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Study towards bioactive pyrone derivatives from the marine red alga *Phacelocarpus labillardieri*

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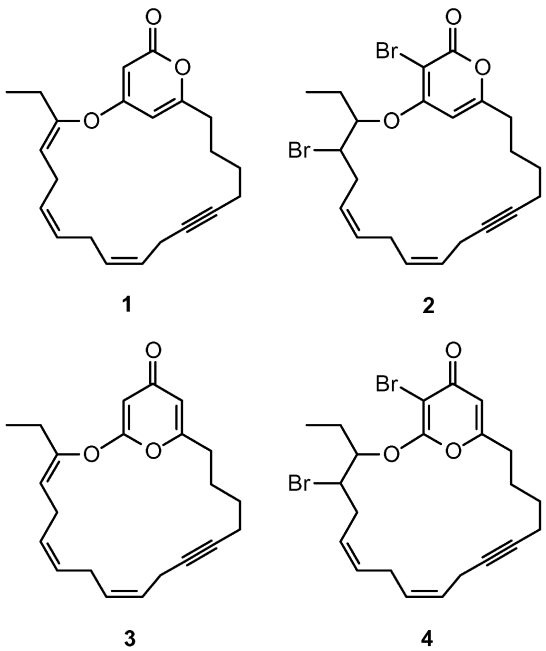
This paper is dedicated with respect and admiration to Professor K. C. Nicolaou as the recipient of the 2003 Tetrahedron Prize

Abstract—Red algae of the genus *Phacelocarpus labillardieri* produce a structurally rather unique class of macrocyclic pyrone derivatives with phospholipase A_2 inhibiting properties and potential neuromuscular blocking activity. They were also shown to be potent feeding inhibitors for various marine herbivorous gastropods. Described herein is the first preparative study towards these conspicuous secondary metabolites. Their carbon skeleton has been assembled in a few straightforward steps using ring closing alkyne metathesis (RCAM) catalyzed by the Schrock alkylidyne complex $(t\mathrm{BuO})_3\mathrm{W}{\equiv}\mathrm{CCMe}_3$ to forge the *meta*-cyclophane core with high efficiency.

1. Introduction

The red alga *Phacelocarpus labillardieri* commonly found in South Australian waters turned out to be a unique source of the acetate-derived secondary metabolites **1**–**4** featuring a pyrone ring embedded into a polyunsaturated macrocyclic skeleton.[1,2] While the somewhat variable ratio of the individual members of this family in different collections is deemed to reflect seasonal and/or regional variations in the algae's metabolism, there is little doubt that all of them derive from a common linear diketoacid precursor that can cyclize along two different pathways to give either the α- or the γ-pyrone motif.[2]

Compound **3** acts as potent deterrent to herbivorous shells, snails and other gastropods and is therefore likely involved in the chemical defense of the algae against predators.[3] The crude extracts of *P. labillardieri* were also found to exhibit neuromuscular blocking activity, which might be caused by pyrones of this type.[1a] Moreover, compound **4** exhibits promising phospholipase A_2 inhibiting properties (93% inhibition of bee venom PLA_2 at 4.4 μM).[4] This interesting biological profile together with the rather unusual structures prompted us to target these marine natural products as part of our investigations on the synthesis and evaluation of bioactive heterocycles.[5,6] Outlined below is a preliminary study showing that ring closing alkyne metathesis (RCAM)[7]



is an adequate tool for the construction of their *meta*-cyclophane skeleton.[8]

2. Results and discussion

The highly conserved triple bond within the core structures of **1**–**4** suggests the use of RCAM for the construction of the macrocyclic scaffold.[7,9] Though discovered only recently, RCAM has already borne scrutiny in target oriented

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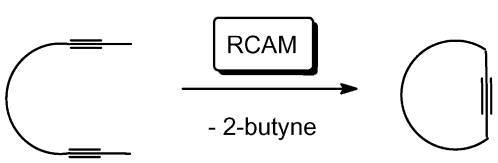
syntheses on several occasions,[10,11] not least because of the exceedingly high tolerance of the commonly used catalysts[12–14] towards many polar functional groups. Moreover, these catalysts are distinguished by a remarkable chemoselectivity profile in that they select exclusively for alkynes while leaving pre-existing olefins in a given substrate unaffected.[15–17] This ability to differentiate between different π-bonds promises a successful application of RCAM to the present series as well (Scheme 1).

However, since no secured information on the relative and absolute configuration of compounds **2** and **4** is available to date, only a highly flexible approach to this class of pyrone ether derivatives can ultimately be successful as it might be necessary to prepare the full set of stereoisomers for comparison with the natural products. Therefore, an interim goal consists in establishing an efficient and concise route to their common core structure.

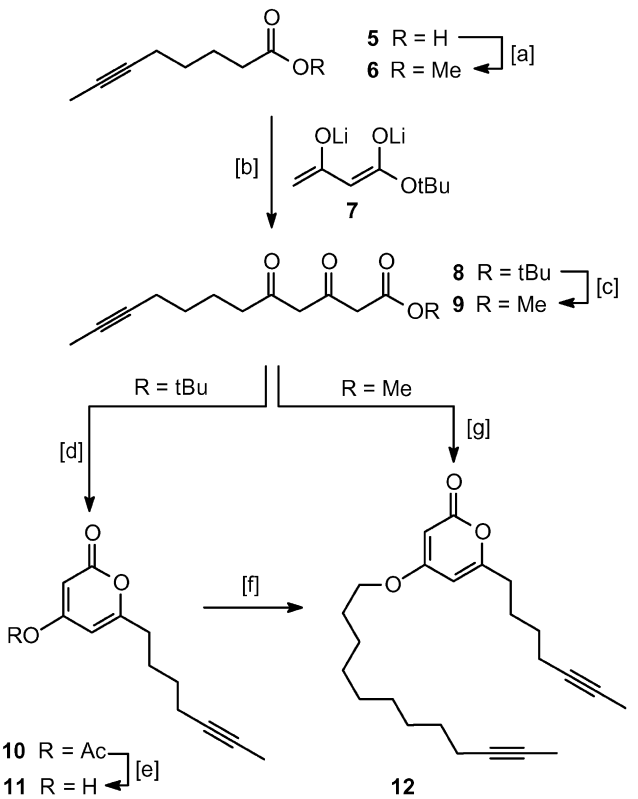
This model study commenced with commercial 6-heptynoic acid, which was *C*-alkylated with MeI prior to esterification of the resulting acid **5** with (trimethylsilyl)-diazomethane. Reaction of ester **6** thus formed with dianion **7** gave the tricarbonyl compound **8**; thereby, an extra equivalent of base (*n*-BuLi) was necessary to ensure that the product formed does not quench the reagent via proton transfer.[18] Attempts to use methyl acetoacetate resulted in lower yields (ca. 30%) of the corresponding tricarbonyl derivative **9** due to competing attack of residual nucleophile to the emerging product.

For the sake of brevity, we envisaged conversion of compound **8** to the required metathesis precursor **12** by a cascade combining the cyclization of the β,δ-diketoester to the corresponding α-pyrone[19] with a subsequent in situ *O*-alkylation reaction. Unfortunately, however, the *tert*-butyl ester **8** remained completely unchanged under the standard reaction conditions (DBU, toluene, reflux). Cyclization of this compound could only be achieved in a stepwise fashion by cleavage of the *tert*-butyl group followed by dehydration of the resulting diketoacid with Ac_2O.[20] Since this procedure leads to a concomitant acetylation of the 4-OH group on the heterocyclic ring, the alkylation had to be carried out separately (**10**→**11**→**12**, cf. Scheme 2). In marked contrast, however, the corresponding methyl ester **9** was converted to the 4-alkylated pyrone derivative **12** in one-pot on treatment with DBU followed by addition of 12-bromo-2-dodecyne **13**. Since the direct synthesis of **9** from **6** and methyl acetoacetate is unsatisfactory (see above), access to this key intermediate had to be secured by transesterification of **8** under standard conditions.[21]

With diyne **12** in hand, the formation of the macrocyclic ring by RCAM was investigated. Gratifyingly, this reaction

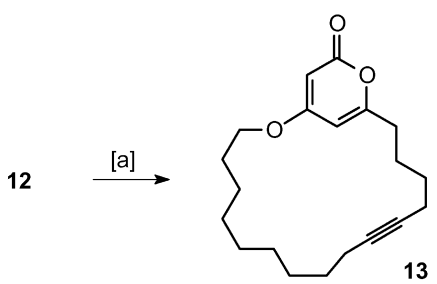


Scheme 1. Basic principle of ring closing alkyne metathesis (RCAM).



Scheme 2. [a] $TMSCHN_2$, pentane–MeOH, 85%; [b] *tert*-butyl acetoacetate, LDA (2 equiv.), TMEDA, THF, then BuLi (see text), 0°C, 58%; [c] (i) F_3CCOOH, CH_2Cl_2; (ii) $TMSCHN_2$, MeOH, 71%; [d] (i) F_3CCOOH, CH_2Cl_2; (ii) Ac_2O; [e] K_2CO_3 cat., MeOH, 70% (over three steps); [f] 12-bromo-2-dodecyne **13**, Et_3N, MeCN, 56%; [g] (i) DBU, toluene, reflux; (ii) bromide **13**, MeCN, rt, 53%.

occurred smoothly on exposure of the substrate to catalytic amounts of Schrock's tungsten alkylidyne complex $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$[12] in toluene at 80°C (Scheme 3). Thereby, the yield of the resulting cycloalkyne **13** strongly correlated with the chosen dilution, with best results being obtained at c=0.001 M (84% isolated yield). This fact is deemed to reflect the strain inherent to the *meta*-pyronophane skeleton of this particular compound. Its molecular structure in the solid state is depicted in Figure 1. In contrast to the excellent results obtained with Schrock's complex, applications of the 'in situ' catalyst system (comprising $Mo(CO)_6$ and phenol additives) pioneered by Mortreux et al. and subsequently modified by others[14] invariably gave rather poor results (<40% yield) which could not be improved any further by lowering the concentration.



Scheme 3. Ring closing alkyne metathesis of diyne **13**. [a] $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$ cat., toluene, 80°C, 50 min, 84%.

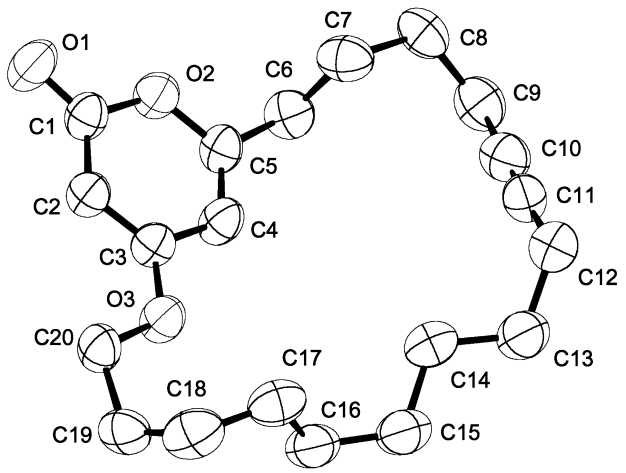


Figure 1. Molecular structure of cycloalkyne **13** obtained from single-crystal structure determination. Anisotropic displacement parameters are shown at the 50% probability level.

In summary, a model for the core structure of the marine pyrone derivatives isolated from *P. labillardieri* has been prepared by a route which comprises only six steps, including the crucial RCAM reaction forging the macrocyclic ring with high efficiency. Due to its brevity and flexibility, this entry should qualify for the envisaged total synthesis of these bioactive natural products and derivatives thereof. Studies along these lines are currently in progress and will be reported in due course.

3. Experimental

3.1. General

All reactions were carried out under Ar. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg–anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N, pyridine, DMF (CaH_2), MeOH (Mg), hexane, pentane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a Bruker DPX 300 or AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), HRMS: Finnigan MAT 95. Melting points: Büchi melting point apparatus (uncorrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Lancaster, Fluka, Aldrich) were used as received.

3.1.1. 6-Octynoic acid (5). Hept-6-ynoic acid (5 mL, 39.8 mmol) was added dropwise to a solution of LDA (freshly prepared from diisopropylamine (11.7 mL, 83.3 mmol) and *n*-BuLi (52.2 mL, 83.3 mmol, 1.6 M in hexane)) in THF (800 mL) at −78°C. After stirring for 1.5 h, DMPU (9.6 mL, 79.3 mmol) was introduced followed by the addition of MeI (3.7 mL, 59.5 mmol). The reaction mixture was allowed to warm to ambient temperature and stirring was continued for 10 h. After quenching with aq. HCl (6 M), the aqueous layer was repeatedly extracted with Et_2O, the combined organic phases were dried over Na_2SO_4, the solvent was evaporated, and the residue was purified by flash chromatography (hexanes–EtOAc, 6:1+3% AcOH) to give acid **5** as a colorless solid (5.45 g, 98%). Mp 43–44°C; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.37 (t, J=7.6 Hz, 2H), 2.18–2.10 (m, 2H), 1.75 (t, J=2.5 Hz, 3H), 1.80–1.66 (m, 2H), 1.56–1.48 (m, 2H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 180.2, 78.6, 75.9, 33.7, 28.5, 24.0, 18.5, 3.2; IR (neat) 2947, 2875, 1707, 1415, 1269, 936 cm^{-1}; MS (EI) *m/z* (rel. intensity) 140 (M^+, 9), 95 (35), 81 (100), 67 (32), 53 (52), 41 (54), 39 (40); HRMS (CI): ($C_8H_{12}O_2$+H) calcd 141.0916, found 141.0916; $C_8H_{12}O_2$ (140.18) calcd C 68.54, H 8.63; found C 68.28, H 8.54.

3.1.2. 6-Octynoic acid methyl ester (6). To a solution of acid **5** (900 mg, 0.64 mmol) in MeOH (10 mL) and pentane (5 mL) was added (trimethylsilyl)-diazomethane (2.0 M in hexanes, 9.6 mL, 1.93 mmol). After stirring for 30 min, the solution was quenched with acetic acid (2 mL). Evaporation of the solvents and flash chromatography of the residue (hexanes–EtOAc, 4:1) afforded ester **6** as a colorless liquid (841 mg, 85%); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.57 (s, 3H), 2.26–2.21 (m, 2H), 2.08–2.01 (m, 2H), 1.67 (t, J=2.6 Hz, 3H), 1.70–1.58 (m, 2H), 1.45–1.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.7, 78.4, 75.6, 51.3, 33.4, 28.3, 24.0, 18.3, 3.2; IR (neat) 2951, 2922, 2862, 1740, 1437, 1204, 1174, 1152 cm^{-1}; MS (EI) *m/z* (rel. intensity) 154 (M^+, <1), 95 (23), 94 (100), 79 (60), 67 (29), 69 (31), 55 (23), 53 (29), 41 (25); HRMS (CI) ($C_9H_{14}O_2$+H) calcd 155.1072, found 155.1072; $C_9H_{14}O_2$ (154.21) calcd C 70.10, H 9.15, found C 70.19, H 9.11.

3.1.3. 3,5-Dioxo-dodec-10-ynoic acid *tert*-butyl ester (8). To a solution of freshly prepared LDA (from diisopropylamine (280 μL, 2 mmol) and *n*-BuLi (1.25 mL, 2 mmol, 1.6 M in hexane)) at 0°C were added TMEDA (166 μL, 1.1 mmol) followed by *tert*-butylacetoacetate (182 μL, 1.1 mmol). After stirring for 15 min, a first portion of ester **6** (77 mg, 0.5 mmol) was introduced and stirring was continued for 15 min before *n*-BuLi (690 μL, 1 mmol, 1.6 M in hexane) was added to ensure complete deprotonation of the resulting product. After stirring for another 15 min, a second portion of *tert*-butylacetoacetate (250 mg, 1.62 mmol) was added and stirring was continued for 6 h until GC showed complete conversion of the starting material. The reaction was then quenched with aq. HCl (6 M), the aqueous layer was repeatedly extracted with CH_2Cl_2, the combined organic phases were consecutively washed with aq. HCl, aq. sat. $NaHCO_3$ and brine before being dried over Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (pentane–EtOAc, 10:1) gave the tricarbonyl compound **8** as a pale yellow liquid (161 mg, 58%). The product consists of a mixture of the keto- and the enol tautomers (ca. 21:79) in solution. Characteristic data: ^1H NMR ($CDCl_3$, 300 MHz) δ 15.12 (s), 5.56 (s), 3.67 (s), 3.42 (s), 3.21 (s), 2.50 (t, J=7.2 Hz), 2.28 (t, J=7.3 Hz), 2.14–2.08 (m, 2H), 1.73 (t, J=2.4 Hz, 3H), 1.73–1.62 (m, 2H), 1.49–1.39 (m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz, signals of the enol-form) δ 192.9, 187.7, 166.7, 99.7, 81.9, 78.5, 75.9, 46.4, 37.3. 28.4, 27.9 (3C), 24.7, 18.4, 3.4; IR (neat) 2979, 2934, 2864, 1734, 1610, 1456, 1411, 1394, 1369, 1148; MS (EI) *m/z* (rel. intensity) 224 (18), 165 (53), 162 (19), 129 (18), 95 (16), 69 (16), 57 (100), 41 (27); HR-MS (CI) calcd ($C_{16}H_{24}O_4$+H)

281.1754, found 281.1753; $C_{16}H_{24}O_4$ (280.36) calcd C 68.54, H 8.63, found C 68.54, H 8.58.

3.1.4. 3,5-Dioxo-dodec-10-ynoic acid methyl ester (9). To a solution of the *tert*-butyl ester **8** (360 mg, 1.3 mmol) in CH_2Cl_2 (5 mL) was added trifluoroacetic acid and the resulting mixture was stirred for 2 h at ambient temperature. After all volatiles had been evaporated, the residue was dissolved in MeOH (5 mL) and (trimethylsilyl)-diazomethane (0.96 mL, 1.9 mmol, 2.0 M in hexanes) was slowly added. The reaction was then quenched by AcOH, the solvent was evaporated and the residue was purified by flash chromatography to give product **9** as a colorless liquid (216.4 mg, 71%). The product consists of a mixture of the keto- and the enol tautomers in solution (ca. 14:86). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 15.03 (s), 5.24 (s), 3.65 (s, 3H), 3.64 (s), 3.49 (s), 3.16 (s), 2.45 (t, J=7.2 Hz), 2.23 (t, J=7.8 Hz), 2.09–2.02 (m, 2H), 1.68 (t, J=2.3 Hz, 3H), 1.68–1.57 (m, 2H), 1.48–1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, enol-form) δ 192.8, 187.0, 99.2, 77.2, 75.5, 52.2, 49.0, 44.7, 37.1, 28.2 24.6, 18.2, 3.2; IR (neat) 2952, 2922, 1862, 1745, 1606, 1437, 1330, 1262, 1202, 1156, 1017, 915, 776 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 238 (M^+, 2), 220 (48), 143 (39), 165 (78) 101 (100), 69 (69), 55 (34), 43 (41); HRMS (CI) ($C_{13}H_{18}O_4$+H) calcd 239.1284, found 239.1283; $C_{13}H_{18}O_4$ (238.28) calcd C 65.53, H 7.61, found C 65.38, H 7.62.

3.1.5. 6-Hept-5-ynyl-4-hydroxypyran-2-one (11). To a solution of *tert*-butyl ester **8** (509 mg, 1.8 mmol) in CH_2Cl_2 (11 mL) was added TFA (4 mL) and the resulting mixture was stirred for 2 h at ambient temperature. The solvent was then removed in vacuo and the residue was dissolved in Ac_2O (11 mL). After stirring for 24 h, the solvent was evaporated, the residue was dissolved in MeOH (5 mL), and K_2CO_3 (25 mg, 0.18 mmol) was added. The reaction was quenched after 8 h with sat. aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were successively washed with sat. aq. NH_4Cl and brine before being dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography (pentane–EtOAc, 4:1) gave pyrone **11** (260 mg, 70%) as a colorless solid. Mp 96–97°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93 (d, J=2.0 Hz, 1H), 5.52 (d, J=2.0 Hz, 1H), 2.44 (t, J=7.5 Hz, 2H), 2.12–2.06 (m, 2H), 1.70 (t, J=2.5 Hz, 3H), 1.68–1.57 (m, 2H), 1.51–1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 168.4, 167.2, 101.6, 90.0, 78.5, 76.3, 33.3, 28.3, 25.9, 18.5, 3.6; IR (KBr) 3000, 2935, 2861, 1647, 1571, 1249, 837 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 206 (M^+, 6), 189 (5), 178 (19), 163 (20), 150 (22), 136 (25), 121 (18), 111 (76), 69 (100), 55 (45), 41 (37); HR-MS (EI) calcd 206.0943, found 206.0944; $C_{12}H_{14}O_3$ (206.24) calcd C 69.88, H 6.84, found C 69.86, H 6.90.

3.1.6. 4-Dodec-10-ynyloxy-6-hept-5-ynyl-pyran-2-one (12). To a solution methyl ester **9** (137.2 mg, 0.58 mmol) in toluene (10 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 172.2 μL, 1.15 mmol) and the mixture was refluxed for 2 h. After reaching ambient temperature, MeCN (5 mL) and 12-bromo-dodec-2-yne **13** (169.4 mg, 6.91 mmol) were introduced and stirring was continued for 16 h. The reaction was quenched with aq. sat. NH_4Cl solution, the aqueous layer was extracted with Et_2O, the combined organic phases were dried over Na_2SO_4 and evaporated, and the crude product was purified by flash chromatography (hexanes–EtOAc, 4:1) to furnish pyrone **12** as a colorless solid (113.2 mg, 53%). Mp 47–48°C; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 5.78 (d, J=2.2 Hz, 1H), 5.33 (d, J=2.2 Hz, 1H), 3.93 (t, J=6.5 Hz, 2H), 2.44 (t, J=7.3 Hz, 2H), 2.13–2.05 (m, 4H), 1.79–1.67 (m, 4H), 1.75 (t, J=2.5 Hz, 3H), 1.74 (t, J=2.5 Hz, 3H), 1.55–1.29 (m, 14H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 171.8, 166.5, 165.7, 100.9, 88.8, 80.3, 79.5, 76.9, 76.2, 70.1, 34.3, 30.5, 30.32, 30.29, 30.2, 30.0, 29.6, 29.4, 27.0, 26.9, 19.8, 19.5, 4.3 (2C); IR (KBr) 2927, 2855, 1736, 1717, 1650, 1565, 1441, 1260, 1146, 1031, 868, 812 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 370 (M^+, 18), 326 (35), 162 (100), 147 (51), 111 (72), 81 (58), 67 (52), 55 (62); HRMS (EI) ($C_{24}H_{34}O_3$) calcd 370.2508, found 370.2504; $C_{24}H_{34}O_3$ (370.52) calcd C 77.80, H 9.25, found C 77.68, H 9.20.

3.1.7. 2,19-Dioxa-bicyclo[16.3.1]docosa-1(21),18(22)-dien-12-yn-20-one (13). To a solution of diyne **12** (49 mg, 0.12 mmol) in toluene (100 mL) was added (tBuO)$_3$W≡CCMe$_3$ (10 mg, 16 mol%)[12] and the resulting solution was stirred for 50 min at 80°C. Evaporation of the solvent followed by flash chromatography of the residue (pentane–EtOAc, 5:1) gave cycloalkyne **13** as colorless needles (33.3 mg, 84%). Mp 83–84°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (d, J=2.1 Hz, 1H), 5.38 (d, J=2.1 Hz, 1H), 4.02 (t, J=5.2 Hz, 2H), 2.48 (t, J=5.2 Hz, 2H), 2.19–2.13 (m, 4H), 1.79–1.72 (m, 4H), 1.56–1.29 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 165.7, 165.1, 99.9, 88.0, 81.4, 79.4, 69.4, 32.3, 29.3, 29.2, 28.4, 28.0, 27.4, 26.9, 26.8 (2C), 25.1, 18.7, 18.4; IR (KBr) 3074, 2933, 2896, 2854, 1714, 1651, 1572, 1437, 1340, 1257, 1133, 1033, 848, 806 cm^{-1}; MS (EI) *m*/*z* (rel. intensity) 316 (M^+, 21), 272 (83), 192 (45), 162 (87), 146 (41), 111 (86), 69 (100), 55 (69); HRMS (EI) ($C_{20}H_{28}O_3$) calcd 316.2039, found 316.2039; $C_{20}H_{28}O_3$ (316.43) calcd C 75.91, H 8.92, found C 76.05, H 8.87.

3.2. X-Ray crystallographic study

Crystal data for compound **13**: $C_{20}H_{28}O_3$, M=316.42 g mol^{-1}, colorless, crystal dimensions 0.34×0.08×0.02 mm, Monoclinic $P2_1/c$ (no. 14), at 293 K a=14.8897(6) Å, b=5.3874(2) Å, c=23.4353(12) Å, α=90°, β=103.8460(10)°, γ=90°, V=1825.28(14) Å^3, Z=4, ρ=1.151 mg m^{-3}, μ=0.076 mm^{-1}, λ=0.71073 Å. X-Ray diffraction data were collected using a Bruker–Nonius KappaCCD diffractometer employing CCD scans to cover reciprocal space up to 26.53° with 90.1% completeness, integration of raw data yielded a total of 9115 reflections, merged into 3416 unique reflections with Rint=0.20 after applying Lorentz, polarisation and absorption correction. The structure was solved by the direct method using SHELXS-97,[22] and atomic positions and displacement parameters were refined using full matrix least-squares based on Fsqd using SHELXL-97.[23] Refinement of 208 parameters using all reflections converged at R=0.069, wR=0.19, highest residual electron density peak 0.35 Å^3. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number *CCDC 206171*. Copies of the data can be obtained free of charge on application to CCDC,

12 Union Road, Cambridge CB2 1EZ, UK, e-mail: deposit@ccdc.cam.ac.uk.

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