA* in *THF*

Scheme 5



(i) $(COCl)_2$, *DCM*; (ii) 1.45 eq. *TEA*, *THF* (35–50% over the 2 steps)

Scheme 7

one diastereomer of **20** was detected. Its ^{13}C NMR spectrum, showing *two* distinct carbonyl peaks, furnished clear evidence for the *cis* orientation of the two dioxolane rings. The pentacyclic ring system of **20** appears to suffer from elevated strain. As a consequence, it turned out to be impossible to purify **20** by column chromatography; neither did it tolerate a recrystallization attempt. Also, **20** loses one protecting group in $CDCl_3$ over the course of a few hours. Hence, no attempt was made to trimerize it.

This contribution has presented studies on the potential exploitation of published ketene dimerization and trimerization procedures for the synthesis of heavily functionalized, C_2 and C_3 symmetrical cyclobutadiones and cyclohexatriones. While formation of ketene dimers worked well for the two more constrained substrates, dimer-to-trimer conversion did not appear to be a reliable reaction at the here applied millimolar scale, even for the reported tetramethylcyclobuta-1,3-dione (**1**). However, exploration of a large variety of conditions allows us to communicate the following observations: 1. the use of *DMF*, while aiding in substrate consumption and improving reaction reproducibility, tends to favor the formation of unsymmetrical dimers and trimers; 2. switching from conventional heating to mild microwave-assistance even enhances this trend, thus resulting in a more efficient access to the unsymmetrical trimer of dimethyl ketene **13** (61%, starting from commercially available dimer **1**) than the one previously reported (37% from dimer **12** [19]). Even if dehydrochlorination of acid chlorides has been reported for the formation of a number of symmetrical ketene dimers, the nature of the α substituents plays a critical role as illustrated by the failure to transform **14** into dimer **16**. Finally, functionalized symmetrical ketene dimer **6** was synthesized in a one-pot procedure from the free acid, providing good yields on a 3-g scale. Target cyclohexatrione **7**, an unsaturated symmetrical ketene trimer, was isolated, albeit in poor yield, and fully characterized. The low tendency of **6** to convert to **7**, in contrast to its saturated analogs, may be explained with the apparent higher thermodynamic stability of dimer **6**, or the corresponding polymeric ketenes, over trimer **7**.

Experimental

Reagents were purchased from commercial suppliers and used without further purification otherwise mentioned. All solvents except tetrahydrofuran (*THF*), dichloromethane (*DCM*), and triethylamine (*TEA*) were used without purification. *THF*, *DCM*, and *TEA* were introduced into the reactions freshly distilled from sodium-benzophenone, calcium chloride, and calcium hydride. Extra dry dimethylformamide (*DMF*) was purchased from Acros. The relevant following compounds were prepared according to known literature procedures: cyclopent-3-enecarboxylic acid (**10**) [15], cyclopent-3-enecarbonyl chloride (**9**) [24], and 2-allylpent-4-enoic acid (**15**) [20]. NMR spectra were recorded on a Bruker Avance 200 (operating at 200.13 MHz for ^1H and 50.32 MHz for ^{13}C). For ^1H and ^{13}C, chemical shifts (δ) are reported in ppm relative to *TMS*, using the solvent line as secondary internal reference (s: singlet, d: doublet, t: triplet, q: quartet, qt: quintet, m: multiplet, br: broad). All reactions were followed by TLC on Kieselgel 60 F_{254} with detection by UV light and/or with aqueous 10% permanganate solution and heating. Kieselgel 60 (Merck) was used for flash column chromatography. The microwave heating was carried out in closed vials with a CEM-Discover monomode microwave apparatus at 300 W under the conditions (temperature, time) given below. After completion of the reaction, the vessel was cooled down rapidly to 60°C. Varian CP-3800 gas chromatograph equipped with a flame ionization detector, a Varian CP-8400 autosampler and a CP-Sil5CB capillary column (30 m, 0.32 mm internal diameter, 0.25 μm film thickness) was employed. Nitrogen with a flow rate of 2 cm^3/min was used as gas carrier. The oven was programmed from 50°C with 0 min hold and 50°C/min increment to 170°C with 1.8 min hold. After a second temperature ramp (50°C/min) was applied from 170 to 200°C, the oven was maintained at 200°C during 9.7 min. Melting points were measured on a Perkin-Elmer DSC7 microcalorimeter. The IR spectra were recorded on a Mattson 3000 FT-IR spectrometer between 3500 and 500 cm^{-1} using KBr disks (w: weak, m: medium, s: strong, sh: shoulder). Mass spectra were acquired on a ThermoFinnigan LCQ Advantage ion trap instrument, detecting positive ions (+) or negative ions (−) in the ESI mode. Samples (in methanol:*DCM*:water, 45:40:15, *v*:*v*:*v*) were infused directly into the source (5 mm^3/min) using a syringe pump. The following source parameters were applied: spray voltage 3.0–3.5 kV, nitrogen sheath gas flow 5–20 arbitrary units. The heated capillary was held at 200°C. X-Ray crystal data were collected at room temperature on a Nonius Kappa CCD diffractometer using the COLLECT software [25]. Reduction of the data was carried out with DENZO [26]. Frame scaling and unit-cell parameters refinement were made through SCALEPACK [26]. The crystal structures were solved by direct methods with SIR97 [27] and successive difference *Fourier* map analyses. Refinement on *F* was carried out with CRYSTALS [28]. The hydrogen atoms were found in a difference *Fourier* map and included in the refinement using soft restraints on bond lengths and angles to regularize their geometry (C–H in the range 0.93–0.98 Å and O–H = 0.82 Å) and isotropic atomic displacement parameters (U(H) 1.2–1.5 times U_{eq} of the adjacent atom). CCDC-638272 and CCDC-638273 contain the supplementary crystallographic data for compounds **6** ($C_6H_{12}O_2$; unit cell parameters: $a = 8.689(5)$Å, $b = 10.063(5)$Å, $c = 11.821(5)$Å; space group *Pbca*) and **19**

($C_9H_{14}O_4$; unit cell parameters: $a = 5.582(5)$Å, $b = 6.284(5)$Å, $c = 14.678(5)$Å; $\alpha = 83.177(5)°$, $\beta = 82.283(5)°$, $\gamma = 74.235(5)°$; space group P-1). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk/data_request/cif.

Dispiro[4.1.4.1]dodeca-2,9-diene-6,12-dione (**6**, $C_{12}H_{12}O_2$)

Typical Dimerization Procedure Starting from Acyl Chloride ***9***

Cyclopent-3-enecarbonyl chloride **9** (3.11 g, 23.8 mmol), placed in a 100-cm^3 flame-dried *Schlenk*-flask, was diluted with 40 cm^3 *THF* under Argon. Triethylamine (2.3 mol · dm^{-3}, 4.80 cm^3 *TEA*, 15 cm^3 *THF*) was added to the yellow solution over 1 h under vigorous stirring. After only a few drops, a white solid material appeared while the colour slowly turned to orange. The reaction mixture was allowed to react overnight. After dilution with 70 cm^3 Et_2O, the brownish solution was filtered through a fritted funnel and washed with 50 cm^3 1 *N* HCl_{aq}. After extraction of the aqueous layer with 3×25 cm^3 Et_2O, the combined organic phases were washed with 30 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (*n*-hexane:*EtOAc* = 15:1–10:1–8:1–3:1) gave 1.56 g **6** as a white powder (8.29 mmol, 70%). X-Ray quality monocrystals were obtained from recrystallization in a cyclohexane/*EtOAc* mixture. $R_f = 0.34$ (*n*-hexane:*EtOAc*, 5:1). GC retention time: 4.0 min; mp 124°C; IR (KBr): $\bar{\nu} =$ 3072 w, 2910 m, 2841 w, 1745 s, 1718 sh, 1620 w, 1441 m, 1434 m, 1329 w, 1294 m, 1273 w, 1225 s, 1153 w, 1099w, 1038 m, 953 m, 814 w, 661 $s\,cm^{-1}$; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.88$ (s, 8H) 5.59 (s, 4H) ppm; ^{13}C NMR (CD_2Cl_2, 50 MHz): $\delta = 214.0$ (C), 128.1 (CH), 78.0 (CH_2), 39.8 (C) ppm; HR-MS (EI): m/z calcd. for $C_{12}H_{12}O_2$ [M^+] 188.0357, found 188.0835.

One-pot Procedure Starting from Cyclopent-3-enecarboxylic Acid ***10***

Cyclopent-3-enecarboxylic acid **10** (7.01 g, 62.4 mmol), placed in a 250 cm^3 flame-dried 2-neck round-bottomed flask, was diluted with 70 cm^3 *DCM* under Argon. Addition of oxalyl chloride (6.65 cm^3, 74.7 mmol) followed by 3 drops of *DMF* at 0°C gave rise to strong gas evolution. After 1.5 h at 0°C, the temperature was raised to ambient. After *ca.* 2.5 h the system was purged with Argon for 30 min and concentrated *in vacuo* ($T = 20$°C, $P = 50$ mmHg). Two successive additions of 20 cm^3 *DCM* followed by evaporation under reduced pressure helped to get rid of excess oxalyl chloride. After dilution of the brown–green oil in 100 cm^3 *THF*, *TEA* (12.5 cm^3, 89.7 mmol), diluted in 7.5 cm^3 *THF*, was added at room temperature over 1 h and the reaction mixture was stirred overnight. It was then filtered and the solid rinsed with Et_2O (*ca.* 180 cm^3) until complete decoloration. The mother liquor was washed with 50 cm^3 1 *N* HCl_{aq}. After extraction of the aqueous layer with 3×25 cm^3 Et_2O, the combined organic phases were washed with 30 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (*n*-hexane:*EtOAc* = 15:1–10:1; pure *EtOAc*; *EtOAc*/*Me*OH = 9:1) gave 3.22 g **6** as a white powder (17.1 mmol, 55%).

Trispiro[4.1.4.1.4.1]octadeca-2,9,15-triene-6,12,18-trione (**7**, $C_{18}H_{18}O_3$) *and Methyl 1-(cyclopent-3-enecarbonyl) cyclopent-3-enecarboxylate* (**11**, $C_{13}H_{16}O_3$)

Typical Trimerization Procedure under Conventional Heating

Under Argon, dimer **6** (402 mg, 2.13 mmol) and *Me*ONa (23 mg, 0.41 mmol) were placed in a 10-cm^3 2-neck round-bottomed flask connected to a reflux condenser. Addition of 3 cm^3 anhydrous *DMF* resulted in a purple color. Heating at 170–175°C was stopped after exactly 5 min and the crude reaction mixture was cooled down to 0°C under Argon. The resulting dark brown oil was transferred to a separatory funnel using 10 cm^3 *EtOAc* and 15 cm^3 diluted NH_4Cl. After separation, the aqueous layer was extracted with 2×10 cm^3 *EtOAc*. The combined organic phases were washed with 10 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the dark oil by flash chromatography (*n*-hexane: *EtOAc* = 10:1; pure *EtOAc*) afforded 9.5 mg **7** as white crystals (0.034 mmol, 2.4%), 27 mg **11** as a light yellow oil (0.123 mmol, 5.8%), and 240 mg unknown more polar fractions.

Compound **7**: $R_f = 0.32$ (*n*-hexane:*EtOAc*, 5:1); GC retention time: 10.4 min; IR (KBr): $\bar{\nu} = 3060$ w, 2949 w, 2926 m, 2854 w, 1699 s, 1435 w, 1340 m, 1294 sh, 1261 m, 1217 m, 1096 m, 1063 m, 1022 m, 968 m, 951 w, 818 m, 804 sh, 694 sh, 690 m, 660 m, 644 w cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 2.89$ (s, 12H) 5.60 (s, 8H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 206.6$ (C), 127.3 (CH), 66.9 (CH_2), 41.8 (C) ppm; HR-MS (CI): m/z calcd. for $C_{18}H_{18}O_3$ [$M + H^+$] 283.1334, found 283.1331.

Compound **11**: $R_f = 0.45$ (*n*-hexane:*EtOAc*, 5:1); GC retention time: 4.86 min; IR (KBr): $\bar{\nu} = 3059$ m, 2999 w, 2949 m, 2920 m, 2850 m, 1743 s, 1712 s, 1622 w, 1435 m, 1352 m, 1340 m, 1263 s, 1219 s, 1190 m, 1132 m, 1109 sh, 1084 m, 1066 m, 1016 w, 901 w, 881 w, 843 w, 793 w, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.62$ (s, 2H) 5.60 (s, 2H), 3.74 (s, 3H), 3.37 (qt, 1H, $J = 8.3$ Hz) 2.96 (s, 4H), 2.54 (d, 4H, $J = 8.3$ Hz) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 208.7$ (C), 173.5 (C), 128.7 (CH), 127.8 (CH), 65.5 (C), 52.6 (C), 45.7 (CH_3), 39.0 (CH_2), 38.7 (CH_2) ppm; HR-MS (EI): m/z calcd. for $C_{18}H_{18}O_3$ [M^+] 220.1099, found 220.1097.

Typical Trimerization Procedure under Microwave Heating

An 8-cm^3 reactor vial containing a magnetic stirring bar was charged with dimer **6** (502 mg, 2.67 mmol) and *Me*ONa (20 mg, 0.37 mmol). It was then placed inside a 50 cm^3 *Schlenk* tube which was further purged with Argon. After addition of 2 cm^3 of dry *DMF*, the reactor vial was sealed and irradiated with microwave according to the conditions (temperature and time) mentioned in Table 2. The crude mixture was transferred to a separatory funnel containing 15 cm^3 *EtOAc* and 15 cm^3 of diluted NH_4Cl. The layers were separated and the organic phase was washed with 10 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The dark oil was passed through a short pad of silicagel using a 5:1 cyclohexane/*EtOAc* eluant mixture. After evaporation of the solvents, the crude material was dissolved in *DCM* (7 mg/cm^3) and analyzed by GC.

2,2,4,4,6,6-Hexamethylcyclohexane-1,3,5-trione (**2**)*, 3,3-Dimethyl-4-(propan-2-ylidene)oxetan-2-one* (**12**)*, and 3,3,5,5-Tetramethyl-6-(propan-2-ylidene)-dihydro-3H-pyran-2,4-dione* (**13**)

Typical Trimerization Procedure under Conventional Heating

Under Argon, dimer **1** (400 mg, 2.85 mmol) was placed in a 10-cm^3 2-neck round-bottomed flask connected to a reflux condenser. After addition of 1.5 cm^3 anhydrous *DMF*, the reaction mixture was refluxed for 3 min with a pre-heated oil bath ($T = 170–175°C$). Addition of *Me*ONa (20 mg, 0.37 mmol) to the yellow solution initiated a strong exothermic process. The reaction was stopped after exactly 5 min by pouring the contents of the flask into an ice-bath. The crude orange solution was transferred into a separatory funnel containing 10 cm^3 *Et*O*Ac* and 15 cm^3 diluted NH_4Cl. After separation, the aqueous layer was extracted with 2×10 cm^3 *Et*O*Ac*. The combined organic phases were washed with 10 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The orange oil was analyzed by ^1H NMR to determine the relative percentages of compounds **1**, **2**, **12**, and **13**. When no dimer **1** was detected, flash column chromatography (*n*-pentane:Et_2O, 15:1) afforded compounds **2**, **12** and **13** in pure form.

Compound **2**: $R_f = 0.37$ (*n*-hexane:*Et*O*Ac*, 5:1); IR, ^1H, and ^{13}C NMR spectra were found to be identical with the ones described in Ref. [8].

Compound **12**: $R_f = 0.57$ (*n*-pentane:Et_2O, 10:1); IR, ^1H, and ^{13}C NMR spectra were found to be identical with the ones described in Ref. [8]; HR-MS (EI): m/z calcd. for $C_9H_{14}O_4$ [M^+] 140.0837, found 140.0836.

Compound **13**: $R_f = 0.38$ (*n*-pentane:Et_2O, 10:1); IR (KBr): $\bar{\nu} = 2985$ s, 2939 s, 2873 m, 1765 s, 1720 s, 1674 m, 1468 s, 1384 s, 1290 s, 1225 m, 1198 m, 1134 s, 1084 s, 1036 m, 933 w, 876 w, 825 w, 769 w, 586 w cm^{-1}; ^1H NMR spectrum was found to be in good agreement with Ref. [7] (neat); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 1.88$ (s, 3H), 1.84 (s, 3H), 1.44 (s, 6H), 1.39 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 209.5$ (C), 171.4 (C), 143.0 (C), 118.2 (C), 51.7 (C), 48.7 (C), 25.1 (CH_3), 21.7 (CH_3), 20.8 (CH_3), 18.6 (CH_3) ppm; HR-MS (EI): m/z calcd. for $C_9H_{14}O_4$ [M^+] 210.1256, found 210.1252.

Typical Trimerization Procedure under Microwave Heating

An 8-cm^3 reactor vial containing a magnetic stirring bar was charged with dimer **1** (704 mg, 5.02 mmol) and *Me*ONa (20 mg, 0.37 mmol). The vial was then placed inside a 50 cm^3 *Schlenk* tube which was further purged with Argon. After addition of 2 cm^3 dry *DMF*, the reactor vial was sealed and irradiated with microwave according to the conditions (temperature and time) mentioned in Table 3. The crude mixture was transferred to a separatory funnel containing 15 cm^3 *Et*O*Ac* and 15 cm^3 diluted NH_4Cl. The layers were separated and the organic phase was washed with 10 cm^3 brine, dried ($MgSO_4$), and concentrated *in vacuo*. The orange oil was analyzed by ^1H NMR to determine the relative percentages of compounds **1**, **2**, **12**, and **13**.

2-Allylpent-4-enoyl chloride (**14**)

Carboxylic acid **15** (4.60 g, 3.82 mmol) placed in a 100 cm^3 flame-dried *Schlenk* flask was diluted with 35 cm^3 *DCM* under Argon. Addition of oxalyl chloride (3.60 cm^3, 41.3 mmol) followed by 3 drops of *DMF* at 0°C gave rise to strong gas evolution. After 1.5 h at 0°C, the temperature was raised to ambient until no more gas evolution was detected (*ca.* 2 h). The system was purged with Argon for 30 min and concentrated *in vacuo*. The crude orange oil was vacuum distilled to afford 4.14 g acyl chloride **14** as a light yellow oil (26.1 mmol, 80%). Bp = 85–89°C at 50 mmHg [Ref. [29] 64°C (10 torr)]; IR (KBr): $\bar{\nu} = 3082$ m, 2993 w, 2983 m, 2945 w, 2918 w, 1795 s, 1711 w (traces of carboxylic acid), 1643 m, 1443 m, 993 m, 922 s, 897 m, 856 w, 631 w cm^{-1}; ^1H NMR and ^{13}C NMR in $CDCl_3$ identical to Ref. [30].

2-Allylpent-4-enoic anhydride (**17**, $C_{16}H_{22}O_3$)

Acyl chloride **14** (2.00 g, 12.6 mmol) placed in a 50 cm^3 flame-dried *Schlenk*-flask was diluted with 20 cm^3 *THF* under Argon. At room temperature, *TEA* (1.25 mol · dm^{-3}, 2.60 cm^3 *TEA*, 15 cm^3 *THF*) was added to the yellow solution over 1 h under vigorous stirring. After only a few drops, a white solid material appeared while the colour slowly turned to orange. The reaction mixture was allowed to react overnight at room temperature under Argon. The reaction mixture was filtered through a fritted funnel and the remaining brown solid was washed with 35 cm^3 Et_2O. After addition of 25 cm^3 1 *N* HCl_{aq}, the layers were separated. The aqueous phase was extracted with 3×15 cm^3 Et_2O, and the combined organic extracts were washed with 15 cm^3 brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude orange oil was purified by silicagel column chromatography (cyclohexane:*Et*O*Ac* = 10:1–8:1–5:1; pure *Et*O*Ac*) to afford 0.97 g **17** as a colorless oil (3.70 mmol, 59%) and 0.50 g **15** as a colorless oil (3.60 mmol, 29%).

Compound **17**: $R_f = 0.46$ (cyclohexane/*Et*O*Ac*, 5:1); IR (KBr): $\bar{\nu} = 3080$ m, 3003 w, 2981 m, 2941 sh, 2918 m, 2848 w, 1815 s, 1745 s, 1643 m, 1443 m, 1417 w, 1363 w, 1300 w, 1230 w, 1038 s, 997 s, 960 m, 920 s, 849 w, 810 w, 638 w cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 5.77$ (m, 4H), 5.10 (m, 8H), 2.60 (m, 4H), 2.37 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 170.0$ (C), 134.1 (CH), 117.6 (CH_2), 45.6 (CH), 34.8 (CH_2) ppm; HR-MS (CI): m/z calcd. for $C_{16}H_{22}O_3$ [$M + H^+$] 263.1647, found 263.1645.

Compound **15**: $R_f = 0.1$ (cyclohexane/*Et*O*Ac*, 5:1); ^1H NMR and ^{13}C NMR in $CDCl_3$ identical to Ref. [30].

(±)-(3R,4S)-3,4-Dihydroxycyclopentanecarboxylic acid (**18**)

Procedure adapted from Ref. [23]. A 250-cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was charged with 88 cm^3 *tert*-butyl alcohol, 88 cm^3 water, and 24.7 g AD-mix-α. Stirring at room temperature for 15 min produced two clear phases, the lower one appearing red. Carboxylic acid **10** (2.00 g, 17.8 mmol) was added at once and the resulting slurry was stirred vigorously for 3 days. Sodium hydrosulfide (26.5 g, 0.47 mol) was added and stirring was continued for an additional 4 h. The gray slurry was transferred to a separatory funnel containing 80 cm^3 2 *N* HCl and 220 cm^3 *Et*O*Ac*. The layers were separated, and the red aqueous phase was further extracted with 4×220 cm^3 *Et*O*Ac*, while the *pH* was main-

tained at 2 after each extraction by addition of 2 *N* HCl. The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford 1.69 g diol **18** as a white powder (11.57 mmol, 65%) with traces of an unknown product. No attempt was made to determine the stereochemistry of **18** at that stage. ^{1}H NMR (*DMSO*-d_6, 200 MHz): $\delta = 12.00$ (br s, 1H) 4.41 (br s, 2H), 3.86 (m, 2H), 2.88 (m, 1H), 1.79 (m, 4H) ppm; ^{13}C NMR (*DMSO*-d_6, 50 MHz): $\delta = 177.7$ (C), 72.8 (CH), 38.7.0 (CH), 34.4 (CH) ppm.

(±)-(3R,4S)-Isopropyliden-3,4-dioxycyclopentanecarboxylic acid (**19**)

Procedure adapted from Ref. [31]. A 100-cm^3 round-bottomed flask was charged with a solution of diol **18** (3.6 g, 24.6 mmol) in 4 cm^3 *DMSO*, and treated with (+)-camphor-10-sulfonic acid (100 mg, 0.43 mmol). Cyclohexane (30 cm^3) and 2,2-dimethoxypropane (34 cm^3, 274 mmol) were added and the volatile fractions (bp = 51–70°C) were distilled off. The remaining orange oil was concentrated *in vacuo* and purified by column chromatography (cyclohexane:*Et*O*Ac* = 2:1–1:2; pure *Et*O*Ac*) to afford 4.49 g of carboxylic acid **19** as a white crystalline powder (24.1 mmol, 98%). X-Ray quality monocrystals were obtained from recrystallization in $CHCl_3$. $R_f = 0.15$–0.34 (cyclohexane:*Et*O*Ac*, 1:1); mp 121°C; IR (KBr): $\bar{\nu} = 2981$ sh, 2974 s, 2669 sh, 2624 sh, 1703 s, 1468 m, 1450 m, 1429 m, 1377 m, 1319 m, 1279 s, 1253 s, 1219 s, 1205 s, 1178 m, 1132 m,1097 s, 1045 s, 984 m, 964 m, 899 m, 849 w, 832 m, 717 m, 575 w, 519 m cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 11.71$ (br, s, 1H), 4.67 (m, 2H), 3.02 (tt, 1H, $J = 12.0$ Hz, $J = 6.0$ Hz), 2.14 (dd, 2H, $J = 6.0$ Hz, $J = 14.2$ Hz), 1.71 (m, 2H), 1.42 (s, 3H), 1.26 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 180.8$ (C), 109.1 (C), 79.9 (CH), 40.6 (CH), 36.8 (CH_2), 26.0 (CH_3), 23.6 (CH_3) ppm; HR-MS (CI): m/z calcd. for $C_9H_{14}O_4$ [M + H$^+$] 187.0970, found 187.0974.

2,4-Dispiro(isopropyliden-2′,3′-dioxycyclopentyl)cyclobutane-1,3-dione (**20**, $C_{18}H_{24}O_6$)

Same one-pot procedure as described for compound **6** starting with carboxylic acid **19** (675 mg, 3.62 mmol). After work-up with diluted citric acid, the crude mixture was dried under high vacuum to afford 352 mg orange powder containing 60–85% of dimer **20** (0.63–0.89 mmol, 35–50%) according to ^{1}H NMR. ^{1}H NMR (CD_2Cl_2, 200 MHz): $\delta = 4.71$ (m, 4H), 2.31 (d, 4H, $J = 14.4$ Hz), 2.05 (m, 4H), 1.61 (s, 6H), 1.26 (s, 6H) ppm; ^{13}C NMR (CD_2Cl_2, 50 MHz): $\delta = 213.3$ (C), 207.3 (C), 111.5 (C), 81.8 (CH), 80.3 (C), 39.3 (CH_2), 26.1 (CH_3), 24.4 (CH_3) ppm; HR-MS (ESI): m/z calcd. for $C_{18}H_{24}O_6Na$ [M + Na$^+$] 359.1471, found 359.1471.

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