3-Functionalized Tetronic Acids From Domino Rearrangement/Cyclization/ Ring-Opening Reactions of Allyl Tetronates

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Allyl tetronates **1** thermally rearrange to stable 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2** (R^3 = H, Aryl), which can be ring-opened with O-, N-, S- and C-nucleophiles to give 3-substituted tetronic acids **3**–**7**. Compounds **2** with R^3 = Alkyl are not isolable, but are interceptable intermediates in formal [2,3]-sigmatropic rearrangements of allyl tetronates. The vinylogous hexadienyl tetronate **17** undergoes a different domino [3,5]-rearrangement/cyclization reaction to give the 2*H*,5*H*-furano[4,3-*b*]oxepin-6-one **19**.

Introduction

3,5-Disubstituted tetronic acids are of medical interest as potential antibiotic, antiviral and antineoplastic agents.[1−6] We have recently reported an expeditious synthesis of the 3-[(*syn*-1′-methyl-2′-alkoxy)alkyl]tetronic acids **3** from allyl tetronates **1**.[7] An unusual thermal domino Claisen−Conia rearrangement[8] of **1** furnished the 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2**, which were isolable in cases of residues R^3 lacking α-hydrogen atoms and which could be selectively ring-opened with water or alcohols to give **3** (Scheme 1). Tetronates **1** were in turn readily available from a domino addition/intramolecular Wittig alkenation between the corresponding α-hydroxyallyl esters and the phosphorus ylide $Ph_3P{=}C{=}C{=}O$. We have also communicated[7] that the 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2** with residues R^3 bearing α-hydrogen atoms, though not isolable, are likely intermediates in the so-called "abnormal" Claisen rearrangements of allyl tetronates. Here we report on new evidence for this assumption, on the scope of ring-opening reactions of stable derivatives of **2** with O-, N-, S- and C-nucleophiles, and on a domino [3,5]-sigmatropic rearrangement/cyclization reaction of a penta-2,4-dienyl tetronate to give a furano[4,3-*b*]dihydrooxepine.

Results and Discussion

Ring-Opening of 3-(Spirocyclopropyl)dihydrofuran-2,4-diones with O-, N-, S- and C-Nucleophiles

1-Methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione [(±)-**2a**] ($R^{1/2}$ = $-[CH_2]_5-$; R^3 = Ph) was chosen as a stereochemically simple standard system, prepared as described earlier,[8,9] and was treated with a variety of alcohols, amines, thiols, Grignard compounds and cyanocuprates of the Knochel and Normant types. Heating of mixtures of **2a** and these nucleophiles at reflux in an inert solvent produced the corresponding 3-(1′-methyl-2′-nucleophile-2′-phenyl)ethyltetronic acids **3**−**6** in good yields (Scheme 1, Table 1). 5-Monosubstituted 3-(spirocyclopropyl)dihydrofuran-2,4-diones reacted in the same way. Ring opening of the 5-phenyl derivative **2b** (R^1 = H, R^2 = R^3 = Ph) with methanol, for instance, gave the corresponding tetronic acid **3c** in 65% yield. From earlier single-crystal X-ray structural analyses[7] of tetronic acids **3** with R^3 = Ph, we know that vicinal coupling constants ^3J(1′-H/2′-H) of ≈ 2−4 Hz are indicative of a *syn* configuration of the stereocentres in the side chain at C-3. Accordingly, compounds **3**−**5** were also formed exclusively in *syn* configurations, which can be explained in terms of a selective attack of the nucleophile on the benzylic carbon atom in the intact three-membered ring from the face of the adjacent methyl group. Treatment of (±)-**2a** with the "hard" Grignard reagents EtMgBr and BuMgBr, however, resulted in the exclusive formation of a single diastereoisomer, which in the case of **6b** was assigned the *anti* configuration, due to ^3J(1′-H/2′-H) > 10 Hz. Treatment with the "softer" Knochel cuprate $H_3CCu(CN)ZnI$ gave an easily separable 1:1 mixture of *syn* and *anti* diastereoisomers of **6c**. These findings can be explained by assuming an attack of the nucleophilic portion of the organometallic reagent on the cyclopropane ring at an advanced stage of opening, giving rise to *syn*/*anti* mixtures, or even on a planar benzylium cation, affording solely the *anti* isomer.

Mechanistically, it is very likely that all of these ring-opening reactions are electrophilically driven and initiated by a preceding protonation/metalation of the oxo oxygen atom of **2**. Treatment of stable solutions of **2a** in acetonitrile

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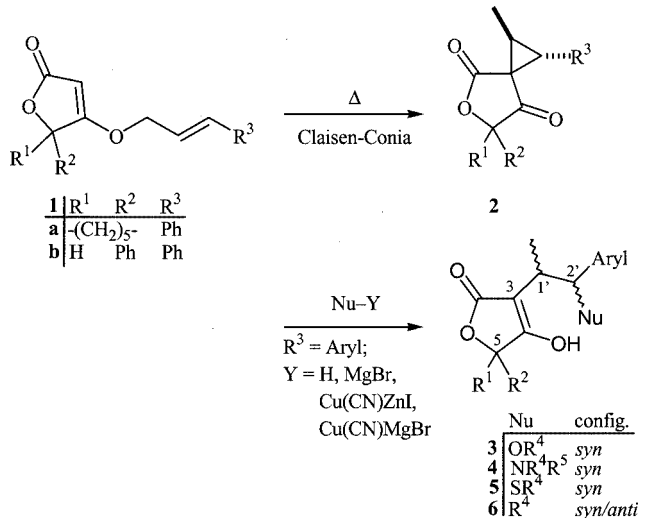
containing traces of water with catalytic amounts of ytterbium triflate resulted in the precipitation of the *anti*-configured acetamide **7a** as shown by the vicinal coupling constant $^3J(1'\text{-H}/2'\text{-H}) = 10.5$ Hz. The lanthanoid Lewis acid is obviously required for strong polarisation of the C3−C2′bond in the cyclopropane, facilitating an S_N1-like attack of the "hard" nitrile nitrogen atom. Water eventually adds to the C−N triple bond in **8** and liberates the catalyst. This reaction was found to be fairly general, working for various representative alkyl and aryl nitriles (Scheme 2). In the absence of water, no products arising from intramolecular cyclizations of **8** were obtained, but only the retro-Conia[8] product of **2a**, a 3-allyltetronic acid. Products originating from attack on the oxo carbonyl carbon atom could not be detected in any of the above reactions, although ab initio calculations suggested the coefficients along the cyclopropane bond and at the carbonyl carbon atom in the LUMO of **2a** were of similar magnitude. A conceivable attack on the ester carbonyl carbon atom, resulting in cleavage of the lactone ring and formation of a cyclopropanecarboxylate, was observed on only one occasion, when **2a** was heated at 100 °C in a mixture of methanol and THF under single-mode microwave conditions (300 W, 5 min). This preference for selective opening of the three-membered ring thus provides a short and general route to functionalized 3,5-disubstituted tetronic acids.

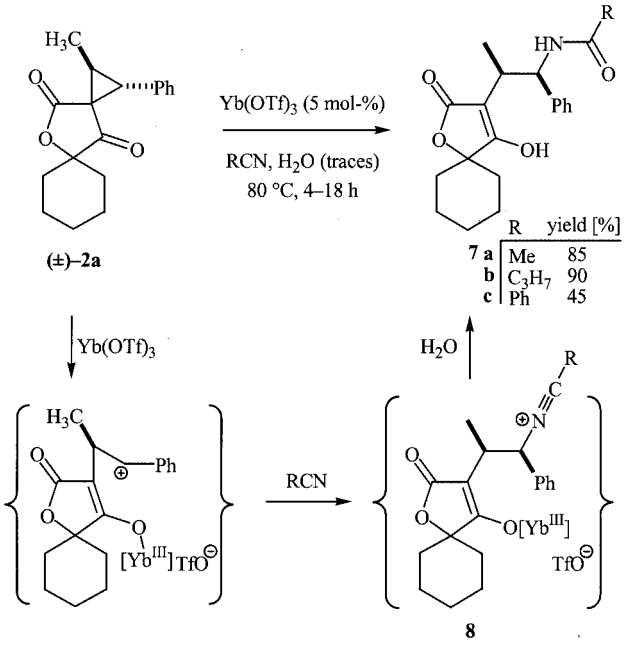


1	R^1	R^2	R^3
a	$-(CH_2)_5-$		Ph
b	H	Ph	Ph

2

	Nu	config.
3	OR^4	*syn*
4	NR^4R^5	*syn*
5	SR^4	*syn*
6	R^4	*syn/anti*

Scheme 1



R	yield [%]
Me	85
C_3H_7	90
Ph	45

7 a b c

8

Scheme 2

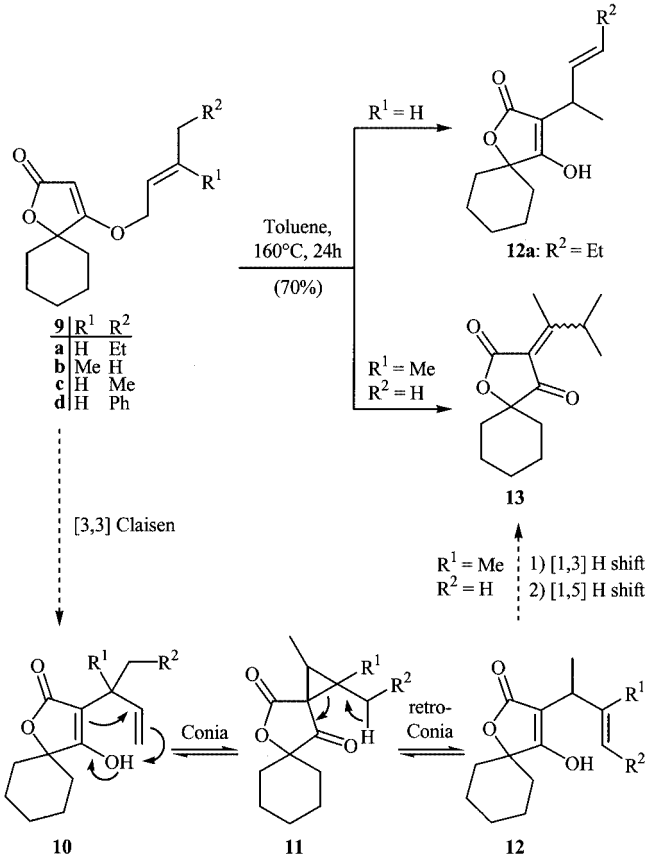
The Intermediacy of 3-(Spirocyclopropyl)dihydrofuran-2,4-diones in Formal [2,3]-Sigmatropic Rearrangements of Allyl Tetronates

The 3-(Spirocyclopropyl)dihydrofuran-2,4-diones **2** with residues R^3 bearing α-hydrogen atoms have not as yet been isolated from rearrangements of allyl tetronates. Derivatives **9** bearing two or three alkyl substituents on the alkene are instead converted directly into [2,3]-rearranged 3-alkylidenetetronic acids under thermal conditions (sealed bomb tube, 140−180 °C or microwave, 120 °C). The dimethyl derivative **9b** had previously been found to give the 3-(1′,2′-dimethylpropylidene)-5-spirodihydrofuran-2,4-dione **13** as

Table 1. 3-Substituted tetronic acids **3**−**6** from 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2a** or **2b** and nucleophiles Nu−Y

	Y−Nu	R^1/R^2	Conditions	M.p. [°C]	Yield [%]
3a	H−$OCH_2CH{=}CMe_2$	$-[CH_2]_5-$	CH_2Cl_2, 16 h, reflux	131	53
3b	H−OPr	$-[CH_2]_5-$	excess PrOH, PTSA, 16 h, 80 °C	151	72
3c	H−OMe	H/Ph	excess MeOH, $CHCl_3$, 12 h, reflux	59	65
4a	H−NEt_2	$-[CH_2]_5-$	$CHCl_3$, 16 h, room temp.	116	64
4b	H−NHEt	$-[CH_2]_5-$	$CHCl_3$, 16 h, room temp.	112	78
4c	H−NHBn	$-[CH_2]_5-$	CH_2Cl_2, 18 h, reflux	63	80
4d	H−NHBu	$-[CH_2]_5-$	$CHCl_3$, 16 h, room temp.	124	67
5a	H−SEt	$-[CH_2]_5-$	$CHCl_3$, 16 h, 70 °C, sealed tube	189	55
6a	BrMg−Bu	$-[CH_2]_5-$	Et_2O, 16 h, reflux	148	61
6b	BrMg−Et	$-[CH_2]_5-$	Et_2O/THF, 24 h, reflux	125	42
6cy	IZnCu(CN)−Me	$-[CH_2]_5-$	THF, −78 °C → 50 °C (16 h)	67−69[a]	55
6dy	BrMgCu(CN)−Ph	$-[CH_2]_5-$	Et_2O/THF, 16 h, 45 °C	209	72

[a] Mixture of diastereoisomers (*syn*/*anti* = 1:1); m.p. (*anti* isomer) 87 °C.



Scheme 3. [2,3]-Rearrangement of allyl tetronates to give 3-alkenyltetronic acids **12** and **13**

an unassigned 2:1 mixture of (*Z*) and (*E*) isomers when heated at 180 °C in a bomb tube.[8] A plausible mechanism is outlined in Scheme 3. An initial [3,3]-sigmatropic Claisen rearrangement produces the 3-allyltetronic acid **10b**, which is not isolable but undergoes a subsequent Conia-type oxa-ene reaction to give the elusive spirocyclopropane **11b**. This can then open the three-membered ring by making use of H atoms either from the newly created methyl group, returning to the Claisen product **10b**, or from one of either adjacent geminal methyl groups, giving rise to the retro-Conia product **12b**. The latter product is thermodynamically favoured, so the equilibrium lies far to the right under thermal conditions. Alternatively, the conversion **11** → **12** might follow a polar E1-type elimination pathway involving zwitterionic carbenium tetronate intermediates. While, in the bomb tube, **12b** rearranges quickly and quantitatively to the 3-(1′,2′-dimethylpropylidene)-5-spirodihydrofuran-2,4-dione **13** through two consecutive H-shifts, it can be isolated as the end product under microwave conditions (190 °C, toluene, 20 min). The driving force for these final H-shift steps is the formation firstly of a tetrasubstituted alkene and eventually of an alkene in conjugation to both carbonyl groups. It was interesting to see whether a similar preference for the ring opening of spirocyclopropane intermediates of type **11**, bearing just one *n*-alkyl substituent, would exist. When tetronate **9a** (R^1 = H, R^2 = Et) was kept at ca. 160 °C overnight, the (*E*)-configured olefin

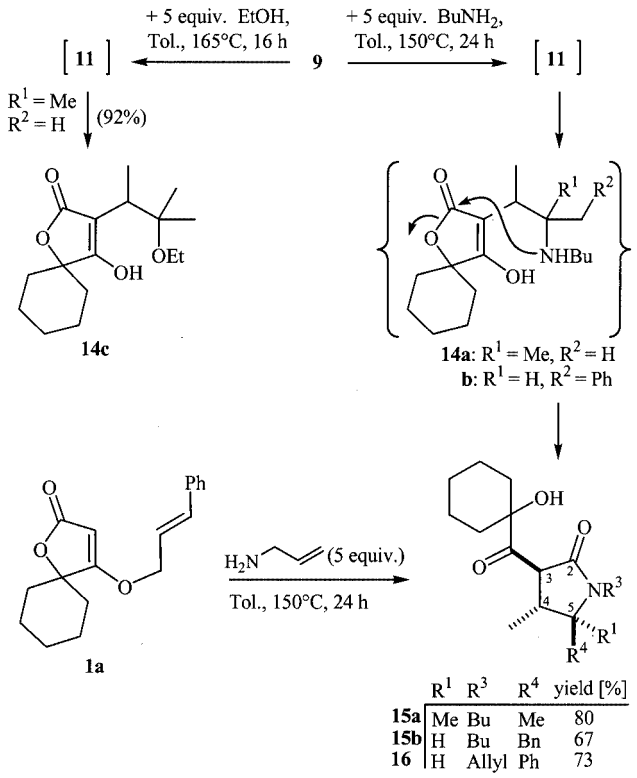
Table 2. 3-Allyltetronic acids **12** from allyl tetronates **9**

12	R^1	R^2	M.p. [°C]	Yield [%]
a[a]	H	Et	112	70
b[b]	Me	H	159	58
c[a]	H	Me	135	98
d[a]	H	Ph	159	84

[a] Conditions: toluene, 150−160 °C, 16−24 h, sealed bomb tube. [b] Conditions: toluene, 190 °C, 20 min, microwave.

12a was formed as the sole and stable product, which means that the Conia intermediate **11a** had undergone retro-Conia ring opening exclusively by H-abstraction from the methylene group, producing the thermodynamically more stable internal alkene. Compound **12a** is not prone to further H-shifts like **12b**, as this would merely furnish a trisubstituted olefin. Table 2 shows additional examples. Thanks to their selectivity and predictability, these [2,3]-rearrangement reactions offer convenient access to various types of 3-alkylidenetetronic acids and -furan-2,4-diones. It is worthy of note that the congenerous benzo-annulated six-membered systems (i.e., 4-allyloxycoumarins and 4-allyloxyquinolones) undergo [3s,3s]-sigmatropic rearrangement reactions. This can be explained by the reluctance of these systems to enter into the Conia cyclopropanation through shifting of the C=C bond out of conjugation with the benzene core and loss of an sp^2-carbon atom in the heterocycle. Allyloxybenzenes[10−12] and 4-allyloxytetrahydroazepin-2-ones,[13] on the other hand, are known to follow a [2,3]-sigmatropic rearrangement pathway, which is totally in line with the above reasoning.

Though not isolable, the intermediate spirocyclopropanes **11** could be intercepted by ring-opening reactions with amines and alcohols, showing their intermediacy in [2,3]-sigmatropic rearrangements and also opening synthetic routes to functionalized 3-alkyltetronic acids with alkyl instead of aryl residues at C^β of the side chain. When a mixture of allyl tetronate **9b** and 5 equiv. of ethanol was heated under nitrogen to 165 °C for 16 h in a sealed bomb tube, the corresponding 3-(β-ethoxy)propylfuran-2,4-dione **14c** was obtained in an excellent 92% yield. Treatment of allyl tetronates **9** with a fivefold excess of butylamine under similar conditions, however, did not furnish the corresponding 3-(β-*N*-butylamino)ethylfuran-2,4-diones **14a** or **14b**, as these underwent subsequent intramolecular lactone → lactam conversions to give the 3,4,5-trisubstituted butyrolactams **15** in 70−80% yield (Scheme 4). As the NMR spectra of **15** can easily be mistaken for those of the oxo tautomers of intermediates **14**, single crystals of the analogous lactam **16** suitable for an X-ray structural analysis (Figure 1), prepared under identical conditions from allyl tetronate **1a**[8] and allylamine, were grown. The all-*trans* configuration of the residues at C-3, C-4 and C-5 fits with the vicinal coupling constants ^3J(3-H/4-H) = 10.0 Hz and ^3J(4-H/5-H) = 8.5 Hz. Similar values were found for **15b**. Obviously, at elevated temperatures an excess of the polar amine opens a cyclopropane ring with a considerably weakened, if not en-



Scheme 4. Trapping of intermediate 3-(spirocyclopropyl)dihydrofuran-2,4-diones **11** and synthesis of γ-lactams **15/16**

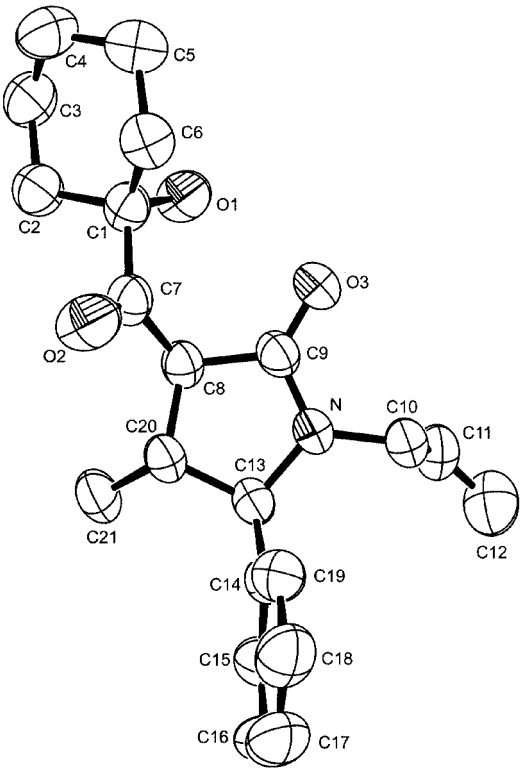
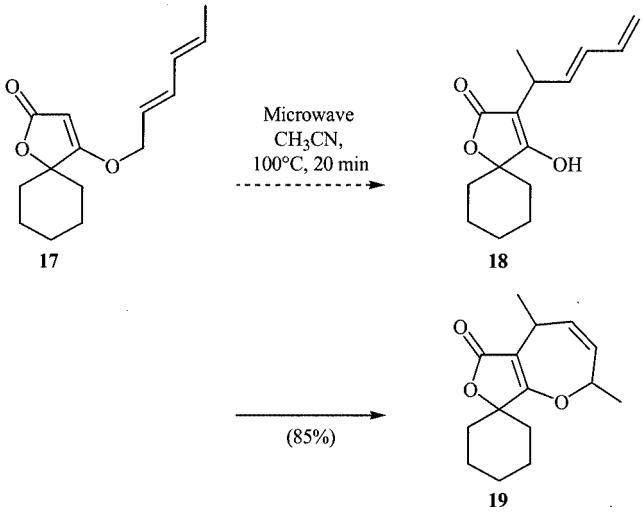


Figure 1. Molecular structure of (±)-**16** (ORTEP representation, 50% probability ellipsoids); hydrogen atoms are omitted; selected bond lengths [Å] and dihedral angles [°]: C9−O3 1.2300(19), C9−N 1.338(2), C13−N 1.468(2), C10−N 1.464(2), C33-C20 1.547(2), C8−C20 1.525(2), C8−C9 1.523(2), C21−C20−C13−C14 87.89(18), C7−C8−C20−C21 92.12(19), C14−C13−N−C10 55.0(2), C2−C20−C13−N 149.48(14)

tirely broken, C−C bond and a good deal of carbenium ion character of the more highly substituted atom C-2′. This is in contrast to the *syn*-selective ring opening of **2a** with amines in CH_2Cl_2 or $CHCl_3$ at ambient temperature or slightly above to give **4**.

The Vinylogous Case: Domino [3,5]-Rearrangement/ Cyclization of a Pentadienyl Tetronate

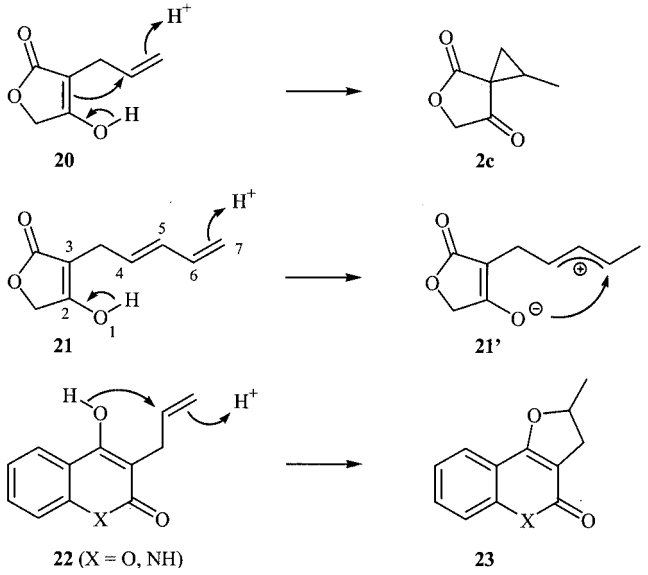
3-(Penta-2′,4′-dienyl)tetronic acids are the vinylogues of 3-allyltetronic acids and could in principle undergo the same thermally induced Conia rearrangement to produce the 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2** (R^3 = vinyl), a (3,6) oxa-ene reaction to furnish 3-(spirocyclopentenyl)dihydrofuran-2,4-diones, a [2+4] cycloaddition, or an addition of the OH group onto either C=C bond. When hexadienyl tetronate **17** was heated in acetonitrile to 100 °C for 20 min under microwave conditions (300 W) the 2*H*,5*H*-furano[4,3-*b*]oxepin-6-one **19** was formed in 85% yield, whereas heating of **17** in a bomb tube resulted only in uncontrolled decomposition. A plausible mechanism assumes an initial [3,5]- (or [2,3]-) sigmatropic rearrangement of **17** to give **18**, which then undergoes a rapid cyclization to **19** by a Markovnikov-type addition of the OH group across



Scheme 5. A sigmatropic-cationic domino synthesis of 2*H*,5*H*-furano[4,3-*b*]oxepin-6-one **19**

the terminal C=C bond (Scheme 5). Whether this is a general reaction remains to be seen. The use of acetonitrile as the solvent seemed to be crucial both for the rearrangement step and for the cyclization sequence formally comprised of protonation/allyl cation formation/charge-controlled tetronate attack.

Conversely, 3-allyltetronic acids such as **20** furnish the spirocyclopropanes **2** as the products of an orbital-controlled Conia rearrangement, but only upon prolonged heating in acetonitrile or preferentially in toluene at 150 °C. No charge-controlled addition of the OH group onto the C=C bond in **20** and similar systems has ever been observed, probably because of the instability of an intermediate carbenium ion in relation to the allyl cation in **21′**



Scheme 6

(Scheme 6). It has already been pointed out that 3-allyl-4-hydroxycoumarins and -quinolones **22** do not undergo Conia-type spirocyclopropanation but rather addition of the OH group onto the C=C bond to give furano derivatives **23** at high temperatures, despite the involvement of a relatively unstabilized cation.

Further work is now in progress on the ring opening of the stable 3-(spirocyclopropyl)dihydrofuran-2,4-diones **2** with difunctional nucleophiles such as enolates and enamines to allow domino ring opening/recyclization processes.

Experimental Section

General Information: Tetronate **1a**,[8] 1-methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione [(±)-**2a**],[8] 1-hydroxycyclohexanecarboxylic acid[14,15] and tetronate **9b**[7] were prepared by literature procedures. All other starting compounds were purchased from Aldrich and used as such without further purification. All reactions were carried out under argon. Solvents were dried and distilled under argon by standard procedures prior to use. Microwave: 300-W focused single-mode system (Discover, CEM). Melting points were recorded with a Gallenkamp apparatus and are not corrected. NMR: Jeol JNM-EX 270, Bruker DRX 500 and AC 300; δ given in ppm; TMS as internal standard. IR: Perkin−Elmer 983G; recorded as potassium bromide (KBr) disks or films (film). MS: Double Focusing Triple Sector VG Auto Spec, and Varian MAT CH-7 (EI). MA: Perkin−Elmer 2400 CHN.

1. Synthesis of 1-Methyl-2,5-diphenyl-6-oxaspiro[2.4]hexane-4,7-dione [(±)-2b]

(±)-(*E*)-5-Phenyl-4-[(3′-phenylprop-2′-enyl)oxy]furan-2(5*H*)-one (1b): White solid (3.52 g, 12.05 mmol, 59%) from (*E*)-3-phenylprop-2-enyl mandelate (5.56 g, 20.75 mmol) and ketenylidenetriphenylphosphorane (8.14 g, 26.95 mmol) heated at reflux in THF (150 mL) for 12 h; m.p. 116 °C. IR (KBr): $\tilde{\nu}$ = 3025 cm^{-1}, 2928, 1740, 1618, 1449. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.66 (m, 2 H, OCH_2), 5.19 (d, ^4J = 1.08 Hz, 1 H, 5-H), 5.70 (d, ^4J = 1.08 Hz, 1 H, 3-H), 6.19 (dt, ^3J= 15.92, 6.29 Hz, 1 H, C*H*=CH), 6.59 (dt, ^3J = 15.92 Hz, ^4J = 1.33 Hz, 1 H, CH=C*H*), 7.24−7.40 (m, 10 H, Ph) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 73.3 (OCH_2), 80.4 (C-3), 88.9 (C-5), 120.7 (*C*H=CH), 126.6, 126.7, 128.6, 128.7, 128.8, 129.3 (CH-*ar*), 134.1 and 135.4 (C-*ipso*), 135.7 (CH=*C*H), 172.6 (C-2), 180.2 (C-4) ppm. MS (EI, 70 eV): *m/z* (%) = 293 (1) [M^+ + 1], 292 (5) [M^+], 274 (5), 129 (12), 117 (100). $C_{19}H_{16}O_3$ (292.33): accurate mass: calcd. 292.10990; found 292.15418.

1-Methyl-2,5-diphenyl-6-oxaspiro[2.4]hexane-4,7-dione [(±)-2b]: Yellow, crystalline solid (461 mg, 1.58 mmol, 77%) from (±)-(*E*)-5-phenyl-4-(3′-phenylprop-2′-enyloxy)-(5*H*)furan-2-one (600 mg, 2.05 mmol), dissolved in dry toluene and heated to 165 °C in a sealed tube for 36 h; 8(α)/5(β) mixture of diastereoisomers; R_f = 0.52 (diethyl ether/hexane, 1:1, v/v), m.p. 169 °C. IR (KBr): $\tilde{\nu}$ = 3048 cm^{-1}, 2928, 1786, 1736, 1452, 1206. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (d, ^3J = 6.17 Hz, 3 H, 1-CH_3^{α}), 1.61 (d, ^3J = 6.19 Hz, 3 H, 1-CH_3^{β}), 2.85 (dq, ^3J = 9.38, 6.19 Hz, 1 H, 1-H^{β}), 3.09 (dq, ^3J = 9.34, 6.17 Hz, 1 H, 1-H^{α}), 3.49 (d, ^3J = 9.34 Hz, 1 H, 2-H^{α}), 3.61 (d, ^3J = 9.38 Hz, 1 H, 2-H^{β}), 5.27 (s, 1 H, 5-H^{β}), 5.65 (s, 1 H, 5-H^{α}), 7.14−7.47 (m, 10 H, $Ph^{\alpha,\beta}$) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 11.4 (1-CH_3^{α}), 12.1 (1-CH_3^{β}), 38.0 (C^{α}-1), 38.7 (C^{β}-1), 39.0 ($C^{\alpha,\beta}$-3), 51.1 (C^{α}-2), 52.4 (C^{β}-2), 84.0, 84.4 ($C^{\alpha,\beta}$-5), 125.3, 125.7, 128.0, 128.1, 128.4, 128.5, 128.8, 129.1, 129.9 (CH-*ar*), 132.0, 132.1, 133.4 (C-*ipso*), 171.4 ($C^{\alpha,\beta}$-7), 203.3 ($C^{\alpha,\beta}$-4) ppm. MS (EI, 70 eV): *m/z* (%) = 293 (1) [M^+ + 1], 292 (13) [M^+], 277 (6), 129 (11), 118 (100). $C_{19}H_{16}O_3$ (292.33): accurate mass: calcd. 292.10990; found 292.15422.

2. Synthesis of Tetronic Acids 3−6

General Procedure for the Nucleophilic Ring Opening of 2: A solution of 1-methyl-2-phenyl-11-oxadispiro[2.1.5.2]dodecane-4,12-dione (**2a**) (568 mg, 2.00 mmol) or **2b** (585 mg, 2.00 mmol) in an appropriate solvent was treated with the appropriate amine, thiol, alcohol or organometallic compound and stirred overnight with exclusion of air and moisture, either at ambient temperature or at gentle reflux. All volatile components were then removed in vacuo and the obtained residue was taken up in CH_2Cl_2. In cases of reactions with organometallic compounds, the resulting solution was washed with water, dried with magnesium sulfate and concentrated again before purification by column chromatography (silica gel 60, solvent as indicated). Accurate conditions and quantities for the individual derivatives were as indicated below.

4-Hydroxy-3-{*syn*-[1′-methyl-2′-(3′′-methylbut-2′′-enyloxy)-2′-phenyl]ethyl}-1-oxaspiro[4.5]dec-3-en-2-one (3a): This compound (389 mg, 0.95 mmol, 53%) was obtained from 3-methylbut-2-en-1-ol (950 mg, 11.10 mmol); solution in dry dichloromethane (40 mL) heated at reflux for 16 h; white crystalline solid; m.p. 131 °C (hexane); R_f = 0.52 (ethyl acetate/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1}, 2936, 1700, 1659, 1604, 1455, 1324, 1164. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, ^3J = 7.35, 3 H, 1′-CH_3), 1.55−1.85 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 1.57 (s, 3 H, =CCH_3-*cis*), 1.78 (s, 3 H, =CCH_3-*trans*), 2.82 (dq, ^3J = 7.35 Hz, 2.17 Hz, 1 H, 1′-H), 3.91 (dd, ^2J = 11.40, ^3J = 8.39 Hz, 1 H, OCH^{α}), 4.08 (dd, ^2J = 11.40, ^3J = 6.64 Hz, 1 H, OCH^{β}), 4.71 (d, ^3J = 2.17 Hz, 1 H, 2′-H), 5.36 (m, 1 H, =CH), 7.26−7.39 (m, 5 H, Ph), 10.54 (br., 1 H, OH) ppm. ^{13}CNMR (75.4 MHz, $CDCl_3$): δ = 11.4 (1′-CH_3), 18.0 (=C*C*H_3-*cis*), 21.8, 22.0 (C-7, C-9), 24.5 (C-8), 25.9 (=C*C*H_3-*trans*), 32.7, 33.3 (C-6, C-10), 35.7 (C-1′), 65.8 (OCH_2), 81.8 (C-5-*spiro*), 84.5 (C-2′), 102.9 (C-3), 118.3 (H*C*=C), 126.8, 127.8, 128.4 (CH-*ar*), 138.0 (C-*ipso*), 140.6 [*C*(CH_3)2], 173.5, 179.8 (C-2, C-4) ppm. MS (EI, 70 eV): *m/z* (%) = 369 (3) [M^+ − 1], 301 (9), 197 (16), 196 (94), 195 (64), 178 (29), 177 (56), 118 (28), 109 (55), 107 (58), 81 (24), 85 (20), 69 (100). $C_{23}H_{30}O_4$: accurate mass: calcd. 370.2144; found 370.2153.

4-Hydroxy-3-[*syn*-(1′-methyl-2′-phenyl-2′-propoxy)ethyl]-1-oxaspiro[4.5]dec-3-en-2-one (3b): This compound (497 mg, 1.44 mmol, 72%) was obtained from propanol (50 mL); mixture treated with *p*-toluenesulfonic acid (170 mg, 1.00 mmol) and heated at 80 °C for 16 h; white, crystalline solid; m.p. 151 °C; R_f = 0.32 (dichloromethane). IR (KBr): $\tilde{\nu}$ = 3430 cm^{-1}, 2937, 1701, 1657, 1604, 1451, 1322, 1162. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.48 Hz, 3 H, CH_2CH_3), 0.93 (d, ^3J = 7.39 Hz, 3 H, 1′-CH_3), 1.15−1.92 (m, 12 H, 6-H, 7-H, 8-H, 9-H, 10 H, CH_2CH_3), 2.80 (dq, ^3J = 7.39 Hz, 2.11 Hz, 1 H, 1′-H), 3.37 (ddd, ^2J = 9.45, ^3J = 7.48, 5.74 Hz, 1 H, OCHH), 3.51 (dt, ^2J = 9.45, ^3J = 7.48 Hz, 1 H, OCHH), 4.66 (d, ^3J = 2.11 Hz, 1 H, 2′-H), 7.25−7.40 (m, 5 H, Ph), 10.29 (s, 1 H, OH) ppm. ^{13}CNMR (68 MHz, $CDCl_3$): δ = 10.3 (CH_2CH_3), 18.3 (1′-CH_3), 21.8 and 21.9 (C-7, C-9), 22.7 ($OCCH_2$), 24.8 (C-8), 32.7, 33.2 (C-6, C-10), 35.8 (C-1′), 71.3 (OCH_2), 81.9 (C-5-*spiro*), 85.6 (C-2′), 102.8 (C-3), 126.7, 127.8, 127.9, 128.3, 128.4 (CH-*ar*), 138.7 (C-*ipso*), 173.4 (C-2), 179.7 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 345 (1) [M^+ + 1], 344 (2) [M^+], 301 (3) [$M^+ - C_3H_7$], 149 (100), 107 (66). $C_{21}H_{28}O_4$ (344.44): calcd. C 73.23, H 8.19; found C 73.36, H 8.12.

4-Hydroxy-3-[*syn*-2′-methoxy-1′-methyl-2′-phenylethyl]-5-phenyl-(5*H*)furan-2-one (3c): White solid (417 mg, 1.12 mmol, 65%) from **2b** and methanol (5 mL) heated at reflux in dry chloroform (15 mL) for 12 h; 5(α)/3(β) mixture of diastereoisomers; m.p. 59 °C; R_f = 0.21 (diethyl ether/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3576 cm^{-1}, 1748, 1656, 1454, 1194. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, ^3J = 7.27 Hz, 3 H, 1′-CH_3^{α}), 1.03 (d, ^3J = 5.91 Hz, 3 H, 1′-CH_3^{β}), 2.90 (dt, ^3J = 7.27, 1.66 Hz, 1 H, 1′-H^{α}), 2.97−3.02 (m, 1 H, 1′-H^{β}), 3.32 (s, 3 H, OCH_3^{β}), 3.40 (s, 3 H, OCH_3^{α}), 4.60 (d, ^3J = 1.70 Hz, 1 H, 2′-H^{β}), 4.66 (d, ^3J = 1.66 Hz, 1 H, 2′-H^{α}), 5.64 (s, 2 H, 5-$H^{\alpha,\beta}$), 7.23−7.40 (m, 10 H, $Ph^{\alpha,\beta}$), 10.62 (s, 1 H, OH^{β}), 10.68 (s, 1 H, OH^{α}) ppm. ^{13}CNMR (75.5 MHz, $CDCl_3$): δ = 11.6 (1′-$CH_3^{\alpha,\beta}$), 36.1, 36.2 (C-1′), 57.2, 58.3 (OCH_3), 78.7, 78.8 (C-2′), 87.3, 89.3 (C-5), 104.3 (C-3), 126.7, 126.8, 128.2, 128.9, 129.2, 129.3 (CH-*ar*), 134.5, 134.9 (C-*ipso*), 137.6 (C-*ipso*), 173.9 and 174.8 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 325 (1) [M^+ + 1], 324 (3) [M^+], 309 (1), 122 (10), 121 (100). $C_{20}H_{20}O_4$ (324.38): calcd. C 74.06, H 6.21; found C 74.26, H 6.19.

3-[*syn*-(2′-Diethylamino-1′-methyl)-2′-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (4a): This compound (457 mg, 1.28 mmol, 64%) was obtained from diethylamine (150 mg, 2.0 mmol); mixture in dry chloroform (10 mL) stirred for 16 h at room temp.; white crystalline solid; m.p. 116 °C; R_f = 0.46 (acetonitrile). IR (KBr): $\tilde{\nu}$ = 3442 cm^{-1}, 2980, 2938, 1709, 1605, 1403, 1030, 766. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.05 (d, ^3J = 6.86 Hz, 3 H, 1′-CH_3), 1.14−1.32 (m, 6 H, $NCCH_3$), 1.51−1.89 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.45−2.63 (m, 1 H, NCH_2), 2.81−3.02 (m, 1 H, NCH_2), 3.27 (dq, ^3J = 6.86 Hz, 2.19 Hz, 1′-H), 3.87 (d, ^3J = 2.19, 1 H, 2′-H), 7.25−7.42 (m, 5 H, Ph) ppm. ^{13}CNMR (68 MHz, $CDCl_3$): δ = 16.7 (1′-CH_3), 22.0, 22.2 ($NCCH_3$), 24.8 (C-7, C-9), 31.6 (C-8), 33.0 (C-6, C-10), 33.2 (C-1′), 42.8 (NCH_2), 71.1 (C-2′), 82.0 (C-5-*spiro*), 91.5 (C-3), 128.8, 129.2, 130.1 (CH-*ar*), 134.0 (C-*ipso*), 176.0 (C-2), 187.9 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 358 (2) [M^+ + 1], 357 (3) [M^+], 356 (1) [M^+ − 1], 284 (8), 266 (6), 163 (53), 162 (100), 134 (92). $C_{22}H_{31}NO_3$ (357.49): calcd. C 73.91, H 8.74, N 3.92; found C 74.02, H 8.70, N 3.98.

3-[*syn*-(2′-Ethylamino-1′-methyl)-2′-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (4b): This compound (497 mg, 1.54 mmol, 78%) was obtained from ethylamine (87 mg, 2.0 mmol); mixture in dry chloroform (10 mL) stirred at room temp. for 16 h; white crystalline solid; m.p. 112 °C; R_f = 0.27 (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3429 cm^{-1}, 2934, 1730, 1682, 1563, 1453, 1024, 755. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.99 (d, ^3J = 7.08 Hz, 3 H, 1′-CH_3), 1.18 (t, ^3J = 7.29 Hz, 3 H, $NCCH_3$), 1.39−1.83 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.65 (dq, ^3J = 7.1 Hz, 2.1 Hz, 1 H, 1′-H), 2.75−2.94 (q, ^3J = 7.29 Hz, 2 H, NCH_2), 4.04 (m, 1 H, 2′-H), 7.19−7.38 (m, 5 H, Ph) ppm. ^{13}CNMR (68 MHz, $CDCl_3$): δ = 18.4 (1′-CH_3), 20.0 (C-7, C-9), 28.4 (C-8), 28.5 ($NCCH_3$), 31.1 (C-6, C-10), 39.3 (C-1′), 42.7 (NCH_2), 71.0 (C-2′), 88.8 (C-5-*spiro*), 105.5 (C-3), 133.1, 134.3, 135.3 (CH-*ar*), 144.2 (C-*ipso*), 181.5 (C-2), 190.5 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 330 (5) [M^+ + 1], 329 (29) [M^+], 328 (3), 135 (64), 134 (100), 106 (88). $C_{20}H_{27}NO_3$ (329.43): calcd. C 72.92, H 8.26, N 4.25; found C 72.86, H 8.22, N 4.33.

3-[*syn*-(2′-Benzylamino-1′-methyl)-2′-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (4c): This compound (630 mg, 1.62 mmol, 80%) was obtained from benzylamine (435 mg, 4.0 mmol); mixture in dry dichloromethane (25 mL) heated at reflux for 18 h; compound purified by filtration through a short plug of neutral alumina; white crystalline solid; m.p. 63 °C. IR (KBr): $\tilde{\nu}$ = 3422 cm^{-1}, 3063, 2932, 2855, 1735, 1684, 1655, 1558, 1456, 1026, 962, 749. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, ^3J = 7.29 Hz, 3 H, 1′-CH_3), 1.28−1.86 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.83 (dq, ^3J = 7.29 Hz, 2.19 Hz, 1 H, 1′-H), 3.58 (d, ^2J = 12.65 Hz, 1 H, $NCH^{\alpha}Ph$), 3.83 (d, ^2J = 12.65 Hz, 1 H, $NCH^{\beta}Ph$), 4.07 (d, ^3J = 2.19 Hz, 1 H, 2′-H), 7.24−7.45 (m, 10 H, Ph), 15.98 (s, 1 H, OH) ppm. ^{13}CNMR (75.4 MHz, $CDCl_3$): δ = 11.1 (1′-CH_3), 21.0, 21.1 (C-7, C-9), 23.7 (C-8), 31.7, 32.1 (C-6, C-10), 34.8 (C-1′), 49.1 (NCH_2), 63.5 (C-2′), 81.5 (C-5-*spiro*), 96.8 (C-3), 125.9, 126.1, 127.1, 127.2, 127.9, 128.4, 133.2 (CH-*ar*), 136.3 (C-*ipso*), 174.7, 185.4 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 392 (2) [M^+ + 1], 391 (4) [M^+], 372 (1) [$M^+ - H_2O$], 266 (8), 265 (16), 197 (17), 196 (67), 130 (11), 118 (14), 107 (22), 106 (62), 91 (61), 84 (16), 75 (16), 65 (18), 55 (77), 51 (82), 47 (58), 39 (54), 32 (72), 28 (100). $C_{25}H_{29}NO_3$: accurate mass: calcd. 391.2147; found 391.2133.

3-[*syn*-(2′-Butylamino-1′-methyl)-2′-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (4d): This compound (480 mg, 1.33 mmol, 67%) was obtained from butylamine (167 mg, 2.33 mmol); mixture in dry chloroform (20 mL) stirred for 16 h at room temp.; white crystalline solid; m.p. 124 °C; R_f = 0.48 (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3448 cm^{-1}, 2934, 1738, 1681, 1582, 1429, 1050, 963. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.50 Hz, 3 H, CH_2CH_3), 0.95 (d, ^3J = 7.29 Hz, 3 H, 1′-CH_3), 1.32 (mc, 2 H, CH_2CH_3), 1.41−1.88 (m, 12 H, 6-H, 7-H, 8-H, 9-H, 10-H, $NCCH_2$), 2.50−2.73 (m, 2 H, NCH_2), 2.83 (dq, ^3J = 7.29 Hz, 2.19 Hz, 1 H, 1′-H), 4.03 (m, 1 H, 2′-H), 7.17−7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.0 (CH_2CH_3), 13.7 (1′-CH_3), 20.2 (CH_2CH_3), 21.9 (C-7, C-9), 24.6 (C-8), 30.0 ($NCCH_2$), 32.7 (C-6, C-10), 36.1 (C-1′), 46.4 (NCH_2), 65.3 (C-2′), 82.6 (C-5-*spiro*), 97.6 (C-3), 126.8, 127.9, 128.8 (CH-*ar*), 137.3 (C-*ipso*), 175.7 (C-2), 186.2 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 358 (2) [M^+ + 1], 357 (4) [M^+], 163 (47), 162 (100), 106 (90). $C_{22}H_{31}NO_3$ (357.49): calcd. C 73.91, H 8.74, N 3.92; found C 74.06, H 8.72, N 4.03.

3-[*syn*-(2′-Ethylthio-1′-methyl)-2′-phenylethyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (5a): This compound (362 mg, 1.06 mmol, 55%) was obtained from ethanethiol (1 mL); mixture in dry chloroform (10 mL) heated to 70 °C for 16 h in a sealed bomb tube; white crystalline solid; m.p. 189 °C; R_f = 0.32 (ethyl acetate/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3419 cm^{-1}, 2937, 1701, 1661, 1635, 1455, 1264, 1156. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.38 Hz, 3 H, $SCCH_3$), 1.29 (d, ^3J = 7.08 Hz, 3 H, 1′-CH_3), 1.30−1.80 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.42 (q, ^3J = 7.38 Hz, 2 H, SCH_2), 3.10 (dq, ^3J = 7.08, 4.92 Hz, 1 H, 1′-H), 4.19 (d, ^3J = 4.92 Hz, 1 H, 2′-H), 7.20−7.43 (m, 5 H, Ph), 10.01 (s, 1 H, OH)

ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.7 (1′-CH_3), 15.5 (SC*C*H$_3$), 22.2, 22.3 (C-7, C-9), 24.8 (C-8), 26.2 (S*C*H$_2$), 33.0, 33.1 (C-6, C-10), 36.4 (C-1′), 54.6 (C-2′), 82.9 (C-5-*spiro*), 103.3 (C-3), 128.0, 128.4, 128.8 (CH-*ar*), 142.0 (C-*ipso*), 174.5, 178.6 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 346 (16) [M$^+$], 318 (11), 290 (16), 284 (5), 178 (39), 177 (85), 152 (21), 151 (100), 130 (11), 118 (16), 117 (18), 103 (10). $C_{20}H_{26}O_3S$: accurate mass: calcd. 346.1602; found 346.1598.

4-Hydroxy-3-[(1′-methyl-2′-phenyl)hexyl]-1-oxaspiro[4.5]dec-3-en-2-one (6a): This compound (420 mg, 1.23 mmol, 61%) was obtained from butylmagnesium bromide, prepared from Mg turnings (73 mg, 3.00 mmol), and butyl bromide (410 mg, 0.32 mL, 3.00 mmol); mixture in dry diethyl ether (20 mL) heated at reflux for 16 h; white crystalline solid; m.p. 148 °C; R_f = 0.75 (ethyl acetate/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3414 cm^{-1}, 3184, 2931, 1712, 1629, 1452, 1267, 1154. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.76 (t, ^3J = 7.33 Hz, 3 H, 6′-H), 1.23 (d, ^3J = 6.45 Hz, 3 H, 1′-CH_3), 0.84−1.72 (m, 16 H, 6-H, 7-H, 8-H, 9-H, 10-H, 3′-H, 4′-H, 5′-H), 2.76−2.80 (m, 2 H, 1′-H, 2′-H), 6.99−7.30 (m, 5 H, Ph), 11.0 (s, 1 H, OH) ppm. ^{13}C NMR (JMOD, 68 MHz, $CDCl_3$): δ = 13.9 (C-6′), 16.6 (1′-CH_3), 21.4, 21.5 (C-7, C-9), 22.1 (C-5′), 23.9 (C-4′), 25.7 (C-8), 31.8, 31.9 (C-6, C-10), 32.6 (C-1′), 32.9 (C-3′), 48.3 (C-2′), 80.2 (C-5), 102.3 (C-3), 125.5, 127.8, 128.0 (CH-*ar*), 144.8 (C-*ipso*), 171.7, 176.8 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 342 (1) [M$^+$], 196 (64), 174 (65), 169 (45), 147 (18), 132 (79), 91 (100). $C_{22}H_{30}O_3$: accurate mass: calcd. 342.2195; found 342.2195.

4-Hydroxy-3-[*anti*-(1′-methyl-2′-phenyl)butyl]-1-oxaspiro[4.5]dec-3-en-2-one (6b): This compound (266 mg, 0.85 mmol, 42%) was obtained from ethylmagnesium bromide, prepared from Mg turnings (73 mg, 3.00 mmol), and ethyl bromide (327 mg, 3.00 mmol); mixture in dry diethyl ether (10 mL) and THF (10 mL) heated at reflux for 24 h; white crystalline solid; m.p. 125 °C; R_f = 0.62 (ethyl acetate/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3486 cm^{-1}, 3056, 2936, 1712, 1646, 1496, 1309. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.85 (d, ^3J = 7.50 Hz, 3 H, 1′-CH_3), 1.17−1.35 (m, 15 H, 6-H, 7-H, 8-H, 9-H, 10-H, 3′-H, 4′-H), 1.50−1.98 (m, 2 H, 3′-H), 2.72−2.90 (m, 1 H, 2′-H), 3.45 (dq, ^3J = 10.6, 7.50 Hz, 1 H, 1′-H), 7.13−7.28 (m, 5 H, Ph), 8.44 (s, 1 H, OH) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.3 (C-4′), 16.9 (1′-CH_3), 21.8, 21.9 (C-7, C-9), 24.5 (C-8), 26.7 (C-3′), 32.2, 32.3 (C-6, C-10), 33.5 (C-1′), 51.0 (C-2′), 82.6 (C-5), 104.0 (C-3), 125.8, 127.8, 129.0 (CH-*ar*), 144.8 (C-*ipso*), 175.0, 178.4 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 314 (2) [M$^+$], 296 (3), 286 (10), 196 (44), 169 (70), 146 (100). $C_{20}H_{26}O_3$ (314.2): calcd. C 76.40, H 8.33; found C 76.47, H 8.54.

4-Hydroxy-3-(1′-methyl-2′-phenyl)propyl-1-oxaspiro[4.5]dec-3-en-2-one (6c): This compound (333 mg, 1.11 mmol, 55%) was obtained from MeCu(CN)ZnI, prepared[16] from MeI (370 mg, 2.60 mmol), Zn dust (245 mg, 3.75 mmol), CuCN (214 mg, 2.39 mmol) and LiCl (204 mg, 4.81 mmol); mixture in dry THF (10 mL) stirred at 50 °C for 16 h; 1:1 mixture of *syn*/*anti* isomers as colourless solid of m.p. 67−69 °C and of R_f = 0.29 (diethyl ether/pentane, 1:1, v/v). Crystals of pure *anti* isomer were obtained as first crop from benzene; m.p. 87 °C. ***anti* Isomer:** IR (KBr): $\tilde{\nu}$ = 3414 cm^{-1}, 3036, 1708, 1640, 1395, 1310, 1273. ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 0.78 (d, ^3J = 6.86 Hz, 3 H, 1′-CH_3), 1.17 (d, ^3J = 6.65 Hz, 3 H, 3′-H), 1.05−2.00 (m, 10 H), 2.77 (dq, ^3J = 10.72, 6.65 Hz, 1 H, 2′-H), 2.92 (dq, ^3J = 10.72, 6.86 Hz, 1 H, 1′-H), 7.14−7.37 (m, 5 H, Ph), 11.57 (s, 1 H, OH) ppm. ^{13}C NMR (68 MHz, [D$_6$]DMSO): δ = 16.9 (1′-Me), 21.0 (C-3′), 21.5 (C-7, C-9), 23.9 (C-8), 32.3, 32.6 (C-6, C-10), 33.4 (C-1′), 42.4 (C-2′), 80.8 (C-5-*spiro*), 100.9 (C-3), 125.9, 127.2, 128.2, 128.2 (CH-ar), 146.4 (C-*ipso*), 174.6, 178.4 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 300 (1) [M$^+$], 196 (23), 195 (10), 177 (10), 169 (48), 132 (64), 105 (100). $C_{19}H_{24}O_3$ (300.4): calcd. C 75.97, H 8.05; found C 76.07, H 8.14.

4-Hydroxy-3-(1′-methyl-2′,2′-diphenyl)ethyl-1-oxaspiro[4.5]dec-3-en-2-one (6d): This compound (522 mg, 1.44 mmol, 72%) was obtained from PhCu(CN)MgBr, prepared[17] from Mg turnings (66 mg, 2.70 mmol), bromobenzene (361 mg, 242μL, 2.30 mmol) and CuCN (19 mg, 10 mol %); mixture in dry diethyl ether (10 mL) and THF (10 mL) stirred at 45 °C for 16 h to give a white precipitate of **6d**, which was successively washed with 5 mL each of THF, H_2O, THF, Et_2O and finally dried in vacuo; white solid; m.p. 209 °C. IR (KBr): $\tilde{\nu}$ = 3433 cm^{-1}, 3027, 2938, 1704, 1660, 1631, 1309. ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 0.95 (d, ^3J = 6.65 Hz, 3 H, 1′-CH_3), 0.90−1.80 (m, 10 H), 3.81 (dq, ^3J = 11.58, 6.65 Hz, 1 H, 1′-H), 4.26 (d, ^3J = 11.58 Hz, 1 H, 2′-H), 6.97−7.50 (m, 10 H, Ph) ppm. ^{13}CNMR (75 MHz, [D$_6$]DMSO): δ = 17.2 (Me), 21.5, 21.6 (C-7, C-9), 24.0 (C-8), 30.8 (C-1′), 32.0 (C-6, C-10), 54.9 (C-2′), 80.5 (C-5-*spiro*), 100.0 (C-3), 125.5, 125.9, 127.6, 127.7, 127.8, 128.4 (CH-*ar*), 144.5, 145.0 (C-*ipso*), 169.3 (C-2), 172.2 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 362 (4) [M$^+$], 194 (60), 167 (100), 165 (17). $C_{24}H_{26}O_3$ (362.5): calcd. C 79.53, H 7.23; found C 79.47, H 7.34.

3.

***N*-[2-(4′-Hydroxy-2′-oxo-1′-oxaspiro[4.5]dec-3′-en-3′-yl)-1-phenylpropyl]acetamide (7a):** Compound **2a** (250 mg, 0.88 mmol) was dissolved in freshly distilled acetonitrile (10 mL) and treated with ytterbium triflate (30 mg, 5 mol %), and the mixture was heated at 80 °C overnight. The supernatant was decanted and the precipitate was repeatedly washed with acetonitrile, filtered and dried in vacuo to yield 257 mg (85%) of **7a** as colourless crystals; decomp. > 300 °C; R_f = 0.12 (diethyl ether/hexane/methanol, 3:6:1, v/v/v). IR (KBr): $\tilde{\nu}$ = 3462 cm^{-1}, 3287, 2938, 1716, 1654, 1588, 1329. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.60−1.10 (m, 2 H), 1.15 (d, ^3J = 6.72 Hz, 3 H, 1′-CH_3), 1.18−1.75 (m, 8 H), 1.81 (s, 3 H, H_3CCO), 2.87 (dq, ^3J = 6.72, 10.5 Hz, 1 H, 1′-H), 3.30 (s, 1 H, NH), 5.02−5.12 (m, 1 H, 2′-H), 7.05−7.25 (m, 5 H, Ph), 11.25 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 15.8 (1′-Me), 21.5 (C-7, C-9), 22.7 (*C*H$_3$CO), 23.9 (C-8), 31.6, 31.7 (C-6, C-10), 32.8 (C-1′), 55.0 (C-2′), 80.6 (C-5-*spiro*), 100.0 (C-3), 126.6, 127.1, 127.7 (CH-*ar*), 143.0 (C-*ipso*), 168.3, 171.8, 178.2 (C-2, C-4, CON) ppm. MS (EI, 70 eV): *m*/*z* (%) = 343 (1) [M$^+$], 176 (8), 149 (63), 148 (80), 106 (100). $C_{20}H_{25}NO_4$ (343.4): calcd. C 69.95, H 7.34, N 4.08; found C 70.10, H 7.28, N 3.98.

***N*-[2-(4′-Hydroxy-2′-oxo-1′-oxaspiro[4.5]dec-3′-en-3′-yl)-1-phenylpropyl]butyramide (7b):** This compound (235 mg, 0.63 mmol, 90%) was obtained by heating of a mixture of **2a** (200 mg, 0.70 mmol), ytterbium triflate (30 mg, 7 mol %) and butyronitrile (20 mL) at 80 °C for 18 h. Workup as for **7a**; colourless solid; m.p. (decomp.) 305 °C; R_f = 0.10 (diethyl ether/hexane/methanol, 10:20:1, v/v/v). IR (KBr): $\tilde{\nu}$ = 3291 cm^{-1}, 2940, 1716, 1653, 1591, 1303. ^{1}H NMR (270 MHz, [D$_6$]DMSO): δ = 0.80 (t, ^3J = 7.18 Hz, 3 H, CH_2CH_3), 0.95−1.05 (m, 2 H), 1.15 (d, ^3J = 6.86 Hz, 3 H, $CHCH_3$), 1.25−1.75 (m, 8 H), 1.85−2.20 (m, 4 H), 2.90 (dq, ^3J = 10.5, 6.86 Hz, 1 H, MeC*H*), 3.30 (s, 1 H, NH), 5.02−5.15 (m, 1 H, C*H*NH), 7.05−7.25 (m, 5 H, Ph), 11.2 (br. s, 1 H, OH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 14.1, 15.9 (Me), 19.3, 22.0 (*C*H$_2$Me), 22.1, 24.5 (C-7, C-8, C-9), 32.2, 32.3 (C-6, C-10), 33.3 (*C*HMe), 38.1 (CO*C*H$_2$), 55.6 (C-2′), 79.2 (C-5-*spiro*), 100.9 (C-3), 126.7, 127.4, 127.8 (CH-*ar*), 143.5 (C-*ipso*), 172.1, 172.6, 178.5 (C-2, C-4, CON) ppm. MS (EI, 70 eV): *m*/*z* (%) = 371 (0.2) [M$^+$], 300 (5), 176 (50), 149 (5), 106 (100). $C_{22}H_{29}NO_4$ (371.5): calcd. C 71.13, H 7.87, N 3.77; found C 71.03, H 7.88, N 3.71.

***N*-[2-(4′-Hydroxy-2′-oxo-1′-oxaspiro[4.5]dec-3′-en-3′-yl)-1-phenylpropyl]benzamide (7c):** This compound (125 mg, 0.31 mmol, 45%)

was obtained by heating of a mixture of **2a** (200 mg, 0.70 mmol), ytterbium triflate (30 mg, 7 mol %) and benzonitrile (20 mL) at 80 °C for 16 h. Workup as for **7a**; colourless solid; m.p. 313 °C. IR (KBr): $\tilde{\nu}$ = 3313 cm^{-1}, 2937, 1723, 1674, 1631, 1554, 1389. ^1H NMR (300 MHz, [D_6]DMSO): δ = 0.70−0.90 (m, 2 H), 1.20 (d, ^3J = 6.7 Hz, 3 H, Me), 1.21−1.70 (m, 8 H), 3.33 (s, 1 H, N*H*), 3.60 (dq, ^3J = 9.2, 6.7 Hz, 1 H, MeC*H*), 5.30−5.50 (m, 1 H, C*H*N), 6.90−7.60 (m, 10 H, Ph), 11.4 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 15.9 (Me), 21.5 (C-7, C-9), 23.9 (C-8), 31.7 (C-6, C-10), 32.2 (C-1′), 56.1 (CHN), 80.7 (C-5-*spiro*), 106.6 (C-3), 125.5, 126.1, 126.5, 127.2, 127.4, 127.5, 127.9, 128.2, 129.5, 130.9, 131.0 (CH-*ar*), 134.7, 143.1 (C-*ipso*), 165.1, 165.9, 172.0 (C-2, C-4, CON) ppm. MS (EI, 70 eV): *m*/*z* (%) = 405 (1) [M^+], 300 (8), 238 (16), 210 (54), 105 (100). $C_{25}H_{27}NO_4$ (405.5): calcd. C 74.05, H 6.71, N 3.45; found C 74.17, H 6.78, N 3.34.

4. Synthesis of Tetronates 9 and 17[18]

4.1.

(2′*E*)-Hexenyl 1-Hydroxycyclohexanecarboxylate: This compound (4.05 g, 17.9 mmol, 90%) was obtained from 1-hydroxycyclohexanecarboxylic acid (4.52 g, 20.0 mmol), (2*E*)-hexen-1-ol (2.50 g, 25.0 mmol) and *N*,*N*-dicyclohexylcarbodiimide (5.15 g, 25.0 mmol); colourless, viscous liquid; R_f = 0.72 (diethyl ether/*n*-hexane, 1:1, v/v). IR (film): $\tilde{\nu}$ = 3520 cm^{-1}, 2932, 1726, 1540, 1232, 1156, 1041. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.41 Hz, 3 H, CH_3), 1.41 (sext, ^3J = 7.41 Hz, 2 H, 5′-H), 1.30−1.79 (m, 10 H, *cyc*-CH_2), 2.02−2.05 (m, 2 H, 4′-H), 2.88 (s, 1 H, OH), 4.60 (dt, ^3J = 6.36, ^4J = 0.78 Hz, 2 H, OCH_2), 5.56 (dtt, ^3J = 15.40, 6.36, ^4J = 1.34 Hz, 1 H, 2′-H), 5.78 (dt, ^3J = 6.70, 15.40 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 13.6 (CH_3), 21.2 (C-3, C-5), 22.1 (C-5′), 25.3 (C-5), 34.3 (C-2, C-6), 34.8 (C-4′), 66.3 (OCH_2), 73.6 (C-1), 123.4 (C-2′), 136.9 (C-3′), 177.2 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 226 (4) [M^+], 225 (11) [MH^+ − 1], 208 (6), 144 (16), 143 (28), 138 (68), 98 (61), 56 (100). $C_{13}H_{22}O_3$ (226.3): calcd. C 68.99, H 9.80; found C 69.10, H 9.88.

4-[(2′*E*)-Hexenyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (9a): This compound (900 mg, 3.60 mmol; 90%) was obtained from (2′*E*)-hexenyl 1-hydroxycyclohexanecarboxylate (900 mg, 3.98 mmol) and ketenylidenetriphenylphosphorane (1.66 g, 5.50 mmol) in dry THF (40 mL); colourless, viscous oil; R_f = 0.46 (diethyl ether/hexane, 1:1, v/v). IR (film): $\tilde{\nu}$ = 2935 cm^{-1}, 2863, 1753, 1628, 1338, 1192, 804. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.41 Hz, 3 H, CH_3), 1.41 (sex, ^3J = 7.41 Hz, 2 H, 5′-H), 1.25−1.76 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.04−2.11 (m, 2 H, 4′-H), 4.46 (dd, ^3J = 6.36, ^4J = 1.06 Hz, 2 H, OCH_2), 4.92 (s, 1 H, 3-H), 5.60 (dtt, ^3J = 15.40, 6.36, ^4J = 1.06 Hz, 1 H, CH=C*H*), 5.84 (dt, ^3J = 15.40, 6.36 Hz, 1 H, C*H*=CH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.6 (C-6′), 21.7, 21.9 (C-7, C-9), 23.5 (C-8), 24.5 (C-5′), 33.1 (C-6, C-10), 34.3 (C-4′), 73.1 (OCH_2), 84.0 (C-5), 87.4 (C-3), 122.3 (*C*H=CH), 138.2 (CH=*C*H), 172.4 (C-2), 185.0 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 251 (6) [M^+ + 1], 203 (11), 170 (24), 169 (74), 168 (19), 151 (17), 150 (16), 124 (21), 122 (24), 105 (37), 86 (68), 83 (100). $C_{15}H_{22}O_3$ (250.3): calcd. C 71.97, H 8.86; found C 71.84, H 8.72. accurate mass: calcd. 250.1568; found 250.1562.

4.2.

(2′*E*)-Pentenyl 1-Hydroxycyclohexanecarboxylate: This compound (4.21 g, 19.8 mmol, 86%) was obtained from 1-hydroxycyclohexanecarboxylic acid (5.20 g, 23.0 mmol), (2*E*)-penten-1-ol (2.00 g, 23.0 mmol), *N*,*N*-dicyclohexylcarbodiimide (4.80 g, 23.0 mmol) and a catalytic amount of copper(II) chloride; clear oil; R_f = 0.27 (*n*-hexane). IR (film): $\tilde{\nu}$ = 3517 cm^{-1}, 2934, 1726, 1630, 1450, 1233. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.40 Hz, 3 H, CH_3), 1.20−1.78 (m, 10 H, 2-H, 3-H, 4-H, 5-H, 6-H), 2.01−2.12 (dq, ^3J = 6.96, 7.40 Hz, 2 H, C$H_2$$CH_3$), 2.84 (s, 1 H, OH), 4.58 (d, ^3J = 6.43 Hz, 2 H, OCH_2), 5.53 (dt, ^3J = 15.24, 6.43 Hz, 1 H, C*H*=CH), 5.82 (dt, ^3J = 15.24, 6.96 Hz, 1 H, CH=C*H*) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 13.2 (CH_3), 20.8 (*C*$H_2$$CH_3$), 21.2 (C-3, C-5), 25.3 (C-4), 34.8 (C-2, C-6), 66.4 (OCH_2), 73.6 (C-1), 122.4 (*C*H=CH), 138.5 (CH=*C*H), 177.2 (CO_2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 212 (1) [M^+], 109 (58), 100 (65), 99 (100). $C_{12}H_{20}O_3$ (212.3): calcd. C 67.98, H 9.50; found C 68.10, H 9.58.

4-[(2′*E*)-Pentenyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (9c): This compound (1.45 g, 6.15 mmol; 93%) was obtained from (2′*E*)-pentenyl 1-hydroxycyclohexanecarboxylate (1.40 g, 6.60 mmol) and ketenylidenetriphenylphosphorane (2.59 g, 8.60 mmol) in dry THF (100 mL), heated at reflux for 48 h; colourless viscous oil; R_f = 0.79 (ethyl acetate/hexane, 1:1, v/v). IR (film): $\tilde{\nu}$ = 3115 cm^{-1}, 2936, 1752, 1627, 1340. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.43 Hz, 3 H, CH_3), 1.15−1.73 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.09 (qddt, ^3J = 7.43, 6.25, ^4J = 1.60, $^{\varepsilon}$ = 1.06 Hz, 2 H, 4′-H), 4.43 (ddt, ^3J = 6.39, ^4J = 1.19, ^5J = 1.06 Hz, 2 H, OCH_2), 4.89 (s, 1 H, 3-H), 5.56 (dtt, ^3J = 15.43, ^3J = 6.39, ^4J = 1.60 Hz, 1 H, 2′-H), 5.87 (dtt, ^3J = 15.43, ^3J = 6.25, ^4J = 1.19 Hz, 1 H, 3′-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.0 (C-5′), 21.7 (C-7, C-9), 24.4 (C-8), 25.3 (C-4′), 33.1 (C-6, C-10), 73.1 (OCH_2), 84.0 (C-5), 86.9 (C-3), 121.2 (C-2′), 139.7 (C-3′), 172.4 (C-2), 185.0 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 237 (1) [M^+ + 1], 236 (3) [M^+], 208 (1), 169 (48), 69 (100). $C_{14}H_{20}O_3$ (236.3): calcd. C 71.16, H 8.53; found C 70.98, H 8.22.

4.3.

(2′*E*)-4′-Phenylbutenyl 1-Hydroxycyclohexanecarboxylate: This compound (2.88 g, 10.5 mmol, 76%) was obtained from 1-hydroxycyclohexanecarboxylic acid (2.00 g, 13.85 mmol), (2*E*)-4-phenylbutene-1-ol (2.05 g, 13.85 mmol) and *p*-toluenesulfonic acid (247 mg, 1.38 mmol), heated at reflux in toluene under a Dean−Stark apparatus for 24 h; colourless oil; R_f = 0.25 (diethyl ether/*n*-hexane, 1:1, v/v). IR (film): $\tilde{\nu}$ = 3504 cm^{-1}, 2935, 1726, 1450, 1234. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.18−1.82 (m, 10 H, 2-H, 3-H, 4-H, 5-H, 6-H), 3.28 (br. s, 1 H, OH), 3.40 (d, ^3J = 6.65 Hz, 2 H, CH_2Ph), 4.62 (d, ^3J = 6.22 Hz, 2 H, OCH_2), 5.62 (dt, ^3J = 15.22, 6.22 Hz, 1 H, C*H*=CH), 5.94 (dt, ^3J = 15.22, 6.65 Hz, 1 H, CH=C*H*), 7.15−7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.1, 21.4 (C-7, C-9), 25.2 (C-8), 34.7, 35.0 (C-6, C-10), 38.6 (CH_2Ph), 65.8 (OCH_2), 73.6 (COH), 125.2 (=CH), 126.3, 126.7, 128.3, 128.5, 128.9 (CH-ar), 135.1 (=CH), 139.4 (C-*ipso*), 177.1 (CO2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 197 (1), 130 (38), 103 (13), 99 (100), 91 (29), 81 (75). $C_{17}H_{22}O_3$ (274.4): calcd. C 74.42, H 8.08; found C 74.29, H 8.01.

4-[(2′*E*)-4′-Phenylbutenyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (9d): This compound (717 mg, 2.41 mmol; 75%) was obtained from (2′*E*)-4′-phenylbutenyl 1-hydroxycyclohexanecarboxylate (880 mg, 3.21 mmol) and ketenylidenetriphenylphosphorane (1.26 g, 4.18 mmol) in dry THF (75 mL), heated at reflux for 16 h; colourless oil. IR (film): $\tilde{\nu}$ = 3038 cm^{-1}, 2936, 2860, 1746, 1623, 1338, 1192. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.19−1.71 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.42 (d, ^3J = 6.65 Hz, 2 H, CH_2Ph), 4.46 (d, ^3J = 6.22 Hz, 2 H, OCH_2), 5.66 (dt, ^3J = 15.29, 6.22 Hz, 1 H, C*H*=CH), 5.99 (dt, ^3J = 15.29, 6.65 Hz, 1 H, CH=C*H*), 7.15−7.37 (m, 5 H, Ph) ^{13}C NMR (68 MHz, $CDCl_3$): δ = 21.7 (C-7, C-9), 24.4 (C-8), 33.1 (C-6, C-10), 38.6 (CH_2Ph), 72.7 (OCH_2), 84.1 (C-5), 87.5 (C-3), 123.5 (CH=*C*H), 127.0 (*C*H=CH), 126.4, 128.6, 128.7, 128.8 (CH-*ar*), 136.3 (C-*ipso*), 172.3 (C-2), 185.0 (C-4) ppm.

MS (EI, 70 eV): *m*/*z* (%) = 299 (0.2), 298 (0.1) [M^+], 280 (0.1), 272 (5), 132 (41), 131 (100), 130 (83), 116 (16), 105 (99). $C_{19}H_{22}O_3$ (298.39): calcd. C 76.48, H 7.43; found C 76.24, H 7.38.

4.4.

(2′*E*,4′*E*)-Hexadienyl 1-Hydroxycyclohexanecarboxylate: This compound (1.71 g, 7.63 mmol, 50%) was obtained from 1-hydroxycyclohexanecarboxylic acid (2.18 g, 15.20 mmol), (2*E*,4*E*)-hexadien-1-ol (1.50 g, 15.20 mmol) and *N*,*N*-dicyclohexylcarbodiimide (3.15 g, 15.20 mmol); yellowish liquid; R_f = 0.69 (ethyl acetate/*n*-hexane, 1:2, v/v). IR (film): $\tilde{\nu}$ = 3520 cm^{-1}, 2932, 1726, 1630, 1448, 1235, 1153, 1042, 996. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.35 (d, ^3J = 6.64 Hz, 3 H, CH_3), 1.59−1.72 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.87 (s, 1 H, OH), 4.64 (d, ^3J = 6.64 Hz, 2 H, 1′-H), 5.11−5.26 (m, 1 H, 2′-H), 5.37−5.46 (m, 1 H, 5′-H), 5.60−5.80 (m, 1 H, 4′-H), 6.17−6.35 (m, 1 H, 3′-H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.1 (CH_3), 21.2 (C-3, C-5), 25.3 (C-4), 34.7 (C-2, C-6), 66.1 (OCH_2), 73.5 (C-1), 132.1 (C-2′), 132.5 (C-5′), 135.4 (C-4′), 135.9 (C-3′), 176.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 224 (24) [M^+], 207 (5) [$MH^+ - H_2O$], 206 (20), 110 (14), 99 (92), 81 (100). $C_{13}H_{20}O_3$ (224.14): calcd. C 69.61, H 8.99; found C 69.80, H 7.06.

4-[(2′*E*,4′*E*)-Hexadienyloxy]-1-oxaspiro[4.5]dec-3-en-2-one (17): This compound (770 mg, 3.10 mmol; 43%) was obtained from (2′*E*,4′*E*)-hexadienyl 1-hydroxycyclohexanecarboxylate (1.63 g, 7.23 mmol) and ketenylidenetriphenylphosphorane (2.90 g, 9.60 mmol) in dry THF (60 mL), heated at reflux for 16 h; colourless solid; R_f = 0.35 (ethyl acetate/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1}, 2847, 1751, 1628, 1450, 1334. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.38 (d, ^3J = 6.40 Hz, 3 H, CH_3), 1.11−1.72 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 4.82 (d, ^3J = 4.33 Hz, 2 H, OCH_2), 5.16 (s, 1 H, 3-H), 5.50−5.59 (m, 1 H, 5′-H), 5.86−5.96 (m, 1 H, 2′-H), 6.13−6.26 (m, 2 H, 3′-H and 4′-H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 17.8 (Me), 24.4, 24.6 (C-7, C-9), 25.7 (C-8), 33.1, 33.6 (C-6, C-10), 71.9 (OCH_2), 79.3 (C-5-*spiro*), 88.0 (C-3), 128.1 (C-5′), 130.8 (C-4′), 131.3 (C-3′), 135.4 (C-2′), 172.8 (C-2), 185.8 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 248 (87) [M^+], 233 (9), 230 (43), 215 (30), 122 (100). $C_{15}H_{20}O_3$ (248.3): calcd. C 72.55, H 8.12; found C 72.64, H 8.26.

5. Synthesis of 3-Allyltetronic Acids 12

5.1.

4-Hydroxy-3-[(2′*E*)-1′-methylpentenyl]-1-oxaspiro[4.5]dec-3-en-2-one (12a): A solution of **9a** (540 mg, 2.16 mmol) in toluene (15 mL) was heated at 150 °C in a sealed glass bomb tube for 24 h. The mixture was then cooled to room temp., all volatile components were evaporated in vacuo, and the resulting residue was finally purified by column chromatography on silica gel 60, to afford a white, crystalline solid (375 mg, 1.50 mmol, 70%); m.p. 112 °C; R_f = 0.16 (diethyl ether/*n*-hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3421 cm^{-1}, 2936, 2862, 1699, 1636, 1451, 1388, 1270, 960. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.49 Hz, 3 H, 5′-H), 1.26 (d, ^3J = 7.06 Hz, 3 H, 1′-CH_3), 1.55−1.89 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.05 (dt, ^3J = 7.49, 5.67 Hz, 2 H, 4′-H), 3.32 (m, 1 H, 1′-H), 5.62 (dd, ^3J = 5.67, 15.87 Hz, 1 H, 2′-H), 5.71 (dt, ^3J = 5.67, 15.87 Hz, 1 H, 3′-H), 9.07 (s, 1 H, OH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.1 (C-5′), 18.8 (1′-CH_3), 21.4, 22.2 (C-7, C-9), 23.0 (C-8), 24.7 (C-1′), 25.7 (C-4′), 30.9, 33.1 (C-6, C-10), 83.1 (C-5), 103.3 (C-3), 131.0 (C-3′), 133.1 (C-2′), 174.8, 178.8 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 251 (14) [M^+ + 1], 250 (25) [M^+], 235 (10), 232 (14), 221 (5), 217 (47), 203 (13), 195 (19), 177 (19), 170 (20), 169 (82), 124 (29), 123 (42), 110 (53), 109 (47), 96 (43), 95 (61), 82 (100). $C_{17}H_{18}O_3$: accurate mass: calcd. 250.1568; found 250.1565.

5.2.

4-Hydroxy-3-[3′-methylbut-3′-en-2′-yl]-1-oxaspiro[4.5]dec-3-en-2-one (12b): A solution of **9b** (500 mg, 2.12 mmol) in toluene (6 mL) was heated in a sealed vial in a single-mode microwave oven (200 W) at 190 °C and 3.5 bar for 20 min. The mixture was then cooled to room temp. and stored in a refridgerator overnight, whereupon colourless crystals of **12b** precipitated. These were washed three times with dry toluene and dried in vacuo to leave 290 mg (58%); m.p. 159 °C. IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1}, 2937, 1702, 1643, 1443, 1384, 1267. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.10−1.30 (m, 2 H, 8-H), 1.27 (d, ^3J = 6.99 Hz, 3 H, 1′-H), 1.55−1.85 (m, 8 H, 6-H, 7-H, 9-H, 10-H), 1.76 (s, 3 H, 3′-CH_3), 3.12 (q, ^3J = 6.99, 1 H, 2′-H), 5.00−5.10 (m, 2 H, 4′-H), 7.64 (s, 1 H, OH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.9 (C-1′), 21.6, 21.7 (C-7, C-9), 22.3 (3′-CH_3), 24.3 (C-8), 32.6, 32.7 (C-6, C-10), 34.5 (C-2′), 82.4 (C-5), 101.6 (C-3), 110.9 (C-4′), 148.4 (C-3′), 173.8, 178.2 (C-4, C-2) ppm. MS (EI, 70 eV): *m*/*z* (%) = 237 (75) [M^+ + 1], 221 (18), 218 (47), 203 (65), 190 (10), 175 (37), 95 (100). $C_{14}H_{20}O_3$ (236.31): calcd. C 71.16, H 8.53; found C 71.24, H 8.51.

5.3.

4-Hydroxy-3-[(2′*E*)-1′-methylbutenyl]-1-oxaspiro[4.5]dec-3-en-2-one (12c): This compound (638 mg, 2.70 mmol, 98%) was obtained from **9c** (650 mg, 2.75 mmol) treated as described above for **9a**; white, crystalline solid; m.p. 135 °C; R_f = 0.29 (ethyl acetate/*n*-hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3406 cm^{-1}, 2937, 1700, 1652, 1389, 1271. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.23 (d, ^3J = 7.08 Hz, 3 H, 1′-CH_3), 1.52−1.75 (m, 13 H, 6-H, 7-H, 8-H, 9-H, 10-H, 4′-CH_3), 3.19−3.25 (m, 1 H, 1′-H), 5.70−5.75 (m, 2 H, CH=CH), 10.21 (s, 1 H, OH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.4 (C-4′), 19.6 (1′-C), 21.7, 21.8 (C-7, C-9), 24.4 (C-8), 30.7 (C-1′), 32.9, 33.0 (C-6, C-10), 82.0 (C-5), 102.9 (C-3), 127.2 (C-3′), 132.7 (C-2′), 172.0, 177.3 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 237 (1), 236 (5) [M^+], 218 (3), 203 (6), 169 (46), 110 (78), 95 (100). $C_{14}H_{20}O_3$ (236.31): calcd. C 71.16, H 8.53; found C 71.32, H 8.49.

5.4.

4-Hydroxy-3-[(2′*E*)-1′-methyl-3′-phenylpropenyl]-1-oxaspiro[4.5]-dec-3-en-2-one (12d): This compound (318 mg, 1.07 mmol, 84%) was obtained from **9d** (380 mg, 1.28 mmol), heated in a sealed glass bomb tube at 150 °C for 24 h; white crystalline solid; m.p. 159 °C; R_f = 0.13 (diethyl ether/*n*-hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3417 cm^{-1}, 2933, 1698, 1639, 1389, 962. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.38 (d, ^3J = 7.05 Hz, 3 H, 1′-CH_3), 1.17−1.88 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 3.54 (dq, ^3J = 7.05, 5.13 Hz, 1 H, 1′-H), 6.49 (dd, ^3J = 16.29, 5.13 Hz, 1 H, 2′-H), 6.60 (d, ^3J = 16.29, 1 H, 3′-H), 7.21−7.42 (m, 5 H, Ph) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.5 (1′-CH_3), 21.9 (C-7, C-9), 24.4 (C-8), 31.2 (C-1′), 32.8 (C-6, C-10), 83.2 (C-5), 126.3, 126.4 (CH-*ortho*), 127.4 (CH-*para*), 128.6, 128.7 (CH-*meta*), 129.9 (C-3′), 131.7 (C-2′), 137.0 (C-*ipso*), 174.7 (C-2), 179.2 (C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 299 (3), 298 (24) [M^+], 280 (21), 254 (9), 188 (19), 171 (89), 143 (78), 131 (100), 129 (57), 128 (44), 110 (57). $C_{19}H_{22}O_3$ (298.38): calcd. C 76.48, H 7.43; found C 76.42, H 7.39.

6.

(2*H*,5*H*,6*H*,8*H*)-2,5-Dimethyl-8-(spirocyclohexyl)furano[4,3-*b*]oxepin-6-one (19): A solution of **17** (300 mg, 1.20 mmol) in acetonitrile (15 mL) was placed in a microwave source (focused single-mode, 300 W) and irradiated at 100 °C for 20 min. The solution

was cooled to room temp., all volatile components were evaporated in vacuo, and the obtained residue was eventually purified by column chromatography on silica gel 60 to afford a colourless liquid (255 mg, 1.03 mmol, 85%); R_f = 0.84 (ethyl acetate/*n*-hexane, 1:2, v/v). IR (film): $\tilde{\nu}$ = 2935 cm^{-1}, 1748, 1663, 1448, 1397, 1266, 974. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.31 (d, ^3J = 7.13 Hz, 3 H, $OCCH_3$), 1.45 (d, ^3J = 6.25 Hz, 3 H, 5-CH_3), 1.55−1.74 (m, 10 H, CH_2), 3.09 (qui, ^3J = 7.13, 1 H, OCH), 5.05 (qui, ^3J = 6.25 Hz, 1 H, 5-H), 5.56 (dd, ^3J = 7.13, 10.62 Hz, 1 H, 3-H), 6.12 (dd, ^3J = 6.25, ^3J = 10.62 Hz, 1 H, 4-H) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 20.9 ($OCCH_3$), 21.0 (5-CH_3), 21.7, 21.9, 24.4, 32.8, 33.3 (CH_2), 29.2 (C-5), 75.2 (C-2), 82.7 (C-8), 102.7 (C-5a), 130.0 (C-3), 140.0 (C-4), 173.4, 179.0 (C=O, OC=) ppm. MS (EI, 70 eV): *m*/*z* (%) = 248 (43) [M^+], 233 (9) [$M^+ - CH_3$], 230 (34), 215 (34), 202 (15), 187 (12), 175 (11), 122 (100). $C_{15}H_{20}O_3$ (248.32): calcd. C 72.55, H 8.12; found C 72.44, H 8.14.

7. Trapping of Spirocyclopropane Intermediates 11

General Procedure: A solution of the appropriate 4-allyl tetronate **9** (1.0 mmol) and either *n*-butylamine (400 mg, 5.50 mmol) or ethanol (230 mg, 5.00 mmol) in toluene (30 mL) was heated to 150−165 °C with exclusion of air and moisture in a sealed glass tube overnight. The mixture was then cooled to room temperature, the solvent was evaporated in a rotary evaporator, and the resulting residue was purified by column chromatography (silica gel 60, solvent as indicated).

***trans*-1-Butyl-3-[(1′-hydroxycyclohexyl)carbonyl]-4,5,5-trimethylpyrrolidin-2-one (15a):** This compound (224 mg, 0.80 mmol; 80%) was obtained from **9b** (235 mg); white crystalline solid; m.p. 77 °C; R_f = 0.42 (ethyl acetate). IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1}, 2937, 2861, 1713, 1644, 1422, 1378, 1097. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (d, ^3J = 6.87 Hz, 3 H, 4-CH_3), 0.89 (t, ^3J = 7.23 Hz, 3 H, CH_2CH_3), 1.03 (s, 3 H, 5-CH_3), 1.26 (s, 3 H, 5-CH_3), 1.19−1.81 (m, 14 H, *cyc*-H, Me-CH_2, MeCCH_2), 2.57 (dq, ^3J = 11.45 Hz, 6.87 Hz, 1 H, 4-H), 2.92 (ddd, ^2J = 13.76, ^3J = 9.96, 5.75 Hz, 1 H, NC*H*H), 3.22 (ddd, ^2J = 13.76, ^3J = 9.96, 5.85 Hz, 1 H, NCH*H*), 4.05 (d, ^3J = 11.45 Hz, 1 H, 3-H), 5.84 (d, ^4J = 2.12 Hz, 1 H, OH) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 12.5 (CH_2CH_3), 13.7 (4-CH_3), 20.5, 20.7, 20.8 (C-4′, C-6′, CH_2CH_3), 21.1 (5-Me), 25.4 (C-5′), 26.1 (5-Me′), 31.6 (NCCH_2), 33.8, 33.9 (C-3′, C-7′), 39.3 (C-4), 40.4 (NCH_2), 56.7 (C-3), 62.6 (C-5), 79.0 (C-2′), 171.1 (C-2), 211.1 (C-1′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 310 (1) [M^+ + 1], 309 (1) [M^+], 294 (1), 281 (4), 266 (2), 184 (20), 183 (100), 169 (18), 168 (99). $C_{18}H_{31}NO_3$ (309.44): calcd. C 69.86, H 10.10, N 4.53; found C 70.02, H 10.06, N 4.50.

***trans*,*trans*-1-Butyl-3-[(1′-hydroxycyclohexyl)carbonyl]-4-methyl-5-benzylpyrrolidin-2-one (15b):** This compound (257 mg, 0.67 mmol; 67%) was obtained from **9d** (300 mg); clear crystalline solid; m.p. 148 °C; R_f = 0.29 (diethyl ether/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3418 cm^{-1}, 2934, 2864, 1697, 1639, 1493, 1387, 1262. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 7.29 Hz, 3 H, CH_3CH$_2$), 0.93−1.63 (m, 14 H, *cyc*-H, MeCH_2, MeCCH_2), 1.11 (d, ^3J = 6.27 Hz, 3 H, 4-CH_3), 2.46−2.54 (m, 1 H, PhC*H*H), 2.74−2.90 (m, 3 H, PhCH*H*, NC*H*H, 4-H), 3.30−3.48 (m, 2 H, NCH*H*, 5-H), 4.24 (d, ^3J = 7.55 Hz, 1 H, 3-H), 5.79 (d, ^4J = 2.11 Hz, 1 H, OH), 7.05−7.22 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3CH_2), 19.1 (4-CH_3), 20.0 (CH_3CH_2), 20.7, 20.8 (C-4′, C-6′), 25.3 (C-5′), 29.1 (MeCCH_2), 33.6, 34.3 (C-3′, C-7′), 39.5 (PhCH_2), 40.4 (NCH_2), 41.2 (C-4), 56.7 (C-3), 57.9 (C-5), 79.1 (C-2′), 126.6, 128.6, 129.1 (C-*ar*), 138.1 (C-*ipso*), 170.5 (C-2), 210.2 (C-1′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 371 (0.2) [M^+], 353 (0.5), 343 (1), 245 (64), 155 (46), 154 (100). $C_{23}H_{33}NO_3$ (371.51): calcd. C 73.36, H 8.95, N 3.77; found C 73.38, H 9.02, N 3.74.

3-[2′-Ethoxy-1′,2′-dimethylpropyl]-4-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (14c): This compound (260 mg, 0.92 mmol; 92%) was obtained from **9b** (237 mg) and ethanol (230 mg, 5.0 mmol); white solid; m.p. 74 °C; R_f = 0.46 (diethyl ether/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3476 cm^{-1}, 2980, 2938, 1752, 1662, 1450, 1373, 1050. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, ^3J = 7.15 Hz, 3 H, 1′-CH_3), 1.18 (s, 3 H, 2′-CH_3), 1.29 (t, ^3J = 7.02 Hz, 3 H, CH_2CH_3), 1.33 (s, 3 H, 2′-CH_3), 1.71−2.56 (m, 10 H, 6-H, 7-H, 8-H, 9-H, 10-H), 2.55 (q, ^3J = 7.15 Hz, 1 H, 1′-H), 3.51−3.68 (m, 2 H, CH_2CH_3), 11.01 (s, 1 H, OH) ppm. ^{13}C NMR (68 MHz, $CDCl_3$): δ = 14.1 (1′-Me), 15.3 (CH_2CH_3), 21.8, 21.9 (C-7, C-9), 23.2 and 24.2 (2′-Me), 24.6 (C-8), 32.6, 33.3 (C-6, C-10), 40.4 (C-1′), 57.8 (OCH_2), 79.3 (C-2′), 81.7 (C-5), 101.6 (C-3), 174.2, 178.3 (C-2, C-4) ppm. MS (EI, 70 eV): *m*/*z* (%) = 283 (1) [M^+ + 1], 282 (4) [M^+], 237 (2), 203 (19), 175 (11), 137 (6), 87 (100). $C_{14}H_{20}O_3$ (282.2); accurate mass: calcd. 282.18311; found 282.19228.

8.

***trans*,*trans*-1-Allyl-3-[(1′-hydroxycyclohexyl)carbonyl]-4-methyl-5-phenylpyrrolidin-2-one (16):** This compound (249 mg, 0.73 mmol; 73%) was obtained from cinnamyl tetronate **1a** (284 mg, 1.00 mmol) and allylamine (290 mg, 5.10 mmol), treated as described above; white crystalline solid; m.p. 107 °C; R_f = 0.57 (diethyl ether/hexane, 1:1, v/v). IR (KBr): $\tilde{\nu}$ = 3455 cm^{-1}, 2939, 2852 1708, 1667, 1456, 1366, 1038. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, ^3J = 6.71 Hz, 3 H, 4-CH_3), 1.16−1.80 (m, 10 H, 3′-H, 4′-H, 5′-H, 6′-H, 7′-H), 2.82 (ddq, ^3J = 10.04, 8.45, 6.71 Hz, 4-H), 3.01 (dd, ^2J = 15.04, ^3J = 7.58, 1 H, NCH*H*), 4.07 (d, ^3J = 8.45 Hz, 1 H, 5-H), 4.16 (ddt, ^2J = 15.04, ^3J = 4.89, 1 H, NC*H*H), 4.22 (d, ^3J = 10.04 Hz, 1 H, 3-H), 4.84 (d, ^3J = 17.06, 1 H, =CH*Htrans*), 5.05 (d, ^3J = 10.15 Hz, 1 H, =CH*Hcis*), 5.48−5.58 (m, 1 H, C*H*=CH_2), 5.60 (d, ^4J = 2.04 Hz, 1 H, OH), 7.18−7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 16.3 (4-Me), 20.6, 20.8 (C-4′, C-6′), 25.4 (C-5′), 33.9, 34.0 (C-3′, C-7′), 38.0 (C-4), 43.9 (NCH_2), 58.4 (C-3), 68.3 (C-5), 79.1 (C-2′), 118.9 (=CH_2), 127.9, 128.7, 128.9 (C-*ar*), 130.9 (CH=), 138.0 (C-*ipso*), 172.0 (C-2), 210.3 (C-1′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 341 (0.1) [M^+], 313 (1), 216 (15), 215 (100), 200 (51), 174 (9). $C_{21}H_{27}NO_3$ (341.54): calcd. C 73.86, H 7.97, N 4.10; found C 73.98, H 812, N 3.96.

9.

X-ray Crystal Structure Analysis of (±)−16:[19] Clear, colourless crystals were obtained from diethyl ether/hexane solutions on cooling to 0 °C. Empirical formula $C_{21}H_{27}NO_3$, formula mass 341.44, crystal size 0.22 × 0.17 × 0.09 mm, *a* = 5.9991(12), *b* = 11.495(2), *c* = 14.318(3) Å, α = 91.28(3), β = 95.95(3), γ = 100.10(3)°, *V* = 966.0(3) $Å^3$, *T* = 293(2) K; $\delta_{calcd.}$ = 1.174 g cm^{-3}, μ = 0.078 cm^{-1}, *Z* = 2, triclinic, space group *P*1, Siemens P4 diffractometer, λ = 0.71037 Å, Θ-range 2.25−26.01°; ω/Θ scans, index ranges $-6 \le h \le 6$, $-14 \le k \le 13$, $-17 \le l \le 17$, 6781 collected reflections, 3499 reflections [$I > 2\sigma(I)$], 226 refined parameters, no absorption correction. Structure solution: direct methods (SHELXS-97); structure refinement: full-matrix least squares on F^2 (SHELXL-97); *R*1 = 0.0718, *wR*2 = 0.1183 (all data), largest diff. peak and hole 0.141 and −0.136 e·$Å^{-3}$.

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[19] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-213176. Copies of the data can be obtained free of charge on applicaton to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]

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