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Furanylidene systems from a tosylic acid-mediated, tandem desilylation-cyclization reaction of silyl ethers of monoalkynylated β-keto carbonyls

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Abstract

Single isomers of the furanylidene system **8** were synthesized in four steps. The synthesis begins with the dianion of β-keto carbonyls and culminates in a mild, tandem desilylation-cyclization reaction using tosylic acid. Compounds synthesized in this study have the potential for further diversification at the alkyne, carbonyl and enol-ether moieties. Hence, the furanylidenes from this study are prospective building blocks for biologically active, furan-containing natural products and their analogs.

Keywords: desilylation; furanylidene; silyl ether; tosylic acid.

Introduction

Furanylidene units are core structures in several compounds with important biological activity (Wright, 2005), for example, anti-parasitic (Epifanio et al., 2005; Lim et al., 2006), antibacterial (Levy et al., 2003; Berg et al., 2006; Brændvang et al., 2009) and cytotoxic activities (Cateni et al., 2006) (Figure 1). Previous reports have detailed acid-mediated syntheses of furanylidene systems from 6-hydroxy-1,3-dicarbonyls and their alcohol-protected derivatives (Bryson, 1973; Lygo, 1988; Sato et al., 1991; Kim et al., 2000; Solladié et al., 2000) (Scheme 1). In all cases, only the more stable *E*-furanylidene was produced. While the furanylidenes were accessed in moderate to good yields, most of the reported syntheses were limited to furanylidene esters with hydrogen or methyl substituents at the α-position (Bryson, 1973; Lygo, 1988; Sato et al., 1991; Solladié et al., 2000). Here, we report the synthesis of furanylidene building blocks with the built-in potential for further diversification at α-propargyl groups in addition to the carbonyl and enol-ether moieties in the molecules.

Results and discussion

During the synthesis of unique alkynes for a gold-catalysis project we discovered that the tosylic acid-mediated desilylation of silyl ether **7a** at room temperature results in the formation of furanylidene system **8a** with the 'acid-labile' alkyne moiety still intact (Scheme 2). In line with previous reports (Bryson, 1973; Lygo, 1988; Sato et al., 1991; Kim et al., 2000; Solladié et al., 2000), ^{13}C-NMR data confirmed that only one isomer of the furanylidene **8a** was formed in the process.

The study by Sato et al., an acid-mediated desilylation-cyclization reaction, is closely related to our work (Sato et al., 1991). They have reported isolating a furanylidene methyl ester as a byproduct in 28% yield. Given that the furanylidene was not their target, the adaptability of the furanylidene chemistry to a variety of substrates was not explored. With the built-in potential for further diversification at the enol-ether, the carbonyl and the alkyne of the α-propargyl group, furanylidene systems such as **8a** are potential building blocks for biologically active, furan-containing natural products and their analogs. As such, we decided to explore the adaptability of desilylation-cyclization chemistry with different carbonyls in substrates **7**: esters **7a–b**, amide **7c** and ketone **7d** (Scheme 2).

Our four-step synthesis of the furanylidene compounds **8** begins with the treatment of the dianion of the β-keto carbonyl **4** with (*R*)-propylene oxide to provide compound **5** (Scheme 2). Conversion of **5** to the *t*-butyldimethylsilyl ether **6** followed by monoalkynylation with propargyl bromide produces the monoalkynylated compound **7**. In the final step of the synthesis, a tandem desilylation-cyclization with tosylic acid monohydrate at room temperature yields the furanylidene system **8** as one isomer. The esters **7a**, **7b** and ketone **7d** cyclized to form furanylidenes **8a**, **8b** and **8d**, respectively (Scheme 2, Table 1). Compounds **9/9′a** and **9/9′b** were never observed. ^{1}H NMR spectra indicated that trace amounts of a non-furanylidene compound, possibly the monoalkynylated 6-hydroxy 1,3-diketone **9/9′d**, was produced in the reaction with **7d** but this byproduct was never isolated. At this time the geometry of the double bond in furanylidenes **8a**, **8b** and **8d** is not known. However, the literature suggests that we have synthesized the *E*-isomers (Bryson, 1973; Lygo, 1988; Sato et al., 1991; Kim et al., 2000; Solladié et al., 2000).

Amide **7c** is the only substrate that did not cyclize upon treatment with the tosylic acid. We attempted the desilylation-cyclization of **7c** at room temperature and under reflux conditions. However, due perhaps to the lower acidity of the α-proton in an amide relative to that of esters and ketones, compound **7c** only desilylated. Based on our analyses of NMR spectra, we theorized that **9′c** was produced instead (Scheme 2). Furanylidene **8c** was never observed.

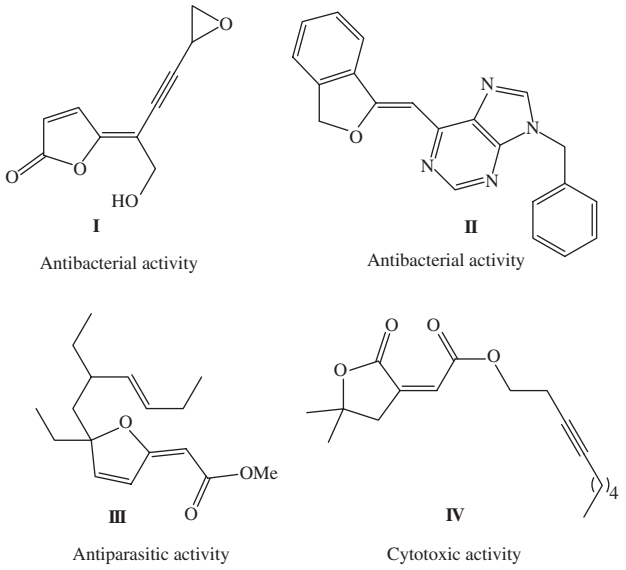


Figure 1 Biologically active compounds with furanylidene moieties (**I**: Levy et al., 2003; **II**: Brændvang et al., 2009; **III**: Lim et al., 2006; **IV**: Cateni et al., 2006).

Evidence suggests that the tosylic acid is a catalyst in the reaction and water is necessary for removal/trapping of the silyl group. In initial studies with two equivalents of the acid monohydrate relative to substrates **7a–d**, the reactions were complete within 1 h. When the reaction was attempted with 0.5 equivalent of acid with substrates **7a–c**, the reaction time increased from 1 h to 8 h and the yields improved significantly, from 45% to 69% for **8a**, 47% to 59% for **8b**, 57% to 89% for **8c**. Lower equivalents of the acid monohydrate (<0.5 Eq) resulted in incomplete conversion of the substrates to products during 8 h of reaction time.

In conclusion, we report that a mild, tandem desilylation-cyclization of silyl ethers of monoalkynylated β-keto carbonyls with tosylic acid monohydrate results in the formation of furanylidenes that are potential building blocks for biologically active furan-containing natural products and their analogs. Only one isomer of the furanylidenes results from the reaction and the alkyne moiety remains intact. Our results suggest that amides present a limitation to this chemistry in that only desilylation, without cyclization, will occur. The method, however, works well with ester and ketone carbonyls.

Experimental

General

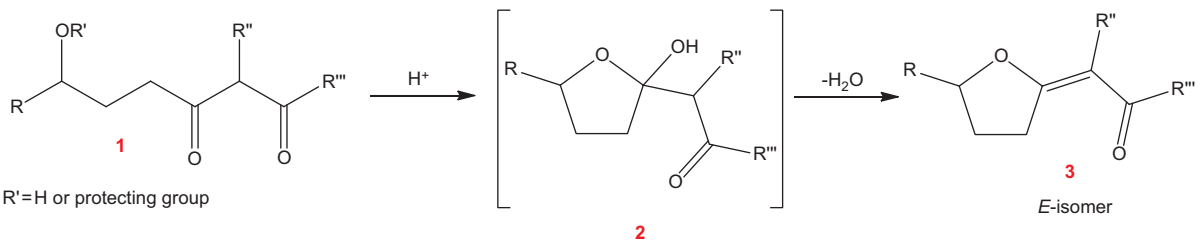
Unless noted, all reactions were performed under an atmosphere of argon in oven-dried glassware. Solvents for the reaction were obtained from commercial sources and purified with the MBraun Manual Solvent Purification System prior to use. Diisobutylamine was distilled over sodium hydroxide pellets. All other chemicals were obtained from commercial sources without further purification. Chromatography was performed with Selecto Scientific Si-gel (particle size 100–200 microns) and the chromatography solvents were purchased from commercial sources and used without further purification. NMR spectra were recorded in $CDCl_3$ solution on a Bruker 250 MHz Multi-Nuclear NMR instrument or a Varian 400 MHz Multi-Nuclear NMR instrument. High resolution mass spectrometry was performed using Waters Micromass Q-Tof micro Mass Spectrometer, ESI, positive ion mode.

General procedure for synthesis 6a–d

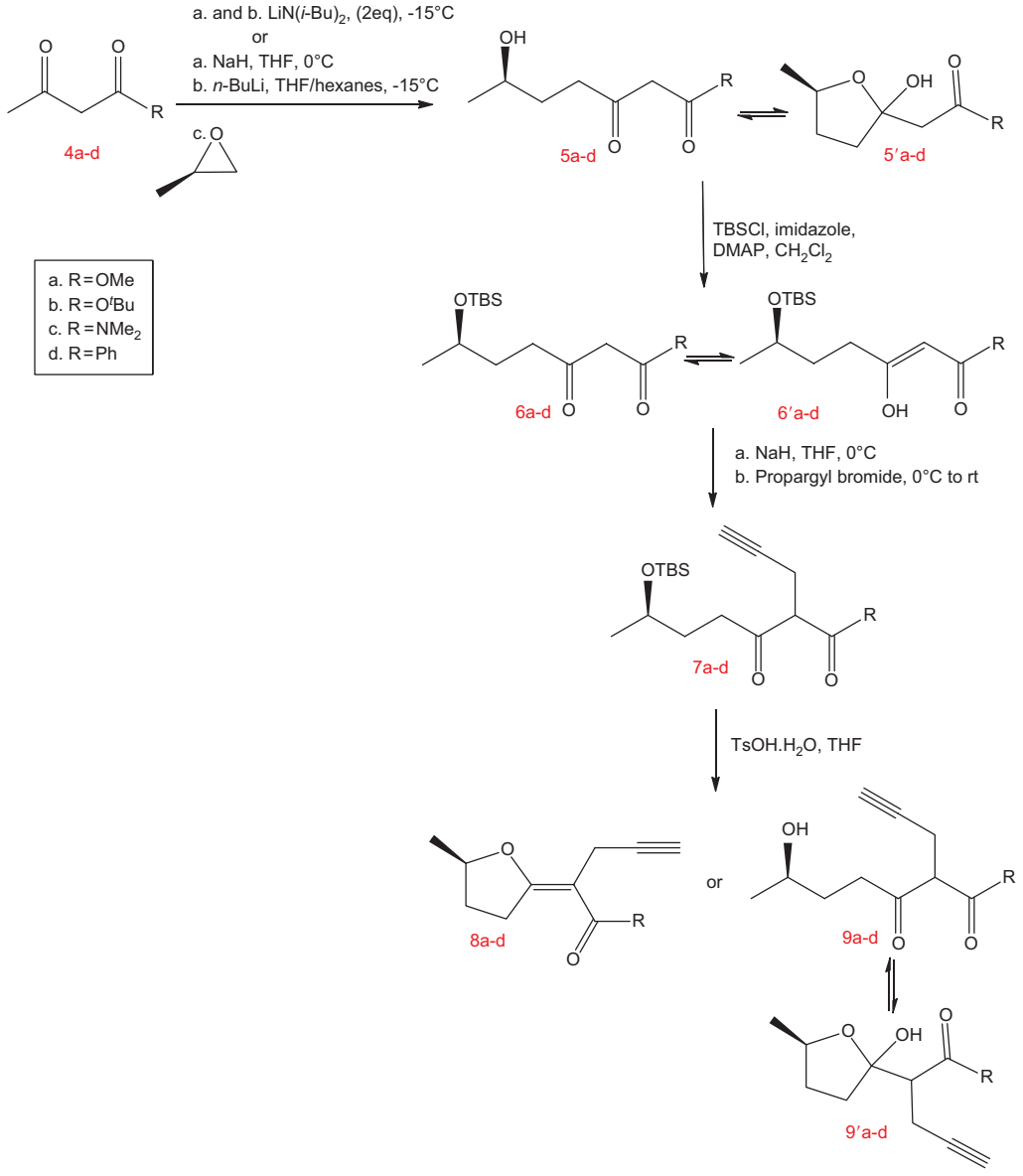
Part I: synthesis of 5a–d

Compounds **5a–c** were synthesized according to a known procedure with one modification (Lygo and O'Connor, 1992). Modification: the final reaction mixture was cooled in an ice-water bath (0°C) and quenched with an aqueous solution of saturated ammonium chloride. Following isolation from the reaction mixture compounds **5a–c** were used in the synthesis of **6a-c** without further purification.

6-Hydroxy-1-phenyl-1,3-heptanedione (5d) An oven-dried round-bottom flask equipped with a stir bar and argon-inlet was charged with freshly distilled diisobutylamine (4.3 mL, 25.0 mmol) in THF (20 mL). The solution was cooled with an ice-water bath (0°C) and treated dropwise with *n*-butyllithium (2.5 M in hexanes, 9.2 mL, 23.0 mmol). After 30 min, the resulting transparent yellow solution was cooled with an ice-salt-water bath (-15°C) and benzoylacetone **4d** (1.62 g, 10.0 mmol) in a solution of THF (10 mL) was added dropwise. The resulting solution had an intense orange color. After 45 min, the reaction mixture was treated dropwise with (*R*)-propylene oxide (1.05 mL, 15.0 mmol). The mixture was stirred overnight, quenched with an aqueous solution of saturated ammonium chloride (10 mL), and extracted twice with ethyl acetate (60 mL). The combined organic extract was washed with water (10 mL) followed by brine (10 mL), and dried with sodium sulfate. The dried organic extract was concentrated under reduced pressure and the crude orange product was purified by flash chromatography (20% ethyl acetate in hexanes followed by 50% ethyl acetate in hexanes) to provide **5d**, an orange oil, (1.89 g, 86%) which was used in the synthesis of **6d**. Compound **5d** has been synthesized previously by an independent method (Cannon et al., 1952).



Scheme 1 *E*-Furanylidene from acid-mediated cyclization of 6-hydroxy-1,3-dicarbonyls.



Scheme 2 Tosylic acid-mediated desilylation of silyl ethers **7a–d**.

Part II: synthesis of 6a–d

An oven-dried round-bottom flask equipped with a stir bar and argon-inlet was charged with dichloromethane (30 mL), imidazole (1.91 g, 28.1 mmol) and DMAP (50 mg, 0.41 mmol). After the solids dissolved completely, the solution was treated with *t*-butyldimethylchlorosilane (1.91 g, 12.7 mmol) followed by **5a–d** (11.5 mmol) in a solution of dichloromethane (10 mL). The resulting white suspension was stirred vigorously for 18 h. The mixture was quenched with water (15 mL) and the product was extracted twice with diethyl ether (70 mL). The combined extracts were washed with brine (15 mL), then dried with sodium sulfate and concentrated under reduced pressure. The crude yellow product **6a–d** was purified by flash chromatography.

Table 1 Tosylic acid catalyzed desilylation of silyl ether **7**.

Entry	Silyl ether	R	Isolated yield%			
			2 Eq $TsOH \cdot H_2O$		0.5 Eq $TsOH \cdot H_2O$	
			8	**9/9′**	**8**	**9/9′**
1	**7a**	OMe	45	0	69	0
2	**7b**	O^{t}Bu	47	0	59	0
3	**7c**	NMe_2	0	57	0	89
4	**7d**	Ph	57	0	–	–

Methyl 6-(*t*-butyldimethylsilyloxy)-3-oxoheptanoate (6a) This product was eluted with 2% ethyl acetate in hexanes, R_f=0.06, followed by 3% ethyl acetate in hexanes: a pale yellow oil; yield 1.80 g (42% over two steps). Characterization for **6a** is in agreement with that previously reported (Sato et al., 1991).

***t*-Butyl 6-(*t*-butyldimethylsilyloxy)-3-oxoheptanoate (6b)** This product was eluted with 2% ethyl acetate in hexanes, R_f=0.09: a pale

yellow oil; yield 56% over two steps; ^{1}H NMR (250 MHz): δ 3.80 (m, 1H), 3.37 (m, 2H), 2.59 (m, 2H), 1.70 (m, 2H), 1.48 (s, 9H), 1.14 (d, 3H, *J*=6.1 Hz), 0.92 (s, 9H), 0.06, (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz): δ 209.4, 172.4, 80.8, 67.9, 39.1, 37.5, 33.4, 29.5, 28.4, 26.2, 24.0, 18.4, -4.1, -4.5; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 331.2305, found: 331.2295.

6-(*t*-Butyldimethylsilyloxy)-*N,N*-dimethyl-3-oxoheptanamide (6c) This product was eluted with 25% ethyl acetate in hexanes followed by 60% ethyl acetate in hexanes, R_f=0.50: an orange oil; yield 29% over two steps; ^{1}H NMR (250 MHz): δ 3.83 (m, 1H), 3.57 (s, 2H), 2.96–3.04 (broad, 6H), 2.64 (m, 1H), 2.29 (m, 1H), 1.72 (m, 2H), 1.55 (d, 2H, *J*=6.1 Hz), 0.92 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (63 MHz): δ 204.5, 167.0, 67.3, 49.1, 39.0, 37.8, 35.4, 32.8, 25.7, 23.5, 17.9, -4.5, -4.8; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 302.2151, found: 302.2148.

6-(*t*-Butyldimethylsilyloxy)-3-hydroxy-1-phenylhept-2-ene-1-one (6′d) This product was eluted with 2% ethyl acetate in hexanes, R_f=0.27: an orange oil; yield 47% over two steps; ^{1}H NMR (250 MHz): δ 7.90 (d, 2H, *J*=8.3 Hz), 7.44–7.55 (m, 3H), 6.21 (s, 1H), 3.92 (m, 1H), 2.51 (m, 2H), 1.82 (m, 2H), 1.20 (d, 3H, *J*=6.1 Hz), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (63 MHz): δ 197.4, 182.7, 134.8, 132.2, 128.6, 126.9, 96.0, 76.9, 35.5, 35.0, 25.8, 23.7, 17.9, -4.4, -4.8; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 335.2042, found: 335.2054.

General procedure for synthesis of 7a–d

Methyl 6-(*t*-butyldimethylsilyloxy)-3-oxo-2-(2-propynyl)heptanoate (7a) Sodium hydride (60% oil dispersion, 137 mg, 3.42 mmol) was added under an argon atmosphere to THF (15 mL) in an oven-dried round-bottom flask equipped with a stir bar. The resulting white suspension was cooled in an ice-water bath (0°C) and treated dropwise with a solution of **6a–d** (880 mg, 3.04 mmol) in THF (5 mL). After 30 min, the mixture was treated dropwise with propargyl bromide (80% toluene solution, 0.49 mL, 3.35 mmol). The mixture was stirred overnight at 0°C and then allowed to warm to room temperature. The resulting orange-brown suspension was quenched with water (20 mL) and the crude product was extracted twice with ethyl acetate (60 mL). The extracts were washed with brine (20 mL), dried with sodium sulfate, and then concentrated under reduced pressure. The crude product was purified by chromatography.

Methyl 6-(*t*-butyldimethylsilyloxy)-3-oxo-2-(2-propynyl)heptanoate (7a) This product was eluted with 10% ethyl acetate in hexanes, R_f=0.38: a pale yellow oil; yield 0.89 g (89%); ^{1}H NMR (250 MHz): δ 3.85 (m, 1H), 3.73–3.79 (broad, 4H), 2.72–2.77 (b, 4H), 2.02 (t, 1H, *J*=1.4 Hz), 1.60–1.85 (m, 2H) 1.15 (d, 3H, *J*=6.1 Hz), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (63 MHz): δ 203.5, 168.5, 80.3, 70.1, 67.2, 57.3, 52.5, 38.7, 32.5, 25.7, 23.5, 17.9, 17.4, -4.5, -4.9; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 327.1992, found: 327.1996.

***t*-Butyl 6-(*t*-butyldimethylsilyloxy)-3-oxo-2-(2-propynyl)heptanoate (7b)** This product was eluted with 10% ethyl acetate in hexanes: a pale yellow oil; yield 94%; ^{1}H NMR (250 MHz) δ 3.86 (m, 1H), 3.64 (t, 1H, *J*=7.6 Hz), 2.40–2.89 (broad, 4H), 1.99 (broad s, 1H), 1.74(m, 2H), 1.49 (s, 9H), 1.15 (d, 3H, *J*=6.1 Hz), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (63 MHz): δ 203.8, 167.2, 82.4, 80.7, 69.9, 67.3, 58.4, 38.5, 32.7, 27.7, 25.7, 23.5, 17.9, 17.3, -4.5, -4.9; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 369.2461, found: 369.2459.

6-(*t*-Butyldimethylsilyloxy)-*N,N*-dimethyl-3-oxo-2-(prop-2-yn-1-yl)heptanamide (7c) This product was eluted with 50% ethyl acetate in hexanes, R_f=0.5: an orange oil; yield 87%; ^{1}H NMR (250 MHz): δ 3.92 (m, 1H), 3.82 (m, 1H), 3.17 (s, 3H), 2.99 (s, 3H), 2.53–2.96 (broad, 4H), 2.01 (t, 1H, *J*=2.6 Hz), 1.70 (m, 2H), 1.13 (d, 3H, *J*=6.1 Hz), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (63 MHz): δ 204.3, 167.5, 82.0, 70.2, 67.4, 55.3, 37.8, 36.1, 35.9, 32.7, 25.7, 23.6, 18.3, 17.9, -4.9, -4.7; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 340.2308, found: 340.2310.

6-(*t*-Butyldimethylsilyloxy)-1-phenyl-2-(prop-2-yn-1-yl)heptane-1,3-dione (7d) This product was eluted with 1% ethyl acetate in hexanes, followed by 3% ethyl acetate in hexanes, R_f=0.1: an orange oil; yield 37%; ^{1}H NMR (250 MHz): δ 8.09 (d, 2H, *J*=8.7 Hz), 7.70–7.80 (m, 1H), 7.52–7.60 (m, 2H), 4.76 (t, 1H, *J*=7.2 Hz), 3.77 (m, 1H), 2.55–2.91 (b, m, 2H), 2.50 (m, 2H), 1.99 (broad s, 1H), 1.67 (m, 2H), 1.07 (d, 3H, *J*=6.0 Hz). 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (63 MHz): δ 203.7, 194.6, 136.1, 133.8, 128.8 (4C), 80.6, 70.6, 67.2, 60.6, 37.6, 32.6, 25.7, 23.5, 18.2, 17.9, -4.5, -4.8; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 373.2199, found: 373.2199.

General procedure for synthesis of 8a, 8b, 8d and 9′c

An oven-dried 15 mL vial equipped with a stir bar was charged with *p*-toluenesulfonic acid monohydrate (*p*-TsOH; 190 mg, 0.99 mmol) and THF (0.5 mL). Once all of the acid dissolved, **7a–d** (0.5 mmol) was added as a solution in THF (1.0 mL). The mixture was stirred vigorously for 1 h, then diluted with ethyl acetate (5 mL) and washed sequentially with saturated sodium bicarbonate (2.5 mL), water (2.5 mL) and brine (2.5 mL). The organic solution was dried with sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography. The above procedure was also performed with 0.5 Eq of *p*-TsOH (47.5 mg, 0.25 mmol). The mixture was stirred for 8 h.

Methyl (2*E*)-2-(dihydro-5-methyl-2(3*H*)-furanylidene)-4-pentynoate (8a) This product was eluted with 5% ethyl acetate in hexanes, R_f=0.08, to yield **8a** as a pale yellow oil: yield 44 mg (45%) with 2 Eq *p*-TsOH and 67 mg (69%) with 0.5 Eq *p*-TsOH; ^{1}H NMR (250 MHz): δ 4.63 (m, 1H), 3.67(s, 3H), 3.10–3.40 (broad, 3H), 3.00 (dt, 1H, *J*=9.2, 18.2 Hz), 2.21 (m, 1H), 1.91(t, 1H, *J*=2.4 Hz), 1.73(m, 1H), 1.39(d, 3H, *J*=6.2 Hz); ^{13}C NMR (63 MHz): δ 172.1, 168.3, 97.1, 83.5, 80.5, 66.1, 50.9, 31.6, 31.3, 20.4, 15.6; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 195.1021, found: 195.1028.

***t*-Butyl (2*E*)-2-(dihydro-5-methyl-2(3*H*)-furanylidene)-4-pentynoate (8b)** This product was eluted with 3% ethyl acetate in hexanes, R_f=0.10, as a pale yellow oil; yield 47% with 2 Eq *p*-TsOH and 59% with 0.5 Eq *p*-TsOH; ^{1}H NMR (250 MHz): δ 4.57 (m, 1H), 3.15–3.40 (broad m, 3H), 2.94 (m, 1H), 2.22 (m, 1H), 1.91 (t, 1H, *J*=2.5 Hz), 1.67 (m, 1H), 1.52 (s, 9H), 1.38 (d, 3H, *J*=6.2 Hz); ^{13}C NMR (63 MHz): δ 170.6, 167.3, 98.7, 83.8, 80.0, 79.5, 65.8, 31.5, 31.4, 27.9, 20.5, 15.9; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 237.1491, found: 237.1487.

(2*E*)-2-(5-Methyldihydrofuran-2(3*H*)-ylidene)-1-phenylpent-4-yn-1-one (8d) This product was eluted with 5% ethyl acetate in hexanes, R_f=0.10, as a pale yellow oil; yield 57% with 2 Eq *p*-Ts-OH. Trace amounts of **9/9′d** proved difficult to separate from

8d. ^{1}H NMR (250 MHz): δ 7.65 (d, 2H, *J*=9.3 Hz), 7.39–7.49 (m, 3H), 4.65 (m, 1H), 3.30–3.40 (broad, 2H), 2.71 (m, 2H), 2.18 (m, 1H), 1.96 (t, 1H, *J*=2.7 Hz), 1.64 (m, 1H), 1.44 (d, 3H, *J*=9.1 Hz); ^{13}C NMR (63 MHz): δ 197.0, 172.0, 142.0, 130.7, 128.2, 127.6, 107.0, 83.0, 80.5, 66.8, 32.3, 31.7, 20.5, 17.3; HRMS (ESI, positive ion mode): $[M+H]^+$ *m/z* calculated: 241.1229, found: 241.1226.

2-(2-Hydroxy-5-methyltetrahydrofuran-2-yl)-*N,N*-dimethylpent-4-ynamide (9′c) This product was eluted with 20% ethyl acetate in hexanes, followed by 100% ethyl acetate, R_f=0.50 as oily white crystals: yield 57% with 2 Eq *p*-Ts-OH and 89% with 0.5 Eq *p*-TsOH. ^{1}H NMR (250 MHz) δ 4.45 (m) 4.35 (m), 4.14(m), 3.15–3.22 (broad), 3.00–3.10 (broad), 2.74 (m), 2.52 (dd, *J*=2.7, 4.3 Hz), 2.45 (dd, *J*=2.7, 4.3 Hz), 2.09–2.22 (broad), 1.75–2.07 (broad), 1.45 (m), 1.34 (m), 1.19 (d, *J*=6.2 Hz); ^{13}C NMR (63 MHz) δ 174.5, 106.2, 81.8, 74.2, 69.6, 47.4, 38.1, 35.9, 35.7, 31.5, 21.3, 19.5.

Acknowledgments

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