

Free radical 5-*exo*-dig cyclization as the key step in the synthesis of *bis*-butyrolactone natural products: experimental and theoretical studies†‡Gangavaram V. M. Sharma,^{*a} Devoju Harinada Chary,^a Nagula Chandramouli,^a Florian Achraimer,^b Sateesh Patrudu^b and Hendrik Zipse^{*b}

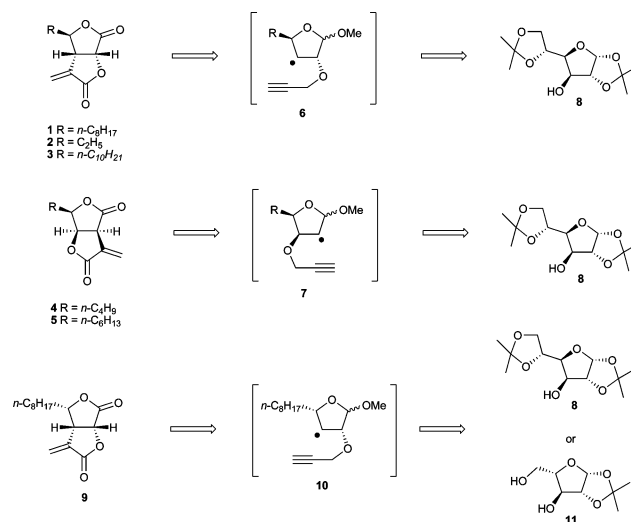
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Radical cyclization reactions were performed by 5-*exo*-dig mode to yield *cis*-fused bicyclic systems, leading to the synthesis of *bis*-butyrolactone class of natural products. The study was aimed at understanding the impact of alkyl side chains of furanoside ring systems in *L-ara* configuration on the radical cyclization. It was amply demonstrated by experimental studies that the increase in the length of the alkyl side chain has an effect on the cyclization: while efficient cyclization reactions could be realized with methyl and ethyl side chains, the yields were significantly reduced in the case of *n*-pentyl side chain. Theoretical studies using DFT and (RO)MP2 methods were carried out to analyze the influence of the substitution pattern on the cyclization barriers.

Introduction

Radical cyclization reactions¹ for the synthesis of cyclic carbon frameworks, particularly the *cis*-fused bicyclic system, is a simple and prominent protocol. Utilization of a 5-*exo*-dig² mode of cyclization of a suitably substituted 5-hexynyl radical onto the alkyne is usually a highly regioselective reaction and efficient at introducing an *exo*-methylene group. Application of radical cyclization on carbohydrate derived precursors has found wide utility, while the above strategies were successfully adopted by our group for the synthesis of natural products containing *bis*-butyrolactone moieties. In our earlier studies, a 5-*exo*-dig radical cyclization approach was efficiently utilized for the synthesis of avenaciolide³ (**1**), 4-*epi*-ethisolide⁴ (**2**), discosiolide⁵ (**3**), canadensolide^{6,7} (**4**) and sporothriolide⁴ (**5**), besides xylobovide.⁸ For the synthesis of **1–5** (Scheme 1), the corresponding radical intermediates **6** and **7** were derived from diacetone glucose (DAG) **8**. The cyclization was found to be successful in giving the *cis*-fused bicyclic systems along with the concomitant introduction of the *exo*-methylene group. In further studies, a similar strategy was used for the synthesis of *iso*-avenaciolide⁹ (**9**), a structurally related natural product, wherein the attempt at the cyclization of the radical intermediate **10**, generated from **8** or *L*-arabinose

Scheme 1 Retrosynthetic analysis of **1–5** and **9**.

derivative **11**,^{9c} met with failure and the synthesis of **9** could not be achieved by the above protocol.

Results and discussion

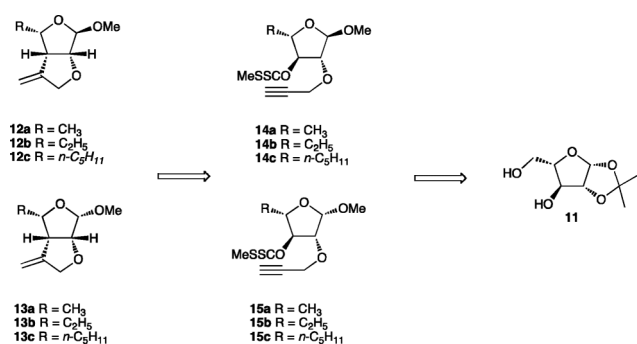
The successful synthesis of **1–5** (Scheme 1), and failure to attain **9** inferred that: (a) the systems with *D-xylo* configuration undergo a facile cyclization and (b) the systems with *L-ara* configuration resisted doing so. The above observations on the resistance of **10** to undergo radical cyclization prompted us to study the impact of the side chain on radical cyclization reactions. Based on the retrosynthetic analysis (Scheme 2), synthesis of *cis*-fused bicyclic systems **12a–12c** and **13a–13c** could be achieved through the

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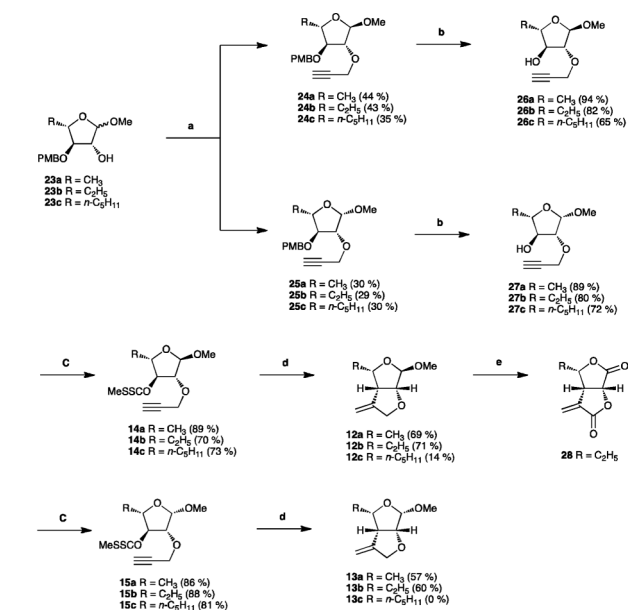
† This work is dedicated to the memory of Athel Beckwith, a great teacher and a true pioneer in the area of radical chemistry.

‡ Electronic supplementary information (ESI) available: Analytical data and synthetic details for all synthesized compounds, energies and structures obtained in DFT and *ab initio* calculations. See DOI: 10.1039/c1ob00019e

Scheme 2 Retrosynthetic analysis of **12** and **13**.

xanthates **14a–14c** and **15a–15c**, which in turn could be derived from **11**.

Anomeric mixtures of **23a**, **23b** and **23c** (Scheme 3), prepared from *L*-arabinose (see ESI[†]),¹⁰ independently on reaction with propargyl bromide in the presence of NaH in dry THF furnished the required propargyl derivatives **24a–c** and **25a–c** respectively. Both the β -anomers **24a–c** and α -anomers **25a–c** were independently subjected to oxidative deprotection of the PMB group with DDQ in wet CH₂Cl₂ to give alcohols **26a–c** and **27a–c** respectively. The alcohols **26a–c** and **27a–c** on reaction with NaH and carbon disulfide followed by methyl iodide were converted into the corresponding xanthate esters **14a–c** and **15a–c** respectively.



Reagents and conditions: (a) NaH, propargyl bromide, THF, RT, 4 h; (b) DDQ, CH₂Cl₂:H₂O (19:1), RT, 2 h; (c) NaH, CS₂, CH₃I, THF, 0 °C, RT, 2 h; (d) *n*-Bu₃SnH, AIBN, benzene, reflux, 12 h; (e) Ref 11.

Scheme 3 Synthesis of intermediates **12** and **13**.

Having prepared the radical precursors, the stage was set for radical cyclization reactions. Accordingly, **14a** and **15a** (Scheme 3), with a methyl side chain were subjected to radical reaction with *n*-Bu₃SnH in the presence of catalytic amounts of AIBN in dry benzene at reflux for 12 h. Interestingly, unlike **10** with the *n*-octyl side chain, both **14a** and **15a** underwent cyclization to give the respective cyclized products **12a** (69%) and **13a** (57%) (Scheme 3). Further, radical cyclization was next attempted on **14b** (β -) and **15b** (α -) with an ethyl side chain, which resulted in

the successful synthesis of *cis*-fused bicyclic systems **12b** (71%) and **13b** (60%) respectively. A similar study was conducted on the radical precursors **14c** (β -) and **15c** (α -). Unlike in the case of **14a–b** and **15a–b**, the β -anomer **14c** underwent radical cyclization reaction to give *cis*-fused bicyclic system albeit in a very poor yield (14%), while **15c** totally resisted undergoing cyclization. Thus, it is pertinent to mention that cyclization products with methyl or ethyl side chains were obtained in better yields from the β -anomers over the α -anomers. In the case of *n*-pentyl side chain, the α -anomer failed to give the cyclization product and the β -anomer gave the product in very poor yield. These results on the *n*-pentyl side chain very well complement the results obtained earlier with an *n*-octyl side chain. Thus, it is evident to mention that the side chain in *L*-ara configuration has a role to play in the 5-*exo*-dig radical cyclizations.

Synthesis of ethisolide

Ethisolide (**28**), *iso*-avenaciolide (**9**) and avenaciolide (**1**) are three *bis*-lactone secondary mold metabolites isolated from broths of *Aspergillus* and *Penicillium* species, and have been reported to possess antifungal and antibacterial activities. Ethisolide (**28**) has similar structural features to *iso*-avenaciolide (**9**), except for an ethyl side chain. However, it differs from avenaciolide (**1**) and 4-*epi*-ethisolide (**2**) in being a positional isomer. During the studies, the radical reactions with different side chains, synthesis of **12b** and **13b** (Scheme 3) has been achieved successfully. The conversion of **12b** into ethisolide (**28**) has already been reported¹¹ in the literature, and this study thus formally concludes the total synthesis of ethisolide **28**.

Theoretical studies on 5-*exo*-dig cyclizations in selected systems derived from the tetrahydrofuran skeleton

In order to shed some light on the influence of the substituents present in precursor **15** on the efficiency of the subsequent 5-*exo*-dig cyclization processes, theoretical studies were undertaken for a series of radicals in which the α -configuration of the methoxy group at C-5 was kept constant, while the stereochemistry and the substitution pattern at the C-2 position was allowed to vary (Scheme 4). The influence of the configuration at the C-2 position on the reaction barrier and reaction enthalpy for the cyclization step was first studied for R = CH₃ (Table 1). As

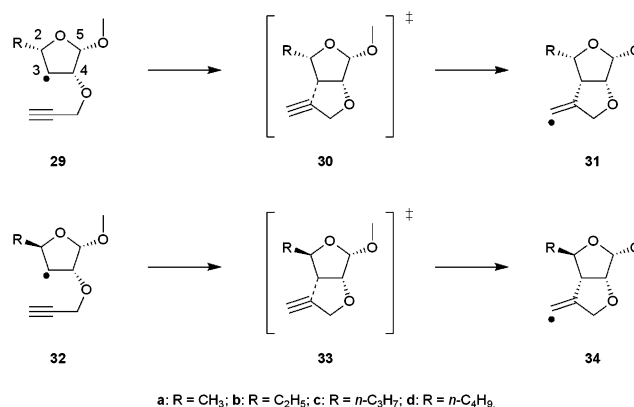
Scheme 4 5-*Exo*-dig cyclizations in selected systems derived from the tetrahydrofuran skeleton.

Table 1 Boltzmann-averaged activation and reaction enthalpies for the systems described in Scheme 4 (in kJ mol⁻¹)

	$\Delta H^\ddagger_{298}(\mathbf{30a-29a})$	$\Delta H_{298}(\mathbf{31-29})$	$\Delta H^\ddagger_{298}(\mathbf{33-32})$	$\Delta H_{298}(\mathbf{34-32})$
a: R = CH₃				
UB3LYP ^a	+33.51	-64.90	+29.10	-74.02
ROMP2 ^b	+25.60	-78.86	+22.63	-86.03
b: R = C₂H₅				
UB3LYP ^a	+32.30	-64.82	n/a	n/a
ROMP2 ^b	+23.83	-78.81	n/a	n/a
c: R = <i>n</i>-C₃H₇				
UB3LYP ^a	+33.15	-64.24	n/a	n/a
ROMP2 ^b	+24.44	-78.75	n/a	n/a
d: R = <i>n</i>-C₄H₉				
UB3LYP ^a	+33.72	-63.81	n/a	n/a
ROMP2 ^b	+24.79	-78.66	n/a	n/a

^a UB3LYP/6-311+G(d,p)//UB3LYP/6-31G(d).
^b (RO)MP2(FC)/G3MP2large//UB3LYP/6-31G(d).

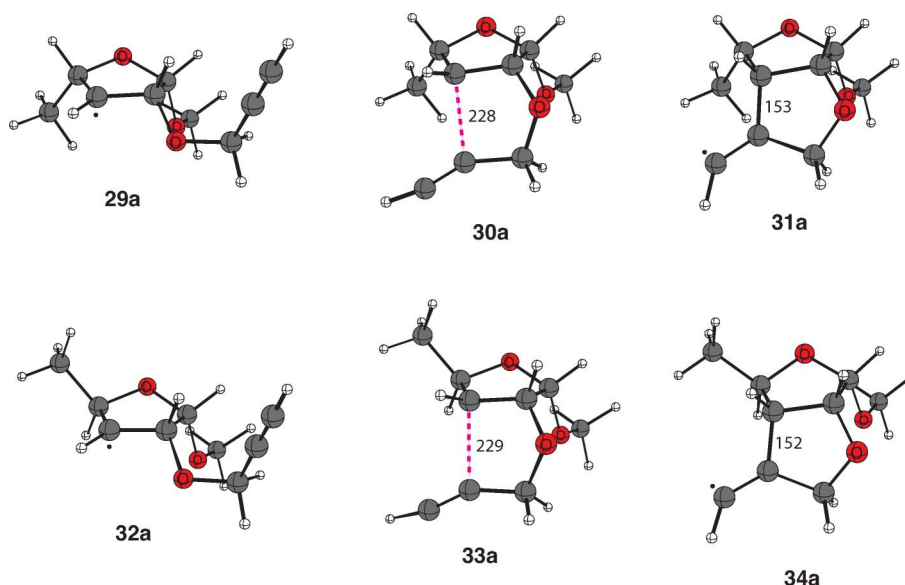
previously anticipated we find here that the reaction barrier for cyclization of radical **29a** is somewhat larger at $\Delta H^\ddagger_{298}(\mathbf{30a-29a}) = +33.51$ kJ mol⁻¹ as compared to the barrier for cyclization of radical **32a** with $\Delta H^\ddagger_{298}(\mathbf{33a-32a}) = +29.10$ kJ mol⁻¹ at UB3LYP/6-311+G(d,p) level of theory. The higher barrier for cyclization of **29a** is undoubtedly due to the *all-cis* stereochemistry in this system, which is also reflected in the reaction energy for formation of product **31a**. Comparing the differences in barriers of $\Delta\Delta H^\ddagger_{298}(\mathbf{30a-33a}) = +4.41$ kJ mol⁻¹ with differences in reaction energies of $\Delta\Delta H_{298}(\mathbf{31a-34a}) = +9.12$ kJ mol⁻¹ we may also conclude that approx. 50% of the strain energy present in the product radicals is already present in the respective transition states. According to the Eyring equation, the cyclization rates depend on the activation energies in an exponential manner. Assuming identical activation entropies for both processes we can use the expression $k_{34a}/k_{31a} = \exp((\Delta H^\ddagger_{34a} - \Delta H^\ddagger_{31a})/RT) = 5.8$ to predict that the cyclization rate for **32a** will be 5.8 times faster than that for **29a** at a temperature of 298.15 K. Assuming

equal intermolecular trapping rates for radicals **31a** and **34a** with hydrogen donors, this indicates that cyclization of **29a** may be low yielding under conditions optimized for the reaction of **32a**.

In Fig. 1 the most stable conformers of **29a** and **32a** are shown together with the respective transition states and reaction products. Only one low energy conformation could be found for the orientation of the methoxy group at C5 due to the presence of a strong *exo*-anomeric effect. For the cyclized product radicals two configurations at the newly formed double bond are possible. For both products **31a** and **34a** we find that the *Z*-configuration is more favourable than the *E*-configuration (see ESI† for further details).

In order to explore possible reasons for the unusual chain length dependence observed in radical cyclization reactions involving precursor **15a–15c**, the reaction pathways of *all-cis* substituted tetrahydrofuran models **29a–d** were examined varying the size of the side chain from methyl, ethyl, *n*-propyl to *n*-butyl. At the UB3LYP/6-311+G(d,p)//UB3LYP/6-31G(d) level of theory we find that extending the side chain from R = Me to R = Et leads to marginally lower barriers, in full agreement with the experimental studies. However, further extension of the sidechain to R = *n*-propyl or *n*-butyl led to only marginally higher barriers. These largely similar reaction barriers are accompanied by equally similar reaction energies (Table 1).

Since the DFT hybrid functional UB3LYP does not take dispersion effects into account properly we also performed restricted open-shell MP2 ((RO)MP2) single point calculations using the large G3MP2large basis set.¹² Reaction barriers calculated at (RO)MP2 level are uniformly lower than UB3LYP barriers by approx. 10 kJ mol⁻¹ and reaction energies are larger by approx. 14 kJ mol⁻¹ in all cases. However, also at ROMP2 level the barrier differences for cyclization of radicals **29a–d** remain quite small. Thus, while the calculated reaction barriers and reaction energies for cyclization of radicals **29a** and **32a** clearly respond to the stereochemistry selected at C2, the calculations performed for cyclization of radicals **29a–d** do not provide an answer for the

**Fig. 1** Structures of the most stable conformers of **29a** and **32a** together with the corresponding transition states and reaction products as obtained at UB3LYP/6-31G(d) level of theory (distances are given in pm).

largely reduced yields in cyclization reactions of radicals **29** with longer alkyl substituents at C2 position. These may, of course, not only be due to problems with the actual cyclization step, but may also reflect problems with other steps of the radical chain reaction.

Conclusion

The manuscript describes theoretical and experimental studies on the impact of the side chains at the C2 and C5 positions on 5-*exo*-dig radical cyclization reactions in radicals derived from L-arabinose. While the stereochemistry at the anomeric C5 position remains without much consequence in the cyclization reactions, the length of the substituent at the C2 position has a marked effect on cyclization yields: while extension of the C2 substituent from methyl to ethyl leads to slightly increased yields, the cyclization becomes much more difficult for the *n*-pentyl substituted system. Theoretical studies of cyclization reactions indicate that the stereochemistry at the C2 position has a significant impact on the cyclization barriers. The theoretical studies also indicate that variation of the substituent from methyl to ethyl leads to a minor reduction in reaction barriers, in full agreement with experiment. Further extension of the C2 substituent to *n*-propyl and *n*-butyl does not lead to drastically altered cyclization barriers and suggests that the largely reduced reaction yields observed experimentally are due to other factors in the overall chain reaction.

Experimental part

General experimental details

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification. All reactions were performed under Nitrogen. ¹H NMR (200 MHz, 300 MHz, 400 MHz and 500 MHz) and ¹³C NMR (75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz and Inova-500 MHz with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in Hz. Chemical shifts were reported in ppm relative to the solvent signal. Multiplicities are indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); quin (quintet). All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na₂SO₄ and concentrated below 40 °C in *vacuo*. IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

(2*S*,3*S*,4*R*,5*R*)-3-(4-Methoxybenzyloxy)-tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan (24a) and (2*S*,3*S*,4*R*,5*S*)-3-(4-methoxybenzyloxy)-tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan (25a). A stirred suspension of sodium hydride (0.04 g, 2.14 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of **23a** (0.25 g, 0.93 mmol) in THF (3 mL) at 0 °C and stirred for 15 min. Propargyl bromide (0.08 mL,

0.93 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for 4 h. Reaction mixture was quenched with aq. NH₄Cl solution (3 mL) and extracted with ethyl acetate (2 × 10 mL). Organic layer was washed with water (5 mL), brine (5 mL), dried (Na₂SO₄), evaporated and the residue was purified by column chromatography. First eluted (60–120 Silica gel; ethyl acetate–*n*-hexane, 1.2 : 8.8) was **24a** (0.13 g, 45%) as a liquid; [α]_D = –218.2 (*c* 0.66, chloroform); IR (neat): ν_{\max} 3451, 3282, 2924, 1720, 1611, 1513, 1248, 1100, 1065, 1050, 943, 771 cm^{–1}; ¹H NMR (300 MHz, CDCl₃): δ 1.25 (d, 3H, *J* = 6.0 Hz, CH₃), 2.42 (t, 1H, *J* = 2.2 Hz, acetylenic), 3.33 (s, 3H, OCH₃), 3.42–3.46 (q, 1H, *J* = 3.7, 7.5 Hz, H-3), 3.77 (s, 3H, Ar–OCH₃), 3.94–4.19 (m, 4H, H-2, H-4 and OCH₂), 4.43–4.62 (dd, 2H, *J* = 11.7 Hz, Ar–OCH₂), 4.77 (s, 1H, H-5), 6.82 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.22 (d, 2H, *J* = 8.6 Hz, Ar–H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.1, 129.8, 129.3 (2C), 113.7 (2C), 106.5, 88.4, 87.9, 76.6, 74.9, 71.8, 57.2, 54.6, 54.5, 18.6; HRMS (ESI): *m/z* calculated for C₁₇H₂₂NaO₅(M⁺+Na) 329.1364, found 329.1354.

Second eluted (60–120 Silica gel; ethyl acetate–*n*-hexane, 1.2 : 8.8) was **25a** (0.09 g, 31%) as colourless liquid; [α]_D = +129.0 (*c* 0.36, chloroform); IR (neat): ν_{\max} 3448, 3282, 1720, 1636, 771, 600 cm^{–1}; ¹H NMR (300 MHz, CDCl₃): δ 1.28 (d, 3H, *J* = 6.4 Hz, CH₃), 2.42 (t, 1H, *J* = 2.2 Hz, acetylenic), 3.38 (s, 3H, OCH₃), 3.78 (s, 3H, Ar–OCH₃), 3.85 (t, 1H, *J* = 6.4 Hz, H-3), 3.95 (p, 1H, *J* = 6.0, 12.4 Hz, H-2), 4.15–4.31 (m, 3H, H-4, OCH₂), 4.45–4.64 (dd, 2H, *J* = 11.3 Hz, Ar–OCH₂), 4.83 (d, 1H, *J* = 4.1 Hz, H-5), 6.82 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.22 (d, 2H, *J* = 8.6 Hz, Ar–H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 130.1, 129.4 (2C), 113.8 (2C), 101.2, 86.4, 83.7, 77.6, 75.1, 72.0, 57.5, 55.2, 54.7, 22.1; HRMS (ESI): *m/z* calculated for C₁₇H₂₂NaO₅(M⁺+Na) 329.1364, found 329.1367.

(2*S*,3*S*,4*R*,5*R*)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-nyloxy)furan-3-ol (26a). A solution of **24a** (0.22 g, 0.71 mmol) in aq. CH₂Cl₂ (1 : 19, H₂O–CH₂Cl₂, 10 mL) was treated with DDQ (0.32 g, 1.43 mmol) at 0 °C and stirred for 2 h. The reaction mixture was quenched with aq. NaHCO₃ solution (7 mL) and extracted with CH₂Cl₂ (2 × 15 mL). Organic layer was washed with aq. NaHCO₃ solution (10 mL), water (10 mL), brine (10 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of residue obtained by chromatography (60–120 Silica gel; ethyl acetate–*n*-hexane, 1 : 4) afforded **26a** (0.12 g, 94%) as a liquid; [α]_D = –65.2 (*c* 1.53, CDCl₃); IR (neat): ν_{\max} 3447, 2925, 2854, 1741, 1219, 771 cm^{–1}; ¹H NMR (200 MHz, CDCl₃): δ 1.29 (d, 3H, *J* = 6.2 Hz, CH₃), 2.44 (t, 1H, *J* = 2.5 Hz, acetylenic), 2.66 (bd, 1H, OH), 3.36 (s, 3H, OCH₃), 3.69 (bs, 1H, H-3), 3.90 (d, 1H, *J* = 2.9 Hz, H-2), 3.99 (t, 1H, *J* = 5.8 Hz, H-4), 4.22 (t, 2H, *J* = 2.5 Hz, OCH₂), 4.84 (s, 1H, H-5); ¹³C NMR (CDCl₃, 75 MHz): δ 106.4, 88.8, 80.5, 80.1, 75.0, 57.4, 54.7, 29.6, 18.6; HRMS (ESI): *m/z* calculated for C₉H₁₄NaO₄(M⁺+Na) 209.0789, found 209.0793.

(2*S*,3*S*,4*R*,5*S*)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-nyloxy)furan-3-ol (27a). A solution of **25a** (0.39 g, 1.27 mmol) in aq. CH₂Cl₂ (1 : 19, H₂O–CH₂Cl₂, 10 mL) was treated with DDQ (0.58 g, 2.54 mmol) at 0 °C as described for **26a**. Work up and purification by column chromatography (60–120 Silica gel; ethyl acetate–*n*-hexane, 1 : 4) afforded **27a** (0.21 g, 89%) as a liquid; [α]_D = +284.1 (*c* 0.44, CDCl₃); IR (neat): ν_{\max} 3437, 2926, 2856, 1737, 1219, 1051, 769 cm^{–1}; ¹H NMR (300 MHz, CDCl₃): δ 1.33 (d, 3H, *J* = 6.4 Hz, CH₃), 2.45 (t, 1H, *J* = 2.2 Hz, acetylenic), 3.38

(s, 3H, OCH₃), 3.87 (p, 1H, *J* = 6.42, 12.8 Hz, H-3), 4.07–3.95 (m, 2H, H-2, H-4), 4.16–4.38 (ddd, 2H, *J* = 2.2, 16.2 Hz, OCH₂), 4.81 (d, 1H, *J* = 3.8 Hz, H-5); ¹³C NMR (CDCl₃, 75 MHz): δ 100.7, 84.1, 79.2, 77.9, 75.2, 57.6, 54.6, 31.5, 21.0; HRMS (ESI): *m/z* calculated for C₉H₁₄NaO₄(M⁺+Na) 209.0789, found 209.0797.

***O*-(2*S*,3*S*,4*R*,5*R*)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan-3-yl-*S*-methyl carbonodithioate (14a).** A stirred suspension of NaH (0.05 g, 2.25 mmol) in dry THF (3 mL) under N₂ atmosphere was treated with a solution of **26a** (0.14 g, 0.75 mmol) in THF (3 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulfide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was quenched with aq. NH₄Cl solution (4 mL) and extracted with ethyl acetate (3 × 5 mL). Organic layer was washed with water (6 mL), brine (6 mL), dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (60–120 Silica gel; ethyl acetate–*n*-hexane, 1 : 9) afforded **14a** (0.18 g, 89%) as light yellow liquid; [α]_D²⁰ = –304.2 (*c* 1.04, CDCl₃); IR (neat): ν_{max} 3448, 2921, 2851, 1724, 1460, 1250, 1071, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.43 (d, 3H, *J* = 6.2 Hz, CH₃), 2.47 (t, 1H, *J* = 2.2 Hz, acetylenic), 2.57 (s, 3H, SCH₃), 3.38 (s, 4H, H-2, OCH₃), 4.19 (s, 1H, H-4), 4.30 (s, 2H, OCH₂), 5.0 (s, 1H, H-5), 5.61 (d, 1H, *J* = 3.3 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz): δ 214.7, 107.3, 96.3, 86.3, 84.5, 76.3, 75.3, 57.8, 55.2, 18.9, 15.8; HRMS (ESI): *m/z* calculated for C₁₁H₁₆NaO₄S₂(M⁺+Na) 299.0387, found 299.0391.

***O*-(2*S*,3*S*,4*R*,5*S*)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan-3-yl-*S*-methyl carbonodithioate (15a).** A stirred suspension of NaH (0.05 g, 2.25 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of **27a** (0.14 g, 0.75 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulfide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.12 mmol) was added at 0 °C as described for **14a** and purification of the residue by column chromatography (60–120 Silica gel; ethyl acetate–*n*-hexane, 1 : 9) afforded **15a** (0.18 g, 86%) as light yellow liquid; [α]_D²⁰ = +285.1 (*c* 0.44, CDCl₃); IR (neat): ν_{max} 3285, 2924, 2858, 2120, 1712, 1446, 1210, 1064, 669 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.50 (d, 3H, *J* = 6.4 Hz, CH₃), 2.42 (t, 1H, *J* = 2.2 Hz, acetylenic), 2.58 (s, 3H, SCH₃), 3.44 (s, 3H, OCH₃), 4.06 (m, 1H, H-2), 4.25 (t, 2H, *J* = 2.2 Hz, OCH₂), 4.45 (t, 1H, *J* = 5.2 Hz, H-4), 4.95 (d, 1H, *J* = 4.5 Hz, H-5), 5.90 (q, 1H, *J* = 4.1 Hz, H-3); ¹³C NMR (CDCl₃, 100 MHz): δ 214.9, 106.9, 88.7, 86.3, 78.7, 78.3, 75.3, 57.7, 54.6, 19.1 (2C); HRMS (ESI): *m/z* calculated for C₁₁H₁₆NaO₄S₂(M⁺+Na) 299.0387, found 299.0389.

(3*aR*,4*S*,6*S*,6*aR*)-Hexahydro-6-methoxy-4-methyl-3-methylenefuro[3,4-*b*]furan (12a). A solution of **14a** (0.18 g, 0.67 mmol) in dry benzene (25 mL) under N₂ atmosphere was treated with *n*-Bu₃SnH (0.36 mL, 1.34 mmol) at room temperature and heated at reflux for 30 min. After 30 min, a catalytic amount of AIBN was added at reflux and continued the reflux for 12 h. The reaction mixture was cooled to room temperature, benzene evaporated under reduced pressure and residue purified by column chromatography (60–120 Silica gel; ethyl acetate–*n*-hexane, 1.2 : 8.8) to afford **12a** (0.08 g, 69%) as a colorless liquid; [α]_D²⁰ = –21.70 (*c* 0.41, CDCl₃); IR (neat): ν_{max} 2925, 2852, 1731, 1654, 1463, 1265, 1100, 771 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 1.25 (d, 3H, *J* = 9.0 Hz, CH₃), 3.18 (t, 1H, *J* = 6.8 Hz, H-3a), 3.31–3.40 (m, 4H, H-4, OCH₃), 4.19–4.30 (m, 2H, OCH₂), 4.53 (d, 1H, *J* = 3.8 Hz, H-6a), 4.81 (s, 1H, H-6), 4.90 (d, 1H, *J* = 1.5 Hz, olefinic), 5.08 (d, 1H, *J* = 2.2 Hz, olefinic); ¹³C NMR (CDCl₃, 75 MHz): δ 146.3, 107.5, 106.2, 85.2, 74.5, 73.0, 54.7, 52.8, 29.6; HRMS (ESI): *m/z* calculated for C₉H₁₅O₃(M⁺+H) 171.1021, found 171.1023.

(3*aR*,4*S*,6*R*,6*aR*)-Hexahydro-6-methoxy-4-methyl-3-methylenefuro[3,4-*b*]furan (13a). A solution of **15a** (0.85 g, 3.07 mmol) in dry benzene (25 mL) under N₂ atmosphere was treated with *n*-Bu₃SnH (1.65 mL, 6.15 mmol) as described for **12a**. Work up and column chromatographic purification (60–120 Silica gel, ethyl acetate–*n*-hexane, 0.7 : 9.3) gave **13a** (0.30 g, 57%) as a colorless liquid; [α]_D²⁰ = –2.44 (*c* 0.33, CDCl₃); IR (neat): ν_{max} 2923, 2853, 1732, 1654, 1461, 1261, 1029, 869, 723 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.23 (d, 3H, *J* = 6.5 Hz, CH₃), 3.23 (t, 1H, *J* = 5.8 Hz, H-3a), 3.50 (s, 3H, OCH₃), 4.06 (m, 1H, H-4), 4.28–4.38 (m, 2H, OCH₂), 4.61 (q, 1H, H-6a), 4.67 (d, 1H, *J* = 3.6 Hz, H-6), 4.89 (d, 1H, *J* = 2.1 Hz, olefinic), 5.08 (d, 1H, *J* = 2.1 Hz, olefinic); ¹³C NMR (CDCl₃, 75 MHz): δ 146.3, 108.0, 105.2, 83.7, 73.9, 73.7, 57.7, 50.5, 29.4; HRMS (ESI): *m/z* calculated for C₉H₁₄NaO₃(M⁺+Na) 193.0840, found 193.0839.

(3*aR*,4*S*,6*R*,6*aR*)-4-Ethyl-hexahydro-6-methoxy-3-methylenefuro[3,4-*b*]furan (12b). A solution of **14b** (0.10 g, 0.34 mmol) in dry benzene (25 mL) on reaction with *n*-Bu₃SnH (0.18 mL, 0.68 mmol) and catalytic amount of AIBN as described for **12a**. Work up and column chromatographic purification (60–120 Silica gel, ethyl acetate–*n*-hexane, 0.7 : 9.3) gave **12b** (0.04 g, 71%) as a colorless liquid; [α]_D²⁰ = –49.2 (*c* 0.23, CDCl₃); IR (neat): ν_{max} 3437, 2926, 2856, 1737, 1219, 1051, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.01 (t, 3H, *J* = 7.3 Hz, CH₃), 1.49 (m, 2H, CH₂), 3.19 (t, 1H, *J* = 7.1 Hz, H-3a), 3.29 (s, 3H, OCH₃), 3.94 (m, 1H, H-4), 4.16 (m, 2H, *J* = 1.7, 3.5 Hz, OCH₂), 4.53 (d, 1H, *J* = 6.4 Hz, H-6a), 4.81 (s, 1H, H-6), 4.92 (q, 1H, *J* = 1.7 Hz, olefinic) 5.06 (q, 1H, *J* = 1.5 Hz, olefinic); ¹³C NMR (CDCl₃, 75 MHz): δ 147.1, 107.7, 96.2, 88.5, 80.9, 72.6, 54.1, 50.0, 24.3, 11.4; HRMS (ESI): *m/z* calculated for C₁₀H₁₇O₃(M⁺+H) 185.1177, found 185.1170.

(3*aR*,4*S*,6*S*,6*aR*)-4-Ethyl-hexahydro-6-methoxy-3-methylenefuro[3,4-*b*]furan (13b). A solution of **15b** (0.10 g, 0.34 mmol) in dry benzene (25 mL) on reaction with *n*-Bu₃SnH (0.18 mL, 0.68 mmol) and catalytic amount of AIBN as described for **13a**. Work up and column chromatographic purification (60–120 Silica gel, ethyl acetate–*n*-hexane, 0.9 : 9.1) gave **13b** (0.03 g, 60%) as a colorless liquid; [α]_D²⁰ = –285.8 (*c* 0.23, CDCl₃); IR (neat): ν_{max} 3412, 2891, 2797, 1764, 1176, 1083, 804 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.02 (t, 3H, *J* = 7.3 Hz, CH₃), 1.55 (m, 2H, CH₂), 3.26 (t, 1H, *J* = 7.3 Hz, H-3a), 3.51 (s, 3H, OCH₃), 3.74 (m, 1H, H-4), 4.25–4.35 (q, 2H, *J* = 12.1 Hz, OCH₂), 4.60 (m, 1H, H-6a), 4.67 (d, 1H, *J* = 3.6 Hz, H-6), 4.91 (s, 1H, olefinic), 5.06 (s, 1H, olefinic); ¹³C NMR (CDCl₃, 75 MHz): δ 146.6, 107.8, 105.1, 83.5, 78.6, 74.0, 57.5, 50.1, 24.9, 11.2; HRMS (ESI): *m/z* calculated for C₁₀H₁₇O₃(M⁺+H) 185.1177, found 185.1175.

(3*aR*,4*S*,6*R*,6*aR*)-Hexahydro-6-methoxy-3-methylene-4-pentylfuro[3,4-*b*]furan (12c). A solution of **14c** (0.08 g, 0.24 mmol) in dry benzene (25 mL) on reaction with *n*-Bu₃SnH (0.13 mL, 0.48 mmol) and catalytic amount of AIBN as described for **12a**. Work up and column chromatographic purification (60–120 Silica

gel, ethyl acetate–*n*-hexane, 0.5:9.5) gave **12c** (0.008 g, 14%) as a colorless liquid; $[\alpha]_D = -249.7$ (c 0.26, CDCl_3); IR (neat): ν_{max} 3367, 2832, 2165, 1167, 762 cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3): 0.89 (t, 3H, $J = 6.6$ Hz, CH_3), 1.28–1.58 (m, 8H, alkyl chain), 3.23 (t, 1H, $J = 6.2$ Hz, H-3a), 3.33 (s, 3H, OCH_3), 4.08 (m, 1H, H-4), 4.21 (q, 2H, $J = 12.3$ Hz, OCH_2), 4.59 (d, 1H, $J = 6.1$ Hz, H-6a), 4.89 (s, 1H, H-6), 4.95 (s, 1H, olefinic), δ 5.09 (s, 1H, olefinic); $^{13}\text{C NMR}$ (CDCl_3 , 150 MHz): δ 146.5, 108.0, 107.6, 88.3, 79.3, 72.5, 54.1, 49.8, 31.8, 31.0, 26.5, 22.6, 14.0; HRMS (ESI): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NaO}_3(\text{M}^+ + \text{Na})$ 249.1466, found 249.1456.

Theoretical methods

In order to study the intramolecular 5-*exo*-dig-cyclization reaction in propargyloxy-substituted radicals **29** and **32** for each stage along the reaction pathway the conformational space has been searched extensively with the MM3* force field¹³ and the systematic search routine implemented in *MACROMODEL* 9.7¹⁴ in order to identify all possible low energy conformations. Geometry optimizations have then been performed at the UB3LYP/6-31G(d) level of theory. Thermal corrections to enthalpies at 298.15 K have been calculated at the same level using the rigid rotor/harmonic oscillator model. Single point energies have subsequently been calculated at the UB3LYP/6-311+G(d,p) level of theory. Combination of these total energies with thermal corrections calculated at UB3LYP/6-31G(d) level yield the enthalpies “ H_{298} ” discussed in the text. Single point calculations have also been performed at the (RO)MP2(FC)/G3MP2large level and combined with thermochemical corrections to 298.15 K obtained at UB3LYP/6-31G(d) level using a scaling factor of 0.9806. These results are termed as “ROMP2” in the text. The G3MP2large basis set is a large triple-zeta basis set used in the G3(MP2) compound energy scheme.¹² All calculations have been performed with *Gaussian 03*.¹⁵

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