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On the Regioselectivity of the Intramolecular [2 + 2]-Photocycloaddition of Alk-3-enyl Tetronates

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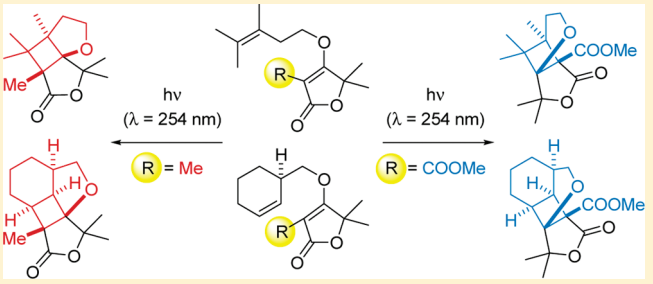
Supporting Information

ABSTRACT: The simple diastereoselectivity and the regioselectivity of the [2 + 2]-photocycloaddition of alk-3-enyl tetronates were studied, depending on the nature of the substituent R in the α-position. Fourteen tetronates were synthesized and their intramolecular photocycloaddition reactions performed. If R was an alkoxycarbonyl group and if the olefin, which underwent the intramolecular addition, was sterically congested, crossed photoproducts prevailed and were formed in yields between 35 and 65%. In all other cases, the straight photoproducts were obtained as the main reaction products in yields ranging from 39 to 84%. The structures of the photochemical products were thoroughly investigated by one- and two-dimensional NMR experiments. In all cases, the diastereoselectivitiy was excellent and only a single diastereoisomer was formed. A mechanistic model is proposed, which explains the regioselectivity of the [2 + 2]-photocycloaddition reaction.



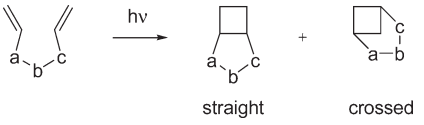
INTRODUCTION

[2 + 2]-Photocycloaddition reactions[1] have shown to be magnificent reactions for the construction of strained molecules, and they can be found as key steps in numerous natural product syntheses.[2] As depicted in Scheme 1, [2 + 2]-photocycloaddition reactions with a three atom tether between the reacting olefins can occur either in a straight or in a crossed fashion.[3] Typically, the straight product, which goes along with the formation of a five-membered ring, prevails or is the only reaction product.[4] This observation was recognized by Srinivasan et al. and Hammond et al., and the term "rule of five" was coined to account for the preferred regioselectivity of [2 + 2]-photocycloaddition reactions.[5]

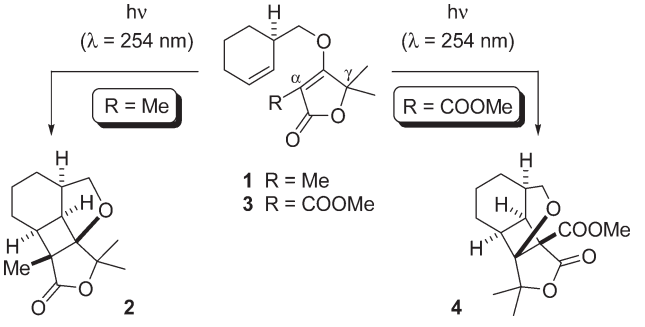
During our studies related to the application of tetronate [2 + 2]-photocycloaddition reactions[6] to the total synthesis of cembranoid natural products,[7] we discovered that the regioselectivity of the photochemical key step was inverted as a result of changing one substituent at the chromophore.[8] As one would anticipate from the rule of five,[5] the [2 + 2]-photocycloaddition of tetronate **1** (R = Me) afforded the tetracyclic cyclobutane **2** as the only reaction product (Scheme 2). In contrast, the tetronate **3** with a methoxycarbonyl substituent in the α-position of the tetronate was regioselectively converted into the crossed photocycloaddition product **4** upon irradiation.

In order to gain insight into the factors that govern the regiochemical outcome of related [2 + 2]-photocycloaddition reactions, we investigated the influence of three structural parameters: (1) substituent R in the α-position of the tetronate; (2) substitution pattern at the alk-3-enyl substituent; (3) influence of the geminal dimethyl group in the γ-position of the tetronic acid unit. Here, we give a full account of our synthetic study, which includes the preparation of six tetronic acids and 14 tetronates that were subsequently submitted to an intramolecular [2 + 2]-photocycloaddition reaction.

Scheme 1. Formation of Straight and Crossed [2 + 2]-Photocycloaddition Products upon Irradiation of Two Olefins, which are Separated by Three Atoms a, b, and c



Scheme 2. Influence of the Substituent R on the Regioselectivity in the Intramolecular [2 + 2]-Photocycloaddition of Tetronates 1 and 3



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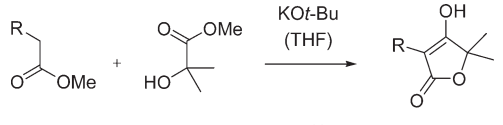
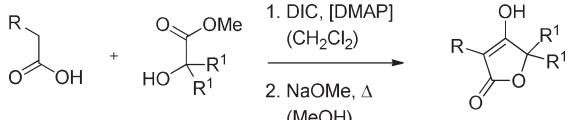
Scheme 3. One-Step Synthesis of Tetronic Acids 5 and 6 by Transesterification and Dieckmann Cyclization



7 R = H, **8** R = Me | **9a** | 48%, 85% | **5** R = H, **6** R = Me

Table 1. Two-Step Synthesis of Tetronic Acids 11−14 by Steglich Esterification and Dieckmann Cyclization



10a-c | **9a/b** | **11-14**

entry	R	R^1	yield step 1 (%)	yield step 2 (%)	product
1	COOMe	Me	70	61	**11**
2	COO*t*-Bu	Me	53	71[a]	**12**
3	CN	Me	31	42	**13**
4	COOMe	H	55	61	**14**

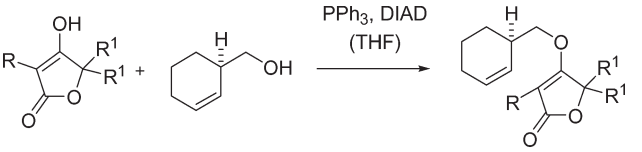
[a]Reaction carried out with KO*t*-Bu in *t*-BuOH.

RESULTS

Synthesis of the Substrates. For the synthesis of tetronic acids **5** and **6**, we adopted a one-step procedure recently published by Le Gall et al.[9] As depicted in Scheme 3, methyl acetate (**7**) or methyl propionate (**8**) were reacted with hydroxyester **9a** in the presence of KO*t*-Bu in THF to give the desired product **5** or **6** in 48 and 85% yield. In order to purify tetronic acids **5** and **6**, but also for the purification of the tetronic acids mentioned below, we took advantage of their hydrophilicity at high pH values. The tetronic acids were dissolved in an aqueous sodium hydroxide solution phase, which was washed with Et_2O to remove any unpolar impurities. After acidification of the aqueous layer, the tetronic acids were extracted into a 5:1 mixture of $CHCl_3$ and *i*-PrOH.

Tetronic acids **11**−**14** with electron-withdrawing substituents in the α-position were not accessible by the method mentioned above. They could, however, be prepared by a sequence of esterification and Dieckmann condensation (Table 1).[10] First, malonic acid monoesters **10a**[11]**/b** (or the respective nitrile **10c**) were condensed with methyl 2-hydroxyisobutyrate (R^1 = Me, **9a**) or methyl 2-hydroxyacetate (R^1 = H, **9b**) by treatment with di-*iso*-propylcarbodiimide (DIC) and catalytic amounts of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (31−70% yield).[12] For the synthesis of nitrile **13**, the reaction preferably led to the formation of an *N*-acylurea accounting for the low yield of the esterification product. A similar yield of compound **13** was obtained by utilizing dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) as coupling reagents.[13] In the second step, the diester intermediates were cyclized by treatment with NaOMe in MeOH to generate the tetronic acids **11**−**14** in 42−71% yield. For the synthesis of *tert*-butyl ester **12**, KO*t*-Bu in *tert*-butyl alcohol was employed as base in order to avoid a transesterification to methyl ester **11**.

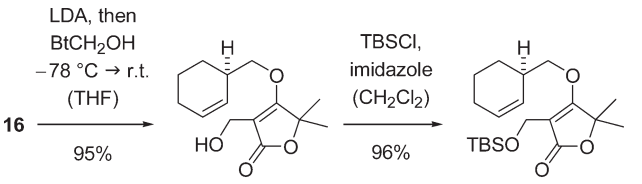
Table 2. Synthesis of Tetronates 1, 3, and 16−19



5, 6, 11-14 | **15** | **1, 3, 16-19**

entry	substrate	R	R^1	product	yield (%)
1	**5**	H	Me	**16**	93
2	**6**	Me	Me	**1**	75
3	**11**	COOMe	Me	**3**	90
4	**12**	COO*t*-Bu	Me	**17**	62
5	**13**	CN	Me	**18**	67
6	**14**	COOMe	H	**19**	24

Scheme 4. Synthesis of Tetronates 20 and 21 Starting from Tetronate 16



16 | **20** | **21**

The coupling of tetronic acids **5**, **6** (entries 1 and 2, Table 2), and **11**−**14** (entries 3−6, Table 2) with cyclohex-2-enemethanol (**15**, accessible from cyclohexene in one step)[14] was successfully accomplished by Mitsunobu reactions (Table 2).[15] The primary alcohol **15** and tetronic acids **5**, **6**, or **11**−**14** were stirred in the presence of triphenylphosphine and di-*iso*-propylazodicarboxylate (DIAD) overnight in THF, and tetronates **1**,[8] **3**,[8] **16**,[8] **17**, **18**, and **19** were conveniently obtained after column chromatography. These reactions worked reasonably well in yields ranging from 62 to 93%. In the case of tetronic acid **14**, the reaction was cumbersome and the required tetronate **19** could only be isolated in a yield of 24%.

It is known that γ,γ-disubstituted tetronates can be deprotonated in the α-position with lithium di-*iso*-propylamide (LDA).[16] After deprotonation, tetronate **16** was treated with 1-benzotriazolylmethanol ($BtCH_2OH$),[17] which is a source of formaldehyde under basic conditions,[18] and the hydroxymethylated tetronate **20** was obtained.[8] Contrary to the examples mentioned by Bischoff et al., which took place at −78 °C,[18] it was essential to warm the reaction mixture to room temperature to achieve complete conversion. A subsequent silylation of alcohol **20** with *tert*-butyldimethylsilyl chloride (TBSCl) afforded the TBS ether **21** (Scheme 4).

In order to study the influence of the substituents at the olefinic side chain, several esters of tetronic acids **6** and **11** were synthesized. A Mitsunobu reaction of tetronic acid **6** with but-3-enol (**22a**) generated tetronate **23a** in a yield of 74%.[15] Tetronate **23b** with a tetrasubstituted olefin was obtained from the same tetronic acid **6** and the literature known bromide **24**[19] by a cesium fluoride mediated O-alkylation reaction in DMF

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Scheme 5. Synthesis of Tetronate 23a by Mitsunobu Reaction of Alcohol 22a and Tetronic Acid 6 and Synthesis of 23b by Nucleophilic Substitution of Bromide 24 with Tetronic Acid 6

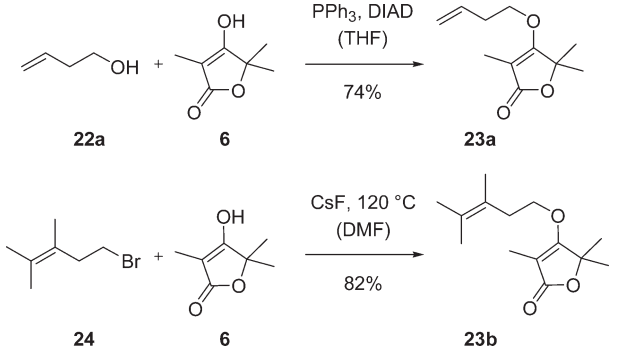
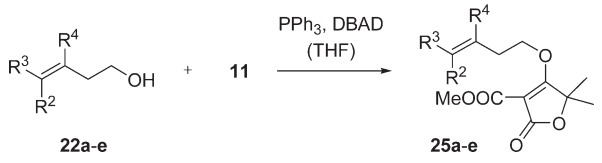


Table 3. Synthesis of Tetronates 25a−25e by Mitsunobu Reaction of Alcohol 22a−e and Tetronic Acid 11



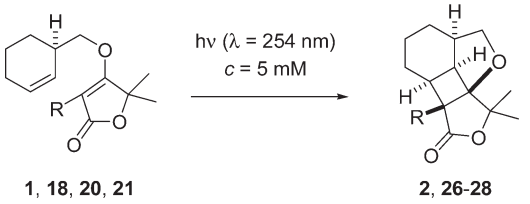
entry	alcohol	R^2	R^3	R^4	product	yield (%)
1	**22a**	H	H	H	**25a**	88
2	**22b**	H	H	Me	**25b**	75
3	**22c**	Me	Me	H	**25c**	83
4	**22d**	H	$-(CH_2)_4-$		**25d**	68[a]
5	**22e**	Me	Me	Me	**25e**	86

[a]DIAD was used instead of DBAD.

(Scheme 5).[20] Although these substitution reactions between tetronic acids and alkyl bromides normally take place at room temperature, a temperature of 120 °C was necessary to obtain full conversion.

Mitsunobu reactions were also applied to synthesize tetronates **25a−e** (Table 3).[15] The required alcohols **22a** and **22b** are commercially available, whereas alcohols **22c**[21] and **22d**[22] were prepared according to literature precedence. Alcohol **22e** was obtained from bromide **24** by acetoxylation and hydrolysis of the acetate (see Experimental Section). Except for tetronate **25d** (entry 4), it was difficult to separate the products of the Mitsunobu reaction from *N,N′*-di-*iso*-propoxycarbonylhydrazine (formed by reduction of DIAD). Thus, di-*tert*-butylazodicarboxylate[23] (DBAD) was employed instead of DIAD for the synthesis of tetronates **25a−c** and **25e**. The hydrazine resulting from DBAD could easily be removed by column chromatography. The tetronates **25a−c** were isolated in yields between 75 and 88% (entries 1−3 and 5). Initially, we attempted to synthesize tetronate **25e** from bromide **24** and tetronic acid **11** by using cesium fluoride as a base.[20] As opposed to the related reaction of tetronate **6** with the same bromide (Scheme 5), only low yields (<10%) of tetronate **25e** could be obtained, even at high temperatures and after long reaction times.

Table 4. Formation of Straight Products 2 and 26-28 by [2 + 2]-Photocycloaddition of Tetronates 1, 18, 20, and 21



entry	tetronate	R	solvent	product	yield (%)
1	**1**	Me	*t*-BuOH	**2**	39
2	**1**	Me	*i*-PrOH	**2**	42
3	**20**	CH_2OH	*t*-BuOH	**26**	55
4	**21**	CH_2OTBS	*t*-BuOH	**27**	36[a]
5	**18**	CN	Et_2O	**28**	54

[a]With 17% starting material **21** reisolated.

[2 + 2]-Photocycloaddition Reactions. It has been previously reported that the [2 + 2]-photocycloaddition of tetronates **1** and **20** proceeds smoothly to afford the cyclobutanes **2** and **26** with straight constitution.[8] The reaction of compound **1** was almost equally effective in *t*-BuOH and *i*-PrOH (Table 4, entries 1 and 2). For tetronate **20**, only *t*-BuOH and Et_2O were investigated as solvents, and the better yield was obtained in *t*-BuOH (55%, entry 3). Upon irradiation of the TBS ether **21**, the same regioselectivity was found and the photocycloaddition product **27** was generated in 36% yield (entry 4). The reaction was hampered by the fact that full conversion of the starting material could not be achieved. If the irradiation was continued until all of the starting material **21** was consumed, only diminished yields of cyclobutane **27** were found, presumably due to severe decomposition. However, product **27** could conveniently be separated from starting material **21** by column chromatography, so it was beneficial to stop the reaction after 8 h (for the irradiation conditions, see general procedure C in the Experimental Section and ref 6f). An irradiation at longer wavelength (λ = 300 nm) did not lead to any conversion in the case of α-alkyl-substituted tetronates, such as compound **1**. Treatment of silyl ether **27** with tetrabutylammonium fluoride in THF led to the formation of alcohol **26** in 91% yield. Not only cyclohex-2-enylmethyl tetronates with electron-donating substituents afforded the straight photocycloaddition product, but also the nitrile **18** gave a straight photoproduct, compound **28** (entry 5). In this case, Et_2O was superior to alcoholic solvents. While a reaction time of 8 h was necessary for a full conversion of tetronates **1** and **20**, the nitrile **18** was fully converted in only 1 h. It has to be stressed that all of the reactions in Table 4 afforded the straight photocycloaddition product as the only defined low molecular weight product. In particular, there was no indication for the formation of a crossed product in the crude ^1H NMR. There was no detectable influence of the solvent on the regioselectivity in all cases we studied.

In contrast to the regioselectivity observed for the [2 + 2]-photocycloaddition reactions mentioned above, the compounds **3** and **17** with a carboxylate group in the α-position afforded selectively the crossed products **4**[8] and **29** in 65 and 37% yield (Scheme 6). Both reactions worked best if *t*-BuOH was employed as the solvent, and both reactions were complete after

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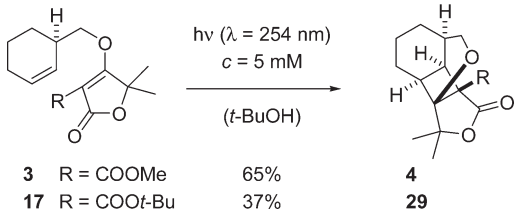
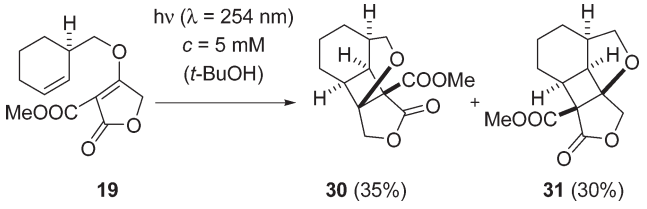
Scheme 6. Formation of Crossed Products 4 and 29 by [2 + 2]-Photocycloaddition of Tetronates 3 and 17



Scheme 7. Formation of Crossed Product 30 and Straight Product 31 by [2 + 2]-Photocycloaddition of Tetronate 19



30 min. According to the ^{1}H NMR spectra of the crude reaction products, there was no evidence for the formation of straight photocycloaddition products. It should be noted that the reaction of tetronate **3** also proceeded at λ = 300 nm in *t*-BuOH, but a reaction time of 16 h was necessary for full conversion and the yield was disappointingly low (37%). In the presence of 10 equiv of acetone as a sensitizer, the photochemical reaction at λ = 300 nm in *t*-BuOH was completed much more rapidly (1 h), thus indicating a triplet mechanism as previously suggested for other tetronates.[6b] The higher reaction rate under nonsensitized conditions as compared to tetronates **1**, **20**, and **21** is attributed to the better absorption properties of the alkoxycarbonyl-substituted tetronates. While substrate **1** for example exhibits an absorption coefficient ε of 420 M^{-1} cm^{-1} at λ = 254 nm, the absorption of tetronate **3** is in *tert*-butyl alcohol about six times higher (ε = 2600 M^{-1} cm^{-1}). The cyano-substituted substrate **18** (Table 4), which exhibits a similar bathochromic shift, showed a similar reaction rate as tetronate **3** (vide supra).

We next turned our attention to the influence of the geminal dimethyl group in the γ-position of the tetronic acid unit on the regioselectivity of the [2 + 2]-photocycloaddition (Scheme 7). Irradiation of tetronate **19**, which lacks the two methyl groups, led to the formation of two cyclobutanes in 35 and 30% yield. The reaction products were identified as the crossed product **30** and its straight counterpart **31**.

It was questionable whether the special behavior of the tetronates with carboxylate groups in the α-position was limited to cyclohex-2-enylmethyl tetronates. Thus, the series of previously prepared acyclic alk-3-enyl tetronates **23** and **25** was subjected to irradiation at λ = 254 nm. Our studies commenced with the [2 + 2]-photocycloaddition of the α-methyl-substituted tetronates **23a** and **23b** (Scheme 8). In both cases, a straight photocycloaddition took place, and the cyclobutanes **32a** and **32b** were formed as single diastereoisomers in 52 and 46% yield. No other reaction products could be detected. Similar to our observations mentioned above, the regioselectivity was inverted

Scheme 8. Formation of Straight Products 32a and 32b by [2 + 2]-Photocycloaddition of Tetronates 23a and 23b and Formation of Crossed Product 33 from Tetronate 25e

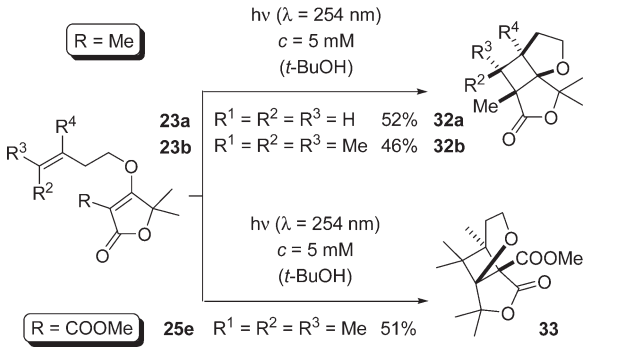
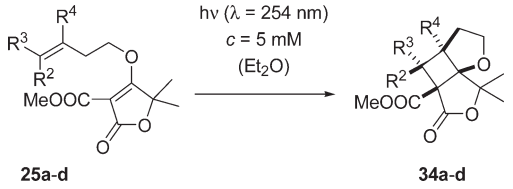


Table 5. Formation of Straight Products 34a-d by [2 + 2]-Photocycloaddition of Tetronates 25a-d



entry	substrate	R^2	R^3	R^4	product	yield (%)
1	**25a**	H	H	H	**34a**	78[a]
2	**25b**	H	H	Me	**34b**	75
3	**25c**	Me	Me	H	**34c**	53[b]
4	**25d**	H	$-(CH_2)_4-$		**34d**	84[a]

[a] A 90:10 (^{1}H NMR) mixture of isomers; the minor product is tentatively assigned as the crossed regioisomer. [b] A second isomer (tentatively assigned as the crossed regioisomer) was formed according to crude ^{1}H NMR (ratio = 88:12) but could be separated by column chromatography.

for tetronate **25e** with a tetrasubstituted olefin, if the methyl substituent in the α-position was replaced with a methoxycarbonyl group. In this case, only the crossed photocycloaddition product **33** was obtained in a yield of 51%. Once again, it was formed diastereomerically pure, and there was no evidence for another reaction product.

Subsequently, the influence of the substituents R^2, R^3, and R^4 at the olefinic side chain of the α-methoxycarbonyl-substituted tetronates was studied (Table 5). As opposed to tetronate **25e** with a tetrasubstituted double bond, the less substituted alk-3-enyl tetronates **25a**−**d** afforded the straight photocycloaddition products **34a**−**d** as the main products in 53−84% yield. According to ^{1}H NMR data, the least substituted tetronate **25a** (entry 1), the tetronate **25c** with a terminal dimethyl group (entry 3), and the tetronate **25d** with a cyclic disubstitution at positions R^3 and R^4 (entry 4) also afforded a small quantity of another isomer (ratio = 90:10) upon irradiation. We assume that the second isomer is the crossed isomer. However, due to the small amounts formed, and due to the difficulties obtaining the side products in pure form, we could not unambiguously determine their molecular structures. Interestingly, the amount of the second reaction

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product formed from the cyclohexenyl-substituted tetronate **25d** inreased slightly if the reaction was carried out at −60 °C (90% yield, ratio = 83:17). If *t*-BuOH was selected as the solvent for the irradiation of substrate **25d**, a 67:33 ratio of straight photocycloaddition product **34d** and the second isomer was formed (72% overall yield).

While cyclobutane **34a** was inseperable from the minor product, compounds **34c** and **34d** could be purified by column chromatography. If the terminal position was unsubstituted and one methyl group was present as R^4 (compound **25b**, entry 2), the [2 + 2]-photocycloaddition proceeded diastereo- and regioselectively to generate cyclobutane **34b** as a single reaction product in a yield of 75%.

Structural Assignment of the [2 + 2]-Photocycloaddition Products. The structural assignment of the photocycloaddition products was mainly based on two-dimensional NMR experiments. In particular, NOE experiments turned out to be very helpful to determine the constitution and configuration of the photochemical reaction products. Furthermore, the molecular structure of the methyl derivative **2** and that of the methoxycarbonyl derivative **4** were proven by single-crystal X-ray diffraction.[8] For the structure determination of the photocycloaddition products **2**, **4**, and **26**−**29**, it was most advisible to investigate the methine proton which bears an NOE correlation to the *endo* methyl group. If this methyl group showed an NOE contact to the methine proton C13−H, a straight constitution was assigned to the product depicted on the left in Figure 1. If the *endo* methyl group had an NOE correlation to the methine proton C1−H, a crossed constitution was assigned (Figure 1, right).

These diagnostic NOE correlations are highlighted with an asterisk in Figure 1. Apart from that, the multiplicities and coupling constants of the signals in the ^{1}H NMR were compared. Table 6 presents a comparison of three representative ^{1}H NMR signals: The proton C1−H and the diastereotopic protons at C8−H (straight products **2**, **26**, and **31**) or C13−H (crossed products **4**, **29**, and **30**). Proton C1−H of the straight products typically couples with three vicinal protons with ^3J-coupling constants of ca. 9, 8, and 3.5 Hz, while the same proton of the crossed isomers only couples with two vicinal protons with coupling constants of ca. 5 Hz each.

The protons C8−H^α of the straight products appear as virtual triplets with a ^2J- and a ^3J-coupling constant of ca. 9 Hz for the straight photocycloaddition products, while the corresponding protons C13−H^α of the crossed isomers appear as doublets of doublets of doublets with ^2J-coupling constants of ca. 12 Hz and ^3J-coupling constants of ca. 6 and 1.5 Hz. The values of the ^2J-coupling constants mentioned above are in good agreement with those typically obtained for the respective positions in tetrahydrofurans (^2J < 10 Hz)[24] and tetrahydropyrans (^2J > 10 Hz).[25] Apart from the ^2J-coupling to C8−H^α, the protons C8−H^β of the straight isomers couple to the vicinal proton with coupling constants of ca. 8 Hz. Thus, they typically appear as doublets of doublets, while the protons C13−H^β of the crossed isomers only couple to the diastereotopic protons C13−H^α, resulting in a doublet multiplicity.

The structural assignment of the [2 + 2]-photocycloaddition products of tetronates with acyclic alkene units is exemplarily demonstrated for the cyclobutanes **32b**, **33**, and **34c**. Analogous to the structure determination mentioned above, the signals in the ^{1}H and ^{13}C NMR spectra were carefully analyzed with HMQC (heteronuclear multiple quantum coherence) and HMBC (heteronuclear multiple bond coherence) experiments in order to establish the connectivities. As for the cyclohexyl-substituted cyclobutanes, the ^2J-coupling constants for the methylene protons next to the oxygen atom of the tetrahydrofuran unit in the straight photocycloaddition products were lower than 10 Hz. For the assignment of the constitution and relative configuration, NOE experiments were a valuable tool. The characteristic NOE contacts of compounds **32b**, **33**, and **34c** are shown in Figure 2.

In the case of photocycloaddition product **32b**, the relative configuration could easily be proven by means of the depicted NOE correlations. Unfortunately, the chemical shifts of the ^{1}H NMR signal of the *endo* methyl group at C2 and the methyl group attached to C7 are almost identical, so an unequivocal NOE signal between these two methyl groups could not be determined. Still, the connectivity could be established with the help of the HMBC spectrum of compound **32b** (see Supporting Information for details). The NOE experiments of crossed photocycloaddition product **33** and straight product **34c** were more rewarding. Apart from an unambiguous assignment of the relative configuration on the basis of NOE cross peaks, the

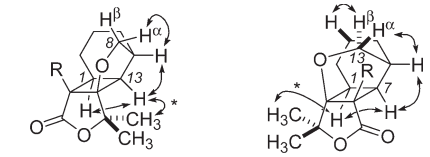

Figure 1. Characteristic NOE signals of the [2 + 2]-photocycloaddition products of cyclohex-2-enylmethyl tetronates.

Table 6. Chemical Shift δ (ppm), Multiplicities, and Coupling Constants J (Hz) of Representative ^{1}H NMR Signals of Straight Photocycloaddition Products 2, 26, and 31 and of Crossed Isomers 4, 29, and 30

proton	2	26	31	4	29	30
C1−H	2.37	2.46	2.61−2.74	2.92	2.86	2.26
	ddd	ddd	m	virtual t	virtual t	virtual t
	8.7, 8.3, 3.7	9.0, 7.8, 3.4		∼5.1	∼5.1	∼5.5
C8−H^α or C13−H^α	4.12	4.18	4.15	4.04	4.11	4.01
	virtual t	virtual t	virtual t	ddd	ddd	ddd
	∼8.9	∼9.0	∼9.1	12.2, 6.2, 1.7	12.1, 6.1, 1.5	12.2, 6.2, 1.7
C8−H^β or C13−H^β	3.85	3.92	3.83	3.83	3.83	3.82
	dd	dd	virtual t	d	d	d
	8.9, 8.0	9.0, 8.0	∼9.5	12.2	12.1	12.2

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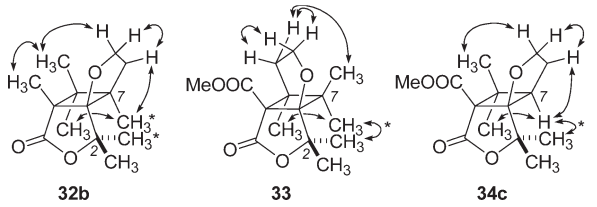
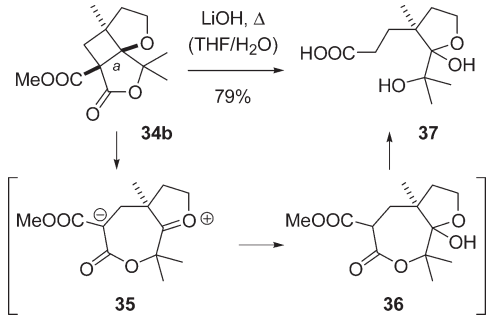


Figure 2. Characteristic NOE signals of the [2 + 2]-photocycloaddition products **32b**, **33**, and **34c**.

Scheme 9. Formation of Hydroxy Acid 37 from Cyclobutane 34b by Fragmentation of Bond *a*, Nucleophilic Attack of a Hydroxide Ion, Hydrolysis, and Decarboxylation



constitution could be determined based on the diagnostic signal of the *endo* methyl group at C2 to the methyl group (for compound **33**) or proton (for compound **34c**) attached to C7. This NOE contact is highlighted with an asterisk in Figure 2.

The structure of the cyclobutane **34b** could not be unambiguously assigned by means of one- and two-dimensional NMR experiments. In order to elucidate the structure, we resorted to a fragmentation reaction similar to that previously observed for compound **4**.[8] Treatment of diester **34b** with lithium hydroxide in a boiling mixture of THF and water led to a fragmentation of bond *a* (Scheme 9). Supposedly, the resulting carboxonium ion **35** was trapped by a hydroxide ion to generate compound **36**, and after two-fold hydrolysis of the ester groups and decarboxylation, the hydroxyacid **37** was formed. The NMR data of this compound are in agreement with structure **37** and differ clearly from the set of signals that would be expected from the corresponding reaction product (a tetrahydropyran-2-ol) of the crossed isomer of compound **34b**.

DISCUSSION

For discussing the outcome of the [2 + 2]-photocycloaddition, it appears sensible to consider the potential 1,4-biradicals, which are formed by C−C bond formation from the excited triplet state of the respective tetronate. These species have been shown to be involved as intermediates in photocycloaddition reactions, and they have a decisive impact on the regioselectivity.[26] The above-mentioned rule of five suggests a preferred formation of intermediates **I** and **I′** due to the fast ring closure to a five-membered ring in the initial step (Figure 3).[5,27] Diastereoisomer **I** is competent to undergo a subsequent ring closure explaining the formation of all straight products **2**, **26**, **27**, **28**, **31**, **32a**, **32b**, and **34a**−**d** with the given relative configuration. In diastereoisomer **I′**, the *trans*-orientation of the two radical centers at the tetrahydrofuran ring makes the cyclobutane ring formation

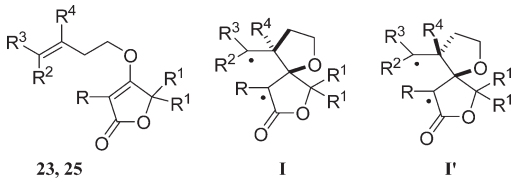


Figure 3. 1,4-Biradicals **I** and **I′** formed as intermediates by five-membered ring closure from tetronate precursors in an intramolecular [2 + 2]-photocycloaddition.

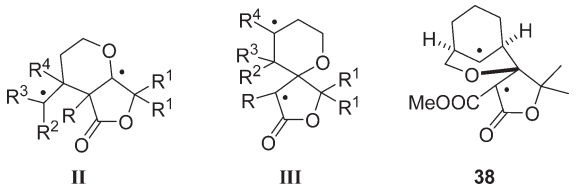


Figure 4. General structures **II** and **III** and specific structure **38** of 1,4-biradicals formed as intermediates in a six-membered ring closure from tetronate precursors.

impossible, and this 1,4-biradical is consequently forced to reverse the C−C bond forming event leading to the formation of starting materials.[5c,26]

The formation of crossed photocycloaddition products proceeds via biradicals **II** or **III** (Figure 4). Given that in all crossed products the substituent R is an alkoxycarbonyl group (R = COOMe, COO*t*-Bu), which stabilizes an adjacent radical, biradical **III** seems to be the more likely intermediate. In addition, this biradical should be formed as a single stereoisomer because the former terminal alkene carbon atom is not stereogenic ($R^2 = R^3$) or is part of a cyclic ring system. The latter statement is illustrated by 1,4-biradical **38**, which is the putative intermediate responsible for formation of product **4**.

What makes the reaction pathway leading to straight products different from the pathway leading to crossed products? The major influence is certainly exerted by the substituent R, which provides a stabilization of the adjacent radical center. In cases in which sterically congested bonds would be formed, cleavage of the 1,4-biradicals provides a route to access thermodynamically more favorable constitutions and configurations.[28] The sterically relatively demanding (compared to cyano) alkoxycarbonyl group exerts this effect in a prominent way. With substrates **1**, **3**, **17**, **18**, **20**, and **21**, a formation of the crossed product is only observed for compounds **3** and **17** which bear a methoxycarbonyl or *tert*-butoxycarbonyl group as substituent R. Inspection of molecular models supports the notion that there is severe steric repulsion in straight photocycloaddition products between the substituents R^1 and R^4 and between the substituents R^2/R^3 and R. While the short-lived 1,4-biradicals derived from α-alkyl-substituted tetronates (R = Me, CH_2OH, CH_2OTBS) exhibit only limited retrocleavage from **I**, and while the relatively small cyano group (R = CN) does not interfere strongly with R^2/R^3, the effects are notable in the reaction of tetronate **25e**, in which both the alkene and the tetronate are highly substituted. As a consequence, a pathway via the sterically less encumbered intermediate **III** is presumably taken, resulting in the crossed photocycloaddition product **33**. The unselective outcome in the reaction of substrate **19** (Scheme 7) can be explained by the reduced steric bulk in the γ-position of the tetronate (R^1 = H), making the steric

interaction between R^1 and R^4 less severe than in substrate **3**. The two regioisomeric products **30** and **31** are formed in close to equal amounts.

CONCLUSION

In summary, an array of tetronates was synthesized in order to study the parameters responsible for the formation of straight or crossed [2 + 2]-photocycloaddition products. While all α-alkyl tetronates selectively afforded straight photocycloaddition products, it turned out that some α-alkoxycarbonyl-substituted tetronates were converted to crossed cyclobutanes upon irradiation. Several factors play a role for the observed regioselectivities, the most prominent being the substituent in the α-position of the tetronate. The steric bulk of both the substituent in the γ-position and the olefinic side chain was also found to have an influence on the regiochemical outcome of the [2 + 2]-photocycloaddition. The results were explained with a mechanistic model that takes into account that the primarily formed 1, 4-biradical may revert to the starting material if the subsequent ring closure is thermodynamically unfavorable. In sterically encumbered situations, it appears as if the α-alkoxycarbonyl-substituted tetronates employ this pathway to avoid formation of the straight photocycloaddition products.

EXPERIMENTAL SECTION

General Methods. All reactions sensitive to air or moisture were carried out in flame-dried glassware under a positive pressure of argon using standard Schlenk techniques. Dry tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethylether (Et_2O) were obtained from a solvent purification system. Other dry solvents were purchased in the highest purity available and used without further purification. Technical solvents used for aqueous workup and for column chromatography [*n*-pentane (P), ethyl acetate (EtOAc), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), isopropyl alcohol (*i*-PrOH), chloroform ($CHCl_3$)] were distilled prior to use. Flash chromatography was performed on silica gel 60 (230−400 mesh) with the indicated eluent mixtures. Thin layer chromatography (TLC) was performed on silica-coated glass plates (silica gel 60 F 254); CAM (cerium ammonium molybdate solution) or $KMnO_4$ solution was used as staining agent. ^1H and ^{13}C NMR spectra were recorded at 298 K and calibrated to the residual solvent signals. Apparent multiplets which occur as a result of accidental equality of coupling constants to those of magnetically non-equivalent protons are marked as virtual (*virt.*). Hydrogen multiplicities of ^{13}C NMR were determined by DEPT and 2D HMQC experiments. Melting points (mp) are not corrected.

*3,5,5-Trimethyltetronic Acid (**6**):* Methyl propionate (**8**, 2.88 mL, 2.63 g, 30.0 mmol) and methyl 2-hydroxy-*iso*-butyrate (**9a**, 4.01 mL, 4.13 g, 35.0 mmol) were dissolved in 150 mL of THF, KO*t*-Bu (7.40 g, 66.0 mmol) was added, and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure; the residue was taken up in 1 M aqueous NaOH solution (50 mL) and Et_2O (50 mL); the phases were separated, and the aqueous phase was extracted with Et_2O (50 mL) again. Concentrated HCl was added at 0 °C to adjust pH 1. The acidified aqueous solution was extracted with a $CHCl_3$/*i*-PrOH (5:1) mixture (3 × 50 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. Tetronic acid **6** (3.63 g, 25.5 mmol, 85%) was obtained as a light yellow solid in >95% purity: mp = 140 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.50 (s, 6H), 1.72 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 5.8 (CH_3), 24.0 (2C, CH_3), 82.7 (C), 94.6 (C), 177.4 (C), 180.3 (C). The spectroscopic data are in agreement with those reported in the literature.[29]

*5,5-Dimethyltetronic Acid (**5**):* Methyl acetate (**7**, 11.7 mL, 10.9 g, 147 mmol) and methyl 2-hydroxy-*iso*-butyrate (**9a**, 20.0 mL, 20.6 g, 176 mmol) were dissolved in 250 mL of THF, KO*t*-Bu (36.3 g, 323 mmol) was added, and the mixture was heated to reflux overnight. The solvent was removed under reduced pressure; the residue was taken up in 1 M aqueous NaOH solution (100 mL) and Et_2O (100 mL); the phases were separated, and the aqueous phase was extracted with Et_2O (100 mL) again. Concentrated HCl was added at 0 °C to adjust pH 1. The acidified aqueous solution was extracted with a $CHCl_3$/*i*-PrOH (5:1) mixture (6 × 25 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. After recrystallization from Et_2O and MeOH, tetronic acid **5** (8.95 g, 69.9 mmol, 48%) was obtained as a yellow solid: mp = 140 °C; ^1H NMR (360 MHz, DMSO) δ (ppm) = 1.37 (s, 6H), 4.78 (s, 1H), 12.64 (br s, 1H); ^{13}C NMR (90.6 MHz, DMSO) δ (ppm) = 24.0 (2C, CH_3), 81.3 (C), 85.9 (CH), 171.8 (C), 185.2 (C). The spectroscopic data are in agreement with those reported in the literature.[10a]

General Procedure A: Syntheses of Tetronic Acids by Esterification and Cyclization. I. A solution of the monomethyl malonate (**10a**)[11] or cyanoacetic acid (**10c**) (13.0 mmol) in 40 mL of CH_2Cl_2 was cooled to 0 °C, hydroxy ester **9a**/**b** (10.0 mmol), DIC (11.0 mmol), and DMAP (1.00 mmol) were added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered; the solvents were removed under reduced pressure; the residue was suspended in Et_2O (80 mL), filtered again, and washed with 1 M aqueous HCl. The aqueous phase was extracted with Et_2O, the combined organic phases were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The crude malonate was purified by distillation or column chromatography.

II. The purified malonate (10 mmol) was dissolved in 20 mL of MeOH, a freshly prepared 1 M solution of NaOMe in MeOH (15 mL, 15 mmol) was added, and the mixture was heated to reflux overnight. The solvent was removed under reduced pressure; the residue was taken up in 1 M aqueous NaOH solution (25 mL) and Et_2O (25 mL); the phases were separated, and the aqueous phase was extracted with Et_2O (25 mL) again. Concentrated HCl was added at 0 °C to adjust pH 1. The acidified aqueous solution was extracted with a $CHCl_3$/*i*-PrOH (5:1) mixture (5 × 25 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure.

Methyl-2-(2-methoxycarbonyl-acetoxy)-2-methyl Propionate: Colorless oil, obtained from monomethyl malonate (**10a**)[11] and 2-hydroxy-*iso*-butyrate (**9a**) in 70% yield according to General Procedure A-I: bp 112−114 °C (5.0 mbar); ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.57 (s, 6H), 3.38 (s, 2H), 3.72 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 24.4 (2C, CH_3), 41.3 (CH_2), 52.4 (2C, CH_3), 79.4 (C), 165.3 (C), 166.7 (C), 172.5 (C). The spectroscopic data are in agreement with those reported in the literature.[30]

*3-Methoxycarbonyl-5,5-dimethyltetronic Acid (**11**):* Yellow solid, obtained from methyl-2-(2-methoxycarbonyl-acetoxy)-2-methyl propionate in 61% yield according to General Procedure A-II: mp = 126 °C (lit.[10a] 118−120 °C); ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.55 (s, 6H), 3.93 (s, 3H), 9.87 (s, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 23.8 (2C, CH_3), 52.5 (CH_3), 80.9 (C), 93.0 (C), 164.9 (C), 166.9 (C), 194.6 (C). The spectroscopic data are in agreement with those reported in the literature.[10a]

Methyl-2-(2-tert-butoxycarbonyl-acetoxy)-2-methyl Propionate: Colorless oil, obtained from mono-*tert*-butyl malonate (**10b**) and 2-hydroxy-*iso*-butyrate (**9a**) in 53% yield according to General Procedure A-I: TLC R_f = 0.35 (P/Et_2O 3:1); bp 95 °C (0.1 mbar); IR (ATR) $\tilde{\nu}$ = 2987 (w, C−H), 1750 (s, C═O), 1730 (s, C═O), 1455 (w, C−H); ^1H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.47 (s, 9H), 1.57 (s, 6H), 3.28 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 24.4 (2C, CH_3), 27.9 (3C, CH_3), 43.0 (CH_2), 52.4 (CH_3), 79.1 (C), 82.0 (C), 165.3 (C), 165.7 (C), 172.6 (C); MS (EI, 70 eV) *m*/*z* (%) = 229

(2) [(M − CH_3O)$^+$], 201 (11) [(M − $C_2H_3O_2$)$^+$], 187 (20) [(M − C_4H_9O)$^+$], 101 (55) [$C_5H_9O_2^+$], 73 (6) [$C_4H_9O^+$], 57 (100); HRMS (EI, 70 eV) calcd for $C_{11}H_{17}O_5^+$ [(M − OCH_3)$^+$] 229.1071; found 229.1076.

*3-tert-Butoxycarbonyl-5,5-dimethyltetronic Acid (**12**):* Orange solid, obtained from methyl-2-(2-*tert*-butoxycarbonyl-acetoxy)-2-methyl propionate in 71% yield (ca. 90% purity) according to General Procedure A-II: mp = 150 °C; IR (ATR) $\tilde{\nu}$ = 3205 (br s, O−H), 2982 (w, C−H), 2938 (w, C−H), 1765 (s, C═O), 1671 (s, C═O), 1625 (s, C═C−O), 1474 (w, C−H), 1441 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.54 (s, 6H), 1.59 (s, 9H), OH proton not visible; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 23.8 (3C, CH_3), 28.1 (2C, CH_3), 80.4 (C), 84.3 (C), 93.9 (C), 165.6 (C), 166.1 (C), 194.2 (C); MS (EI, 70 eV) *m*/*z* (%) = 171 (36) [(M − C_4H_9)$^+$], 127 (39) [(M − C_4H_9 − CO_2)$^+$], 112 (34) [(M − C_4H_9 − CH_3 − CO_2)$^+$], 86 (26) [$C_4H_6O_2^+$], 70 (100); HRMS (ESI) calcd for $C_7H_9O_5^+$ [(M − C_4H_9 + 2H)$^+$] 173.0444; found 173.0441.

Methyl-2-(2-cyanoacetoxy)-2-methyl Propionate: Yellow oil, obtained from cyanoacetic acid (**10c**) and 2-hydroxy-*iso*-butyrate (**9a**) in 31% yield according to General Procedure A-I: TLC R_f = 0.64 (P/EtOAc 1:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2957 (w, C−H), 2923 (w, C−H), 1740 (s, C═O), 1440 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.61 (s, 6H), 3.47 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 24.4 (CH_3), 24.9 (CH_3), 27.2 (CH_2), 52.7 (CH_3), 81.1 (C), 112.7 (C), 161.9 (C), 171.8 (C); MS (EI, 70 eV) *m*/*z* (%) = 185 (1) [M$^+$], 154 (2) [(M − CH_3O)$^+$], 126 (25) [$C_6H_8NO_2^+$], 68 (9) [$C_3H_2NO^+$], 59 (100) [$C_3H_6O^+$]; HRMS (EI, 70 eV) calcd for $C_7H_8NO_3^+$ [(M − OCH_3)$^+$] 154.0499; found 154.0502.

*3-Cyano-5,5-dimethyltetronic Acid (**13**):* Beige solid, obtained from methyl-2-(2-cyanoacetoxy)-2-methyl propionate in 42% yield according to General Procedure A-II: mp 175−177 °C; IR (ATR) $\tilde{\nu}$ = 3447 (w, C═C), 2997 (w, C−H), 2943 (w, C−H), 2337 (w, C≡N), 1697 (s, C═O), 1474 (s, C−H); ^{1}H NMR (360 MHz, DMSO-d_6) δ (ppm) = 1.50 (s, 6H), 3.86 (s, 1H), 8.00 (br s, 1H), additional signals due to tautomeric equilibrium; ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (ppm) = 23.9 (2C, CH_3), 70.6 (C), 83.0 (C), 112.1 (C), 165.6 (C), 177.8 (C); MS (EI, 70 eV) *m*/*z* (%) = 153 (12) [M$^+$], 59 (20) [$C_3H_7O^+$], 43 (100); HRMS (EI, 70 eV) calcd for $C_7H_7NO_3^+$ [M$^+$] 153.0420; found 153.0426.

Methyl-2-(2-methoxycarbonylacetoxy)acetate: Colorless oil, obtained from monomethyl malonate[11] and 2-hydroxyacetate (**9b**) in 55% yield according to General Procedure A-I: bp 119 °C (7.0 mbar); IR (ATR) $\tilde{\nu}$ = 2997 (w, C−H), 2957 (w, C−H), 1736 (s, C═O), 1440 (m, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 3.51 (s, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 4.68 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 40.9 (CH_2), 52.5 (CH_3), 52.8 (CH_3), 61.4 (CH_2), 166.0 (C), 166.5 (C), 167.7 (C); MS (EI, 70 eV) *m*/*z* (%) = 159 (11) [(M − CH_3O)$^+$], 101 (100) [$C_4H_5O_3^+$], 59 (69) [$C_2H_3O_2^+$]; HRMS (EI, 70 eV) calcd for $C_6H_7O_5^+$ [M$^+$] 159.0288; found 159.0296.

*3-Methoxycarbonyltetronic Acid (**14**):* Yellow solid, obtained from methyl-2-(2-methoxycarbonylacetoxy)acetate in 61% yield according to General Procedure A-II: mp = 162−163 °C (lit.[30] 166−167 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 3.96 (s, 3H), 4.80 (s, 2H); OH proton not visible; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 52.6 (CH_3), 66.2 (CH_2), 95.2 (C), 166.6 (C), 169.1 (C), 189.3 (C). The spectroscopic data are in agreement with those reported in the literature.[30]

General Procedure B: Mitsunobu Reactions of Tetronic Acids with Primary Alcohols. The tetronic acid (10.0 mmol) was dissolved in THF (100 mL) followed by the addition of the primary alcohol (10.0 mmol). The mixture was cooled to 0 °C, triphenylphosphine (11.0 mmol) and di-*iso*-propyl azodicarboxylate (11.0 mmol) were added, and the reaction was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography.

*3-tert-Butoxycarbonyl-4-(cyclohex-2-enylmethoxy)-5,5-dimethyl-2-oxo-2,5-dihydrofuran (**17**):* Yellow oil, obtained from alcohol **15** and tetronic acid **12** in 62% yield according to General Procedure B: TLC R_f = 0.41 (P/Et_2O = 3:1), IR (ATR) $\tilde{\nu}$ = 2982 (w, C−H), 2928 (w, C−H), 1761 (s, C═O), 1707 (s, C═O), 1644 (s, C═C−O), 1465 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.33−1.43 (m, 2H), 1.48 (s, 3H), 1.48 (s, 3H), 1.54 (s, 9H), 1.69−1.87 (m, 2H), 1.99−2.06 (m, 2H), 2.51−2.61 (m, 1H), 4.25 (dd, ^2J = 9.7 Hz, ^3J = 7.2 Hz, 1H), 4.29 (dd, ^2J = 9.7 Hz, ^3J = 6.3 Hz, 1H), 5.53 (ddd, ^3J = 10.2 Hz, ^3J = 4.4 Hz, ^4J = 2.1 Hz, 1H), 5.85 (ddd, ^3J = 9.9 Hz, ^3J = 6.2 Hz, ^3J = 3.6 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 20.5 (CH_2), 24.4 (2C, CH_3), 25.0 (CH_2), 25.3 (CH_2), 28.0 (3C, CH_3), 35.3 (CH), 77.8 (CH_2), 81.1 (C), 82.9 (C), 97.5 (C), 125.5 (CH), 130.5 (CH), 161.7 (C), 168.0 (C), 180.7 (C); MS (EI, 70 eV) 322 (1) [M$^+$], 266 (2) [(M − C_4H_9)$^+$], 222 (21) [(M − CO_2 − C_4H_9)$^+$], 95 (100) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}O_5^+$ [M$^+$] 322.1775; found 322.1770.

*4-(Cyclohex-2-enylmethoxy)-3-cyano-5,5-dimethyl-2-oxo-2,5-dihydrofuran (**18**):* Yellow oil, obtained from alcohol **15** and tetronic acid **13** in 67% yield according to General Procedure B: TLC R_f = 0.42 (P/EtOAc 1:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2987 (w, C−H), 2938 (w, C−H), 2235 (w, C≡N), 1765 (m, C═O), 1634 (s, C═C−O), 1465 (C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.39−1.48 (m, 1H), 1.53 (s, 3H), 1.54 (s, 3H), 1.59−1.68 (m, 1H), 1.74−1.83 (m, 1H), 1.85−1.93 (m, 1H), 2.02−2.07 (m, 2H), 2.66−2.74 (m, 1H), 4.55 (d, ^3J = 6.7 Hz, 2H), 5.57 (dd, ^3J = 10.0 Hz, ^3J = 2.2 Hz, 1H), 5.92 (ddd, ^3J = 10.0, ^3J = 6.0, ^3J = 3.6 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 20.3 (CH_2), 24.2 (CH_2), 24.2 (CH_2), 24.9 (2C, CH_3), 35.0 (CH), 76.8 (CH_2), 78.1 (C), 83.2 (C), 111.4 (C), 124.4 (CH), 131.3 (CH), 165.9 (C), 188.0 (C); MS (EI, 70 eV) *m*/*z* (%) = 247 (1) [M$^+$], 220 (1) [(M − CN)$^+$], 188 (2) [$C_{11}H_{13}NO_2^+$], 136 (3) [$C_7H_7NO_2^+$], 95 (100) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{14}H_{17}NO_3^+$ [M$^+$] 247.1203; found 247.1207.

*4-(Cyclohex-2-enylmethoxy)-3-methoxycarbonyl-2-oxo-2,5-dihydrofuran (**19**):* Yellow oil, obtained from alcohol **15** and tetronic acid **14** in 24% yield according to General Procedure B: TLC R_f = 0.27 (Et_2O) mp = 82−83 °C; IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2938 (w, C−H), 2860 (w, C−H), 1775 (s, C═O), 1750 (s, C═O), 1712 (s, C═O), 1615 (s, C═C−O), 1445 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.40−1.47 (m, 1H), 1.56−1.64 (m, 1H), 1.71−1.77 (m, 1H), 1.85−1.90 (m, 1H), 2.01−2.06 (m, 2H), 2.62−2.70 (m, 1H), 3.84 (s, 3H), 4.12 (dd, ^2J = 8.6 Hz, ^3J = 6.7 Hz, 1H), 4.15 (dd, ^2J = 8.6 Hz, ^3J = 5.7 Hz, 1H), 4.76 (s, 2H), 5.55 (ddd, ^3J = 10.0 Hz, ^3J = 4.4 Hz, ^4J = 2.2 Hz, 1H), 5.89 (d *virt.* td, ^3J = 10.0 Hz, $^3J \approx {}^4J \approx$ 3.7 Hz, ^4J = 2.5 Hz, 1 H, C3′-H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 20.2 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 35.3 (CH), 51.9 (CH_3), 65.2 (CH_2), 76.6 (CH_2), 96.6 (C), 124.9 (CH), 131.1 (CH), 161.2 (C) 168.8 (C), 182.2 (C); MS (ESI) *m*/*z* = 527 [(2 M + Na)$^+$], 275 [(M + Na)$^+$], 253 [(M + H)$^+$]; HRMS (ESI) calcd for $C_{13}H_{16}NaO_5^+$ [(M + Na)$^+$] 275.0890; found 275.0890.

*3-[(tert-Butyldimethylsilyloxy)methyl]-4-(cyclohex-2-enylmethoxy)-5,5-dimethylfuran-2-(5H)-one (**21**).* 4-(Cyclohex-2-enylmethoxy)-3-(hydroxymethyl)-5,5-dimethylfuran-2-(5*H*)-on (**20**, 1.67 g, 6.62 mmol) was dissolved in 66 mL of CH_2Cl_2 and cooled to 0 °C, *tert*-butyldimethylsilyl chloride (1.50 g, 9.93 mmol) and imidazole (1.35 g, 19.9 mmol) were added, and the reaction mixture was stirred for 10 h at room temperature. Saturated aqueous NH_4Cl (50 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (P/Et_2O 6:1 → 4:1) afforded TBS-ether **21** (2.33 g, 6.36 mmol, 96%) as a light yellow oil: TLC R_f = 0.26 (P/Et_2O 6:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2933 (m, C−H), 2890 (w, C−H), 2856 (w, C−H), 1755 (s, C═O), 1649 (s, C═C−O); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 0.08 (s, 6H), 0.87 (s, 9H), 1.44 (s, 6H), 1.46−1.90 (m, 4H), 1.97−2.08 (m, 2H), 2.49−2.64 (m, 1H),

4.37 (s, 2H), 4.43−4.48 (m, 2H), 5.57 (dd, ^3J = 9.9 Hz, 2.2 Hz, 1H), 5.81−5.90 (m, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = −5.2 (CH_3), −5.2 (CH_3), 18.0 (C), 20.5 (CH_2), 24.4 (2C, CH_3), 25.1 (CH_2), 25.3 (CH_2), 25.8 (3C, CH_3), 35.7 (CH), 54.0 (CH_2), 75.6 (CH_2), 80.7 (C), 99.1 (C), 126.0 (CH), 130.1 (CH), 172.7 (C), 180.4 (C); MS (EI, 70 eV) m/z (%) = 351 (1) [$(M - CH_3)^+$], 309 (20) [$(M - C_4H_9)^+$], 271 (6) [$(M - C_7H_{11})^+$], 215 (100), 95 (50) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{16}H_{25}O_4Si^+$ [$(M - C_4H_9)^+$] 309.1517; found 309.1518.

*4-But-3-enyloxy-3,5,5-trimethyl-furan-2(5H)-one (**23a**):* Light yellow oil, obtained from alcohol **22a** and tetronic acid **6** in 74% yield according to General Procedure B: TLC R_f = 0.29 (P/Et_2O 3:2); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2982 (w, C−H), 2933 (w, C−H), 1745 (s, C═O), 1663 (s, C═C−O), 1469 (w, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.39 (s, 6H), 1.94 (s, 3H), 2.48 (*virt.* q, $^3J \approx 6.6$ Hz, 2H), 4.39 (t, ^3J = 6.6 Hz, 2H), 5.10−5.20 (m, 2H), 5.80 (ddt, ^3J = 17.0 Hz, ^3J = 10.2 Hz, ^3J = 6.6 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 8.6 (CH_3), 24.5 (2C, CH_3), 33.9 (CH_2), 70.3 (CH_2), 80.8 (C), 94.7 (C), 118.0 (CH_2), 132.9 (CH), 174.0 (s), 176.2 (s); MS (EI, 70 eV) m/z (%) = 196 (3) [M^+], 181 (1) [$(M - CH_3)^+$], 125 (4) [$(M - C_4H_7O)^+$], 110 (21) [$(M - C_4H_6O_2)^+$], 55 (100) [$C_4H_7^+$]; HRMS (EI, 70 eV) calcd for $C_{11}H_{16}O_3^+$ [M^+] 196.1094; found 196.1100.

*4-((3,4-Dimethylpent-3-en-1-yl)oxy)-3,5,5-trimethylfuran-2(5H)-one (**23b**).* 3,5,5-Trimethyltetronic acid (**6**, 40.1 mg, 282 μmol) was dissolved in 4 mL of DMF followed by the addition of 5-bromo-2,3-dimethylpent-2-ene[19] (**24**, 95.2 mg, 564 μmol) and CsF (94.3 mg, 621 μmol). The reaction mixture was stirred at 120 °C for 24 h, cooled to room temperature, and water (30 mL) was added. The mixture was extracted with EtOAc (4 × 30 mL), the comined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (P/Et_2O 2:1 → 1:1) afforded tetronate **23b** (55.3 mg, 232 μmol, 82%) as a light yellow oil: TLC R_f = 0.41 (P/Et_2O = 1:1); IR (ATR) $\tilde{\nu}$ = 2982 (w, C−H), 2933 (w, C−H), 1750 (s, C═O), 1663 (s, C═C−O), 1465 (w, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.38 (s, 6H), 1.67 (s, 3H), 1.69 (s, 6H), 1.94 (s, 3H), 2.47 (t, ^3J = 7.0 Hz, 2H), 4.34 (t, ^3J = 7.0 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 8.6 (CH_3), 18.7 (CH_3), 20.4 (CH_3), 20.7 (CH_3), 24.5 (CH_3), 30.9 (CH_3), 34.6 (CH_2), 70.0 (CH_2), 80.8 (C), 94.6 (C), 122.2 (C), 128.0 (C), 174.2 (C), 176.6 (C); MS (EI, 70 eV) m/z (%) = 238 (4) [M^+], 169 (25) [$(M - C_5H_9)^+$], 55 (100) [$C_4H_7^+$]; HRMS (EI, 70 eV) calcd for $C_{14}H_{22}O_3^+$ [M^+] 238.1563; found 238.1568.

*3,4-Dimethylpent-3-en-1-ol (**22e**).* 5-Bromo-2,3-dimethyl-pent-2-ene[19] (**24**, 512 mg, 2.89 mmol) was dissolved in DMF, and NaOAc (474 mg, 5.78 mmol) was added. After stirring at 80 °C for 14 h, water (100 mL) and Et_2O (100 mL) were added; the phases were separated; the aqueous phase was extracted with Et_2O (100 mL), and the combined organic phases were washed with water (200 mL). The solvents were removed under reduced pressure, NaOH (6 mL, 1 M) and MeOH (27 mL) were added, and the reaction mixture was stirred at room temperature for 1 h. Most of the organic solvent was removed under reduced pressure, and the residue was extracted with EtOAc (50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Purification by column chromatography (P/Et_2O 2:1) afforded alcohol **22e** (255 mg, 2.23 mmol, 77%) as a colorless liquid: TLC R_f = 0.27 (P/Et_2O = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.65 (s, 3H), 1.67 (s, 3H), 1.69 (s, 3H), 2.34 (t, ^3J = 6.8 Hz, 2H), 3.63 (t, ^3J = 6.8 Hz, 2H) OH proton not visible; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 18.3 (CH_3), 20.3 (CH_3), 20.7 (CH_3), 37.5 (CH_2), 60.8 (CH_2), 123.4 (C), 127.6 (C). The spectroscopic data are in agreement with those reported in the literature.[31]

*4-(But-3-enyloxy)-3-methoxycarbonyl-5,5-dimethyl-2-oxo-2,5-dihydrofuran (**25a**):* Light yellow oil, obtained from alcohol **22a** and tetronic acid **11** in 88% yield according to General Procedure B, with the exception that DBAD was used instead of DIAD: TLC R_f = 0.20 (P/Et_2O 3:2); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2987 (w, C−H), 2952 (w, C−H), 1766 (s, C═O), 1716 (s, C═O), 1469 (m, C−H), 1435 (m, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.47 (s, 6H), 2.50 (*virt.* q, $J \approx 6.4$ Hz, 2H), 3.85 (s, 3H), 4.50 (t, ^3J = 6.4 Hz, 2H), 5.11−5.18 (m, 2H), 5.77 (ddt, ^3J = 17.1 Hz, ^3J = 10.3 Hz, ^3J = 6.7 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 24.4 (2C, CH_3), 33.5 (CH_2), 52.5 (CH_3), 74.1 (CH_2), 81.4 (C), 95.6 (C), 118.2 (CH_2), 132.7 (CH), 162.8 (C), 167.6 (C), 183.5 (C); MS (EI, 70 eV) m/z (%) = 240 (1) [M^+], 209 (5) [$(M - CH_3O)^+$], 196 (4) [$(M - CO_2)^+$], 55 (100); HRMS (EI, 70 eV) calcd for $C_{11}H_{13}O_4^+$ [$(M - CH_3O)^+$] 209.0808; found 209.0816.

*3-Methoxycarbonyl-5,5-dimethyl-4-(4-methylpent-3-enyloxy)-2-oxo-2,5-dihydrofuran (**25b**):* Light yellow oil, obtained from alcohol **22b** and tetronic acid **11** in 75% yield according to General Procedure B, with the exception that DBAD was used instead of DIAD: TLC R_f = 0.26 (P/Et_2O 1:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2982 (w, C−H), 2952 (w, C−H), 1760 (s, C═O), 1716 (s, C═O), 1634 (s, C═C−O), 1441 (m, C−H), ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 6H), 1.74−1.76 (m, 3H), 2.45 (t, ^3J = 6.5 Hz, 2H), 3.86 (s, 3H), 4.56 (t, ^3J = 6.5 Hz, 2H), 4.73−4.76 (m, 1H), 4.84−4.87 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) = 22.3 (CH_3), 24.4 (2C, CH_3), 37.0 (CH_2), 52.6 (CH_3), 73.1 (CH_2), 81.4 (C), 95.3 (C), 113.1 (CH_2), 140.2 (C), 162.8 (C), 167.7 (C), 183.6 (C); MS (EI, 70 eV) m/z (%) = 254 (5) [M^+], 224 (2) [$M - C_2H_6$], 69 (98) [$C_5H_9^+$], 41 (100) [$C_3H_5^+$]; HRMS (EI, 70 eV) calcd for $C_{13}H_{18}O_5^+$ [M^+] 254.1149; found 254.1150.

*3-Methoxycarbonyl-5,5-dimethyl-4-(3-methylbut-3-enyloxy)-2-oxo-2,5-dihydrofuran (**25c**):* Light yellow oil, obtained from alcohol **22c** and tetronic acid **11** in 83% yield according to General Procedure B, with the exception that DBAD was used instead of DIAD: TLC R_f = 0.28 (P/Et_2O 1:1); IR (ATR) $\tilde{\nu}$ = 2977 (w, C−H), 2928 (w, C−H), 1765 (s, C═O), 1716 (s, C═O), 1634 (s, C═C−O), 1436 (m, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 6H), 1.63 (s, 3H), 1.71 (s, 3H), 2.43 (*virt.* q, ^3J = 6.7 Hz, 2H), 3.85 (s, 3H), 4.41 (t, ^3J = 6.7 Hz, 2H), 5.06−5.10 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 17.9 (CH_3), 24.3 (2C, CH_3), 25.7 (CH_3), 28.1 (CH_2), 52.6 (CH_3), 75.0 (CH_2), 81.4 (C), 95.3 (C), 118.1 (C), 135.6 (CH), 163.0 (C), 167.8 (C), 183.8 (C); MS (EI, 70 eV) m/z (%) = 268 (1) [M^+], 237 (5) [$(M - CH_3O)^+$], 155 (21) [$C_7H_7O_4^+$], 82 (100) [$C_6H_{10}^+$], 55 (53) [$C_4H_7^+$]; HRMS (EI, 70 eV) calcd for $C_{13}H_{17}O_4^+$ [$(M - CH_3O)^+$] 237.1121; found 237.1120.

*3-Methoxycarbonyl-5,5-dimethyl-4-(2-(cyclohex-1-en-1-yl)ethoxy)-2-oxo-2,5-dihydrofuran (**25d**):* Light yellow oil, obtained from alcohol **22d** and tetronic acid **11** in 68% yield according to General Procedure B: TLC R_f = 0.30 (P/EtOAc 1:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2982 (w, C−H), 2933 (m, C−H), 1765 (s, C═O), 1716 (s, C═O), 1634 (s, C═C−O), 1465 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 6H), 1.52−1.66 (m, 4H), 1.92−1.99 (m, 4H), 2.36 (t, ^3J = 6.4 Hz, 2H), 3.86 (s, 3H), 4.52 (t, ^3J = 6.4 Hz, 2H), 5.48 (m, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 19.6 (CH_2), 22.2 (CH_2), 22.7 (CH_2), 24.4 (CH_3), 25.2 (CH_3), 28.2 (CH_2), 37.4 (CH_2), 52.6 (CH_3), 73.5 (CH_2), 81.4 (C), 95.2 (C), 124.6 (CH), 132.4 (C), 162.8 (C), 167.8 (C), 183.8 (C); MS (EI, 70 eV) m/z (%) = 294 (6) [M^+], 263 (2) [$(M - CH_3O)^+$], 187 (100), 155 (91) [$C_7H_7O_4^+$], 108 (81) [$C_8H_{12}^+$]; HRMS (EI, 70 eV) calcd for $C_{16}H_{22}O_5^+$ [M^+] 294.1462; found 294.1465.

*3-Methoxycarbonyl-5,5-dimethyl-4-(3,4-dimethylpent-3-enyloxy)-2-oxo-2,5-dihydrofuran (**25e**):* Light yellow oil, obtained from alcohol **22e** and tetronic acid **11** in 86% yield according to General Procedure B, with the exception that DBAD was used instead of DIAD: TLC R_f = 0.31 (P/Et_2O 1:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2982 (w, C−H), 2923 (w, C−H), 1765 (s, C═O), 1716 (s, C═O), 1634 (s, C═C−O), 1469 (s, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.46 (s, 3H), 1.47 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 2.50 (t, ^3J = 6.8 Hz, 2H), 3.86 (s, 3H), 4.46 (t, ^3J = 6.8 Hz, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 18.5 (CH_3),

20.4 (CH_3), 20.7 (CH_3), 24.3 (CH_3), 28.1 (CH_3), 34.0 (CH_2), 52.6 (CH_3), 73.8 (CH_2), 81.4 (C), 100.0 (C), 121.9 (C), 128.2 (C), 162.8 (C), 162.9 (C), 183.9 (C); MS (EI, 70 eV) *m*/*z* (%) = 282 (1) [M^+], 251 (3) [$(M - CH_3O)^+$], 186 (35) [$(M - C_7H_{12})^+$], 96 (100) [$C_7H_{12}^+$]; HRMS (EI, 70 eV) calcd for $C_{14}H_{19}O_4^+$ [$(M - CH_3O)^+$] 251.1278; found 251.1283.

General Procedure C: [2 + 2]-Photocycloaddition Reactions. The tetronate was dissolved in *t*-BuOH or Et_2O, degassed by purging with Ar in an ultrasonicator for 15 min, and irradiated in a Rayonet RPR 100 merry-go-round reactor, equipped with 16 Rayonet RPR 2537 Å lamps (λ = 254 nm). Unless otherwise stated, the reaction was stopped when the starting material was fully consumed according to TLC and GC analysis. Then the solvent was removed and the residue was purified by column chromatography. Except as otherwise noted, only one reaction product could be determined. Typically, an immobile spot could be seen on TLC, which we tentatively attribute to polymeric side-products.

*2-[(tert-Butyldimethylsilyloxy)methyl]-5,5-dimethyl-4,7-dioxatetracyclo[7.3.1.0^{2,6}.0^{6,13}]tridecan-3-one (**27**):* Colorless solid, obtained from tetronate **21** in 36% yield (+ 17% starting material **21**) according to General Procedure C (reaction time = 8 h): mp = 73 °C; TLC R_f = 0.17 (P/Et_2O 4:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2933 (s, C−H), 2856 (m, C−H), 1766 (s, C═O), 1465 (w, C−H), 1087 (s, C−O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 0.07 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.36 (s, 3H), 1.43 (s, 3H), 1.45−1.61 (m, 6H), 2.41−2.46 (m, 1H), 2.52−2.60 (m, 1H), 3.05 (*virt.* t, $^3J \approx$ 9.6 Hz, 1H), 3.88 (d, ^2J = 10.2 Hz, 1H), 3.90 (dd, ^2J = 9.1 Hz, ^3J = 7.4 Hz, 1H) 4.01 (d, ^2J = 10.2 Hz, 1H), 4.16 (*virt.* t, $^2J \approx {}^3J \approx$ 8.9 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = −5.7 (CH_3), −5.6 (CH_3), 18.4 (C), 18.4 (CH_2), 21.1 (CH_2), 22.3 (CH_3), 23.7 (CH_3), 23.8 (CH_2), 25.9 (3C, CH_3), 30.7 (CH), 33.9 (CH), 37.2 (CH), 54.2 (C), 58.2 (CH_2), 76.7 (CH_2), 84.2 (C), 93.0 (C), 178.7 (C); MS (EI, 70 eV) *m*/*z* (%) = 351 (4) [$(M - CH_3)^+$], 309 (100) [$(M - C_4H_9)^+$], 279 (15) [$(M - C_6H_{15}Si)^+$], 235 (8) [$(M - C_6H_{15}OSi)^+$], 95 (74) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{16}H_{25}O_4Si^+$ [$(M - C_4H_9)^+$] 309.1517; found 309.1524.

*2-Hydroxymethyl-5,5-dimethyl-4,7-dioxatetracyclo[7.3.1.0^{2,6}.0^{6,13}]tridecan-3-one (**26**):* TBS ether **27** (784 mg, 2.14 mmol) was dissolved in 40 mL of THF, cooled to 0 °C, tetrabutylammonium fluoride (1.0 M in THF, 3.21 mL, 3.21 mmol) was added, and the reaction mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl (50 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by flash chromatography (P/Et_2O 1:2) afforded alcohol **26** (493 mg, 1.95 mmol, 91%) as a colorless solid. For characterization, see ref 8.

*2-Cyano-5,5-dimethyl-4,7-dioxatetracyclo[7.3.1.0^{2,6}.0^{6,13}]tridecan-3-one (**28**):* Light red oil, obtained from tetronate **18** in 54% yield according to General Procedure C (reaction time = 1 h): TLC R_f = 0.27 (P/EtOAc 3:1); IR (ATR) $\tilde{\nu}$ = 2952 (m, C−H), 2923 (s, C−H), 2356 (w, C≡N), 1775 (s, C═O), 1460 (C−H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.45 (s, 3H), 1.47 (s, 3H), 1.60−1.78 (m, 4H), 1.95−2.07 (m, 2H), 2.64−2.72 (m, 2H), 3.17 (dd, ^3J = 10.2 Hz, ^3J = 8.8 Hz, 1H), 4.18 (*virt.* t, $^2J \approx {}^3J \approx$ 9.4 Hz, 1H), 4.27 (*virt.* t, $^2J \approx {}^3J \approx$ 9.4 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 15.4 (CH_2), 21.3 (CH_3), 21.8 (CH_2), 23.4 (CH_2), 24.6 (CH_3), 33.0 (CH), 33.0 (CH), 39.2 (CH), 46.1 (C) 74.5 (CH_2), 86.2 (C), 91.5 (C), 111.1 (C), 169.0 (C); MS (EI, 70 eV) *m*/*z* (%) = 247 (41) [M^+], 161 (34) [$C_{10}H_{10}NO^+$], 43 (100); HRMS (EI, 70 eV) calcd for $C_{14}H_{17}NO_3^+$ [M^+] 247.1203; found 247.1216.

*6-tert-Butoxycarbonyl-3,3-dimethyl-2,8-oxaethano-4-oxatricyclo-[5.4.0.0^{2,6}]undecan-5-one (**29**):* Colorless solid, obtained from tetronate **17** in 37% yield according to General Procedure C (reaction time = 30 min): TLC R_f = 0.31 (P/Et_2O 3:1); IR (ATR) $\tilde{\nu}$ = 2981 (m, C−H), 2933 (w, C−H), 1762 (s, C═O), 1708 (s, C═O), 1465 (w, C−H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.33 (s, 3H), 1.49 (s, 9H), 1.46−1.59 (m, 3H), 1.61 (s, 3H), 1.70−1.78 (m, 2H), 1.90−2.01 (m, 1H), 2.27 (*virt.* t, $^3J \approx$ 4.8 Hz, 1H), 2.63−2.68 (m, 1H), 2.86 (*virt.* t, $^3J \approx$ 5.1 Hz, 1H), 3.83 (d, ^2J = 12.1 Hz, 1H), 4.11 (ddd, ^2J = 12.1 Hz, ^3J = 6.1 Hz, ^3J = 1.5 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 17.3 (CH_2), 20.2 (CH_2), 21.5 (CH_3), 22.0 (CH_3), 27.7 (3C, CH_3), 28.1 (CH_2), 32.8 (CH), 36.3 (CH), 40.1 (CH), 60.7 (C), 70.1 (CH_2), 83.0 (C), 86.1 (C), 95.1 (C), 165.7 (C), 172.0 (C); MS (EI, 70 eV) *m*/*z* (%) = 322 (15) [M^+], 265 (32) [$(M - C_4H_9)^+$], 221 (24) [$(M - CO_2 - C_4H_9)^+$], 95 (100) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{18}H_{26}O_5^+$ [M^+] 322.1775; found 322.1770.

*6-Methoxycarbonyl-2,8-oxaethano-4-oxatricyclo[5.4.0.0^{2,6}]undecan-5-one (**30**):* Colorless solid, obtained from tetronate **19** in 35% yield according to General Procedure C (reaction time = 30 min): mp = 91−92 °C; TLC R_f = 0.24 (P/Et_2O 3:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2943 (m, C−H), 2917 (m, C−H), 2856 (w, C−H), 1770 (s, C═O), 1716 (s, C═O), 1436 (w, C−H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.45−1.62 (m, 3H), 1.70−1.80 (m, 2H), 1.92−2.01 (m, 1H), 2.26 (*virt.* t, $^3J \approx$ 5.5 Hz, 1H), 2.72 (*virt.* q, $^3J \approx$ 5.0 Hz, 1H), 2.92 (*virt.* t, $^3J \approx$ 5.1 Hz, 1H), 3.80 (s, 3H), 3.82 (d, 1 H, ^2J = 12.2 Hz), 4.01 (ddd, ^2J = 12.2 Hz, ^3J = 6.2 Hz, ^4J = 1.7 Hz, 1H), 4.11 (d, ^2J = 8.7 Hz, 1H), 4.30 (d, ^2J = 8.7 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 17.1 (CH_2), 19.3 (CH_2), 27.7 (CH_2), 32.3 (CH), 37.2 (CH), 39.8 (CH), 52.9 (CH_3), 56.8 (C), 69.5 (CH_2), 70.3 (CH_2), 91.3 (C), 166.6 (C), 172.3 (C); MS (EI, 70 eV) *m*/*z* (%) = 252 (3) [M^+], 237 (6) [$(M - CH_3)^+$], 221 (16) [$(M - CH_3O)^+$], 208 (8) [$(M - CO_2)^+$], 194 (6) [$(M - C_2H_2O_2)^+$], 193 (20) [$(M - C_2H_3O_2)^+$], 95 (100) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{12}H_{13}O_4^+$ [$(M - CH_3O)^+$] 221.0808; found 221.0809.

*2-Methoxycarbonyl-4,7-dioxatetracyclo[7.3.1.0^{2,6}.0^{6,13}]tridecan-3-one (**31**):* Colorless solid, obtained from tetronate **19** in 30% yield according to General Procedure C (reaction time = 30 min): TLC R_f = 0.15 (P/Et_2O 3:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2943 (m, C−H), 2856 (w, C−H), 1770 (s, C═O), 1740 (s, C═O), 1435 (w, C−H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.40−1.61 (m, 4H), 1.69−1.82 (m, 1H), 2.34 (ddd, ^2J = 14.3 Hz, ^3J = 7.4 Hz, ^3J = 3.4 Hz, 1H), 2.61−2.74 (m, 2H), 2.89 (dd, ^3J = 10.1 Hz, ^3J = 8.9 Hz, 1H), 3.79 (s, 3H), 3.83 (*virt.* t, $^2J \approx {}^3J \approx$ 9.5 Hz, 1H), 4.15 (*virt.* t, $^2J \approx {}^3J \approx$ 9.1 Hz, 1H), 4.34 (d, ^2J = 9.6 Hz, 1H), 4.37 (d, ^2J = 9.6 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 16.4 (CH_2), 21.7 (CH_2), 22.4 (CH_2), 33.2 (CH), 33.4 (CH), 42.6 (CH), 52.4 (CH_3), 55.9 (C), 72.6 (CH_2), 74.0 (CH_2), 89.7 (C), 165.5 (C), 174.3 (C); MS (EI, 70 eV) *m*/*z* (%) = 252 (5) [M^+], 237 (1) [$(M - CH_3)^+$], 234 (12) [$(M - H_2O)^+$], 221 (22) [$(M - CH_3O)^+$], 193 (16) [$(M - C_2H_3O_2)^+$], 95 (100) [$C_7H_{11}^+$]; HRMS (EI, 70 eV) calcd for $C_{13}H_{14}O_4^+$ [$(M - H_2O)^+$] 234.0887; found 234.0888.

*2,2,5-Trimethyl-3,10-dioxatricyclo[5.3.0.0^{1,5}]decan-4-one (**32a**):* Colorless solid, obtained from tetronate **23a** in 52% yield according to General Procedure C (reaction time = 6 h): TLC R_f = 0.24 (P/Et_2O 2:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2967 (m, C−H), 2928 (w, C−H), 2880 (w, C−H), 1761 (s, C═O), 1450 (w, C−H); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.28 (s, 3H), 1.32 (s, 6H), 1.52 (dd, ^2J = 12.9 Hz, ^3J = 6.8 Hz, 1H), 1.73−1.85 (m, 2H), 2.32 (dd, ^2J = 12.9 Hz, ^3J = 8.5 Hz, 1H), 3.04 (*virt.* q, $^3J \approx$ 7.5 Hz, 1H), 4.01 (ddd, ^3J = 11.3 Hz, ^2J = 9.1 Hz, ^3J = 5.6 Hz, 1H), 4.25 (*virt.* t, $^2J \approx {}^3J \approx$ 9.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ (ppm) = 16.1 (CH_3), 20.6 (CH_3), 24.2 (CH_3), 30.9 (CH_2), 32.8 (CH_2), 36.3 (CH), 45.8 (C), 69.4 (CH_2), 83.6 (C), 92.4 (C), 180.4 (C); MS (EI, 70 eV) *m*/*z* (%) = 196 (12) [M^+], 181 (4) [$(M - CH_3)^+$], 125 (12) [$(M - C_4H_7O)^+$], 110 (100) [$(M - C_4H_6O_2)^+$], 55 (66) [$C_4H_7^+$]; HRMS (EI, 70 eV) calcd for $C_{11}H_{16}O_3^+$ [M^+] 196.1094; found 196.1095.

*2,2,5,6,6,7-Hexamethyl-3,10-dioxatricyclo[5.3.0.0^{1,5}]decan-4-one (**32b**):* Colorless oil, obtained from tetronate **23b** in 46% yield according to General Procedure C (reaction time = 8 h): TLC

R_f = 0.41 (P/Et_2O 2:1), IR (ATR) $\tilde{\nu}$ = 2967 (w, C−H), 2938 (w, C−H), 1761 (s, C═O), 1460 (w, C−H); ^{1}H NMR (250 MHz, $CDCl_3$, 300 K) δ (ppm) = 1.04 (s, 3H), 1.05 (s, 3H), 1.18 (s, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.47 (s, 3H), 1.66 (ddd, ^2J = 13.3 Hz, ^3J = 10.6 Hz, ^3J = 8.9 Hz, 1H), 2.20 (ddd, ^2J = 13.3 Hz, ^3J = 6.6 Hz, ^3J = 2.1 Hz, 1H), 3.93 (ddd, ^2J = 9.2 Hz, ^3J = 10.6 Hz, ^3J = 6.6 Hz, 1H), 4.12 (*virt.* td, $^2J \approx {}^3J \approx$ 9.0 Hz, ^3J = 2.1 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 300 K) δ (ppm) = 12.1 (CH_3), 20.5 (CH_3), 21.6 (CH_3), 21.8 (CH_3), 23.6 (CH_3), 28.1 (CH_3), 37.9 (CH_2), 38.5 (C), 51.9 (C), 54.1 (C), 68.9 (CH_2), 85.5 (C), 91.6 (C), 179.2 (C); MS (EI, 70 eV) *m*/*z* (%) = 238 (4) [M^+], 223 (1) [$(M - CH_3)^+$], 124 (40) [$C_7H_8O_2^+$], 97 (100) [$C_7H_{13}^+$] 55 (73) [$C_4H_7^+$]; HRMS (EI, 70 eV) calcd for $C_{14}H_{22}O_3^+$ [M^+] 238.1569; found 238.1562.

*5-Methoxycarbonyl-2,2,6,10,10-pentamethyl-3,9-dioxatricyclo-[4.3.1.0^{1,5}]-decan-4-one (**33**):* Colorless oil, obtained from tetronate **25e** in 51% yield according to General Procedure C (reaction time = 45 min): TLC R_f = 0.33 (P/Et_2O 2:1); IR (ATR) $\tilde{\nu}$ = 2978 (C−H), 2952 (C−H), 1761 (s, C═O), 1726 (s, C═O), 1455 (w, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.09 (s, 3H), 1.22 (s, 3H), 1.37 (s, 3H), 1.49 (s, 3H), 1.65 (s, 3H), 2.07 (ddd, ^2J = 13.0 Hz, ^3J = 8.4 Hz, ^3J = 2.5 Hz, 1H), 2.23 (ddd, ^2J = 13.0 Hz, ^3J = 10.0 Hz, ^3J = 9.1 Hz, 1H), 3.82 (s, 3H), 4.00−4.09 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 14.9 (CH_3), 19.8 (CH_3), 21.6 (CH_3), 22.6 (CH_3), 24.7 (CH_3), 34.1 (CH_2), 46.6 (C), 51.0 (C), 52.7 (CH_3), 59.6 (C), 63.1 (CH_2), 87.0 (C), 91.7 (C), 167.8 (C), 172.2 (C); MS (EI, 70 eV) *m*/*z* (%) = 282 (2) [M^+], 251 (2) [$(M - CH_3O)^+$], 209 (1) [$(M - C_2H_5O)^+$], 181 (4) [$C_{11}H_{17}O_2^+$], 96 (100); HRMS (EI, 70 eV) calcd for $C_{15}H_{22}O_5^+$ [M^+] 282.1462; found 282.1467.

*5-Methoxycarbonyl-2,2-dimethyl-3,10-dioxatricyclo[5.3.0.0^{1,5}] decan-4-one (**34a**):* Colorless solid, obtained from tetronate **25a** in 78% yield according to General Procedure C (reaction time = 30 min). Another isomer was present according to ^{1}H NMR (90:10 ratio): TLC R_f = 0.25 (P/Et_2O 3:2); IR (ATR) $\tilde{\nu}$ = 2997 (w, C−H), 2962 (w, C−H), 1765 (s, C═O), 1731 (s, C═O), 1426 (w, C−H); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.34 (s, 3H), 1.45 (s, 3H), 1.78−1.92 (m, 2H), 2.29 (dd, ^2J = 13.3 Hz, ^3J = 8.6 Hz, 1H), 2.49 (dd, ^2J = 13.3 Hz, ^3J = 6.9 Hz, 1H), 3.15 (*virt.* q, $^3J \approx$ 7.5 Hz 1H), 3.79 (s, 3H), 4.13−4.24 (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 20.9 (CH_3), 23.1 (CH_3), 26.8 (CH_2), 30.8 (CH_2), 37.2 (CH), 52.8 (CH_3), 55.5 (C), 70.1 (CH_2), 84.8 (C), 94.7 (C), 166.8 (C), 173.3 (C); MS (EI, 70 eV) *m*/*z* (%) = 240 (5) [M^+], 181 (1) [$(M - COOMe)^+$], 110 (100); HRMS (EI, 70 eV) calcd for $C_{12}H_{16}O_5^+$ [M^+] 240.0992; found 240.1000.

*5-Methoxycarbonyl-2,2,7-trimethyl-3,10-dioxatricyclo[5.3.0.0^{1,5}] decan-4-one (**34b**):* Colorless solid, obtained from tetronate **25b** in 75% yield according to General Procedure C (reaction time = 30 min): TLC R_f = 0.25 (P/Et_2O 3:2); IR (ATR) $\tilde{\nu}$ = 2972 (w, C−H), 2928 (w, C−H), 1770 (s, C═O), 1731 (s, C═O); ^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm) = 1.43 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H) 1.71 (ddd, ^2J = 12.3 Hz, ^3J = 11.9 Hz, ^3J = 8.2 Hz, 1H), 1.91 (dd, ^2J = 12.3 Hz, ^3J = 5.2 Hz, 1H), 1.99 (d, ^2J = 13.0 Hz, 1H), 2.70 (d, ^2J = 13.0 Hz, 1H), 3.77 (s, 3H), 4.13 (*virt.* t, $^2J \approx {}^3J \approx$ 8.6 Hz, 1H), 4.19 (ddd, ^3J = 11.9 Hz, ^2J = 9.3 Hz, ^3J = 5.2 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 21.3 (CH_3), 24.0 (CH_3), 25.5 (CH_3), 34.4 (CH_2), 39.9 (CH_2), 48.8 (C), 52.8 (CH_3), 54.0 (C), 68.3 (CH_2), 86.1 (C), 94.5 (C), 167.3 (C), 173.7 (C); MS (EI, 70 eV) *m*/*z* (%) = 254 (23) [M^+], 239 (4), [$(M - CH_3)^+$], 223 (9) [$(M - CH_3O)^+$], 210 (3) [$(M - CO_2)^+$], 195 (5) [$(M - C_2H_3O_2)^+$], 69 (100) [$C_5H_9^+$]; HRMS (EI, 70 eV) calcd for $C_{13}H_{18}O_5^+$ [M^+] 254.1149; found 254.1156.

*5-Methoxycarbonyl-2,2,6,6-tetramethyl-3,10-dioxatricyclo[5.3.0.0^{1,5}] decan-4-one (**34c**):* Colorless oil, obtained from tetronate **25c** in 53% yield according to General Procedure C (reaction time = 30 min). Another isomer was present in the crude ^{1}H NMR (ratio = 90:10), but could be separated by column chromatography: TLC R_f = 0.32 (P/Et_2O 1:1); IR (ATR) $\tilde{\nu}$ = 2978 (m, C−H), 2957 (m, C−H), 1765 (s, C═O), 1731 (s, C═O), 1436 (m, C−H); ^{1}H NMR (250 MHz, $CDCl_3$, 300 K) δ (ppm) = 1.22 (s, 3H), 1.29 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.86 (dd *virt.* t, ^2J = 13.6 Hz, ^3J = 10.6 Hz, $^3J \approx$ 8.9 Hz, 1H), 2.07 (dd, ^2J = 13.6 Hz, ^3J = 6.4 Hz, 1H), 2.75 (d, ^3J = 8.9 Hz, 1H), 3.76 (s, 3H), 4.02 (ddd, ^2J = 9.2 Hz, ^3J = 10.6 Hz, ^3J = 6.4 Hz, 1H), 4.18 (*virt.* td, $^2J \approx {}^3J \approx$ 8.9 Hz, ^3J = 1.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 300 K) δ (ppm) = 20.7 (CH_3), 21.0 (CH_3), 24.0 (CH_3), 26.3 (CH_2), 28.4 (CH_3), 38.0 (C), 49.2 (CH), 52.2 (CH_3), 60.9 (C), 71.4 (CH_2), 84.8 (C), 91.1 (C), 165.7 (C), 170.8 (C); MS (EI, 70 eV) *m*/*z* (%) = 268 (1) [M^+], 237 (4) [$(M - CH_3O)^+$], 110 (100) [$C_6H_6O_2^+$], 69 (36) [$C_4H_5O^+$]; HRMS (EI, 70 eV) calcd for $C_{13}H_{17}O_4^+$ [$(M - CH_3O)^+$] 237.1121; found 237.1121.

*2-Methoxycarbonyl-5,5-dimethyl-4,7-dioxatetracyclo[8.4.0.0^{2,6}.0^{6,10}]-tetradecan-3-one (**34d**):* Colorless solid, obtained from tetronate **25d** in 84% yield according to General Procedure C (reaction time = 1 h). Another isomer was present according to ^{1}H NMR (90:10 ratio). The minor isomer could be separated by repeated column chromatography: TLC R_f = 0.41 (P/EtOAc 3:1); IR (ATR) $\tilde{\nu}$ = 2933 (w, C−H), 1761 (s, C═O), 1731 (s, C═O), 1466 (w, C−H); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) = 1.25−1.35 (m, 2H), 1.41 (s, 3H), 1.41 (s, 3H), 1.54−1.68 (m, 6H), 2.05−2.13 (m, 2H), 2.87 (*virt.* t, ^3J = 8.2 Hz, 1H), 3.77 (s, 3H), 4.17−4.27 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm) = 18.5 (CH_2), 18.6 (CH_2), 19.9 (CH_2), 21.5 (CH_3), 25.4 (CH_3), 27.4 (CH_2), 37.4 (CH), 38.6 (CH_2), 51.0 (C) 52.8 (CH_3), 59.0 (C), 68.8 (CH_2), 86.3 (C), 95.3 (C), 167.4 (C), 171.5 (C); MS (EI, 70 eV) *m*/*z* (%) = 294 (9) [M^+], 263 (3) [$(M - CH_3O)^+$], 187 (100), 155 (62) [$C_8H_{11}O_3^+$]; HRMS (EI, 70 eV) calcd for $C_{16}H_{22}O_5^+$ [M^+] 294.1462; found 294.1468.

*3-[2-Hydroxy-2-(2-hydroxypropan-2-yl)-3-methyltetrahydrofuran-3-yl]propionic Acid (**37**):* Cyclobutane **34b** (52.6 mg, 207 μmol) was dissolved in 3 mL of THF, aqueous LiOH solution (2 M, 1 mL) was added, and the mixture was heated to reflux for 5 h. The reaction mixture was concentrated to a volume of ca. 1 mL, dissolved in aqueous NaOH solution (1 M, 10 mL) and washed with CH_2Cl_2 (10 mL). Concentrated HCl was added to the aqueous phase to adjust pH 1. The acidified aqueous solution was extracted with a $CHCl_3$/*i*-PrOH (5:1) mixture (5 × 10 mL), dried over Na_2SO_4, and the solvents were removed under reduced pressure. Purification by flash chromatography (CH_2Cl_2/MeOH/HCOOH 95:5:1) afforded hydroxyacid **37** (38.2 mg, 164 μmol, 79%) as a light yellow oil: TLC R_f = 0.17 (DCM/MeOH/HCOOH 95:5:1); IR (ATR) $\tilde{\nu}$ = 3432 (br s, O−H), 2987 (w, C−H), 2938 (w, C−H), 1697 (s, C═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 1.32 (s, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 1.65−1.72 (m, 1H), 1.85 (ddd, ^2J = 14.5 Hz, ^3J = 6.8 Hz, ^3J = 4.2 Hz, 1H), 2.05−2.13 (m, 1H), 2.15−2.24 (m, 2H), 2.55−2.63 (m, 2H), 3.60 (br s, 2H), 4.02−4.07 (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ (ppm) = 24.4 (CH_3), 25.3 (CH_3), 25.9 (CH_2), 27.6 (CH_3), 28.6 (CH_2), 36.4 (CH_2), 42.8 (C), 65.1 (CH_2), 75.4 (C), 116.3 (C), 171.0 (C); MS (EI, 70 eV) *m*/*z* (%) = 199 (3) [$(M - CH_3 - H_2O)^+$], 159 (1) [$C_8H_{15}O_3^+$], 155 (100), 127 (72), 100 (84), 59 (64) [$C_3H_7O^+$]; HRMS (EI, 70 eV) calcd for $C_{10}H_{15}O_4^+$ [$M^+ - CH_3 - H_2O$] 199.0965; found 199.0966.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds **17**−**19**, **21**, **23a**,**b**, **25a**−**e**, **27**−**34d**, **37** and structural assignment of compounds **2**, **4**, **26**−**31**, **32a**,**b**, **33**, **34a**,**c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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