Pergamon

Tetrahedron 54 (1998) 8355–8370

TETRAHEDRON

SYNTHESIS OF FUSED BICYCLIC RINGS BY TANDEM RADICAL RING EXPANSION/CYCLIZATION: EVALUATING COMPETING INTRAMOLECULAR REACTIONS†

Cunxiao Wang, Xin Gu, Marvin S. Yu, and Dennis P. Curran*‡
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

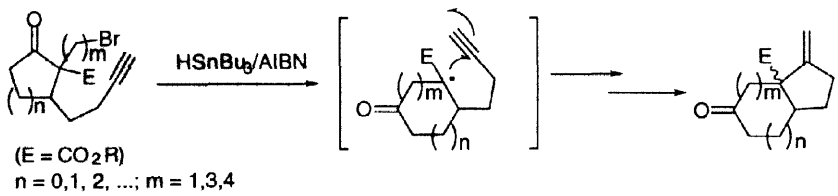
Received 6 March 1998; revised 20 March 1998; accepted 15 May 1998

Summary: One- and three-carbon "Dowd-Beckwith" ring expansions of cyclopentanones and cyclohexanones are generally successful, but tandem expansion/cyclization reactions can be compromised by competing processes. An evaluation of the competition between ring expansion, 1,5-hydrogen transfer, and 6-*exo* cyclization provides information on how to design successful tandem expansion cyclization sequences.

INTRODUCTION

Free radical ring expansion reactions provide attractive approaches to standard, medium-sized and even large rings.[1a] The incorporation of an additional, appropriately positioned radical acceptor can lead to tandem ring expansion/cyclization reactions.[1b] This type of tandem radical reaction has rarely been explored even though it opens interesting avenues to fused bicyclic (or polycyclic) structures (Eq. 1). Boger and Mathvink have built hydrindan-1,4-diones by a tandem expansion/cyclization,[2] while Santagostino and Kilburn have developed a route to spirocyclic systems starting from methylenecyclopropane derivatives.[3] Pattenden has used this strategy in the construction of angular triquinanes from cyclobutanone oximes.[4] However, straightforward and readily available cyclopentanone- or cyclohexanone-based precursors (Eq. 1) have never been studied in this context. We report herein studies on the tandem ring expansion cyclization reactions in Eq. 1, which were undertaken as a foundation for more complex synthetic applications. These studies have identified 1,5-hydrogen transfer as a competing, even dominant, reaction in some cases, and strategies for avoiding hydrogen transfer have been identified.[5] When m = 1, 6-*exo* cyclization can also compete.

Eq. 1



(E = CO_2R)
n = 0,1, 2, ...; m = 1,3,4

†In memory of Professor Paul Dowd, a pioneer in radical ring expansions

‡email: curran+@pitt.edu

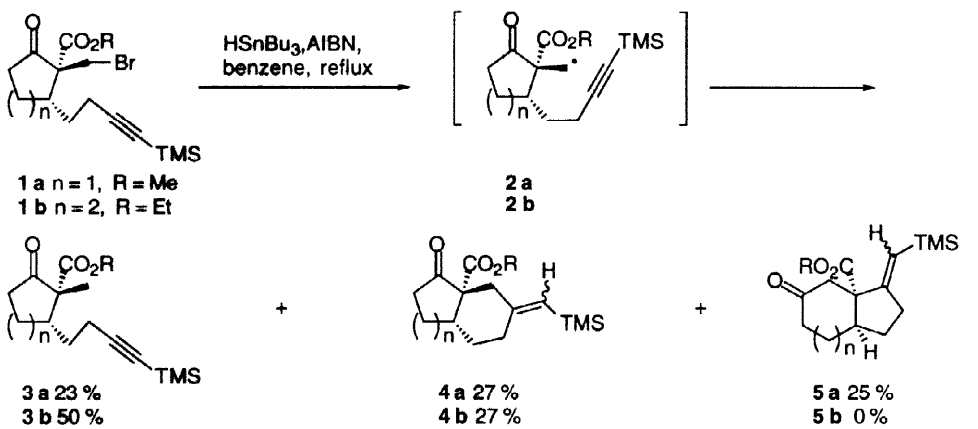
PII: S0040-4020(98)00467-0

RESULTS AND DISCUSSION

We first explored the tandem one-carbon ring expansion/cyclization reaction. Compounds **1a** and **1b** were synthesized from the corresponding cycloalkenone carboxylic acid esters[6] by stepwise conjugate addition[7] and alkylation.[8] Precursors **1a** and **1b** were subjected to typical radical ring expansion conditions,[1] which entailed syringe pump addition of a benzene solution containing 1.2 equiv of tributyltin hydride and 0.1 equiv AIBN to a refluxingsolution of the precursor in benzene. After the reactions were complete, tin byproducts were removed by DBU workup,[9] and the products were purified by chromatography. Reduction of cyclopentanone **1a** provided three products: directly reduced product **3a**, 6-*exo* cyclization product **4a** (1.3/1 mixture of vinyl silane isomers), and ring expansion/cyclization product **5a** (6/1 mixture of vinyl silane isomers). These were isolated in 23%, 27% and 25% yields, respectively. In case of cyclohexanone **1b**, only the reduced **3b** and 6-*exo* **4b** products were isolated in 50% and 27% yields. Compounds **4a,b** and **5a** were additionally characterized by protodesilylation, as described in the Experimental Section.

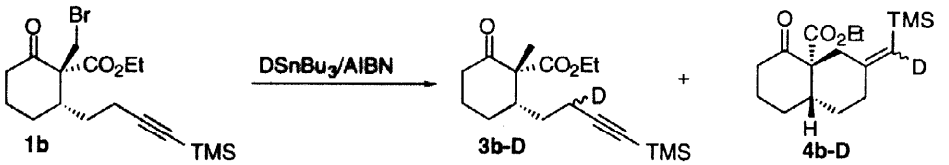
The results show that 6-*exo* cyclization is competitive with ring expansion in the cyclopentanone case and supersedes it in the cyclohexanone case. Perhaps surprising at first glance is the formation of large amounts of reduction product; related compounds (see **7** below) lacking the butynyl side chain are known to undergo ring expansion in high yield under identical conditions. This implied that the formation of large amounts of reduction product was caused by competing intramolecular hydrogen transfer.

Eq. 2



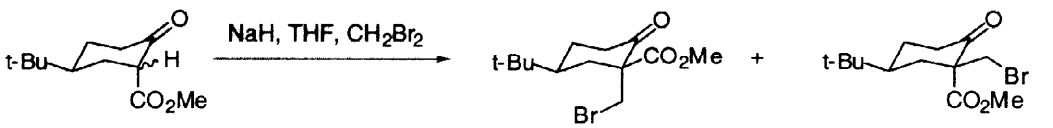
To test this hypothesis, precursor **1b** was treated with DSnBu3/AIBN under the standard conditions; **3b-D** and **4b-D** were isolated in similar yields as above (Eq. 3). ^{1}H and ^{2}H NMR experiments showed that the deuterium in **3b-D** was exclusively incorporated on the carbon next to the triple bond, indicating 1,5-H transfer. As expected, the 6-*exo* product **4b-D** contained deuterium only in the vinyl position. This labeling experiment was not conducted with cyclopentanone precursor **1a**, but it seems probable that most, if not all, of the reduced product **4a** arises from 1,5-hydrogen transfer as well. Apparently, the rigid geometry of the system and the stabilization of the secondary radical by the alkyne allow hydrogen transfer to occur even though the radical and the chain bearing the hydrogen are oriented trans on the cyclohexane ring.

Eq. 3



We next investigated the geometric requirements for this type of one-carbon ring expansion in the cyclohexanone series. The idea was that rigidification of the cyclohexanone ring might be able to promote or inhibit ring expansion. The tandem process is incidental to this question, so we omitted the butynyl side chain. Compounds **7a** and **7e** were prepared in 37 %, and 12% yield[10] by the bromomethylation of 2-methoxycarbonyl 4-t-butylcyclohexanone (**6**) (Eq. 4).[11]

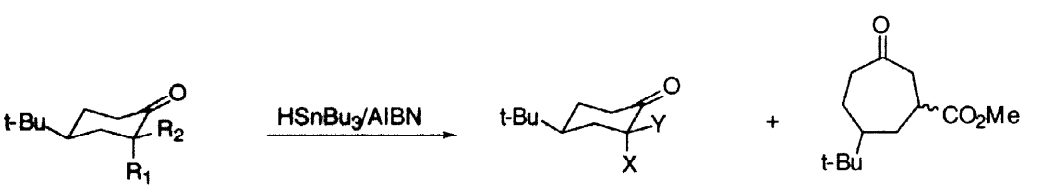
Eq. 4



6 **7a** 37% **7e** 12%

Syringe pump addition of $HSnBu_3$/AIBN to **7a** produced reduction product **8a** and ring expansion product **9** in 4% and 79% yields (Eq. 5). Likewise, under the same conditions, **7e** afforded **8e** and **9** in 5% and 79% yields. The diastereomeric ratio of **9** was determined to be 10/1 based on ^1H NMR (C_6D_6) integration of the crude reaction mixtures.[12] These results showed that under dilute conditions the reduction process does not compete with ring expansion regardless of the configuration of the precursor.

Eq. 5



7a: $R_1 = CH_2Br$, $R_2 = CO_2Me$
7e: $R_1 = CO_2Me$, $R_2 = CH_2Br$

8a: X = Me, Y = CO_2Me, 4%
8e: X = CO_2Me, Y = Me, 5 %

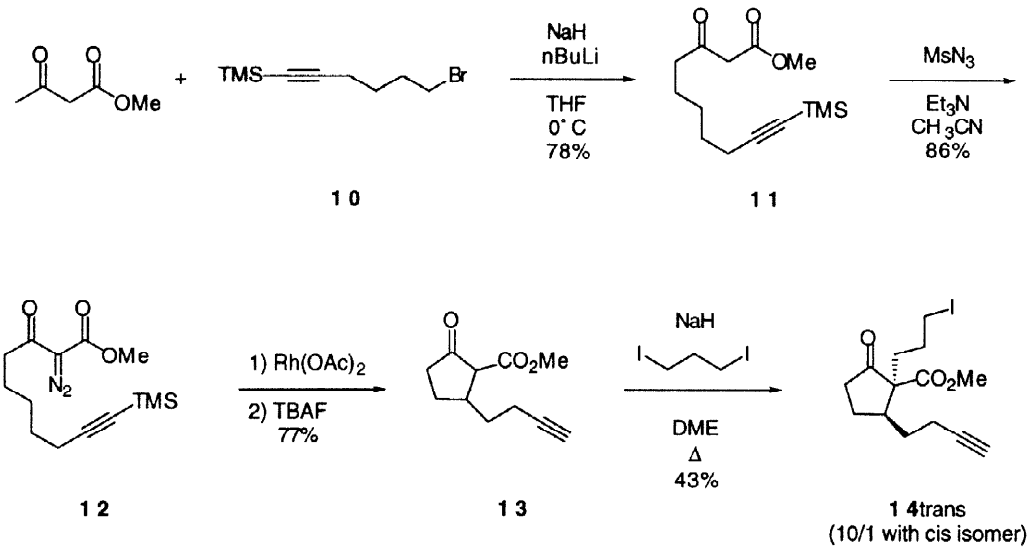
9: 79 %
79 %

Kinetic experiments[13] were carried out to provide estimates of rate constants for the ring expansion of radicals derived from **7a** and **7e**. Heating of a 5 mM solution of precursor **7a** in benzene with 1.5 equiv Bu_3SnH and AIBN at 90°C for 7 h afforded **8a** and **9** in a ratio of 1/1.5. Likewise, reduction of **7e** provide **8e** and **9** in a ratio of 2.60/1. By making the usual calculations,[13] we estimate that the rate constant for 3-*exo* cyclization of the axially oriented radical is about 1×10^4 s^{-1} and that for the equatorially oriented radical is about 3×10^3 s^{-1}. Given the stereoelectronic requirements for this cyclization, it is surprising that the axial radical cyclizes only about 4 times faster than its equatorial isomer.

We next studied the tandem three-carbon expansion/cyclization of precursor **14**, the synthesis of which is shown in Eq. 6. Alkylation of the dianion of methyl acetoacetate with bromide **10**, followed by diazo-transfer[14] (**11** → **12**) and Rh-catalyzed C–H insertion,[15] provided keto-ester **13**. Alkylation of the sodium enolate derived from **13** with 1,3-diiodopropane provided **14** as a 10/1

mixture of stereoisomers. Purification of this mixture by chromatography provided a fraction of the pure trans isomer followed by mixed fractions.

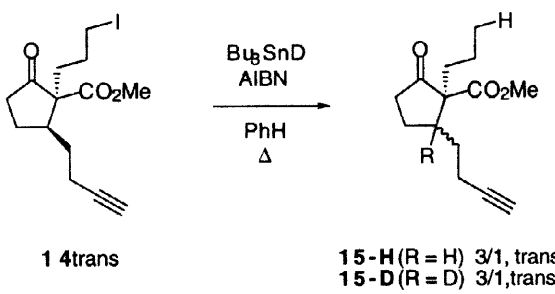
Eq. 6



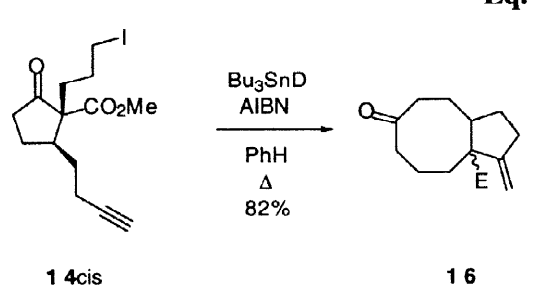
To our surprise, treatment of a 10/1 mixture of **14-trans/cis** with $HSnBu_3$/AIBN gave the reduction products **15-H** as a 3/1 diastereomeric mixture (Eq. 7a). This was a surprise because **14** differs from original substrates studied by Dowd and Beckwith only by the presence of the butynyl group.[7] That the isomer ratio changed from 10/1 to 3/1 clearly implicated hydrogen transfer as the culprit. Indeed, upon treatment of **14-trans** with $DSnBu_3$/AIBN, the deuterium was found exclusively at the tertiary carbon β to the carbonyl (**15-D**).

We suspected that the major stereoisomer **14-trans** might be more susceptible to hydrogen transfer while the minor stereoisomer **14-cis** would be more susceptible to cyclization. A tedious HPLC separation provided a few milligrams of the pure minor isomer **14-cis** which indeed did give a product tentatively identified as **16** on treatment with tin hydride (Eq. 7b). The small amounts of **14-cis** available precluded a thorough study of this reaction but the results hold out the promise that a viable strategy to effect tandem expansion/cyclization has been identified. This strategy calls for the stereoselective preparation of a precursor in which the initial radical precursor and final radical acceptor side chains are cis-oriented.

Eq. 7a



Eq. 7b

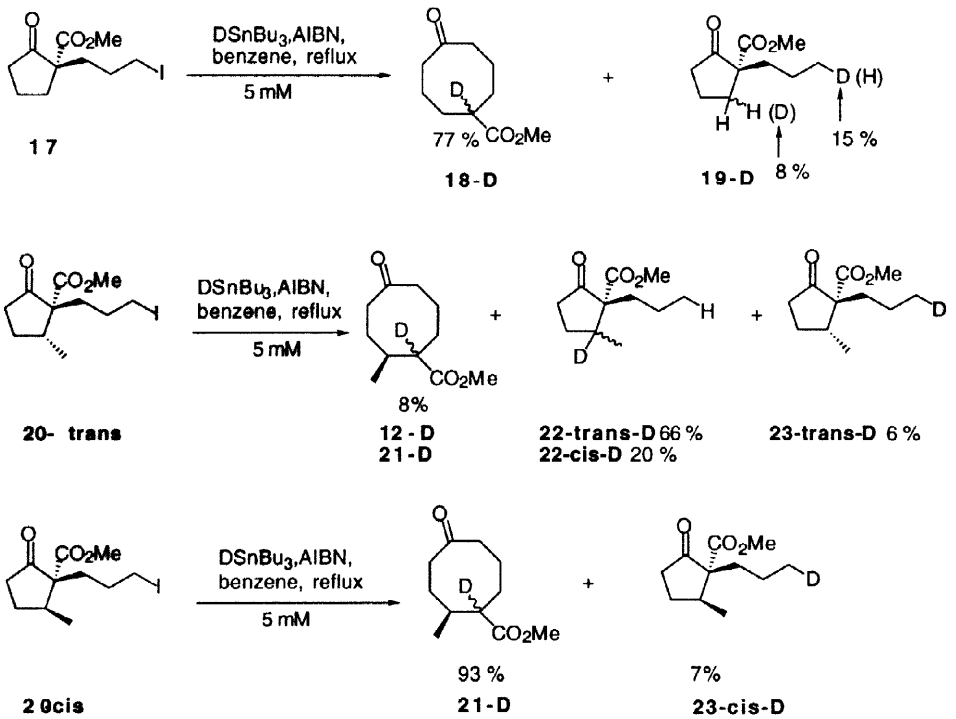


To provide a more detailed understanding of the competition between different radical paths in ring expansion reactions, three compounds **17**, **20-cis**, and **20-trans** were selected for kinetic studies (Eq. 8). Compound **17** is the original substrate of Dowd and Beckwith,[3] so its ring expansion

reaction is already known. Compounds **20-trans** and **20-cis** were prepared by a route analogous to that shown in Eq. 6 (See Experimental). We had initially planned to prepare the cis isomer by a different route to enhance its yield; however, in practice we found that in the methyl series the separation of the cis and trans isomers after alkylation was not difficult, and adequate quantities of both the major trans product and the minor cis product could readily be isolated in pure form.

The three precursors were treated with Bu_3SnD/AIBN in benzene at 80°C for 12 h. The concentration of $DSnBu_3$ in each reaction was chosen to be 5 mM after several trials since this concentration gave suitable product distributions. The results of these labeling experiments, as assessed by ^2H NMR, are shown in Eq. 8. Authentic (non-labeled) products were prepared by standard methods. Since GC and NMR analysis did not provide any evidence for other products than those indicated, the analysis below assumes that the total yield of indicated products is 100%.

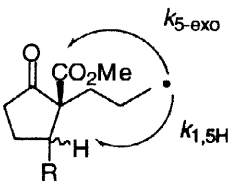
Eq. 8



For the previously studied β-unsubstituted substrate **17**[2] (Eq. 5), the ring expansion product, **18-D** accounted for 77% of the product. In addition, 15% of the directly reduced product (**19-D**) and 8% of reduction product with deuterium incorporated β to the carbonyl were formed. The results show that 1,5-H transfer is occurring even for precursor **17**. This competing reaction has not been previously recognized in the cyclopentanone series although it has been noted for other ring sizes.[7] For the β trans-substituted precursor **20-trans**, ring expansion (**21**), 1,5-hydrogen transfer (**22**), and direct reduction products (**23**) were formed in 8%, 86%, and 6% yields, respectively. Again, 1,5-H transfer dominated as in the case of **14-trans** and this caused epimerization of product **22** (3.3/1 trans/cis). In contrast, reaction of the β cis-substituted compound **20-cis** with $DSnBu_3$/AIBN afforded the ring expansion product **21** in excellent yield (93%). Reduction to **23-cis** was only a minor process, and 1,5-H transfer was not observed. This result shows that when the α-radical carrier and the β-substituent have a cis relationship, 1,5-H transfer can be completely suppressed.

Estimated rate constants derived from these data are shown in Figure 1. We caution that these rate constants are not highly accurate. In addition to the usual errors,[15] we add additional error due to the ^2H NMR analysis, which suffers from broad peaks that overlap and must be deconvoluted in some cases. Nonetheless, the errors cannot be sufficiently large so as to mask the trends. The parent radical **24** cyclizes with a rate constant of about 4 x 10^4 s^{-1}, and this is about six times faster than 1,5-hydrogen transfer. In comparison, the trans isomer of **25** has a significantly faster rate for 1,5-hydrogen transfer coupled with a slightly slower rate for cyclization. This "double whammy" explains the complete failure of the tandem cyclization expansion in Eq. 7a. On the other hand, the cis isomer of **25** cyclizes slightly faster than the parent, and its rate of 1,5-hydrogen transfer is too slow to be estimated. This confirms the tentative conclusion above that cis oriented substrates should be generally good for tandem cyclization/expansion sequences.

Figure 1. Estimated Rate Constants for 5-Exo Cyclization and 1,5-Hydrogen Transfer



Radical	R	$k_{5\text{-exo}}$ (s^{-1})	$k_{1,5H}$ (s^{-1})
24	H	4 x 10^4	7 x 10^3
25-trans	β-CH_3	1 x 10^4	1 x 10^5
25-cis	α-CH_3	1 x 10^5	<10^3

CONCLUSIONS

These results provide insight into the factors controlling the rate of both 3-*exo* and 5-*exo* "Dowd-Beckwith" ring expansion reactions of keto esters and help in planning sequences of reactions. One-carbon ring expansions proceed at a modest rate and can easily be partially or completely derailed in tandem applications by 1,5-hydrogen transfer reactions or 6-*exo* cyclizations. In contrast, competing reactions in a three-carbon expansion/cyclization sequence can be controlled by selecting the configuration of the substrate to favor ring expansion and disfavor hydrogen transfer. These results have formed the basis for planning and executing a series of more complex expansion/cyclization reactions, the results of which will be reported in due course.

Acknowledgments: We thank the National Institutes of Health for Funding of this work. We are grateful to Mr. Daniel Christen for helpful discussions.

EXPERIMENTAL

2-Methoxycarbonylcyclopent-2-enone: Phenylselenyl chloride (2.16 g, 11.3 mmol) was dissolved in dry dichloromethane (50 mL), cooled at 0°C, and treated with pyridine (0.99 mL, 12.2 mmol). After 15 min, a solution of 2-methoxycarbonylcyclopentanone (1.450 g, 10.0 mmol) in CH_2Cl_2 (3 mL) was introduced. The reaction mixture was stirred for 1.5 h at 0°C, and allowed to warm to room temperature in 45 min. The mixture was washed with 10 % HCl (40 mL), saturated $NaHCO_3$ (10 mL), and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil (2.830 g, 95 %): ^1H NMR ($CDCl_3$) δ 1.90–2.70 (6H, m), 3.75 (3H, s), 7.26–7.65 (5H, m).

A solution of this selenide (5.69 g, 19.2 mmol) in methylene chloride (350 mL) was added dropwise over 30 min to 30 % hydrogen peroxide (6.8 mL, 3 equiv) at 0°C with vigorous magnetic stirring. After 30 min at room temperature, the resulting mixture was washed with 2x15 mL of H_2O.

The aqueous portions were combined and back extracted with CH_2Cl_2 (15 mL). The methylene chloride extracts were then dried over Na_2SO_4, filtered, and concentrated to give an orange oil (2.52 g, 94 %). This product was essentially pure (free of $PhSeO_2H$): ^1H NMR ($CDCl_3$) δ 8.44 (1H, s), 3.84 (3H, s), 2.74 (2H, m), 2.57 (2H, m).

2-Ethoxycarbonylcyclohex-2-enone: Phenylselenyl chloride (4.32 g, 22.6 mmol) was dissolved in dry dichloromethane (100 mL), cooled to 0°C, and treated with pyridine (1.98 mL, 24.4 mmol) for 15 min. A solution of 2-ethoxycarbonylcyclohexanone (3.404 g, 20 mmol) in CH_2Cl_2 (6 mL) was introduced. The reaction mixture was stirred at 0°C for 1.5 h, and allowed to warm to room temperature over 45 min. The mixture was washed with 10 % HCl (80 mL), saturated $NaHCO_3$ (20 mL), and dried over $NaSO_4$. Evaporation of the solvent gave an orange oil (5.49 g, 85%): ^1H NMR($CDCl_3$) δ 1.18 (3H, t, J = 7.1 Hz), 1.20–2.70 (8H, m), 4.12 (2H, q, J = 7.1Hz), 7.10–7.60 (5H, m).

A round-bottom flask equipped with a pressure-equalizing dropping funnel and a magnetic stirring bar was charged with the above phenylselenyl chloride (5.49 g, 16.9 mmol) and CH_2Cl_2 (50 mL). The solution was stirred at room temperature, and a few drops of the hydrogen peroxide were added to initiate the reaction. After the exothermic reaction began, the mixture was cooled to 0°C, and stirred vigorously while the H_2O_2 (30 %, 4.02 g, 2.1 eq) was dropwise added over 20 min. After the addition, the mixture was stirred for 15 min at RT, and 15 min at 0°C. The chilled suspension of benzenesulfinic acid was filtered, and the filter cake was washed with CH_2Cl_2 (10 mL). The filtrate was washed with 7 % $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered, and evaporated, providing the pure product as an oil (2.55 g, 90 %): ^1H NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.1 Hz), 2.05 (2H, m), 2.52 (4H, m), 4.26 (2H, q, J = 7.1 Hz), 7.67 (1H, bs); ^{13}C NMR($CDCl_3$) δ 13.6 (q), 21.6 (t), 25.5 (t), 38.2 (t), 60.4 (t), 132.6 (s), 155.5 (d), 164.0 (s), 194.0 (s).

2-Methoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclopentanone: A suspension of zinc dust (1.373 g, 21 mmol) in THF (2 mL) containing 1,2-dibromoethane (80 μL, 0.92 mmol) was heated at reflux for 2 min, cooled to 25°C, and treated with TMSCl (80 μL). After 15 min, a solution of 4-iodo-1-trimethylsilyl-1-butyne (5.044g, 20 mmol) in THF (8 mL) was introduced dropwise over 5 min. The resulting mixture was then heated at 40°C for 16 h. The clear solution was cooled to –15°C and treated with a solution of CuCN/2LiCl (CuCN: 1.98 g; LiCl: 1.90 g) in THF (20 mL) for 15 min. The resulting organocuprate was cooled to –78°C, and treated with 15 mL of a 1M solution of 2-methoxycarbonylcyclopent-2-enone in THF for 3 h. The mixture was warmed to 25°C and stirred overnight. The homogeneous solution was diluted with ether (100 mL), treated with saturated NH_4Cl (50 mL) for 30 min until all the sticky solid became powdery. The organic layer was separated, dried ($MgSO_4$) and concentrated. Column chromatography on silica gel with 1/12 ethyl acetate/hexane gave a colorless oil (2.40 g, 60 %): ^1H NMR ($CDCl_3$) δ 0.08 (9H, s), 1.41–1.76 (3H, m), 2.17–2.36 (5H, m), 2.60 (1H, m), 2.83 (1H, d, J = 11.3), 3.69 (3H, s); ^{13}C NMR ($CDCl_3$) –0.07 (q, J = 119.9), 17.7 (t, J = 128.4), 26.8 (t, J = 132.7), 33.5 (t, J = 130.0), 38.2 (t, J = 132.1), 40.5 (d, J = 130.5), 52.3 (d, J = 147.3), 61.2 (d, J = 126.4), 85.1 (s), 106.0 (s); 169.4 (s), 211.0 (s); IR (neat) 2942 (s), 2163 (m), 1745 (vs), 1720 (vs), 1400 (m), 1244 (vs), 1128 (m), 841 (vs), 756 (m); LRMS m/e (rel intensity) 266 (M^+, 1), 251 (M^+ – Me, 100), 219 (71), 207(17), 191 (54), 109 (36), 89 (62), 73 (67), 59 (29); HRMS (M^+ – Me) 251.1111(found), 251.1103 (calcd).

2-Ethoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclohexanone: By following the same procedure as above, this was obtained as a 2/1 mixture with its enol form in 85 % yield. This product

was contaminated only by a small amount of impurities, but it was used for the next step without further purification.

2-Bromomethyl-2-methoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclopentanone (1a): To a suspension of sodium hydride (60 % oil, 104 mg, 2.6 mmol) in dimethoxyethane (DME) containing HMPA (453 μL, 2.6 mmol) was slowly added a solution of 2-methoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclopentanone (532.6 mg, 2 mmol) in DME (8 mL). After 45 min, dibromomethane (1.40 mL, 20 mmol) was added. The reaction mixture was then refluxed 24 h, cooled to 25°C, diluted with ether (80 mL), washed with water, dried (K_2CO_3), and concentrated to give a yellow oil. Column chromatography on silica gel with 1/7 ethyl acetate and hexane gave 220 mg of a colorless oil (30 %): ^{1}H NMR ($CDCl_3$) δ 0.14 (9H, m), 1.35–1.50 (1H, m), 1.72–1.82 (2H, m), 2.20–2.39 (4H, m), 2.51–2.61 (1H, m), 2.94 (1H, m), 3.62 (1H, d, J = 10.7), 3.71 (3H, s), 3.89 (1H, d, J = 10.7); ^{13}C NMR ($CDCl_3$) δ 0.1 (q, J = 119.7), 17.8 (t, J = 130.5), 25.6 (t, J = 132.6), 29.8 (t, J = 128.7), 31.8 (t, J = 128.7), 38.6 (t, J = 139.2), 41.6 (d, J = 129.5), 52.5 (q, J = 148.3), 63.3 (s), 85.9 (s), 105.4 (s), 169.0 (s), 212.6 (s); IR (neat) 2942 (s), 2162 (m), 1744 (s), 1718 (s), 1425 (m), 1240 (vs), 1075 (w), 1042 (w), 841 (vs), 756 (m); LRMS *m/e* (rel intensity) 360 (M^+, 2), 358 (M^+, 2), 345 (30), 343 (31), 317 (16), 315 (16), 279 (52), 251 (19), 219 (30), 89 (34), 73 (100), 59 (25); HRMS (M^+ – Me): 343.0369 (found), 343.0365 (calcd).

2-Bromomethyl-2-methoxycarbonyl-3-(4-trimethylsilyl-3-but-ynyl)cyclohexanone (1b): Starting from 2-ethoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclohexanone (1.400 g, 4.76 mmol), the same procedure as for **1a** was followed, and **1b** was obtained as an colorless oil (0.743 g, 40 % yield): ^{1}H NMR ($CDCl_3$) δ 0.15 (9H, s), 1.26 (3H, t, J = 7.1), 1.66–1.75 (3H, m), 2.02, 2H, m), 2.20–2.75 (7H, m), 3.62 (1H, d, J = 10.5), 4.18 (3H, m); ^{13}C NMR ($CDCl_3$) δ 0.1 (q, J = 119.7), 13.9 (q, J = 127.1), 17.9 (t, J = 130.8), 22.4 (t, J = 130.0), 25.2 (t, J = 127.5), 29.7 (t, J = 129.7), 32.5 (t, J = 156.9), 39.4 (t, J = 128.7), 40.7 (d, J = 129.7), 61.7 (t, J = 148.5), 64.0 (s), 85.5 (s), 105.5 (s), 168.1 (s), 204.6 (s); IR (neat) 2936 (s), 2163 (m), 1715 (vs), 1242 (s), 1196 (vs), 839 (vs), 756 (m); LRMS *m/e* (rel. intensity) 388 (M^+, 7), 386 (M^+, 7), 373 (50), 371 (49), 327 (22), 307 (85), 233 (48), 73 (100), 59 (42). HRMS (Br^{79}) 386.0904 (found), 386.0912 (calcd).

Reaction of 1a with $HSnBu_3$: To a refluxing solution of **1a** (166 mg, 0.46 mmol) in benzene (50 mL) was added a solution of tributyltin hydride (150 μL, 1.2 eq μL) and AIBN (15 mg) in benzene (10 mL) over 10 h via a syringe pump. The reaction mixture was refluxed for 3 h, cooled and concentrated. The residue was dissolved in ether (12 mL) and treated with a solution of 1,8-diazabicyclo[5.4.o]undec-7-ene (DBU) (77 mg, 1.1 equiv) in ether (12 mL). The ether solution was passed through a 2 inch column of silica gel, and eluted with ether (20 mL). Removal of the ether gave a yellow residue. Column chromatography on silica gel with 1/10 ethyl acetate/hexane afforded three crude products **3a**, **4a**, and **5a**. Further column chromatography of these crude products on silica gel gave pure products. The reduction product **3a** was obtained in 23% yield (30 mg; eluent: CH_2Cl_2), direct cyclization product **4a** was obtained as a 1.3/1 mixture of geometric isomers (35 mg, 27%; eluent: 1/15 ethylacetate/hexane), and **5a** was obtained as a 6/1 mixture of geometric isomers (32 mg, 25%, eluent: 1/20 ethylacetate/methylenechloride). Spectroscopic data for **3a**: ^{1}H NMR ($CDCl_3$) δ 0.14 (9H, s), 1.30 (3H, s), 1.30–1.50 (1H, m), 1.70–1.90 (2H, m), 2.00–2.39 (5H, m), 2.56–2.65 (1H, m), 3.67 (3H, s); ^{13}C NMR ($CDCl_3$) δ 0.1 (q, J = 119.7), 18.0 (t, J = 130.6), 18.7 (q, J = 125.9), 25.7 (t, J = 131.8), 30.0 (t, J = 129.1), 37.6 (t, J = 131.3), 47.9 (d, J = 127.5), 52.0 (q, J =

147.6), 59.0 (s), 85.5 (s), 106.0 (s), 171.2 (s), 216.3 (s); IR (neat) 2944 (s), 2164 (m), 1746 (vs), 1727 (vs), 1449 (m), 1244 (s), 1086 (m), 1045 (m), 841 (vs), 756 (m); LRMS *m/e* (rel intensity) 280 (M^+, 23), 265 (23), 252 (15), 221 (15), 205 (19), 193 (57), 109 (17), 89 (84), 73 (100), 59 (38); HRMS 280.1497 (found), 280.1495 (calcd). Compounds **4a** and **5a** were characterized after the removal of TMS groups.

Desilylation of 4a: To a solution of **4a** (32 mg, 0.11 mmol) in benzene (2.5 mL) was introduced 36 μL of trifluoroacetic acid (4.2 eq) under N_2. After 25 min stirring at RT, the reaction mixture was rotary evaporated, and the residue was chromatographed on silica gel with 1/8 ether and pentane to afford 21 mg of deprotected product (92%): ^{1}H NMR ($CDCl_3$) δ 1.80–2.54 (10H, m), 2.96 (1H, d, J = 13.5), 3.65 (3H, s), 4.77 (1H, s), 4.80 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.6 (t, J = 130. 9), 26.7 (t, J = 130.9), 34.2 (t, J = 122.2), 37.5 (t, J = 130.2), 39.4 (t, J = 140.0), 47.3 (d, J = 121.5), 52.1 (q, J = 147.4), 62.2 (s), 112.1 (t, J = 156.2), 144.1 (s), 168.7 (s), 212.3 (s); IR (neat) 3074 (w), 2980 (s), 1750 (s), 1727 (s), 1650 (w), 1446 (m), 1288 (m), 1264 (s), 1213 (s), 1160 (s), 1079 (m), 1041 (w), 1015 (w), 898 (m); LRMS *m/e* (rel. intensity) 208 (M^+, 35), 190 (8), 149 (65), 121 (18), 106 (100), 93 (31), 91 (31), 79 (15), 77 (18), 65 (8); HRMS 208.1108 (found), 208.1100 (calcd). The silylated structural assignment was further confirmed by a deuterium exchange experiment. Thus, a solution of the deprotected product in CD_3OD was treated with several crystals of $NaOCH_3$ for 5 min; ^{1}H NMR analysis indicated that two protons disappeared in the 2.20–2.60 ppm region. GCMS (*m/e* 210, 192, 151, 106, 91, 79, 77, 75) also showed the incorporation of two deuteriums.

Desilylation of 5a: To a solution of **5a** (42 mg, 0.15 mmol) in benzene (3 mL) was added 56 μL of trifluoroacetic acid under N_2. The mixture was refluxed for 3h, then cooled to RT, and concentrated. The residue was chromatographed with 1/20 ethyl acetate and hexane to afford desilylated product (14 mg, 43 %), and double bond isomerized product (18 mg, 45 %). Spectroscopic data for the desilylated product: ^{1}H NMR ($CDCl_3$) δ 1.50–1.80 (2H, m), 2.00–2.40 (4H, m), 2.45 (1H, d, J = 15.6), 2.53 (2H, m), 2.85 (1H, m), 2.90 (1H, d, J = 15.7), 3.70 (3H, s), 4.91 (1H, s), 5.05 (1H, s); ^{13}C NMR ($CDCl_3$) δ 26.5 (t, J = 127.5), 29.9 (t, J = 129.4), 32.6 (t, J = 130.9), 37.1 (t, J = 127.5), 42.4 (d, J = 133.6), 44.7 (t, J = 130.5), 52.7 (q, J = 147.4), 56.9 (s), 108.5 (t, J = 157.3), 153.8 (s), 175.4 (s), 210.0 (s); IR (neat) 2938 (s), 1721 (broad, vs), 1640 (w), 1451 (w), 1428 (m), 1264 (m), 1206 (s), 1037 (w), 893 (m); LRMS *m/e* (rel. intensity) 208 (M^+, 1), 176 (49), 149 (100), 121 (21), 107 (27), 93 (35), 91 (39), 55 (51); HRMS (M^+ – MeOH) 176.0842 (found), 176.0837 (calcd). After treatment with CD_3OD and several crystals of NaOMe, ^{1}H NMR indicated four protons at δ = 2.83 (1H, d, J=15.4), 2.50 (1H, J = 15.4), 2.30 (1H, m), 2.20 (1H, m) were exchanged. GCMS (*m/e* 212, 180, 153, 125, 109, 93, 79, 56) showed the incorporation of four deuteriums.

Reaction of 1b with $HSnBu_3$: A sample of **1b** (254 mg, 0.656 mmol) was reduced by the same procedure as **1a**. The crude product was chromatographed on silica gel with 1/20 ethyl acetate and hexane to give **3b** (102 mg, 50 %), **4b** (54 mg, 27 %), and other unidentified material (10 mg). Spectroscopic data for **3b**: ^{1}H NMR ($CDCl_3$) δ 0.14 (9H, s), 1.24 (3H, t, J = 7.1), 1.27 (3H, s), 1.57–1.92 (6H, m), 1.97–2.24 (2H, m), 2.26–2.40 (2H, m), 2.65 (1H, dt, J = 6.3, 13.6), 4.14 (2H, q, J = 7.1); ^{13}C NMR ($CDCl_3$) δ 0.0 (q, J = 119.8), 14.0 (q, J = 127.2), 18.6 (q, J = 129.8), 18.7 (t, J = 130.4), 25.3 (t, J = 129.1), 26.7 (t, J = 123.8), 29.8 (t, J = 128.5), 39.9 (t, J = 129.8), 47.5 (d, J = 128.1), 60.5 (s), 60.9 (t, J = 148.0), 85.2 (s), 106.4 (s), 171.3 (s), 207.6 (s); IR (neat) 2936 (s), 2164 (m), 1707 (vs), 1453 (m), 1244 (m), 1194 (m), 1090 (m), 839 (vs), 756 (m); LRMS (CI) *m/e* (rel. intensity) 309 (MH^+, 19),

293 (13), 281 (6), 235 (12), 221 (9), 207 (6), 147 (19), 73 (100), 59 (10); HRMS (M^+ – Me): 293.1565 (found), 293.1573 (calcd).

Desilylation of 4b: A solution of **4b** (32.8 mg, 0.106 mmol) in benzene (2 mL) was treated with trifluoroacetic acid (37 μL, 4.5 eq) for 0.5 h at RT under N_2. The solvent was then evaporated, and the residue was chromatographed on silica gel with 1/10 ether and pentane to give the desilylated product (23 mg, 92%): ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7.1), 1.56–1.69 (4H, m), 1.90–2.42 (8H, m), 2.68 (1H, dd, J = 13.8, 1.4), 4.08–4.21 (2H, m), 4.61 (1H, s), 4.71 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.1 (q, J = 127.1), 26.7 (t, J = 129.4), 28.1 (t, J = 128.2), 29.8 (t, J = 127.4), 34.0 (t, J = 127.2), 39.6 (t, J = 132.3), 40.0 (t, J = 129.5), 47.0 (d, J = 123.8), 60.7 (t, J = 149.9), 63.2 (s), 110.3 (t, J = 115.6), 144.7 (s), 169.7 (s), 206.8 (s); IR (neat) 3074 (w), 2936 (s), 2868 (m), 1742 (s), 1714 (s), 1652 (m), 1450 (m), 1250 (m), 1180 (s), 1075 (m), 1021 (m), 894 (m); LRMS *m/e* (rel. intensity) 236 (M^+, 21), 218 (5), 191 (9), 190 (11), 163 (100), 144 (32), 145 (23), 134 (17), 119 (23), 106 (29), 91 (39), 77 (22), 65 (8); HRMS 236.1418 (found), 236.1412 (calcd).

Reaction of 1b with $DSnBu_3$: Starting from a solution of **1b** (200 mg, 0.516 mmol) in benzene (50 mL) and a solution of $DSnBu_3$ (168 μL, 0.62 mmol) and AIBN (17 mg) in benzene (20 mL), **3b-D** and **4b-D** were obtained in 26 % and 36 % yield, respectively. HH COSY and HC COSY experiments established that the two alkynyl protons of **3b** appeared as two multiplets at 2.15 ppm and 2.40 ppm, respectively, and the corresponding carbon appeared at 18.7 ppm. The ^{2}H NMR spectrum of **3b-D** showed two singlets at 2.12 and 2.29 ppm of equal intensity, indicating the presence of a 1/1 mixture of two diastereomers. The ^{13}C NMR (H-decoupled) spectrum of **3b-D** is the same as that of **3b**, except that the alkynyl carbon peak at 18.7 ppm (singlet) shifted to 18.5 ppm and became a triplet (J = 20.1 Hz).

2-Bromomethyl-2-methoxycarbonyl-4-*tert*-butylcyclohexanones (7a,e): To a suspension of sodium hydride (60 % oil, 1.04 g, 26 mmol) in THF (40 mL) containing HMPA (4.5 mL, 26 mmol) was slowly added a solution of 2-methoxycarbonyl-4-*tert*-butylcyclohexanone (4.246 g, 20 mmol) in THF (80 mL). After 45 min dibromomethane (15 mL, 214 mmol) was added. The reaction mixture was then refluxed. After 23 h, the mixture was cooled, diluted with ether (500 mL), washed with water (3x50 mL), dried (K_2CO_3), and concentrated to give a viscous oil. Crystallization from hexanes (30 mL) gave **7a** as a white needles (1.908 g), m.p. 103.0-104.0°C. More solid (0.222 g) was collected after the mother liquid was allowed to stand overnight at 25°C. The combined yields for **7a** was 2.130 g (37%). The mother liquid was then concentrated and chromatographed on silica gel with ethylacetate/hexanes (1/20) to give **7e** (0.674 g, 12%), and a small amount of unreacted starting material (0.205 g). Spectroscopic data for **7a**: ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 1.40–1.70 (2H, m), 2.00–2.20 (2H, m), 2.30–2.60 (3H, m), 3.77 (1H, d, J = 10.3), 3.79 (3H, s), 3.99 (1H, d, J = 10.3); ^{13}C NMR ($CDCl_3$) δ 27.0 (t, J = 129.9), 27.3 (q, J = 124.7), 32.4 (s), 33.2 (t, J = 151.6), 33.4 (t, J = 134.8), 38.5 (t, J = 130.2), 41.1 (d, J = 131.6), 52.7 (q, J = 147.7), 62.5 (s), 170.1 (s), 206.3 (s); IR (KBr) 2968 (s), 2954 (s), 2868 (m), 1741 (s), 1707 (s), 1460 (m), 1440 (m), 1268 (s), 1212 (m), 1086 (w), 1118 (m), 833 (w), 808 (w); LRMS (CI) *m/e* (rel. intensity) 307 (MH^+, 8), 305 (MH^+, 8), 291 (19), 289 (19), 275 (42), 273 (52), 259 (32), 257 (33), 225 (7), 193 (25), 165 (31), 57 (96); HRMS MH^+ (Br^{79}) 305.0734 (found), 305.0728 (calcd). Spectroscopic data for **7e**: ^{1}H NMR ($CDCl_3$) δ 0.80 (9H, s), 1.18–1.36 (2H, m), 1.59 (1H, tt, J = 12.4, 2.9), 1.93 (1H, m), 2.34 (2H, m), 2.54 (1H, dt, J = 13.3, 3.2), 3.35 (1H, d, J = 10.4), 3.63 (3H, s), 3.66 (1H, d, J = 10.4); ^{13}C NMR($CDCl_3$) δ 27.1 (q, J = 123.4), 27.7

(t, J = 124.1), 32.1 (s), 35.3 (t, J =156.6), 36.3 (t, J = 129.3), 40.2 (t, J = 130.0), 43.1 (d, J = 123.6), 52.5 (q, J = 148.0), 60.2 (s), 169.2 (s), 204.9 (s); IR (neat) 2956 (vs), 2871 (m), 1720 (s), 1436 (s), 1367 (w), 1291 (m), 1232 (s), 1159 (s); LRMS (CI) *m/e* (rel. intensity) 307 (MH^+, 15), 305 (MH^+, 16), 291 (4), 289 (4), 275 (10), 273 (11), 225 (100), 193 (29), 165 (30), 81 (29), 79 (24), 57 (84); HRMS (Br^{79}) 304.0664 (found), 304.0674 (calcd).

Reaction of 7a with $HSnBu_3$: Starting from **7a** (0.456 g, 1.5 mmol), the same radical reaction procedure as **1a** was followed. Column chromatography of the crude products on silica gel with 1/12 ethyl acetate/hexanes afforded reduction product **8a** (12 mg, 4 %),[1] and ring expansion products **9a** (254 mg, 75 %), and **9b** (13 mg, 4 %). Spectroscopic data for **9a**: ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.22–1.38 (2H, m), 1.40–1.60 (1H, m), 1.88–2.00 (1H, m), 2.35–2.50 (2H, m), 2.55–2.70 (2H, m), 2.85–2.98 (1H, m), 3.02 (1H, m), 3.71 (3H, m); ^{13}CNMR ($CDCl_3$) δ 24.4 (t, J = 131.8), 27.1 (q, J = 126.9), 32.5 (t, J = 126.5), 33.2 (s), 38.7 (d, J = 129.1), 42.9 (t, J = 127.9), 43.7 (t, J = 128.9), 47.0 (d, J = 124.0), 51.5 (q, J = 147.1), 174.3 (s), 211.9 (s); IR (neat) 2960 (vs), 2871 (s), 1732 (vs), 1706 (vs), 1436 (s), 1367 (m), 1197 (vs), 1172 (vs); LRMS *m/e* (rel. intensity) 226 (M^+, 29), 195 (11), 179 (27), 169 (52), 167 (14), 142 (31), 127 (67), 111 (87), 87 (70), 57 (100); HRMS 226.1578 (found), 226.1569 (calcd). Spectroscopic data for **9b**: ^{1}H NMR ($CDCl_3$) δ 0.89 (9H, s), 1.05–1.50 (4H, m), 1.90–2.10 (1H, m), 2.25–2.80 (5H, m), 3.70 (3H, s); ^{13}C NMR ($CDCl_3$) δ 25.6 (t, J = 124.9), 27.4 (q, J =124.8), 33.8 (s), 34.6 (t, J = 124.9), 41.9 (d, J = 131.5), 43.1 (t, J = 127.2), 45.6 (t, J = 131.6), 50.7 (d, J = 125.6), 52.1 (q, J = 147.0), 175.4 (s), 212.2 (s); IR (neat) 2956 (vs), 2870 (m), 1737 (vs), 1707 (vs), 1463 (m), 1278 (m), 1171 (m); LRMS *m/e* (rel. intensity) δ 226 (M^+, 17), 195 (8), 179 (22), 170 (24), 169 (24), 142 (29), 127 (54), 111 (71), 87 (53), 57 (100); HRMS 226.1564 (found), 226.1569 (calcd).

Reaction of 7e with $HSnBu_3$: Starting with **7e** (0.152 g, 0.5 mmol), the same procedure as that for **7a** was followed. Column chromatography on silica gel with 1/10 ethyl acetate and hexanes gave reduction product **8e** (6 mg, 5 %), and ring expansion products **9a** (82 mg, 72 %), and **9b** (8 mg, 7 %).

Methyl-3-oxo-10-trimethlysilanyl-9-decynoate (11): Sodium hydride (0.665 g, 27.7 mmol) was suspended in THF (80 mL) and cooled to 0°C. A solution of methylacetoacetate (2.0 mL, 18.5 mmol) in THF (10 mL) was then added dropwise to the stirred suspension. Gas evolution was observed. After 30 min at 0°C, 6-bromo-1-trimethylsilanyl-hexyne (4.75 g, 20.3 mmol) was added. Precipitate formed as the reaction proceeded. After 45 min, the reaction mixture was diluted with ether (100 mL) and the organic layer was washed with water, bicarbonate, and brine. After drying over $MgSO_4$, the product was isolated by column chromatography on silica gel with 15 % ethyl acetate/hexane to give a yellow oil (2.50 g, 50 %): ^{1}H NMR ($CDCl_3$) δ 3.66 (3H, s), 3.39 (2H, s), 2.48 (2H, t, J = 7.2), 2.14 (2H, t, J = 7.0), 1.56–1.32 (6H, m), 0.06 (9H, s); ^{13}C NMR($CDCl_3$) δ 202.4, 167.5, 107.0, 84.3, 52.1, 48.8, 42.6, 28.1, 27.9, 22.7, 19.5, 0.0; IR (neat) 2953, 2174, 1752, 1719, 1458, 1437, 1250, 843; LRMS *m/e*: 268, 253, 221, 193, 179, 89, 73; HRMS (M^+ – Me) *m/e*: 253.1258 (found), 253.1260 (calcd).

Methyl-2-diazo-3-oxo-10-trimethlysilanyl-9-decynoate (12):[13] Methyl-3-oxo-10-trimethyl-silanyl-9-decynoate (2.40 g, 8.90 mmol) and methanesulfonyl azide (1.14 g, 9.39 mmol) were dissolved in acetonitrile (18 mL). Triethylamine (2.48 mL, 17.8 mmol) was then added. After 8 h at room temperature, the reaction mixture was diluted with 1N NaOH (40 mL), and extracted with ethyl

acetate (3x40 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel with 10 % ethyl acetate/hexane to give a clear oil (1.95 g,74 %): ^{1}H NMR ($CDCl_3$) δ 3.82 (3H, s), 2.84 (2H, t, J = 6.4), 2.21 (2H, t, J = 7.1), 1.70–1.35 (6H, m), 0.13 (9H, m); ^{13}C NMR($CDCl_3$) δ 192.4, 161.5, 115.3, 84.3, 75.1, 55.3, 42.3, 29.8, 24.3, 20.8, 1.3; IR (neat) 2952, 2858, 2360, 2140, 1764, 1653, 1315, 1248, 850; LRMS *m/e*: 279 (M^+ – Me), 266, 262, 251, 238, 195, 89, 73; HRMS (M^+ – Me) *m/e*: 279.1148 (found), 279.1164 (calcd).

2-Methoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclopentanone:[15] $Rh_2(OAc)_4$ (148 mg, 0.34 mmol, 5 % mol) was suspended in dry CH_2Cl_2 (40 mL). A solution of **12** (1.80 g, 6.11 mmol) in CH_2Cl_2 (40 mL) was then added dropwise to the stirred slurry of $Rh_2(OAc)_4$ in 3 h. The reaction mixture was then filtered through a fritted funnel to recover the catalyst (115 mg). The solvent was evaporated and the residue was passed through a plug of silica gel with 30 % ethyl acetate/hexane. Concentration and vacuum drying gave a colorless oil (1.60 g, 98 %): ^{1}H NMR ($CDCl_3$) δ 3.73 (3H, s), 2.86 (1H, d, J = 11.3), 2.66 (1H, m), 2.48–2.20 (5H, m), 1.81 (1H, m), 1.68 (1H, m), 1.52 (1H, m), 0.12 (9H, s); ^{13}C NMR($CDCl_3$) δ 202.4, 167.5, 107.1, 88.7, 84.4, 52.2, 42.7, 28.2, 28.0, 22.8, 19.5, 0.01; IR (neat) 2959, 2176, 1757, 1734, 1437; LRMS *m/e*: 251, 219, 207, 191, 179, 175, 163, 154, 149, 145, 141, 135, 131, 117, 109, 89, 73; HRMS (M^+ – Me) 251.1125 (found), 251.1103 (calcd).

2-Methoxycarbonyl-3-(3-butynyl)cyclopentanone (13): 2-Methoxycarbonyl-3-(4-trimethylsilanyl-3-butynyl)cyclopentanone (1.40 g, 5.25 mmol) was dissolved in THF (40 mL) and cooled to 0°C. Tetrabutylammonium fluoride solution (1M in THF) (5.78 m, 5.78 mmol) was then added. After 4 h the reaction mixture was diluted with ether (80 mL), and washed with NH_4Cl (sat.), H_2O, and brine. The combined aqueous solutions were back extracted with EtOAc (40 mL). The organics were dried over $MgSO_4$, concentrated and purified by chromatography on silica gel (15 % ethyl acetate/hexane) to give a colorless oil (0.904 mg, 88 %): ^{1}H NMR ($CDCl_3$) δ 3.70 (3H, s), 2.82 (1H, d, J = 11.4), 2.68 (1H, m), 2.35 (2H, m), 2.24 (3H, m), 1.93 (1H, t, J = 2.6), 1.79 (1H, m), 1.66 (1H, m), 1.48 (1H, m); ^{13}C NMR($CDCl_3$) δ 211.1, 169.5, 83.1, 69.0, 61.2, 52.4, 40.3, 38.2, 33.4, 26.6, 16.3; IR (neat) 3283, 1755, 1724, 1456, 1265, 1136; LRMS *m/e* : 194, 165, 162, 151, 141, 134, 120, 107, 92, 79, 71, 59, 53; HRMS *m/e*: 194.0953 (found), 194.0943 (calcd).

2-Methoxycarbonyl-2-(3-iodopropanyl)-3-(3-butynyl)cyclopentanone (14): Sodium hydride (0.177 g, 6.18 mmol) was suspended in DME (15 mL). 2-Methoxycarbonyl-3-(3-butynyl)cyclopentanone (1.0 g, 5.15 mmol) was then carefully added. After 10 min at room temperature, 1,3-diiodopropane was introduced and the reaction was heated to reflux. After 20 h, the reaction mixture was cooled and diluted with EtOAc (60 mL), and washed with water, sodium bicarbonate solution, and brine (50 mL each). The product was isolated as a mixture of diastereomers by chromatography (SiO_2, 10 % EtOAc/Hexane). HPLC separation gave the pure trans isomer (0.513 g, 27 %): ^{1}H NMR ($CDCl_3$) δ 3.63 (3H, s), 3.20–3.05 (2H, m), 2.61–2.48 (1H, m), 2.42–2.11 (6H, m), 1.97 (1H, t, J = 1.6), 1.94–1.89 (2H, m), 1.71–1.58 (2H, m), 1.42–1.30 (1H, m); ^{13}C NMR($CDCl_3$) δ 215.4, 170.7, 83.1, 69.4, 61.9, 52.0, 43.2, 38.4, 32.9, 29.7, 28.3, 25.5, 16.4, 6.0; IR (neat) 3289, 2947, 1747, 1730, 1462, 1454, 1196; LRMS *m/e*: 362, 334, 275, 235, 175, 133, 91, 79; HRMS *m/e*: 362.0204 (found), 362.0241 (calcd).

Reaction of 2-Methoxycarbonyl-2-(3-iodopropanyl)-3-(3-butynyl)cyclopentanone with $HSnBu_3$: The substrate **14** (0.181 g, 0.40 mmol) was dissolved in benzene (65 mL) and heated to

reflux. A solution of $HSnBu_3$ (121 μL, 0.45 mmol) and AIBN (5 mg) was added over 12 h via syringe pump. After another 3 h of reflux, the reaction mixture was cooled to room temperature and the solvent was evaporated. The residue was taken up in ether (15 mL) and DBU (67 μL, 0.45 mmol) was added. The ether solution was passed through a plug of silica gel and eluted with ether (20 mL). Removal of solvent gave a residue, and column chromatography on silica gel with EtOAc/hexane gave the reduction products as a 3/1 (trans/cis) mixture. Spectra of this mixture: ^1H NMR ($CDCl_3$) δ 3.71 (3H, s, minor), 3.63 (3H, s, major), 2.54 (1H, m), 2.49–2.10 (5H, m), 1.95 (1H, t, J = 1.3), 1.92–1.58 (4H, m), 1.58–1.20 (2H, m), 1.13–0.97 (1H, m), 0.91 (3H, t, J = 7.2); ^{13}C NMR($CDCl_3$) 216.0, 172.6, 171.3, 83.3, 69.1, 68.9, 62.8, 52.3, 51.9, 44.6, 42.5, 38.8, 37.3, 33.7, 30.2, 29.8, 25.6, 25.1, 18.0, 17.4, 16.5, 14.5; IR (neat) 1750, 1732, 1460, 1135, 1086, 830.

Methyl 5-Oxocyclooctane Carboxylate (18): Ring Expansion of Methyl 1-(3-Iodopropyl)-2-oxocyclopentanoate (17):[7a] To a 100 mL round bottom flask were added methyl 1-(3-iodopropyl)-2-oxocyclopentanoate (**17**) (92.6 mg, 0.30 mmol), dry benzene (60 mL), AIBN (10.6 mg, 0.06 mmol) and Bu_3SnH (129 μL, 0.48 mmol) under nitrogen. The reaction mixture was heated at 80°C for 16 h and then cooled to 23°C. The solvent was evaporated and the residual oil was dissolved in CH_2Cl_2 (30 mL) and washed with 10 % KF solution (10 × 1 mL). The organic layer was dried over K_2CO_3, filtered and concentrated. The resulting oil was taken up in acetonitrile (25 mL), washed with with hexane (4 × 5 mL) and concentrated. Flash chromatography (Hexane : EtOAc = 5 : 1) gave **18** (45 mg, 75 %).

α-Diazo Methyl 3-Oxoheptanoate: A flame-dried flask was charged with methyl 3-oxoheptanoate (3.8 g, 24 mmol), methane sulfonyl azide (3.2 g, 26 mmol) and CH_3CN (46 mL). To this solution was added triethylamine (6.7 mL, 48 mmol). The mixture was stirred at 23°C for 3 h, then diluted with 10 % aqueous NaOH and extracted with ethyl ether. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by chromatography on silica gel with Hexane/EtOAc (10/1) to give a clear oil (3.6 g, 80 %): ^1H NMR δ 3.83 (s, 3 H), 2,84 (t, J = 7 Hz, 2 H), 1.64-1.55 (m, 2 H), 1.40-1.37 (m, J = 8 Hz, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMRδ 192.9, 161.8, 75.6, 52.1, 39.9, 26.4, 22.3, 13.8; IR 2959, 2137, 1724, 1659, 1437, 1311, 1211, 1140, 1103; MS (EI) *m/e* 142, 153, 156, 167, 185; HRMS calcd for $C_5H_6N_2O_3$ (M – C_3H_6) 142.0378, found 142.0385.

Methyl 2-Methyl-5-Oxocyclopentane Carboxylate: $Rh_2(OAc)_4$ (56 mg) was suspended in dry CH_2Cl_2 (17 mL), and the diazo compound (0.41 g, 2.2 mmol) in dry CH_2Cl_2 (17 mL) was added by a syringe pump. The solution was filtered and concentrated, and the residue was purified by flash chromatography (Hexane : EtOAc = 6 : 1) to give desired compound as a colorless oil (0.27g, 78 %): ^1H NMR δ 3.73 (s, 3 H), 2.78 (d, J = 12 Hz, 1 H), 2.61 (m, 2 H), 2.42-2.29 (m, 2 H), 2.20 (m, 1 H), 1.49 (m, 1 H), 1.18 (d, J = 7 Hz, 3 H); ^{13}C NMRδ 212.0, 169.7, 63.0, 52.5, 38.9, 36.42, 29.4, 19.4; IR 2959, 1752, 1728, 1458, 1437, 1334, 1290, 1203, 1130; MS (EI) *m/e* 69, 101, 109, 128, 141, 156; HRMS calcd for $C_8H_{12}O_3$ 156.0768, found 156.0768.

Methyl 2-Methyl-5-oxo-1-(2-propenyl)cyclopentane Carboxylate: A solution of the above keto-ester (1.60 g, 10.2 mmol) in THF (7 mL) was added to a suspension of NaH (0.49 g, 12.3 mmol, 60 % suspension in mineral oil) in THF (17 mL) containing HMPA (2.13 mL, 12.3 mmol) at 23°C. The reaction mixture was stirred at 23°C for 1 h, then treated with allyl bromide (1.06 mL, 12.3

mmol). After stirring at 23°C for 12 h, the reaction mixture was diluted with ethyl ether, washed with water, dried over K_2CO_3, filtered and concentrated. Column chromatography on silica gel (Hexane : EtOAc = 10 : 1) gave ***trans*** (1.30 g) and **cis** (0.12 g) products in a total yield of 71 %. **trans**: ^{1}H NMR δ 5.61 (m, 1 H), 5.12-5.07 (m, 2 H), 3.7 (s, 3 H), 2.64-2.46 (m, 3 H), 2.31 (m, 1 H), 2.16-2.02 (m, 2 H), 1.78 (m, 1 H), 1.01 (d, J = 7 Hz, 3 H); ^{13}C NMRδ 215.9, 170.9, 133.1, 119.5, 62.9, 51.8, 38.9, 38.6, 35.7, 28.2, 15.4; IR 3097, 2959, 2878, 1751, 1734, 1642, 1460, 1435, 1381, 1333, 1230, 1167, 1119, 1061, 999, 922; MS (EI) *m/e* 45, 59, 79, 94, 109, 136, 153, 168, 182, 196; HRMS cacld for $C_{11}H_{16}O_3$ 196.1099, found 196.1097. ***cis***: ^{1}H NMR δ 5.80 (m, 1 H), 5.10-5.03 (m, 2 H), 3.70 (s, 3 H), 2.80 (m, 1 H), 2.59-2.32 (m, 4 H), 2.10 (m, 1 H), 1.65 (m, 1 H), 1.06 (d, J = 7 Hz, 3 H); ^{13}C NMRδ 214.5, 171.9, 133.4, 118.4, 63.9, 52.5, 39.6, 37.1, 33.4, 27.6, 14.7; IR 3078, 2959, 1749, 1732, 1639, 1453, 1383, 1292, 1248, 1213, 1167, 1016, 918, 848; MS (EI) *m/e* 81, 94, 109, 121, 136, 164, 168, 178, 181, 196; HRMS calcd for $C_{11}H_{16}O_3$ 196.1095, found 196.1095.

Methyl *cis*-1-(3-Bromopropyl)-2-Methyl-5-oxocyclopentane Carboxylate (20-*cis*): A flame dried flask was charged under argon with the above cis product (0.054 g, 0.28 mmol) and distilled hexane (4 mL). Argon was bubbled through the system for 15 min, and then benzoyl peroxide (5 mg) was introduced. The reaction mixture was cooled to 10°C and HBr was bubbled in for 60 min while maintaining the temperature between 10°C and 20°C. Stirring was continued for additional 1 h, and after that the reaction mixture was poured into ice water and extracted with ether. The ether solution was washed with water, saturated $NaHCO_3$ solution, dried over $MgSO_4$, filtered and evaporated. The resulting oil was purified by flash chromatography on silica gel (Hexane : EtOAc = 6 : 1), affording **20-*cis*** (0.048 g, 63 %) as a pale yellow oil: ^{1}H NMR δ 3.71 (s, 3 H), 3.41 (m, 2 H), 2.72 (m, 1 H), 2.41-2.36 (m, 2 H), 2.12, (m, 1 H), 1.98-1.80 (m, 3 H), 1.78-1.61 (m, 2 H), 1.04 (d, J = 7 Hz, 3 H); ^{13}C NMRδ 214.6, 172.1, 62.9, 52.5, 40.1, 36.9, 34.1, 27.6, 27.4, 26.6, 14.5; IR 2959, 1734, 1726, 1439, 1250, 1165, 1030; MS (EI) *m/e* 81, 137, 165, 191, 197, 248, 261, 276; HRMS calcd for $C_{11}H_{17}O_3$ (M – Br) 197.1152, found 197.1152.

Methyl *trans*-1-(3-Bromopropyl)-2-Methyl-5-oxocyclopentane Carboxylate (20-*trans*). Starting from the above trans product (0.66 g, 3.3 mmol), **20-*trans*** (0.74 g, 80 %) was prepared by following the same procedure for **20-*cis***: ^{1}H NMR δ 3.69 (s, 3 H), 3.40 (m, 2 H), 2.60-2.53 (m, 1 H), 2.25-2.20 (m, 2 H), 2.14-2.06 (m, 2 H), 1.97 (m, 1 H), 1.83-1.73 (m, 3 H), 1.04 (d, J = 7 Hz, 3 H); IR 2959, 1730, 1435, 1383, 1331, 1234, 1167, 1118, 1062, 995, 756; MS (EI) *m/e* 45, 59, 74, 137, 165, 189, 219, 250, 261, 277; HRMS cacld for $C_{11}H_{17}O_3$ (M – Br) 197.1187, found 197.1168.

Kinetic Studies of Radical Ring Expansion with Deuterium Labeling: Halides **17** and **20-*cis*,*trans*** were treated with Bu_3SnD (0.005 M) by following the standard procedure. After KF workup, the resulting oil of each reaction mixture was dissolved in 0.5 mL of $CHCl_3$ with 1 μl of $CDCl_3$ as internal reference for ^{2}H-NMR study.

Methyl 2-Methyl-5-oxocyclooctane Carboxylate (21): A solution of Bu_3SnH (56.6 μl, 0.21 mmol) and AIBN in benzene (4 mL) was added slowly by using a syringe pump to a solution of **20-*cis*** (36.9 mg, 0.13 mmol) in benzene (65 mL) at 80°C over 19 h. After standard KF workup (see general procedure for radical ring expansion), the residual oil was purified by flash chromatography (Hexane : EtOAc = 5 : 1) to give a pair of diasteromers of **21** (1/3.75, 18.0 mg, 70 %). Minor isomer: ^{1}H NMR δ 3.65 (s, 3 H), 2.73 (m, 1 H), 2.55-2.32 (m, 3 H), 2.28-2.16 (m, 4 H), 2.00 (m, 2 H), 1.78 (m, 1

H), 1.60 (m, 1 H), 0.81 (d, J = 7 Hz, 3 H). Major isomer: ^{1}H NMR δ 3.65 (s, 3 H), 2.75 (m, 1 H), 2.52-2.44 (m, 2 H), 2.40-2.23 (m, 2 H), 2.13 (m, 1 H), 2.01-1.87 (m, 2 H), 1.83-1.65 (m, 4 H), 0.91 (d, J = 7 Hz, 3 H); ^{13}C NMRδ 216.6, 177.1, 51.7, 49.4, 40.5, 39.9, 35.1, 30.2, 28.3, 27.8, 18.5; IR 2953, 1734, 1701, 1466, 1458, 1437, 1375, 1334, 1257, 1226, 1170; MS (EI) *m/e* 55, 59, 69, 74, 79, 83, 93, 97, 101, 111, 138, 151, 156, 166, 180, 198; HRMS calcd for $C_{11}H_{18}O_3$ 198.1242, found 198.1242.

Methyl *cis*-2-Methyl-5-oxo-1-propylcyclopentane Carboxylate (22-*cis*): The above cis allyl compound (28 mg, 0.14 mmol) was added into a flask containing a batch of palladium on active carbon suspended in MeOH (5 mL) under nitrogen. A ballon filled with hydrogen was connected to the flask. The flask was evacuated and then filled with hydrogen several times. The reaction mixture was stirred at 23°C for 2 h, filtered through a pad of Celite, and concentrated to give **22-*cis*** (25 mg, 88 %): ^{1}H NMR δ 3.69 (s, 3 H), 2.70 (m, 1 H), 2.34 (m, 2 H), 2.07 (m, 1 H), 1.70-1.50 (m, 3 H), 1.30 (m, 2 H), 1.08 (d, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3 H); ^{13}C NMRδ 215.0, 172.3, 63.7, 52.4, 39.8, 36.9, 30.5, 27.5, 18.1, 14.6, 14.4; IR 3546, 2961, 2876, 1753, 1732, 1464, 1435, 1381, 1279, 1248, 1215, 1167, 1128, 1103, 1074; MS (EI) *m/e* 55, 69, 83, 96, 111, 128, 141, 156, 167, 170, 183, 199; HRMS caclcd for $C_{10}H_{15}O_2$ (M – OCH_3) 167.1072, found 167.1060.

Methyl *trans*-2-Methyl-5-oxo-1-propylcyclopentane Carboxylate (22-*trans*): Alkylation of the above keto ester (93 mg, 0.60 mmol) with 1-iodopropane by following general alkylation procedure gave **22-*trans*** (75 mg, 64 %) after purification by flash chromatography (Hexane : EtOAc = 6 : 1): ^{1}H NMR δ 3.65 (s, 3 H), 2.51 (m, 1 H), 2.30-2.01 (m, 3 H), 1.81-1.67 (m, 3 H), 1.40 (m, 1 H), 1.09 (m, 1 H), 1.01 (d, J = 7 Hz, 3 H), 0.89 (t, J = 7 Hz, 3 H); IR 2961, 2876, 1750, 1732, 1456, 1435, 1381, 1331, 1231, 1192, 1165, 1118, 1065; ^{13}C NMR δ 216.7, 171.4, 63.3, 51.7, 39.4, 39.0, 33.8, 28.2, 17.5, 15.9, 14.7; MS (EI) *m/e* 55, 111, 141, 156, 167, 183, 199.

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