Synthesis of Racemic and Enantiomerically Pure Acetylenic ω-Keto Esters Derived from 2-Methyl-1,3-cycloalkanediones and 2-Methylcycloalkanones Respectively

Philippe Geoffroy,[a] Marie-Paule Ballet,[a] Sidonie Finck,[a,1] Eric Marchioni,[b] Christophe Marcic,[b] Michel Miesch*[a]

[a] Université de Strasbourg, Institut de Chimie, UMR 7177, Laboratoire de Chimie Organique Synthétique, 1 rue Blaise Pascal, BP296/R8, 67008 Strasbourg, France
Fax +33(3)90241754; E-mail: m.miesch@chimie.u-strasbg.fr

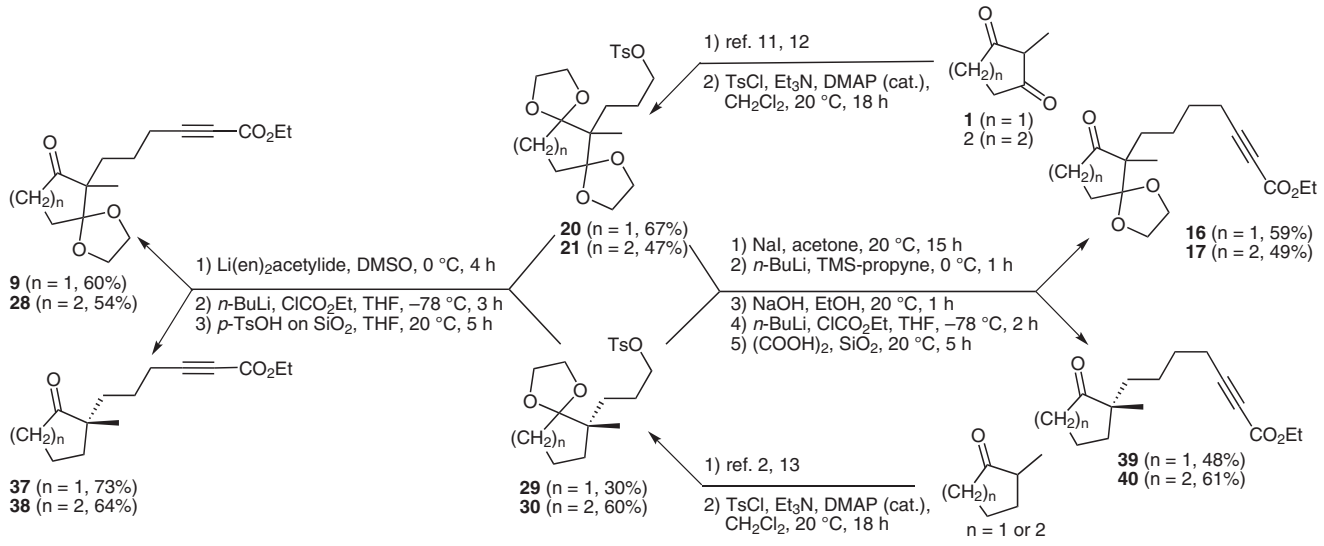
[b] Université de Strasbourg, Faculté de Pharmacie, IPCH, UMR 7178, Laboratoire de Chimie Analytique et Sciences de l'Aliment-74, route du Rhin, 67400 Illkirch, France

Received 6 July 2009; revised 17 July 2009

PSP No 175

Abstract: Racemic and enantiomerically pure alkynyl esters tethered, respectively, to 2-methyl-1,3-cycloalkanediones and 2-methylcycloalkanones were readily obtained starting from common intermediates, which were available on large scale.

Key words: alkynyl ester, enantiomer-chain, elongation, trimethylsilylpropyne, Corey–Fuchs reaction



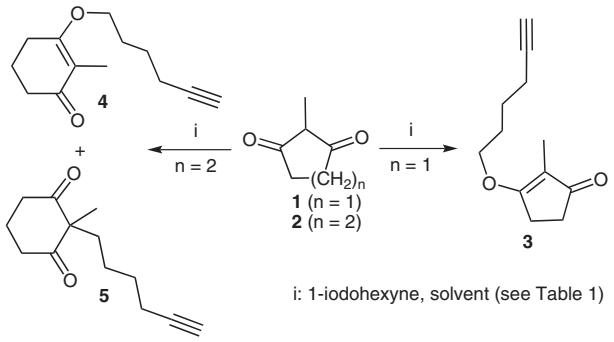
Scheme 1

2-Substituted 2-methyl-1,3-cycloalkanediones and 2,2-disubstituted cycloalkanones derived from optically active imines are useful starting materials for the elaboration of new methodologies.[2,3] For example, compounds derived from non-activated alkynes tethered to 2-methyl-1,3-cyclopentanedione (or -cyclohexanedione) have been used in radical chemistry[4] and organometallic chemistry[5] to set up new cyclisation reactions. Surprisingly, to the best of our knowledge, alkynyl esters tethered to 2-methyl-1,3-cyclopentanedione (or -cyclohexanedione) have not been described in the literature. Being involved in studies on the reactivity of acetylenic ω-keto esters bearing a three- or four-carbon tether toward bases and Lewis acids,[6] we wish to report here different synthetic routes through which to gain access to these types of compound, the final goal being to define the most efficient reaction pathway and to use these reaction conditions for the synthesis of enantiomerically pure acetylenic ω-keto esters (Scheme 1).

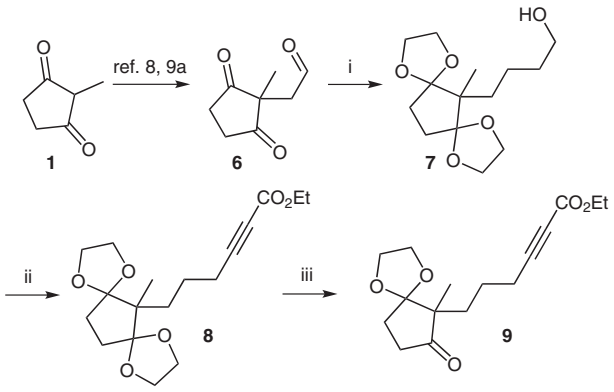
The alkylation reaction of 2-methyl-1,3-cyclopentanedione **1** (or -cyclohexanedione **2**) with 1-iodopentyne (or -hexyne) followed by the introduction of the carbethoxy group proved to be *a priori* the most efficient route to the desired acetylenic ω-keto esters. However, it is known that the alkylation reaction of 2-methyl-1,3-cyclopentanedione (or -cyclohexanedione) can be readily achieved with activated halides such as allyl bromide, propargyl bromide and benzyl bromide.[7] Nevertheless, there are few reports concerning the use of non-activated halides. Moreover, when the latter were involved, chemoselectivity problems (C-alkylation versus O-alkylation) always oc-

SYNTHESIS 2010, No. 1, pp 0171–0179
Advanced online publication: 03.11.2009
DOI: 10.1055/s-0029-1217043; Art ID: Z14609SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: NYU. Copyrighted material.



Scheme 2



Scheme 3 *Reagents and conditions*: i: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 0 °C to 20 °C, 12 h (93%); (b) H_2, Pd/C, AcOEt, 20 °C, 7 h (98%); (c) ethylene glycol, $CH(OMe)_3$, *p*-TsOH, CH_2Cl_2, 40 °C, 20 h (87%); (d) $LiAlH_4$, THF, 20 °C, 10 min (98%); ii: (a) SO_3, Py, Et_3N, DMSO, CH_2Cl_2, 0 °C to 20 °C, 1 h (81%); (b) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0 °C to 20 °C, 2 h (70%); (b) *n*-BuLi, $ClCO_2Et$, THF, –78 °C to 20 °C, 4 h (78%); iii: *p*-TsOH, SiO_2, THF, 20 °C, 5 h (81%).

curred. Indeed, it was shown that the addition of 1-iodohexyne to 2-methyl-1,3-cyclopentanedione **1**, in the presence of TBAF as a base,[8] afforded the O-alkylation product **3** exclusively. Amazingly, when the same reaction was carried out starting from 2-methyl-1,3-cyclohexanedione **2**, a mixture of O-alkylated product **4** and C-alkylated product **5** was obtained (Scheme 2). The ratio of O-alkylated product **4** increased when other base/solvent sytems (*t*-BuOK/THF, NaH/DMF, *n*-BuLi/THF) were utilized (Table 1).

These results prompted us to set up another synthetic route involving an alkylation reaction with an activated

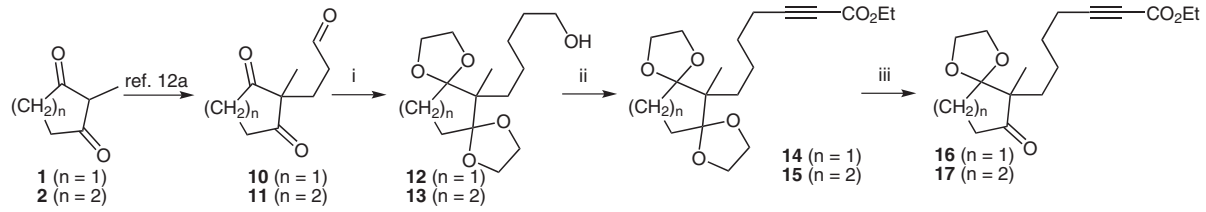
Table 1 C- and O-Alkylation of Diones **1** and **2**

n	Base/Solvent	Ratio C/O-alkylation	Yield (%)
1	TBAF/THF	0:1	quant
2	*t*-BuOK/DMF	1:1.33	70
2	NaH/DMF	1:1.66	48
2	TBAF/THF	1:1.22	89

halide, i.e. allyl bromide. Indeed, the alkylation reaction of 2-methyl-1,3-cyclopentanedione (**1**) with allyl bromide took place readily to yield, after ozonolysis of the double bond, the aldehyde **6** (Scheme 3).[9] A Wittig reaction, followed by a catalytic hydrogenation of the electrophilic double bond, di-protection of the dione and reduction of the carbethoxy group with $LiAlH_4$ afforded the hydroxy derivative **7**. After oxidation of the hydroxy group,[10] a Corey–Fuchs reaction,[11] along with the concomitant introduction of the carbethoxy group delivered, after monodeprotection of the bis-dioxolane **8**, the desired acetylenic ω-keto ester **9** (10 steps, 13% overall yield from **1**) (Scheme 3).

In order to increase the length of the tether, the same strategy was utilized except for the first step, i. e. the alkylation reaction with allyl bromide, which was replaced by a Michael addition of acrolein to 2-methyl-1,3-cyclopentanedione **1** (or -cyclohexane dione **2**) leading respectively to the aldehyde derivatives **10/11** and **12/13**.[12] Using the same reaction sequence described for obtaining the hydroxy derivative **7**, compounds **12/13** were isolated in 72% and 66% overall yields, respectively. After oxidation of the latter into the corresponding aldehydes, a Corey–Fuchs reaction followed by the introduction of the carbethoxy group gave the di-protected diones **14/15**. Monodeprotection of these diones afforded the acetylenic ω-keto esters **16/17** (9 steps, 43% overall yield from **1** and 39% overall yield from **2**) (Scheme 4).

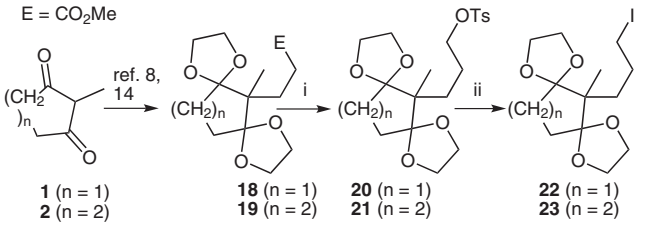
The Corey–Fuchs reaction, which allows the introduction of the alkynyl moiety, represents the key step in the above synthetic route. Nevertheless, these routes are quite long and six chromatographic separations on silica gel were necessary in order to obtain the final products. To improve these time-consuming purifications as well as the overall yields, the alkynyl moiety was directly introduced using acetylides such as lithium acetylide and 3-trimethylsilyl-



Scheme 4 *Reagents and conditions*: i: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 0 °C to 20 °C, 4 h (n = 1: 95%; n = 2: 93%); (b) H_2, Pd/C, AcOEt, 20 °C, 5 h (n = 1: quant; n = 2: quant); (c) ethylene glycol, $CH(OMe)_3$, *p*-TsOH, CH_2Cl_2, 45 °C, 25 h (n = 1: 85%; n = 2: 79%); (d) $LiAlH_4$, THF, 20 °C, 10 min (n = 1: quant; n = 2: quant); ii: (a) SO_3, Py, Et_3N, DMSO, CH_2Cl_2, 0 °C to 20 °C, 1 h (n = 1: 91%; n = 2: 70%); (b) Ph_3P, CBr_4, Et_3N, CH_2Cl_2, 0° C to 20 °C, 12 h (n = 1: 77%; n = 2: 95%); (c) *n*-BuLi, $ClCO_2Et$, THF, –78 °C to 20 °C, 20 h (n = 1: 86%; n = 2: 89%), iii: $(COOH)_2$, SiO_2, CH_2Cl_2, 20 °C, 5 h (n = 1: quant; n = 2: quant).

Downloaded by: NYU. Copyrighted material.

2-propynyllithium. However, it was desirable to start from a common intermediate that would allow the introduction of three or four methylene units. For this purpose, methyl acrylate was added to 2-methyl-1,3-cyclopentanedione **1** (or -cyclohexanedione **2**) to yield, after protection of the diones, compounds **18/19**.[13] After reduction of the carbethoxy groups, the resulting hydroxy derivatives were transformed into the tosylates **20/21** (Scheme 5).



Scheme 5 *Reagents and conditions*: i: (a) $LiAlH_4$, THF, 20 °C, 10 min (n = 1 or 2: quant); (b) TsCl, DMAP (cat), Et_3N, CH_2Cl_2, 0 °C to 20 °C, 12 h (n = 1: 82%; n = 2: 62%); ii: NaI, acetone, 20 °C, 12 h (n = 1 or 2: quant).

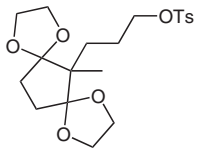
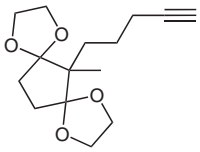
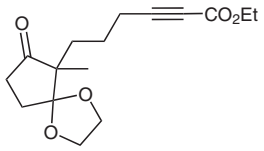
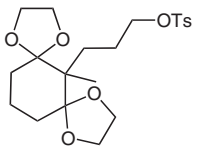
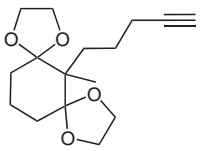
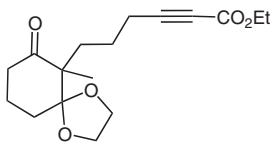
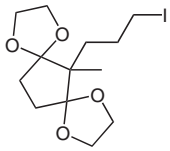
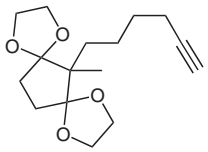
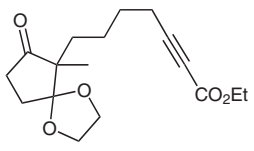
To introduce the three-carbon tether, lithium acetylide was added to the tosylates **20/21** to give the alkynyl derivatives **24/25** (Table 2). Nevertheless, these reaction conditions did not work well for the introduction of the four-carbon tether. The alkynyl derivatives **26/27** only formed from 3-trimethylsilyl-2-propynyllithium if the corresponding iodo derivatives **22/23** were utilized as starting materials. Finally, the introduction of the carbethoxy group and mono-deprotection of the bis-dioxolane afforded the desired acetylenic ω-keto esters **9/28** (7 steps, 40% overall yield from **1** and 25% overall yield from **2**) and **16/17** (9 steps, 39% overall yield from **1** and 23% overall yield from **2**) (Scheme 1). At this stage, it should be noted that the tosylates **20/21** are readily available on a large scale (60 mmol) and that they represent common intermediates for the synthesis of the desired acetylenic ω-keto esters (Scheme 1).

The above synthetic route was also followed using the chiral tosylates **29/30** together with the iodo derivatives **31/32**. Thus, the enantiomerically pure alkynyl derivatives **33/36** were readily obtained and could be easily transformed into the corresponding enantiomerically pure acetylenic ω-keto esters **37**–**40**.[3,15] Only one purification by silica gel chromatography was necessary for the transformation of the tosylates **29/30** or of the iodo derivatives **31/32** into the desired acetylenic ω-keto esters **37**–**40**.

Other synthetic routes were also tested. For example: 1) the addition of the dianion derived from tetrolic acid to the tosylates **20/21** (or iodo derivatives **22/23**),[16] and 2) the substitution of the iodo derivatives **22/23** with the dianion derived from ethyl acetoacetate, followed by the pyrazolone formation and subsequent oxidation with hypervalent iodine reagents.[17] However, a complex mixture of compounds was always obtained in the first case and low yields were observed for the oxidation step in the second case. Therefore, these routes were abandoned.

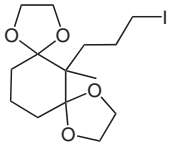
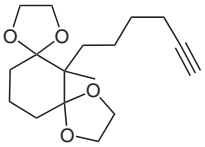
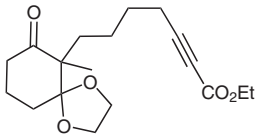
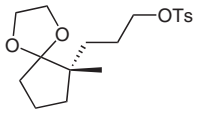
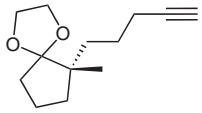
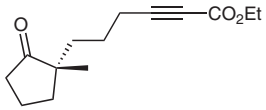
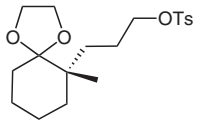
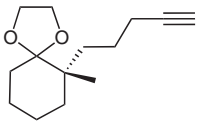
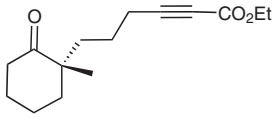
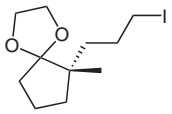
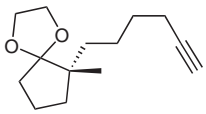
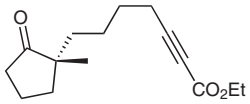
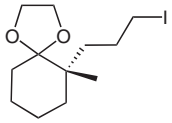
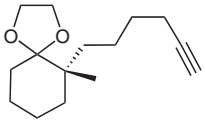
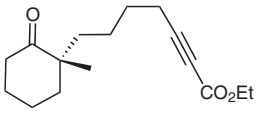
In summary, we have shown that several (enantiomerically pure) acetylenic ω-keto esters can be prepared starting from common intermediates, i.e. the tosylates **20/21** and **29/30**, which are readily available in large scales (60 mmol).

Table 2 Synthesis of Alkynyl Esters Tethered to 2-Methyl-1,3-cycloalkanediones and 2-Methylcycloalkanones

Starting material	Reagent	Product (yield)	Reagent	Product (yield,[a] $[\alpha]_D$)
 **20**	Li(en)$_2$acetylide	 **24** (78%)	1) *n*-BuLi, $ClCO_2Et$ 2) *p*-TsOH/SiO_2	 **9** (77%)
 **21**	Li(en)$_2$acetylide	 **25** (88%)	1) *n*-BuLi, $ClCO_2Et$ 2) *p*-TsOH/SiO_2	 **28** (61%)
 **22**	1) TMS—≡—CH_2Li 2) NaOH	 **26** (66%)	1) *n*-BuLi, $ClCO_2Et$ 2) $(COOH)_2/SiO_2$	 **16** (90%)

Downloaded by: NYU. Copyrighted material.

Table 2 Synthesis of Alkynyl Esters Tethered to 2-Methyl-1,3-cycloalkanediones and 2-Methylcycloalkanones (continued)

Starting material	Reagent	Product (yield)	Reagent	Product (yield,[a] $[\alpha]_D$)
 **23**	1) TMS—≡—CH_2Li 2) NaOH	 **27** (57%)	1) *n*-BuLi, $ClCO_2Et$ 2) $(COOH)_2/SiO_2$	 **17** (87%)
 **29** $[\alpha]_D^{20}$ +1.2 (*c* 1.00, $CHCl_3$)	$Li(en)_2$acetylide	 **33** (80%) $[\alpha]_D^{20}$ +4.6 (*c* 1.00, $CHCl_3$)	1) *n*-BuLi, $ClCO_2Et$ 2) HCl (10%), THF	 **37** (91%) $[\alpha]_D^{20}$ –48.3 (*c* 1.00, $CHCl_3$)
 **30** $[\alpha]_D^{20}$ –3.5 (*c* 1.00, $CHCl_3$)	$Li(en)_2$acetylide	 **34** (88%) $[\alpha]_D^{20}$ –7.2 (*c* 1.00, $CHCl_3$)	1) *n*-BuLi, $ClCO_2Et$ 2) HCl (10%), THF	 **38** (73%) $[\alpha]_D^{20}$ –40.3 (*c* 1.01, $CHCl_3$)
 **31** $[\alpha]_D^{20}$ –1.9 (*c* 1.00, $CHCl_3$)	1) TMS—≡—CH_2Li 2) NaOH	 **35** (quant) $[\alpha]_D^{20}$ +4.6 (*c* 1.00, $CHCl_3$)	1) *n*-BuLi, $ClCO_2Et$ 2) HCl (10%),THF	 $[\alpha]_D^{20}$ +4.0 (*c* 1.00, $CHCl_3$) **39** (48% from **31**)
 **32** $[\alpha]_D^{20}$ –10.6 (*c* 1.00, $CHCl_3$)	1) TMS—≡—CH_2Li 2) NaOH	 **36** (quant) $[\alpha]_D^{20}$ –3.6 (*c* 1.00, $CHCl_3$)	1) *n*-BuLi, $ClCO_2Et$ 2) HCl (10%),THF	 **40** (61% from **32**) $[\alpha]_D^{20}$ –36.6 (*c* 1.00, $CHCl_3$)

[a] Isolated yield.

Et_2O and THF were distilled from Na/benzophenone, CH_2Cl_2 over P_2O_5 and the amines over KOH. Thin-layer chromatography (TLC) was carried out on silica gel plates (Merck $60F_{254}$) and the spots were visualized under a UV lamp (254 or 365 nm) and/or sprayed with an acidic alcoholic solution of vanillin or with phosphomolybdic acid followed by heating on a hot plate. For column chromatography, silica gel (Merck, Si60, 40–60 μm) was used. Melting points (mp) were measured on a hot plate Stuart Scientific SMP 3 apparatus. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at either 75 or 125 MHz on a Bruker AC-300 or ARX-500, respectively, using the signal of the residual non-deuteriated solvent as the internal reference. Significant ^{1}H NMR spectroscopic data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constants (*J*) in Hz, number of protons. The ratios of compounds indicated below were calculated on the basis of the corresponding NMR integrations. High-resolution mass spectra (HRMS) were performed on a Agilent 6520 Accurate Mass Q-TOF. IR spectra were recorded as CCl_4 solutions on a Perkin–Elmer IR-881 and on a Bruker Alpha spectrometer. Microanalysis were carried out by the Service Commun d'Analyses du CNRS, Institut de Chimie-Strasbourg.

Tosylates of Type 20/21 and 29/30; General Procedure (GP1)

A dry vessel equipped with a magnetic stirring bar, a thermometer, a dropping funnel and drying tubes was charged with the appropriate alcohol (~0.4 M in CH_2Cl_2). The solution was cooled to 0 °C and Et_3N (1.5 equiv) was added slowly, followed by the TsCl (1.2 equiv) and DMAP (0.1 equiv). The mixture was allowed to warm to 25 °C over 15 h, then the reaction was quenched with sat. aq NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. A chromatographic purification afforded the products **20**, **21**, **29** and **30**.

Iodides of Type 22/23 and 31/32; General Procedure (GP2)

A dry vessel equipped with a magnetic stirring bar, a thermometer and drying tubes was charged with tosylates of type **20**, **21**, **29** or **30** (~0.12 M in acetone) and NaI (4 equiv). The reaction mixture was stirred for 15 h at r.t., hydrolyzed with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. The iodides were used without purification for the next step.

Downloaded by: NYU. Copyrighted material.

Acetylides of Type 24/25 and 33/34; General Procedure (GP3)
A dry, argon-flushed vessel equipped with a magnetic stirring bar, condenser and dropping funnel was charged with lithium acetylide ethylenediamine complex (1.5 equiv) and cooled to 0 °C. The tosylate (**20**, **21**, **29** or **30**) dissolved in a minimum of anhydrous solvent (DMSO–THF, 2:1, 0.3 M) was added. The reaction mixture was allowed to warm to r.t. over 1.5 to 4.5 h and then hydrolyzed with sat. aq NH_4Cl (50 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. A chromatographic purification afforded the products **24**, **25**, **33** and **34**.

Acetylides of Type 26/27 and 35/36; General Procedure (GP4)
A dry, argon-flushed vessel equipped with a magnetic stirring bar, condenser and dropping funnel was charged with 1-(trimethylsilyl)-1-propyne (~0.16 M in THF, 1.6 equiv) and cooled to 0 °C. *n*-BuLi (1.5 equiv) was added and, after 0.5 h, the THF solution of the iodides **22**, **23**, **31** or **32** (1.0 equiv) was added in one portion at 0 °C. The reaction mixture was allowed to warm to r.t. over 1 h, hydrolyzed with sat. aq NH_4Cl (60 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. A chromatographic purification afforded the substituted products.

These silytated intermediates were dissolved in absolute EtOH (~0.05 M) and treated with NaOH (25 equiv) dissolved in the minimum amount of H_2O during 1 h. Sat. aq NH_4Cl was added and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. A chromatographic purification afforded the products **26**, **27**, **35** and **36**.

Acetylenic Esters of Type 9/28, 37/38 and 16/17, 39/40; General Procedure (GP5)
A dry, argon-flushed vessel equipped with a magnetic stirring bar, condenser and dropping funnel was charged with acetylide (~0.14 M in THF, 1.0 equiv) and cooled to –78 °C. *n*-BuLi (1.2 equiv) was added dropwise. After 0.5 h, $ClCO_2Et$ was added in one portion at –78 °C. The reaction mixture was allowed to warm to r.t. over 2–3 h, hydrolyzed with sat. aq NH_4Cl and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl (50 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. The reaction mixture was treated with a 10% HCl solution in THF (20 mL) for 3 h, extracted with Et_2O (3 × 20 mL) and dried (Na_2SO_4). After filtration, the solvent was removed under reduced pressure. A chromatographic purification afforded the acetylenic esters.

6-Methyl-6-(4-methylbenzenesulfonyloxypropyl)-1,4,8,11-tetraoxadispiro[4.1.4.2]tridecane (20)
According to **GP1**, tosylate derivative **20** was prepared from the corresponding alcohol (11.25 g, 43.5 mmol) and TsCl (9.96 g, 52.2 mmol), Et_3N (9.2 mL, 65.3 mmol) and DMAP (0.53 g, 4.3 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 98:2→85:15 containing 1% of Et_3N) afforded **20**.

Yield: 14.7 g (82%); colorless solid; mp 107–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 3.98 (t, *J* = 6.8 Hz, 2 H), 3.94–3.78 (m, 8 H), 2.44 (s, 3 H), 1.95–1.80 (m, 4 H), 1.72–1.62 (m, 2 H), 1.44–1.28 (m, 2 H), 1.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.52 (ArC), 133.33 (ArC), 129.76 (ArC), 127.92 (ArC), 117.29 (OCO), 71.87 (CH_2O), 64.22 (OCH_2), 64.08 (OCH_2), 49.77 (CCH_3), 32.23 ($OCCH_2$), 25.01 (CH_2), 23.68 (CH_2), 21.64 (CCH_3), 16.89 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_7S$: 435.14480; found: 435.14610.

6-Methyl-6-(4-methylbenzenesulfonyloxypropyl)-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (21)
According to **GP1**, the tosylate derivative **21** was prepared from the corresponding alcohol (5.46 g, 20 mmol) and TsCl (4.59 g, 24.0 mmol), Et_3N (4.2 mL, 30 mmol) and DMAP (0.24g, 2 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 98:2→85:15 containing 1% of Et_3N) afforded **21**.

Yield: 5.36 g (62%); colorless solid; mp 71–72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.3 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 4.01–3.75 (m, 10 H), 2.42 (s, 3 H), 1.85–1.35 (m, 10 H), 1.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.48 (ArC), 133.37 (ArC), 129.75 (ArC), 127.89 (ArC), 113.20 (OCO), 72.20 (CH_2), 65.05 (OCH_2), 63.98 (OCH_2), 48.79 (CCH_3), 29.82 ($OCCH_2$), 26.28 (CH_2), 25.05 (CH_2), 21.62 (CCH_3), 18.48 (CH_2), 15.55 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{30}NaO_7S$: 449.16045; found: 449.16093.

(*S*)-6-Methyl-6-(4-methylbenzenesulfonyloxypropyl)-1,4-dioxaspiro[4.4]nonane (29)
According to **GP1**, the tosylate derivative **29** was prepared from the corresponding alcohol (12 g, 59.8 mmol) and TsCl (13.68 g, 71.1 mmol), Et_3N (12.6 mL, 89.7 mmol) and DMAP (0.73 g, 6 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 98:2→85:15 containing 1% of Et_3N) afforded **29**.

Yield: 16.7 g (78%); colorless liquid; $[\alpha]_D^{20}$ +1.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 4.00 (t, *J* = 6.6 Hz, 2 H), 3.87–3.82 (m, 4 H), 2.44 (s, 3 H), 1.82–1.41 (m, 8 H), 1.32 (dd, *J* = 9.4, 7.5 Hz, 2 H), 0.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.62 (ArC), 133.33 (ArC), 129.81 (ArC), 127.92 (ArC), 119.39 (OCO), 71.69 (CH_2O), 64.76 (OCH_2), 64.51 (OCH_2), 45.39 (CCH_3), 35.43 (CH_2), 33.35 (CH_2), 30.71 (CH_2), 24.59 (CH_2), 21.66 (CCH_3), 20.06 (CH_3), 17.87 (CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}O_5S$: 355.15737; found: 355.15767.

(*S*)-6-Methyl-6-(4-methylbenzenesulfonyloxypropyl)-1,4-dioxaspiro[4.5]decane (30)
According to **GP1**, the tosylate derivative **30** was prepared from the corresponding alcohol (10.4 g, 48.8 mmol) and TsCl (11.17 g, 58.6 mmol), Et_3N (10.3 mL, 73.2 mmol) and DMAP (0.59 g, 4.9 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 98:2→85:15 containing 1% of Et_3N) afforded **30**.

Yield: 16.53 g (91%); colorless liquid; $[\alpha]_D^{20}$ –3.5 (*c* 0.99, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 4.00 (t, *J* = 6.6 Hz, 2 H), 3.94–3.81 (m, 4 H), 2.45 (s, 3 H), 1.62–1.48 (m, 6 H), 1.41–1.33 (m, 6 H), 0.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.58 (ArC), 133.2 (ArC), 129.78 (ArC), 127.89 (ArC), 112.67 (OCO), 71.69 (CH_2O), 64.88 (OCH_2), 64.66 (OCH_2), 40.81 (CCH_3), 34.39 (CH_2), 30.38 (CH_2), 30.38 (CH_2), 23.49 (CH_2), 23.49 (CH_2), 21.62 (CCH_3), 20.75 (CH_2), 19.32 (CH_3).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5S$: 369.17302; found: 369.17268.

6-Methyl-6-(3-iodopropyl)-1,4,8,11-tetraoxadispiro[4.1.4.2]tridecane (22)
According to **GP2**, the addition of NaI (2.82 g, 18.9 mmol) to tosylate **20** (1.94 g, 4.7 mmol) afforded the iodide derivative **22**.

Downloaded by: NYU. Copyrighted material.

Yield: 1.72 g (quant); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.03–3.83 (m, 8 H), 3.14 (t, *J* = 7.1 Hz, 2 H), 1.95–1.80 (m, 6 H), 1.60–1.51 (m, 2 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.38 (OCO), 64.69 (OCH_2), 64.15 (OCH_2), 50.01 (CCH_3), 32.28 ($OCCH_2$), 30.61 (CH_2), 28.58 (CH_2), 17.09 (CH_3), 8.45 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{21}INaO_4$: 391.03767; found: 391.03799.

6-Methyl-6-(3-iodopropyl)-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (23)

According to **GP2**, the addition of NaI (4.79 g, 32 mmol) to tosylate **21** (3.0 g, 8.0 mmol) afforded iodide **23**.

Yield: 2.8 g (quant); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.00–3.87 (m, 8 H), 3.13 (t, *J* = 6.9 Hz, 2 H), 1.98–1.88 (m, 2 H), 1.68–1.51 (m, 8 H), 1.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.28 (OCO), 65.10 (OCH_2), 64.10 (OCH_2), 49.09 (CCH_3), 31.91 (CH_2), 29.90 ($OCCH_2$), 29.70 (CH_2), 18.56 (CH_2), 15.74 (CH_3), 9.38 (CH_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{23}INaO_4$: 405.05332; found: 405.05351.

(*S*)-6-(3-Iodopropyl)-6-methyl-1,4-dioxaspiro[4.4]nonane (31)

According to **GP2**, the addition of NaI (5.92 g, 39.5 mmol) to tosylate **29** (3.5 g, 9.9 mmol) afforded iodide **31**.

Yield: 3.17 g (quant); yellow oil; $[\alpha]_D^{20}$ –1.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94–3.85 (m, 4 H), 3.16 (t, *J* = 7.1 Hz, 2 H), 1.93–1.50 (m, 8 H), 1.44 (dd, *J* = 9.3, 7.5 Hz, 2 H), 0.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.50 (OCO), 64.79 (OCH_2), 64.61 (OCH_2), 45.58 (CCH_3), 36.20 (CH_2), 35.51 (CH_2), 33.39 (CH_2), 29.50 (CH_2), 20.26 (CH_3), 17.94 (CH_2), 8.15 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}IO_2$: 311.05025; found: 311.04984.

(*S*)-6-(3-Iodopropyl)-6-methyl-1,4-dioxaspiro[4.5]decane (32)

According to **GP2**, the addition of NaI (4.45 g, 29.7 mmol) to tosylate **30** (2.73 g, 7.4 mmol) afforded iodide **32**.

Yield: 2.41 g (quant); yellow oil; $[\alpha]_D^{20}$ –10.6 (*c* 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98–3.88 (m, 4 H), 3.16 (md, *J* = 7.0, 8.9 Hz, 2 H), 1.79 (dq, *J* = 9.2, 7.1 Hz, 2 H), 1.63–1.40 (m, 10 H), 0.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.78 (OCO), 64.97 (OCH_2), 64.75 (OCH_2), 41.07 (CCH_3), 35.89 (CH_2), 34.53 (CH_2), 30.48 (CH_2), 28.38 (CH_2), 23.57 (CH_2), 20.85 (CH_2), 19.67 (CH_3), 8.33 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{22}IO_2$: 325.0659; found: 325.06598.

6-Methyl-6-(pent-4-ynyl)-1,4,8,11-tetraoxadispiro[4.1.4.2]tridecane (24)

According to **GP3**, the acetylenic derivative **24** was prepared from the tosylate **20** (3.66 g, 8.7 mmol) and lithium acetylide ethylenediamine complex (1.2 g, 13 mmol) and purified by column chromatography (silica gel; PE–EtOAc, 70:30 containing 1% Et_3N), to afford compound **24**.

Yield: 1.81 g (78%); colorless oil.

IR (ATR): 3286 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.01–3.83 (m, 8 H), 2.14–2.11 (m, 2 H), 1.97–1.82 (m, 5 H), 1.55–1.52 (m, 4 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.52 (OCO), 84.95 (C≡CH), 68.02 (C≡CH), 64.70 (OCH_2), 64.15 (OCH_2), 50.18 (CCH_3), 32.35 ($OCCH_2$), 28.79 (CH_2), 23.39 (CH_2), 19.59 (CH_2), 17.02 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_4$: 289.14103; found: 289.14205.

6-Methyl-6-(pent-4-ynyl)-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (25)

According to **GP3**, the acetylenic derivative **25** was prepared from the tosylate **21** (0.65 g, 2.3 mmol) and lithium acetylide ethylenediamine complex (0.21 g, 3.5 mmol) and purified by column chromatography (silica gel; PE–EtOAc, 70:30 containing 1% Et_3N), furnishing compound **25**.

Yield: 0.38 g (88%); colorless oil.

IR (ATR): 3288 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98–3.86 (m, 8 H), 2.12–2.07 (m, 2 H), 1.90 (t, *J* = 2.7 Hz, 1 H), 1.65–1.53 (m, 10 H), 1.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.40 (OCO), 85.01 (C≡CH), 67.97 (C≡CH), 65.11 (OCH_2), 64.01 (OCH_2), 49.19 (CCH_3), 30.13 (CH_2), 29.99 ($OCCH_2$), 24.61 (CH_2), 19.81 (CH_2), 18.58 (CH_2), 15.56 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_4$: 303.15668; found: 303.15671.

(*R*)-6-Methyl-6-(pent-4-ynyl)-1,4-dioxaspiro[4.4]nonane (33)

According to **GP3**, the acetylenic derivative **33** was prepared from the tosylate **29** (3.29 g, 9.2 mmol) and lithium acetylide ethylenediamine complex (1.11 g, 12 mmol) and purified by column chromatography (silica gel; PE–EtOAc, 95:5 containing 1% Et_3N), furnishing compound **33**.

Yield: 1.55 g (80%); colorless oil; $[\alpha]_D^{20}$ +4.6 (*c* 1.00, $CHCl_3$).

IR (ATR): 3296 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92–3.86 (m, 4 H), 2.16 (td, *J* = 6.7, 2.7 Hz, 2 H), 1.94 (t, *J* = 2.7 Hz, 1 H), 1.88–1.74 (m, 2 H), 1.69–1.39 (m, 8 H), 0.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.66 (OCO), 84.87 (C≡CH), 68.13 (C≡CH), 64.80 (OCH_2), 64.63 (OCH_2), 45.77 (CCH_3), 35.33 (CH_2), 34.33 (CH_2), 33.44 (CH_2), 24.21 (CH_2), 20.07 (CH_3), 19.46 (CH_2), 17.93 (CH_2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}O_2$: 209.15361; found: 209.15344.

(*S*)-6-Methyl-6-(pent-4-ynyl)-1,4-dioxaspiro[4.5]decane (34)

According to **GP3**, the acetylenic derivative **34** was prepared from the tosylate **30** (3.3 g, 9 mmol) and lithium acetylide ethylenediamine complex (1.07 g, 11.6 mmol) and purified by column chromatography (silica gel; PE–EtOAc, 95:5 containing 1% Et_3N), furnishing compound **34**.

Yield: 1.74 g (88%); colorless oil; $[\alpha]_D^{20}$ –7.2 (*c* 1.00, $CHCl_3$).

IR (ATR): 3312 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.87 (m, 4 H), 2.18–2.13 (m, 2 H), 1.95 (t, *J* = 2.6 Hz, 1 H), 1.64–1.37 (m, 12 H), 0.91 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.91 (OCO), 84.86 (C≡CH), 68.10 (C≡CH), 64.94 (OCH_2), 64.73 (OCH_2), 41.12 (CCH_3), 34.29 (CH_2), 33.92 (CH_2), 30.49 (CH_2), 23.60 (CH_2), 23.02 (CH_2), 20.83 (CH_2), 19.47 (CH_2), 19.43 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{23}O_2$: 223.16926; found: 223.16912.

Downloaded by: NYU. Copyrighted material.

Procedure 4

6-Methyl-6-(hex-5-ynyl)-1,4,8,11-tetraoxadispiro[4.1.4.2]tridecane (26)

According to **GP4**, the acetylenic derivative **26** was prepared from the iodide **22** (1.19 g, 3.23 mmol) and 1-(trimethylsilyl)-1-propyne (0.77 mL, 5.17 mmol) with *n*-BuLi (3 mL, 4.84 mmol, 1.6 M in hexanes). The crude mixture was treated with NaOH (3.23 g, 80.7 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 90:10→80:20) afforded compound **26**.

Yield: 0.59 g (66%); colorless oil.

IR (ATR): 3286 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.99–3.84 (m, 8 H), 2.18 (td, *J* = 6.8, 2.7 Hz, 2 H), 1.97–1.82 (m, 4 H), 1.51–1.35 (m, 7 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.62 (OCO), 84.96 (C≡CH), 67.92 (C≡CH), 64.72 (OCH_2), 64.16 (OCH_2), 50.25 (CCH_3), 32.42 ($OCCH_2$), 29.73 (CH_2), 28.69 (CH_2), 23.03 (CH_2), 18.38 (CH_2), 17.08 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{24}NaO_4$: 303.15668; found: 303.15790.

6-Methyl-6-(hex-5-ynyl)-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (27)

According to **GP4**, the acetylenic derivative **27** was prepared from the iodide **23** (1.48 g, 3.87 mmol) and 1-(trimethylsilyl)-1-propyne (0.93 mL, 6.19 mmol) with *n*-BuLi (4.2 mL, 5.81 mmol, 1.38 M in hexanes). The crude mixture was treated with NaOH (3.27 g, 82 mmol). Purification by column chromatography (silica gel; PE–EtOAc, 90:10→80:20) afforded compound **27**.

Yield: 0.69 g (72%); colorless oil.

IR (ATR): 3302 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.99–3.87 (m, 8 H), 2.18 (td, *J* = 6.7, 2.5 Hz, 2 H), 1.91–1.89 (m, 1 H), 1.64–1.45 (m, 12 H), 1.09 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.51 (OCO), 85.03 (C≡CH), 67.89 (C≡CH), 65.13 (OCH_2), 64.09 (OCH_2), 49.25 (CCH_3), 30.15 (CH_2), 30.04 ($OCCH_2$), 24.52 (CH_2), 18.60 (CH_2), 18.46 (CH_2), 15.60 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{26}NaO_4$: 317.17233; found: 317.17298.

(*R*)-6-Methyl-6-(hex-5-ynyl)-1,4-dioxaspiro[4.4]nonane (35)

According to **GP4**, the acetylenic derivative **35** was prepared from the iodide **31** (2.64 g, 8.51 mmol) and 1-(trimethylsilyl)-1-propyne (2 mL, 13.6 mmol) with *n*-BuLi (10 mL, 12.7 mmol, 1.26 M in hexanes). The crude mixture was treated with NaOH (8.5 g, 213 mmol) to afford compound **35**.

Yield: 2.04 g (100%); colorless oil; $[\alpha]_D^{20}$ +4.6 (*c* 1.00, $CHCl_3$).

IR (ATR): 3298 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.92–3.87 (m, 4 H), 2.20 (td, *J* = 7.0, 2.7 Hz, 2 H), 1.93 (t, *J* = 2.6 Hz, 1 H), 1.88–1.28 (m, 12 H), 0.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 119.73 (OCO), 84.75 (C≡CH), 68.08 (C≡CH), 64.77 (OCH_2), 64.62 (OCH_2), 45.90 (CCH_3), 35.19 (CH_2), 34.28 (CH_2), 33.46 (CH_2), 29.51 (CH_2), 23.90 (CH_2), 19.99 (CH_3), 18.42 (CH_2), 17.91 (CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{23}O_2$: 223.16926; found: 223.16956.

(*R*)-6-Methyl-6-(hex-5-ynyl)-1,4-dioxaspiro[4.5]decane (36)

According to **GP4**, the acetylenic derivative **36** was prepared from the iodide **32** (1.09 g, 3.36 mmol) and 1-(trimethylsilyl)-1-propyne (0.81 mL, 5.38 mmol) with *n*-BuLi (3.9 mL, 5 mmol, 1.3 M in hexanes). The crude mixture was treated with NaOH (3.36 g, 84 mmol) to afford compound **36**.

Yield: 0.84 g (100%); colorless oil; $[\alpha]_D^{20}$ –3.6 (*c* 1.00, $CHCl_3$).

IR (ATR): 3308 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.86 (m, 4 H), 1.94 (td, *J* = 7.0, 2.6 Hz, 2 H), 1.67 (t, *J* = 2.7 Hz, 1 H), 1.63–1.28 (m, 14 H), 0.90 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 113.04 (OCO), 84.76 (C≡CH), 68.09 (C≡CH), 64.97 (OCH_2), 64.78 (OCH_2), 41.27 (CCH_3), 34.13 (CH_2), 33.80 (CH_2), 30.52 (CH_2), 29.55 (CH_2), 23.66 (CH_2), 22.62 (CH_2), 20.90 (CH_2), 19.45 (CH_3), 18.45 (CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{25}O_2$: 237.18491; found: 237.18472.

Procedure 5

Ethyl 6-(6-Methyl-7-oxo-1,4-dioxaspiro[4.4]nonan-6-yl)hex-2-ynoate (9)

According to **GP5**, the unsaturated ester **9** was prepared from the acetylenic derivative **24** (1.81 g, 6.83 mmol), *n*-BuLi (5.8 mL, 8.19 mmol, 1.26 M in hexanes), and $ClCO_2Et$ (1.3 mL, 13.65 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 80:20) to yield the corresponding ester as a colorless oil (2.0 g, 90%). Acidic treatment with TsOH adsorbed on silica gel in CH_2Cl_2 afforded the derivative **9**.

Yield: 0.79 g (86%); colorless oil.

IR (ATR): 2233 (s), 1739 (s), 1703(s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (q, *J* = 7.2 Hz, 2 H), 4.04–3.94 (m, 4 H), 2.38 (t, *J* = 8.1 Hz, 2 H), 2.31–2.42 (m, 2 H), 2.17–1.98 (m, 2 H), 1.66–1.54 (m, 4 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.70 (C=O), 153.80 (CO_2Et), 116.13 (OCO), 88.86 (C≡CCO_2Et), 73.41 (C≡CCO_2Et), 65.07 (OCH_2), 64.70 (OCH_2), 61.79 ($CO_2CH_2CH_3$), 53.76 (CCH_3), 35.15 (CH_2), 31.51 (CH_2), 29.95 (CH_2), 22.54 (CH_2), 19.34 (CH_2), 15.72 ($CO_2CH_2CH_3$), 14.04 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{22}NaO_5$: 317.13594; found: 317.13638.

Ethyl 6-(6-Methyl-7-oxo-1,4-dioxaspiro[4.5]decan-6-yl)hex-2-ynoate (28)

According to **GP5**, the unsaturated ester **28** was prepared from the acetylenic derivative **25** (0.37 g, 1.38 mmol), *n*-BuLi (1.15 mL, 1.58 mmol, 1.38 M in hexanes) and $ClCO_2Et$ (0.25 mL, 2.64 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 80:20) yielding the corresponding ester as a colorless oil (0.34 g, 73%). An acidic treatment with TsOH adsorbed on silica gel afforded the derivative **28**.

Yield: 0.34 g (84%); colorless oil.

IR (ATR): 2234 (s), 1703 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 7.2 Hz, 2 H), 3.92–3.86 (m, 4 H), 2.45–2.19 (m, 4 H), 2.08–1.97 (m, 1 H), 1.89 (td, *J* = 12.8, 4.5 Hz, 1 H), 1.80–1.50 (m, 5 H), 1.30–1.15 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.99 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.76 (CO), 153.65 (CO_2Et), 113.61 (OCO), 88.53 (C≡CCO_2Et), 73.60 (C≡CCO_2Et), 65.32 (OCH_2), 65.19 (OCH_2), 61.75 ($CO_2CH_2CH_3$), 58.78 (CCH_3), 37.12 (CH_2), 34.03 (CH_2), 29.49 (CH_2), 22.53 (CH_2), 19.35 (CH_2), 19.15 (CH_2), 14.00 ($CO_2CH_2CH_3$), 13.53 (CH_3).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{24}NaO_5$: 331.15159; found: 331.15304.

Downloaded by: NYU. Copyrighted material.

Ethyl 7-(6-Methyl-7-oxo-1,4-dioxaspiro[4.4]nonan-6-yl)hept-2-ynoate (16)

According to **GP5**, the unsaturated ester **16** was prepared from the acetylenic derivative **26** (0.59 g, 2.11 mmol), *n*-BuLi (1.8 mL, 2.53 mmol, 1.41 M in hexanes) and $ClCO_2Et$ (0.4 mL, 4.24 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 80:20) yielding the corresponding ester as a colorless oil (0.67 g, 90%). An acidic treatment acid with TsOH adsorbed on silica gel afforded the derivative **16**.

Yield: 0.59 g (quant); yellow oil.

IR (ATR): 2233 (s), 1738 (s), 1703 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (q, *J* = 7.2 Hz, 2 H), 4.00–3.98 (m, 4 H), 2.40–2.25 (m, 4 H), 2.20–2.00 (m, 3 H), 1.60–1.35 (m, 5 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 218.03 (CO), 153.83 (CO_2Et), 116.23 (OCO), 89.13 (C≡CCO_2Et), 73.23 (C≡CCO_2Et), 65.11 (OCH_2), 64.65 (OCH_2), 61.77 (OCH_2CH_3), 53.92 (CCH_3), 35.12 (CH_2), 31.72 (CH_2), 30.00 (CH_2), 28.15 (CH_2), 22.96 (CH_2), 18.49 (CH_2), 15.51 (OCH_2CH_3), 14.04 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}O_5$: 309.16965; found: 309.16963.

Ethyl 7-(6-Methyl-7-oxo-1,4-dioxaspiro[4.5]decan-6-yl)hept-2-ynoate (17)

According to **GP5**, the unsaturated ester **17** was prepared from the acetylenic derivative **27** (0.37 g, 1.32 mmol) and *n*-BuLi (1.15 mL, 1.58 mmol, 1.38 M in hexanes), $ClCO_2Et$ (0.25 mL, 2.64 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 80:20) affording the corresponding ester as a colorless oil (0.38 g, 87%). An acidic treatment with TsOH adsorbed on silica gel afforded the derivative **17**.

Yield: 0.35 g (quant); colorless oil.

IR (ATR): 2232 (s), 1703(s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (qd, *J* = 7.2, 1.1 Hz, 2 H), 3.95–3.91 (m, 4 H), 2.47–2.36 (m, 1 H), 2.31 (t, *J* = 7.1 Hz, 2 H), 2.08–2.03 (m, 1 H), 1.88–1.60 (m, 6 H), 1.55 (t, *J* = 7.1 Hz, 2 H), 1.43–1.34 (m, 1 H), 1.29 (t, *J* = 7.1, 0.7 Hz, 3 H), 1.16–1.09 (m, 1 H), 1.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.94 (CO), 153.77 (CO_2Et), 113.77 (OCO), 88.79 (C≡CCO_2Et), 73.40 (C≡CCO_2Et), 65.38 (OCH_2), 65.23 (OCH_2), 61.79 (OCH_2CH_3), 59.03 (CCH_3), 37.28 (CH_2), 34.58 (CH_2), 29.55 (CH_2), 28.05 (CH_2), 23.36 (CH_2), 19.44 (CH_2), 18.45 (CH_2), 14.04 (OCH_2CH_3), 13.33 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_5$: 345.16725; found: 345.16781.

Ethyl (*R*)-6-(1-Methyl-2-oxocyclopentyl)hex-2-ynoate (37)

According to **GP 5**, the unsaturated ester **37** was prepared from the acetylenic derivative **33** (1.47 g, 7 mmol), *n*-BuLi (6.7 mL, 8.47 mmol, 1.26 M in hexanes) and $ClCO_2Et$ (1.35 mL, 14.1 mmol). The mixture was hydrolyzed with a 10% HCl solution and purified by column chromatography (silica gel; PE–EtOAc, 90:10) yielding the corresponding ester **37**.

Yield: 1.51 g (91%); colorless oil; $[\alpha]_D^{20}$ –48.3 (*c* 1.00, $CHCl_3$).

IR (ATR): 2233 (s), 1732 (s), 1703(s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 7.2 Hz, 2 H), 2.36–2.13 (m, 4 H), 1.93–1.41 (m, 8 H), 1.30 (t, *J* = 7.3 Hz, 3 H), 1.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 223.05 (CO), 153.77 (CO_2Et), 88.62 (C≡CCO_2Et), 73.47 (C≡CCO_2Et), 61.82 ($CO_2CH_2CH_3$), 48.04 (CCH_3), 37.56 (CH_2), 35.87 (CH_2), 35.75 (CH_2), 27.74 (CH_2), 21.66 (CO_2CH_2CH), 19.20 (CH_2), 18.66 (CH_2), 14.04 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_3$: 259.13047; found: 259.13175.

Ethyl (*S*)-6-(1-Methyl-2-oxocyclohexyl)hex-2-ynoate (38)

According to **GP5**, the unsaturated ester **38** was prepared from the acetylenic derivative **34** (1.68 g, 7.6 mmol), *n*-BuLi (7 mL, 9.1 mmol, 1.3 M in hexanes) and $ClCO_2Et$ (1.45 mL, 15.2 mmol). The mixture was hydrolyzed with a 10% HCl solution and purified by column chromatography (silica gel; PE–EtOAc, 90:10) affording the corresponding ester **38**.

Yield: 1.39 g (73%); colorless oil; $[\alpha]_D^{20}$ –40.3 (*c* 1.01, $CHCl_3$).

IR (ATR): 2239 (s), 1712 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 7.2 Hz, 2 H), 2.38 (t, *J* = 6.2 Hz, 2 H), 2.33 (t, *J* = 6.8 Hz, 2 H), 1.88–1.37 (m, 10 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.51 (CO), 153.74 (CO_2Et), 88.72 (C≡CCO_2Et), 73.50 (C≡CCO_2Et), 61.79 ($CO_2CH_2CH_3$), 48.35 (CCH_3), 39.19 (CH_2), 38.72 (CH_2), 36.76 (CH_2), 27.44 (CH_2), 22.55 ($CO_2CH_2CH_3$), 22.24 (CH_2), 21.00 (CH_2), 19.23 (CH_2), 14.02 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_3$: 273.14612; found: 273.14714.

Ethyl (*R*)-7-(1-Methyl-2-oxocyclopentyl)hept-2-ynoate (39)

According to **GP5**, the unsaturated ester **39** was prepared from the acetylenic derivative **35** (2.64 g, 8.51 mmol), *n*-BuLi (8.1 mL, 10.21 mmol, 1.26 M in hexanes) and $ClCO_2Et$ (1.62 mL, 17 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 98:2–90:10) affording the corresponding ester as a colorless oil (1.42 g, 57%). An acidic treatment with 10% HCl and purification by column chromatography (silica gel; PE–EtOAc, 98:5) afforded the ester **39**.

Yield: 0.92 g (84%); colorless oil; $[\alpha]_D^{20}$ +4.0 (*c* 1.00, $CHCl_3$).

IR (ATR): 2233 (s), 1733 (s), 1704 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.21 (q, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.0 Hz, 2 H), 2.29–2.13 (m, 2 H), 1.94–1.82 (m, 3 H), 1.79–1.70 (m, 1 H), 1.61–1.36 (m, 6 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.00 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 223.49 (CO), 153.82 (CO_2Et), 88.95 (C≡CCO_2Et), 73.36 (C≡CCO_2Et), 61.79 ($CO_2CH_2CH_3$), 48.20 (CCH_3), 37.65 (CH_2), 35.98 (CH_2), 35.61 (CH_2), 27.98 (CH_2), 23.6 (CH_2), 21.80 ($CO_2CH_2CH_3$), 18.70 (CH_2), 18.55 (CH_2), 14.04 (CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_3$: 273.14612; found: 273.14699.

Ethyl (*R*)-7-(1-Methyl-2-oxocyclohexyl)hept-2-ynoate (40)

According to **GP5**, the unsaturated ester **40** was prepared from the acetylenic derivative **36** (0.84 g, 3.36 mmol), *n*-BuLi (2.5 mL, 4 mmol, 1.6 M in hexanes) and $ClCO_2Et$ (0.64 mL, 6.7 mmol). The mixture was purified by column chromatography (silica gel; PE–EtOAc, 98:2→90:10) yielding the corresponding ester as a colorless oil (0.76 g, 74%). An acidic treatment with 10% HCl and purification by column chromatography (silica gel; PE–EtOAc, 98:5) afforded the ester **40**.

Yield: 0.47 g (83%); colorless oil; $[\alpha]_D^{20}$ –36.6 (*c* 1.00, $CHCl_3$).

IR (ATR): 2232 (s), 1701(s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.20 (q, *J* = 7.3 Hz, 2 H), 2.39–2.30 (m, 4 H), 1.89–1.35 (m, 12 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.88 (CO), 153.81 (CO_2Et), 88.97 (C≡CCO_2Et), 73.36 (C≡CCO_2Et), 61.79 ($CO_2CH_2CH_3$), 48.47 (CCH_3), 39.19 (CH_2), 38.78 (CH_2), 36.92 (CH_2), 28.09 (CH_2),

Downloaded by: NYU. Copyrighted material.

27.46 (CH_2), 23.10 (CH_2), 22.63 ($CO_2CH_2CH_3$), 21.05 (CH_2), 18.55 (CH_2), 14.04 (CH_3).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_3$: 287.16177; found: 287.16247.

Acknowledgment

Support for this work was provided by Université de Strasbourg, CNRS and ANR (N°07-PCVI-0016). M.-P.B. thanks MRT for a research fellowship. The authors thank Dr. Jennifer Wytko for assistance in preparing this manuscript.

References

(1) In part. S.F. achieved the synthesis of compound **17** by using the synthetic route described in Scheme 4.
(2) The Hajos–Parrish–Eder–Sauer–Wiechert reaction is one of the most representative examples of a methodology using 2-substituted 2-methyl-1,3-cycloalkanediones as starting materials, see: (a) Hajos, Z. G.; Parrish, D. R. German Patent DE 2,102,623, **1971**. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (c) Eder, U.; Sauer, G.; Wiechert, R. German Patent DE 2,014,757, **1971**. (d) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int., Ed. Engl.* **1971**, *10*, 496. (e) For a recent application in total synthesis, see: Murata, Y.; Yamashita, D.; Kitahara, K.; Minasako, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 1400.
(3) D'Angelo, J.; Desmaële, D.; Dumas, F.; Guiguant, A. *Tetrahedron: Asymmetry* **1998**, *3*, 459.
(4) (a) Balog, A.; Geib, S. V.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442.
(5) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493.
(6) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem. Eur. J.* **2009**, *15*, 4394; and references cited therein.
(7) (a) Schick, H.; Schwarz, H.; Finger, A. *Tetrahedron* **1982**, *38*, 1279. (b) Nayyar, S.; Trehan, I.; Kaur, J. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2002**, *41*, 2342.
(8) (a) Brooks, D. W.; Mazdiyasni, H.; Chakrabarti, S. *Tetrahedron Lett.* **1984**, *25*, 1241. (b) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223.
(9) (a) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Nakashima, T.; Node, M. *Synlett* **2006**, 2176. (b) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Takeo, M.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1655.
(10) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(11) (a) Corey, E. J.; Fuchs, P. *Tetrahedron Lett.* **1972**, 3769. For the homologation of aldehyde to alkyne see also: (b) Colvin, E. W.; Hammil, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151. (c) Ohira, S. *Synth. Commun.* **1989**, 561. (d) Taber, D. F.; Bai, S.; Guo, P. F. *Tetrahedron Lett.* **2008**, *49*, 6904.
(12) (a) Schick, H.; Roatsch, B.; Schwarz, H.; Hauser, A.; Schwarz, S. *Liebigs Ann. Chem.* **1992**, 419. (b) Rouillard, A.; Deslongchamps, P. *Tetrahedron* **2002**, *58*, 6555. (c) Yamazaki, J.; Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Watanabe, J.; Fuji, K. *Tetrahedron: Asymmetry* **2002**, *13*, 729. (d) Deschamp, J.; Riant, O. *Org. Lett.* **2009**, *11*, 1217.
(13) Schinzer, D.; Muller, N.; Fischer, A. K.; Priess, J. W. *Synlett* **2000**, 1265.
(14) Watanabe, H.; Iwamoto, M.; Nakata, M. J. *J. Org. Chem.* **2005**, *70*, 4652.
(15) Klein, A.; Miesch, M. *Synthesis* **2006**, 2613.
(16) Pitzele, B. S.; Baran, J. S.; Steinman, D. H. *J. Org. Chem.* **1975**, *40*, 269.
(17) (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (b) Moriarty, R. M.; Varid, R. K.; Ravikumar, V. T.; Hopkins, T. E.; Farid, P. *Tetrahedron* **1989**, *45*, 1605.

Downloaded by: NYU. Copyrighted material.