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Stereoselective α-Quaternization of 3-Methoxycycloalk-2-enones via 1,4-Diastereoinduction of Alkoxy Dienolates

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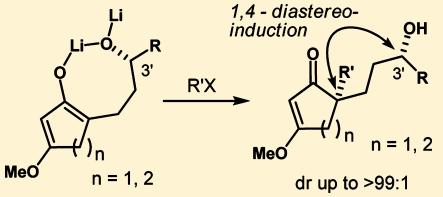
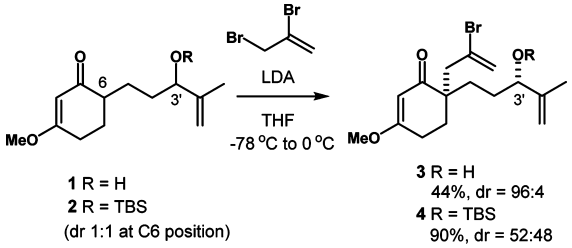
Supporting Information

ABSTRACT: The alkylation of dienolates generated from 3-methoxycycloalk-2-enones having a 3′-hydroxyl alkenyl chain provides the corresponding quaternized cycloalkenones in a highly diastereoselective manner. The high degree of stereocontrol in the α-quaternization possibly implies intervention of a rigid chelating transition state that allows an efficient 1,4-asymmetric induction to take place.



Because of the ubiquity of quaternized carbon in the chemical structures of bioactive natural products, the development of methods for the synthesis of quaternary stereocenters constitutes one of the major objectives in organic synthesis.[1,2] In the course of establishing a route to (±)-platencin, we discovered that 3-methoxycyclohex-2-enone (**1**) possessing a free 3′-hydroxyalkenyl side chain underwent highly diastereoselective alkylation to afford corresponding quaternized product **3** with a ratio of 96:4, whereas TBS-protected substrate **2** did not exert such a high level of selectivity (Scheme 1).[3] The observed stereochemical outcome

Scheme 1. Highly Stereoselective Quaternization of Enone 1

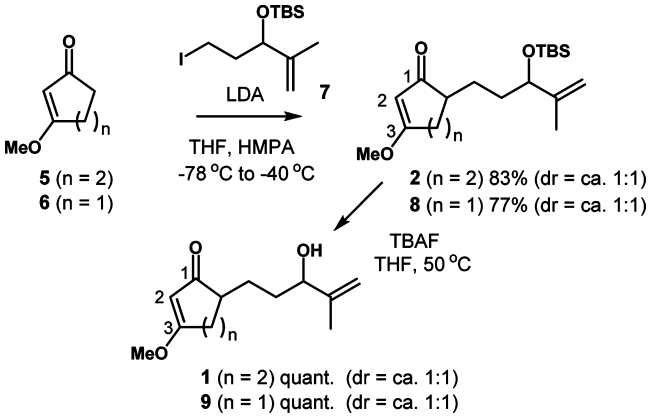


is attributable to the 1,4-diastereoinduction arising from a transition state, in which an eight-membered lithium enolate allows the alkylating agent to access from the less hindered face, leading to essentially single stereoisomer **3**.[4,5]

This discovery prompted us to screen various alkylating agents and substrates and investigate the feasibility of this simple means to access quaternized cycloalkenones, which would serve as useful building blocks for bioactive natural products. In the present study, we report the potential scope of the highly stereoselective 1,4-asymmetric inductive quaternization of 3-methoxycyclohex-2-enone (**1**) and 3-methoxycyclopent-2-enone (**9**) with various alkylating agents.

The stereoselective quaternization was initially evaluated with TBS-protected enones **2**/**8** and hydroxy enones **1**/**9**, which were prepared from 3-methoxycycloalkenones **5** and **6** (Scheme 2). Known enones **5** and **6** were each alkylated with

Scheme 2. Preparation of Substrates



iodide **7** by following standard alkylation protocols to afford enones **2** and **8** in good yields, as an essentially 1:1 diastereomeric mixture. Hydroxy enones **1** and **9** were then successfully derived by desilylation of TBS-protected enones **2** and **8** with TBAF at 50 °C. As the first set of experiments, the alkylative quaternization of TBS-protected enones **2** and **8** was examined with various alkylating agents using 1.5 equiv of LDA (Table 1). In all cases, nearly equal amounts of two diastereomers were produced irrespective of the ring size of the enone or the type of alkylating agent. The low diastereoinduction was consistent with that previously observed for the alkylation of enone **2** with 2,3-dibromopropene.[3]

Then, we evaluated the quaternization of hydroxy enones **1** and **9** under the same conditions except for the slightly larger amount of LDA (3 equiv) (Table 2). In contrast to the above cases, alkylation of the hydroxy enones was highly stereoselective and generally afforded the corresponding quaternized compounds as almost single stereoisomers albeit in moderate yields. Thus, alkoxy dienolates that were generated from enones

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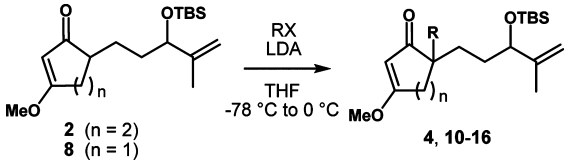
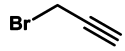
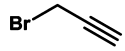
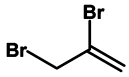
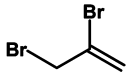
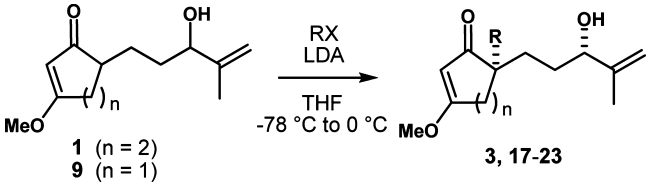
Table 1. Alkylative Quaternization of TBS-Protected Enones 2 and 8

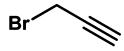
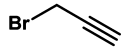
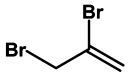
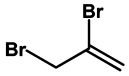


entry	substrate	RX	product	yield (%)[a,b]	dr[c]
1	**8**	MeI	**10**	62 (69)	50:50
2	**2**	MeI	**11**	80 (86)	53:47
3	**8**		**12**	64 (79)	57:43
4	**2**		**13**	74 (80)	58:42
5	**8**		**14**	82 (90)	57:43
6	**2**		**4**	90	52:48[d]
7	**8**	BnBr	**15**	70 (76)	56:44
8	**2**	BnBr	**16**	68 (72)	50:50

[a]RX (5 equiv) and LDA (1.5 equiv) were used. [b]Isolated yields. Yields based on recovered starting enone are given in parentheses. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis. [d]From our published results (see ref 3).

Table 2. Alkylative Quaternization of Hydroxy Enones 1 and 9



entry	substrate	RX	product	yield (%)[a,b]	dr[e]
1	**9**	MeI	**17**	57 (74)	>99:1
2	**1**	MeI	**18**[c]	49 (55)	86:14
3	**9**		**19**	51 (60)	>99:1
4	**1**		**20**	52 (60)	93:7
5	**9**		**21**[d]	53 (65)	88:12
6	**1**		**3**[c]	44 (50)	96:4[f]
7	**9**	BnBr	**22**[d]	50 (57)	93:7
8	**1**	BnBr	**23**[c]	56 (64)	92:8

[a]RX (5 equiv) and LDA (3 equiv) were used. [b]Isolated yields. Yields based on recovered starting enone are given in parentheses. [c]2-Alkylated regioisomers were obtained (9% for entry 2, 11% for entry 6 and 14% for entry 8). See ref 6. [d]4-Alkylated regioisomers were obtained (14% for entry 5 and 16% for entry 7). See ref 6. [e]Diastereomeric ratio was determined by ^{1}H NMR analysis. [f]From our published results (see ref 3).

1 and **9** with 3 equiv of LDA underwent methylation, propargylation, 2-bromoallylation, and benzylation with excellent diastereoselectivities ranging from 86:14 to >99:1. Noteworthy is the fact that methyl iodide, a sterically less demanding alkylating agent, successfully underwent diastereoselective alkylation to give the quaternized products (entries 1 and 2).

The relative stereochemistry of each product was unambiguously determined by analyzing the coupling constants and the NOE correlations of corresponding cyclic compounds **17a**–**23a**, which were readily prepared from products **17**–**23** by acid treatment (Table 3). The large coupling constant between Ha and Hb protons, i.e., J_{ab} = ca. 12 Hz, which was observed for all of the cyclized compounds, indicated the conformation shown in Table 3. Furthermore, NOE analysis allowed us to confirm the proximity of the Hb and the proton of the newly introduced C6 or C5 substituent (numbering based on quaternized products **3**, **17**–**23**). Thus, the stereochemical analysis suggested that in all cases, there was exclusive production of a stereoisomer that possesses *syn*-relationship between C6 or C5 substituent and the hydroxyl group at the side chain. This stereoselectivity strongly implies the intermediacy of a rigid transition state, such as **i** shown in Scheme 3, where the alkylating agents can effectively distinguish the two facial environments of the dienolates. It can thus be postulated again that the chelation structures of the alkoxy dienolates generated in situ by the deprotonation of enones **1** and **9** with LDA are reasonably responsible for exerting the distinct facial selectivities.

With these intriguing results of the quaternization available, we next examined the alkylation of 3-methoxycyclohex-2-enone derivatives **24** and **25**, both of which bear a slightly bulky isopropyl substituent on the side chain, with a view to clarifying the effect of the substituent on the stereoinduction. Isopropyl derivatives **24** and **25** were readily prepared by hydrogenation of enones **1** and **2** with PtO_2 under hydrogen atmosphere in 86% and 65% yield, respectively, and subjected to alkylation. Deprotonation of the enones with LDA, followed by alkylation with 2,3-dibromopropene and benzyl bromide under the established conditions, delivered corresponding quaternized compounds **26**–**29** in moderate yields (Table 4).

The alkylation of hydroxy enone **24** with either 2,3-dibromopropene or benzyl bromide took place with selectivities of 78:22 for both cases to furnish **26** or **28** (entries 1 and 3), whereas that of TBS-protected enone **25** showed no significant diastereoinduction (entries 2 and 4). This result indicates that the 1,4-asymmetric induction is also feasible with an alkyl substituent other than isopropenyl; however, the extent of the 1,4-asymmetric induction may depend on the bulkiness of the group. It seems that the slightly bulky isopropyl substituent

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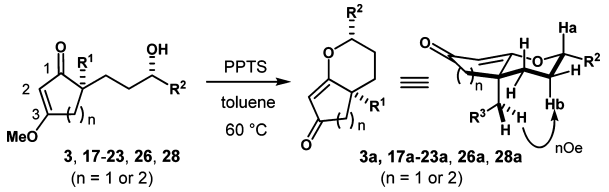
Table 3. Determination of Stereochemistry of Major Isomers



entry	enone	R^1/R^2	product (%)	J_{ab} (Hz)
1	**17**	Me/isopropenyl	**17a** (77%)	12
2	**18**	Me/isopropenyl	**18a** (95%)	11.9
3	**19**	propargyl/isopropenyl	**19a** (81%)	12
4	**20**	propargyl/isopropenyl	**20a** (78%)	11.7
5	**21**	2-bromoallyl/isopropenyl	**21a** (82%)	12.2
6	**22**	Bn/isopropenyl	**22a** (50%)	12
7	**23**	Bn/isopropenyl	**23a** (90%)	12
8	**3**	2-bromoallyl/isopropenyl	**3a** (83%)	11.9 (ref 3)
9	**26**	2-bromoallyl/*i*-Pr	**26a** (90%)	12
10	**28**	Bn/*i*-Pr	**28a** (83%)	12.4

Scheme 3. Plausible Mechanism for Highly Stereoselective Quaternization of Hydroxy Enones 1 and 9

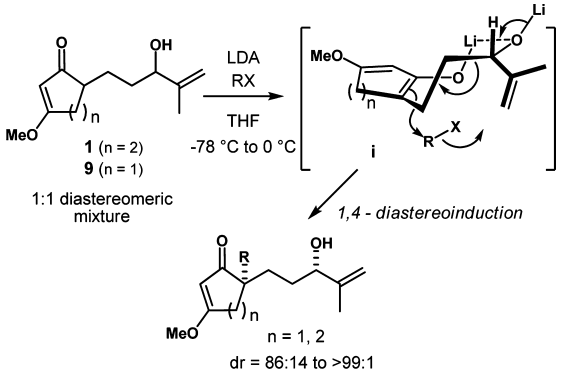
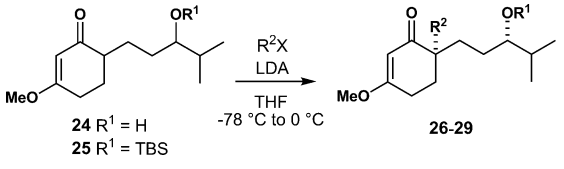
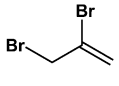
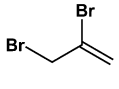


Table 4. Alkylative Quaternization of Enones 24 and 25



entry	substrate	R^2X	product	yield (%)[a]	dr[e]
1	**24**		**26**[b] R^1 = H, R^2 = 2-bromopropenyl	49 (63)	78:22
2	**25**		**27**[c] R^1 = TBS, R^2 = 2-bromopropenyl	60 (79)	51:49
3	**24**	BnBr	**28**[b] R^1 = H, R^2 = Bn	54 (60)[d]	78:22
4	**25**	BnBr	**29**[c] R^1 = TBS, R^2 = Bn	50 (77)	53:47

[a]Isolated yields. Yields based on recovered starting enone are given in parentheses. [b]RX (5 equiv) and LDA (3 equiv) were used. [c]RX (5 equiv) and LDA (1.5 equiv) were used. [d]2-Alkylated regioisomer (10%) was also obtained. See ref 6. [e]Diastereomeric ratio was determined by ^{1}H NMR analysis.

adversely affects the rigidity of the chelation intermediate, leading to undesired erosion of the stereoselectivity.[7]

In conclusion, we have established an expeditious approach to the stereoselective quaternization of cyclic dienolates via 1,4-diastereoinduction, which is expected to find broad application in organic synthesis. Further work to employ the present method for the asymmetric synthesis of natural products bearing quaternary stereocenters is underway.

EXPERIMENTAL SECTION

5-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxycyclopent-2-enone (8). Compounds **8** and **9** were prepared by the protocol reported in ref 2 for compounds **1** and **2**, respectively. Pale yellow oil (dr =1:1): IR (neat) 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.86 (s, 0.5H), 4.85 (s, 0.5H), 4.76 (s, 1H), 4.04−4.00 (m, 1H), 3.82 (s, 3H), 2.74 (dd, 1H, J = 17.6, 7.2 Hz), 2.49−2.43 (m, 1H), 2.26 (dd, 1H, J = 17.6, 2.4 Hz), 1.84−1.72 (m, 1H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.56−1.48 (m, 2H), 1.42−1.34 (m, 1H), 0.881 (s, 4.5H), 0.871 (s, 4.5H), 0.04 (s, 1.5H), 0.03 (s, 1.5H), 0.00 (s, 1.5H), −0.01 (s 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 189.8, 147.3, 147.1, 111.1, 111.0, 103.7, 58.6, 45.3, 45.2, 34.9, 34.6, 33.6, 33.1, 27.2, 25.8, 21.1, 18.2, 17.2, 17.1, −4.8, −5.1; HRMS (FAB) calcd for $C_{18}H_{33}O_3Si$ $(M + H)^+$ 325.2199, found 325.2192.

5-(3-Hydroxy-4-methylpent-4-enyl)-3-methoxycyclopent-2-enone (9). Pale yellow oil (dr =1:1): IR (neat) ν 3412, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.88 (s, 1H), 4.77 (s, 1H), 4.02−3.98 (m, 1H), 3.78 (s, 3H), 2.72 (dd, 1H, J = 18, 7.2 Hz), 2.51−2.43 (m, 1H), 2.25 (dd, 1H, J = 18, 2.4 Hz), 1.85−1.70 (m, 1H), 1.66 (s, 1.5H), 1.65 (s, 1.5H), 1.59−1.51 (m, 2H), 1.47−1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 208.1, 190.4, 190.0, 147.2, 147.0, 111.1, 110.9, 103.6, 103.5, 58.55, 58.53, 44.9, 34.8, 34.6, 32.3, 31.7, 27.6, 27.1, 17.5, 17.4; HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1259.

6-(3-Hydroxy-4-methylpentyl)-3-methoxycyclohex-2-enone (24). To a stirred solution of enone **1** (200 mg, 0.89 mmol) in methanol (5 mL) was added PtO_2 (10 mg, 0.0445 mmol). The mixture was stirred at room temperature under hydrogen atmosphere for 1 h and then filtered through a pad of Celite. After concentration under reduced pressure, the residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:1) to give enone **24** (173 mg, 86%, colorless oil) as a mixture of two diastereomers whose ratio was determined by analyzing the ^{13}C NMR spectrum to be ca. 1:1: IR (neat) 3445, 1624 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1H), 3.69 (s, 3H), 3.37−3.31 (m, 1H), 2.46−2.43 (m, 2H), 2.27−2.23 (m, 1H), 2.10−2.04 (m, 1H), 1.94−1.86 (m, 1H), 1.81−1.75 (m, 1H), 1.68−1.63 (m, 1H), 1.55−1.51 (m, 2H), 1.46−1.39 (m, 1H), 0.92 (d,

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3H, J = 7.0 Hz), 0.91 (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 201.7, 177.8, 177.7, 101.7, 101.68, 55.6, 44.9, 44.88, 33.6, 33.3, 31.5, 31.1, 27.9, 27.6, 26.5, 26.4, 26.1, 25.5, 18.8, 18.7, 17.3, 17.2; HRMS (FAB) calcd for $C_{13}H_{23}O_3$ $(M + H)^+$ 227.1647, found: 227.1643.

6-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpentyl)-3-methoxycyclohex-2-enone (25). This material was obtained as pale yellow oil in 65% yield from enone **2** by the same protocol described for compound **24**: IR (neat) 1661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 3.64 (s, 3H), 3.43−3.40 (m, 1H), 2.39 (t, 2H, J = 6.0 Hz), 2.17−1.99 (m, 2H), 1.88−1.67 (m, 3H), 1.51−1.27 (m, 3H), 0.85 (s, 9H), 0.80 (d, 6H, J = 6.9 Hz), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 201.5, 177.5, 102.0, 101.95, 55.8, 45.6, 45.5, 32.9, 32.5, 30.9, 30.8, 27.9, 27.8, 26.5, 26.49, 26.1, 25.8, 25.5, 18.7, 18.3, 18.2, 18.0, 17.5, −4.0, −4.1, −4.3, −4.32; HRMS (FAB) calcd for $C_{19}H_{37}O_3Si$ $(M + H)^+$ 341.2512, found 341.2510.

Typical Protocol for α-Quaternization of Enones. (*S)-5-((*S**)-3-Hydroxy-4-methylpent-4-enyl)-3-methoxy-5-methylcyclopent-2-enone (17).** To a stirred solution of LDA (1.8 M in heptane/THF/ethylbenzene; 400 μL, 0.72 mmol) in THF (3 mL) at −78 °C was added slowly a solution of enone **9** (50 mg, 0.24 mmol) in THF (2 mL) over a period of 5 min. Then the mixture was stirred at the same temperature for an additional 30 min. Following dropwise addition of methyl iodide (75 μL, 1.2 mmol), the whole mixture was allowed to warm to 0 °C and stirring was continued for further 2 h. Upon addition of satd NH_4Cl, the mixture was transferred to a separatory funnel where it was extracted with Et_2O. The phases were separated, and the organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:2) to yield enone **17** (30.4 mg, 57%, pale yellow oil) as single diastereomer (dr >99:1 determined by ^{1}H NMR analysis). Further elution gave unreacted enone **9** (8 mg, 16% recovered): IR (neat) ν 3393, 1682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 3.99 (dd, 1H, J = 6.5, 6.0 Hz), 3.83 (s, 3H), 2.56 (d, 1H, J = 17.5 Hz), 2.34 (d, 1H, J = 17.5 Hz), 1.69 (s, 3H), 1.55−1.51 (m, 2H), 1.46−1.38 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 188.7, 147.1, 111.4, 102.8, 75.9, 58.5, 47.1, 41.3, 33.5, 29.7, 24.5, 17.5; HRMS (EI) calcd for $C_{13}H_{20}O_3$ (M^+) 224.1413, found 224.1427.

5-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxy-5-methylcyclopent -2-enone (10). Pale yellow oil: IR (neat) 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (s, 1H), 4.76 (brs, 1 H), 4.66 (s, 0.5H), 4.76 (s, 0.5H), 3.91−3.87 (m, 1H), 3.76 (s, 3H), 2.44 (dd, 1H, J = 17.5, 9 Hz), 2.24 (d, 1H, J = 17.5 Hz), 1.56 (s, 1.5H), 1.55 (s, 1.5H), 1.44−1.23 (m, 4H), 1.06 (s, 1.5H), 1.05 (s, 1.5H), 0.81 (s, 4.5H), 0.79 (s, 4.5H), −0.04 (s, 1.5H), −0.06 (s, 1.5H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210, 188.23, 188.16, 146.9, 146.5, 110.8, 110.5, 102.4, 102.2, 58.1, 46.73, 46.72, 41.2, 41.0, 33.2, 32.8, 30.6, 30.3, 25.5, 25.4, 24.0, 23.5, 17.84, 17.82, 16.8, 16.7, −5.1, −5.2, −5.42, −5.44; HRMS (EI) calcd for $C_{19}H_{34}O_3Si$ (M^+) 338.2277, found 338.2263.

6-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxy-6-methylcyclohex-2-enone (11). Pale yellow oil: IR (neat) ν 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.82 (s, 0.5H), 4.80 (s, 0.5H), 4.72 (brs, 1H), 3.96−3.93 (m, 1H), 3.63 (s, 3H), 2.45−2.31 (m, 2H), 1.90−1.83 (m, 1H), 1.73−1.67 (m, 1H), 1.62 (s, 1.5H), 1.61 (s, 1.5H), 1.55−1.28 (m, 4H), 1.04 (s, 1.5H), 1.03 (s, 1.5H), 0.0842 (s, 4.5H), 0.0837 (s, 4.5H), 0.00 (s, 1.5H), −0.02 (s, 1.5H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 203.9, 176.3, 176.2, 147.3, 147.2, 110.79, 110.76, 100.9, 100.7, 55.5, 42.9, 42.8, 32.5, 32.3, 32.1, 32.0, 30.4, 30.2, 25.7, 22.3, 22.0, 18.12, 18.11, 17.2, 17.1, −4.82, −4.84, −5.13, −5.15; HRMS (EI) calcd for $C_{20}H_{36}O_3Si$ (M^+) 352.2434, found 352.2449.

5-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxy-5-(prop-2-ynyl)cyclopent-2-enone (12). Pale yellow oil: IR (neat) 1697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (s, 0.5H), 5.27 (s, 0.5H), 4.84 (s, 1H), 4.77 (s, 0.5H), 4.74 (s, 0.5H), 3.98−3.93 (m, 1H), 3.85 (s, 3H), 2.72 (d, 0.5H, J = 17.5 Hz), 2.71 (d, 0.5H, J = 17.5 Hz), 2.47 (d, 0.5H, J = 17.5 Hz), 2.42 (d, 0.5H, J = 17.5 Hz), 2.39 (dd, 1H, J = 16.5, 2.5 Hz), 2.34 (dd, 1H, J = 16.5, 2.5 Hz), 1.92−1.90 (m, 1H), 1.72−1.66 (m, 1H), 1.62 (s, 3H), 1.54−1.47 (m, 1H), 1.40−1.32 (m, 2H), 0.88 (s, 4.5H), 0.87 (s, 4.5H), 0.03 (s, 1.5H), 0.01 (s, 1.5H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 207.3, 189.1, 189.0, 147.1, 146.4, 111.0, 110.5, 103.3, 103.2, 80.2, 80.1, 69.7, 69.6, 58.4, 49.62, 49.57, 38.4, 38.2, 32.0, 31.5, 30.4, 29.8, 26.7, 26.2, 25.51, 25.49, 17.9, 17.0, 16.9, −5.06, −5.14, −5.4; HRMS (EI) calcd for $C_{21}H_{34}O_3Si$ (M^+) 362.2277, found 362.2294.

6-(3-(*tert*-Butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxy-6-(prop-2-ynyl)cyclohex-2-enone (13). Pale yellow oil: IR (neat) 1653 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.86 (s, 0.5H), 4.84 (s, 0.5H), 4.74 (brs, 1H), 3.99−3.93 (m, 1H), 3.68 (s, 3H), 2.55−2.34 (m, 4H), 2.09−2.03 (m, 2H), 1.97 (dd, 1H, J = 4.5, 4.5 Hz), 1.74−1.66 (m, 1H), 1.64 (s, 3H), 1.56−1.25 (m, 3H), 0.87 (s, 9H), 0.03 (s, 1.5H), 0.00 (s, 1.5H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 176.9, 147.8, 111.11, 111.06, 101.3, 101.2, 97.5, 81.5, 71.0, 70.9, 56.0, 46.04, 46.02, 30.5, 30.4, 30.3, 30.2, 30.1, 26.10, 26.09, 25.90, 25.88, 25.1, 25.0, 18.5, 17.6, −4.4, −4.5, −4.8; HRMS (EI) calcd for $C_{22}H_{36}O_3Si$ (M^+) 376.2434, found 376.2434.

5-(2-Bromoallyl)-5-(3-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxycyclopent-2-enone (14). Pale yellow oil: IR (neat) 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (s, 0.5H), 5.62 (s, 0.5H), 5.54−5.52 (m, 1H), 5.29 (s, 1H), 4.85 (s, 1H), 4.78 (t, 0.5H, J = 1.5 Hz), 4.75 (t, 0.5H, J = 1.5 Hz), 3.99−3.92 (m, 1H), 3.87 (s, 3H), 3.06 (d, 0.5H, J = 18.0 Hz), 3.04 (d, 0.5H, J = 18.0 Hz), 2.73 (d, 1H, J = 14.6 Hz), 2.65 (d, 1H, J = 14.6 Hz), 2.47 (d, 0.5H, J = 18.0 Hz), 2.41 (d, 0.5H, J = 18.0 Hz), 1.64 (s, 3H), 1.57−1.47 (m, 1H), 1.43−1.26 (m, 3H), 0. 90 (s, 4.5H), 0.89 (s, 4.5H), 0.04 (s, 1.5H), 0.03 (s, 1.5H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 208.1, 189.8, 189.6, 147.5, 146.8, 128.8, 128.7, 121.14, 121.05, 111.1, 110.7, 103.9, 103.8, 58.7, 58.6, 50.53, 50.48, 47.7, 47.1, 38.24, 38.20, 32.9, 32.7, 30.5, 29.9, 25.8, 25.78, 18.1, 17.3, 17.2, −4.8, −4.9, −5.10, −5.12; HRMS (EI) calcd for $C_{21}H_{35}BrO_3Si$ (M^+) 442.1539, found 442.1526.

5-Benzyl-5-(3-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxycyclopent−2-enone (15). Pale yellow oil: IR (neat) 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.10 (m, 5H), 5.15 (s, 0.5H), 5.13 (s, 0.5H), 4.85 (s, 0.5H), 4.84 (s, 0.5H), 4.77 (s, 0.5H), 4.74 (s, 0.5H), 3.99−3.93 (m, 1H), 3.70 (s, 1.5H), 3.68 (s, 1.5H), 3.01 (d, 0.5H, J = 13.2 Hz), 2.97 (d, 0.5H, J = 13.2 Hz), 2.65 (d, 0.5H, J = 13.2 Hz), 2.61 (d, 0.5H, J = 13.2 Hz), 2.58 (d, 0.5H, J = 18.0 Hz), 2.55 (d, 0.5H, J = 18.0 Hz), 2.31 (d, 0.5H, J = 18.0 Hz), 2.27 (d, 0.5H, J = 18.0 Hz), 1.65 (s, 1.5H), 1.64 (s, 1.5H), 1.61−1.50 (m, 1H), 1.49−1.29 (m, 3H), 0.88 (s, 4.5H), 0.86 (s, 4.5H), 0.02 (s, 1.5H), 0.01 (s, 1.5H), 0.00 (s, 1.5H), −0.02 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 209.3, 189.3, 189.2, 147.5, 146.9, 137.4, 137.3, 130.18, 130.17, 128.4, 127.99, 127.96, 126.32, 126.28, 111.1, 110.7, 104.22, 104.17, 58.40, 58.36, 51.9, 43.1, 42.4, 37.2, 37.1, 33.5, 33.3, 30.8, 30.3, 25.8, 18.1, 17.2, 17.1, −4.77, −4.84, −5.08, −5.11; HRMS (EI) calcd for $C_{25}H_{38}O_3Si$ (M^+) 414.2590, found 414.2611.

6-Benzyl-6-(3-(*tert*-butyldimethylsilyloxy)-4-methylpent-4-enyl)-3-methoxycyclohex-2-enone (16). Pale yellow oil: IR (neat) 1627 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.11 (m, 5H), 5.30(s, 0.5H), 5.28 (s, 0.5H), 4.84 (brs, 1H), 4.74 (brs, 1H), 3.99−3.95 (m, 1H), 3.65 (s, 1.5H), 3.64 (s, 1.5H), 3.18 (d, 0.5H, J = 13.5 Hz), 3.13 (d, 0.5H, J = 13.5 Hz), 2.60 (d, 0.5H, J = 13.5 Hz), 2.59 (d, 0.5H, J = 13.5 Hz), 2.44−2.30 (m, 2H), 1.78−1.71 (m, 2H), 1.66 (s, 1.5H), 1.64 (s, 1.5H), 1.48−1.25 (m, 3H), 0.87 (s, 4.5H), 0.85 (s, 4.5H), 0.00 (s, 3H), −0.01 (s, 1.5H), −0.02 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) 202.5, 202.47, 176.4, 176.3, 147.6, 147.3, 138.2, 137.9, 130.7, 130.6, 127.9, 127.87, 126.2, 126.1, 110.8, 110.6, 101.8, 101.6, 55.6, 55.5, 47.5, 47.4, 40.9, 40.4, 31.5, 31.0, 30.7, 30.3, 28.9, 28.6, 26.3, 25.8, 25.7, 25.6, 18.1, 17.34, 17.28, −4.7, −4.8, −5.1; HRMS (EI) calcd for $C_{26}H_{40}O_3Si$ (M^+) 428.2747, found 428.2731.

(*S)-6-((*S**)-3-Hydroxy-4-methylpent-4-enyl)-3-methoxy-6-methylcyclohex-2-enone (18).** Pale yellow oil: IR (neat) 3416, 1645 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 5.28 (s, 1H), 4.89 (s, 1H), 4.80 (s, 1H), 3.93 (dd, 1H, J = 6.0, 5.7 Hz), 3.72 (s, 3H), 2.47 (t, 2H, J = 6.3 Hz), 2.00−1.91 (m, 1H), 1.77−1.70 (m, 1H), 1.68 (s, 3H), 1.54−1.41 (m, 4H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 177.5, 148.1, 112.1, 102.0, 101.9, 56.5, 43.9, 33.6, 33.5, 33.0,

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32.96, 30.4, 30.3, 26.7, 23.6, 18.5; HRMS (EI) calcd for $C_{14}H_{22}O_3$ (M^+) 238.1569, found 238.1573.

(*R)-5-((*S**)-3-Hydroxy-4-methylpent-4-enyl)-3-methoxy-5-(prop-2-ynyl)cyclopent-2-enone (19).** Pale yellow oil: IR (neat) 3420, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.93 (s, 1H), 4.84 (s, 1H), 4.00 (t, 1H, J = 6.5 Hz), 3.86 (s, 3H), 2.74 (d, 1H, J = 18.0 Hz), 2.50 (d, 1H, J = 18.0 Hz), 2.41 (dd, 1H, J = 16.5, 2.5 Hz), 2.37 (dd, 1H, J = 16.5, 2.5 Hz), 1.94 (t, 1H, J = 2.5 Hz), 1.74−1.70 (m, 1H), 1.69 (s, 3H), 1.58−1.55 (m, 1H), 1.45−1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 189.6, 147.1, 111.4, 103.6, 80.3, 75.7, 70.1, 58.7, 49.8, 38.5, 32.1, 29.2, 26.9, 17.4; HRMS (EI) calcd for $C_{15}H_{20}O_3$ (M^+) 248.1413, found 248.1420.

(*S)-6-((*S**)-3-Hydroxy-4-methylpent-4-enyl)-3-methoxy-6-(prop-2-ynyl)cyclohex-2-enone (20).** Pale yellow oil: IR (neat) 3302, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.93 (brs, 1H), 4.83 (s, 1H), 3.99 (dd, 1H, J = 6.0, 5.7 Hz), 3.69 (s, 3H), 2.55−2.35 (m, 4H), 2.08−2.04 (m, 2H), 2.00 (dd, 1H, J = 2.7, 2.1 Hz), 1.71 (s, 3H), 1.67−1.62 (m, 2H), 1.52−1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 176.9, 147.1, 111.3, 101.0, 80.9, 75.8, 70.9, 55.7, 45.7, 29.9, 29.8, 29.1, 25.6, 25.1, 17.5; HRMS (EI) calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1574.

(*S)-5-(2-Bromoallyl)-5-((*S**)-3-hydroxy-4-methylpent-4-enyl)-3-methoxycyclopent-2-enone (21).** Pale yellow oil: IR (neat) 3419, 1683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1H), 5.52 (s, 1H), 5.28 (s, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 3.97 (t, 1H, J = 6.5 Hz), 3.85 (s, 3H), 3.05 (d, 1H, J = 17.5 Hz), 2.76 (d, 1H, J = 14.5 Hz), 2.69 (d, 1H, J = 14.5 Hz), 2.47 (d, 1H, J = 17.5 Hz), 1.68 (s, 3H), 1.65−1.58 (m, 1H), 1.57−1.50 (m, 1H), 1.43−1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 189.8, 171.1, 147.1, 121.3, 111.5, 104.0, 60.4, 47.6, 38.2, 32.9, 29.1, 21.0, 17.5, 14.2; HRMS (EI) calcd for $C_{15}H_{21}{}^{79}BrO_3$ (M^+) 328.0674, found 328.0669.

(*R)-5-Benzyl-5-((*S**)-3-hydroxy-4-methylpent-4-enyl)-3-methoxycyclopent-2-enone (22).** Colorless needles: mp 113−114 °C (EtOAc/*n*-hexane); IR (neat) ν 3412, 1681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.17−7.00 (m, 5H), 5.05 (s, 1H), 4.83 (s, 1H), 4.74 (s, 1H), 3.90 (t, 1H, J = 6.5 Hz), 3.58 (s, 3H), 2.92 (d, 1H, J = 13.5 Hz), 2.52 (d, 1H, J = 13.5 Hz), 2.48 (d, 1H, J = 18.0 Hz), 2.24 (d, 1H, J = 18.0 Hz), 1.60 (s, 3H), 1.57−1.54 (m, 1H), 1.52−1.46 (m, 1H), 1.39−1.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 189.5, 147.2, 137.2, 130.2, 128.0, 126.4, 111.4, 104.4, 75.8, 58.4, 51.9, 43.0, 37.0, 33.5, 29.3, 17.4; HRMS (EI) calcd for $C_{19}H_{24}O_3$ (M^+) 300.1726, found 300.1711.

(*S)-6-Benzyl-6-((*S**)-3-hydroxy-4-methylpent-4-enyl)-3-methoxycyclohex-2-enone (23).** Pale yellow oil: IR (neat) ν 3420, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.11 (m, 5H), 5.32 (s, 1H), 4.93 (s,1H), 4.83 (brs, 1H), 3.99 (dd, 1H, J = 5.1, 4.8 Hz), 3.66 (s, 3H), 3.13 (d, 1H, J = 13.2 Hz), 2.62 (d, 1H, J = 13.2 Hz), 2.46−2.36 (m, 2H), 1.84−1.76 (m, 2H), 1.71 (s, 3H), 1.64−1.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 176.6, 147.2, 137.6, 130.5, 127.9, 126.2, 111.0, 101.8, 55.5, 47.5, 41.1, 31.1, 29.3, 28.6, 25.62, 25.59, 17.6; HRMS (EI) calcd for $C_{20}H_{26}O_3$ (M^+) 314.1882, found 314.1892.

(*S)-6-(2-Bromoallyl)-6-((*S**)-3-hydroxy-4-methylpentyl)-3-methoxycyclohex-2-enone (26).** Pale yellow oil: IR (neat) ν 3416, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1H), 5.56 (brs, 1H), 5.31 (s, 1H), 3.69 (s, 3H), 3.29−3.25 (m, 1H), 2.99 (d, 1H, J = 14.5 Hz), 2.61 (d, 1H, J = 14.5 Hz), 2.53−2.46 (m, 2H), 2.19−2.10 (m, 1H), 2.00−1.93 (m, 1H), 1.82−1.76 (m, 1H), 1.69−1.61 (m, 2H), 1.54−1.40 (m, 1H), 1.35−1.27 (m, 1H), 0.90 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 176.7, 128.9, 121.5, 101.4, 55.7, 46.9, 45.4, 33.5, 31.2, 28.8, 28.4, 25.7, 18.9, 17.2; HRMS (FAB) calcd for $C_{16}H_{26}{}^{79}BrO_3$ ($M + H$)$^+$ 345.1065, found 345.1045.

(*S)-6-Benzyl-6-((*S**)-3-hydroxy-4-methylpentyl)-3-methoxycyclohex-2-enone (28).** Pale yellow oil: IR (neat) ν 3408, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.12 (m, 5H), 5.33 (s, 1H), 3.67 (s, 3H), 3.28−3.25 (m, 1H), 3.09 (d, 1H, J = 13.5 Hz), 2.66 (d, 1H, J = 13.5 Hz), 2.48−2.36 (m, 2H), 1.86−1.74 (m, 2H), 1.66−1.61 (m, 2H), 1.53−1.30 (m, 3H), 0.90 (d, 6H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 176.7, 137.7, 130.6, 128.0, 126.3, 101.9, 55.6, 47.6, 41.2, 33.5, 31.5, 28.7, 28.6, 25.7, 18.9, 17.2; HRMS (EI) calcd for $C_{20}H_{28}O_3$ (M^+) 316.2039, found 316.2039.

6-(2-Bromoallyl)-6-(3-(*tert*-butyldimethylsilyloxy)-4-methylpentyl)-3-methoxycyclohex-2-enone (27). Pale yellow oil: IR (neat) ν 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 0.5H), 5.60 (s, 0.5H), 5.54 (brs, 1H), 5.30 (s, 0.5H), 5.29 (s, 0.5H), 3.68 (s, 3H), 3.39−3.32 (m, 1H), 3.13 (d, 0.5H, J = 14.7 Hz), 3.05 (d, 0.5H, J = 14.7 Hz), 2.59−2.43 (m, 2H), 2.23−2.08 (m, 1H), 2.00−1.89 (m, 1H), 1.71−1.63 (m, 2H), 1.51−1.36 (m, 2H), 1.31−1.19 (m, 2H), 0.87 (s, 9H), 0.82 (d, 6H, J = 6.9 Hz), 0.02 (s, 1.5H), 0.01 (s, 1.5H), 0.007 (s, 1.5H), −0.01 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 201.3, 176.33, 176.30, 129.4, 129.3, 121.3, 121.2, 101.3, 101.2, 55.64, 55.61, 47.1, 47.0, 45.1, 44.9, 33.1, 32.6, 31.5, 30.6, 29.7, 28.9, 28.8, 26.9, 26.7, 25.91, 25.87, 25.7, 25.6, 18.09, 18.06, 18.04, 17.9, 17.6, −4.27, −4.30, −4.5; HRMS (FAB) calcd for $C_{22}H_{40}{}^{79}BrO_3Si$ ($M + H$)$^+$ 459.1930, found 459.1917.

6-Benzyl-6-(3-(*tert*-butyldimethylsilyloxy)-4-methylpentyl)-3-methoxycyclohex-2-enone (29). Pale yellow oil: IR (neat) ν 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28−7.11 (m, 5H), 5.31 (s, 0.5H), 5.28 (s, 0.5H), 3.65 (s, 1.5H), 3.64 (s, 1.5H), 3.40−3.35 (m, 1H), 3.20 (d, 0.5H, J = 13.4 Hz), 3.14 (d, 0.5H, J = 13.4 Hz), 2.60 (d, 0.5H, J = 13.4 Hz), 2.57 (d, 0.5H, J = 13.4 Hz), 2.47−2.24 (m, 2H), 1.83−1.65 (m, 4H), 1.59−1.39 (m, 2H), 1.33−1.19 (m, 1H), 0.86 (s, 4.5H), 0.84 (s, 4.5H), 0.82 (d, 6H, J = 6.9 Hz), 0.01 (s, 1.5H), 0.00 (s, 1.5H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 202.5, 176.3, 138.2, 137.9, 130.7, 130.6, 127.92, 127.90, 126.2, 126.1, 101.8, 101.6, 55.6, 55.5, 47.7, 47.6, 40.8, 40.5, 33.1, 32.6, 31.8, 30.9, 29.7, 28.9, 28.7, 27.1, 26.9, 25.91, 25.87, 25.7, 25.6, 18.1, 18.0, 17.8, 17.6, −4.28, −4.32, −4.5; HRMS (FAB) calcd for $C_{26}H_{43}O_3Si$ ($M + H$)$^+$ 431.2981, found 431.2973.

Determination of Stereochemistry of Quaternized Compounds via Acidic Cyclization. Typical Protocol: (2*S,4a*S**)-4a-Methyl-2-(prop-1-en-2-yl)-4,4a,5,6-tetrahydro-2*H*-chromen-7(3*H*)-one (18a).** To a stirred solution of enone **18** (12 mg, 0.05 mmol) in toluene (3 mL) at room temperature was added PPTS (25 mg, 0.10 mmol). The mixture was heated at 60 °C for 35 h. Following addition of satd $NaHCO_3$, the mixture was transferred to a separatory funnel where it was extracted with Et_2O. The phases were separated, and the organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (EtOAc/*n*-hexane 1:3) to yield enone **18a** (9.9 mg, 95%) as a colorless oil: IR (neat) ν 1655 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 5.48 (s, 1H), 5.05 (s, 1H), 4.95 (brs, 1H), 4.24 (dd, 1H, J = 11.9, 2.8 Hz), 5.59−5.49 (m, 1H), 2.42−2.36 (m, 1H), 2.13−2.02 (m, 1H), 1.91−1.83 (m, 1H), 1.81 (s, 3H), 1.79−1.70 (m, 4H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 181.7, 143.7, 112.5, 109.5, 83.7, 36.2, 35.7, 33.8, 33.4, 25.3, 22.9, 17.8; HRMS (EI) calcd for $C_{13}H_{18}O_2$ (M^+) 206.1307, found 206.1333.

(2*S,4a*S**)-4a-Methyl-2-(prop-1-en-2-yl)-3,4,4a,5-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (17a).** Colorless amorphous solid: IR (neat) ν 1637 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 5.36 (s, 1H), 5.10 (s, 1H), 5.00 (brs, 1H), 4.37 (dd, 1H, J = 12.0, 2.7 Hz), 2.40 (d, 1H, J = 17.4 Hz), 2.34 (d, 1H, J = 17.4 Hz), 2.17−2.06 (m, 1H), 2.03−1.95 (m, 1H), 1.85 (s, 3H), 1.83−1.76 (m, 2H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 195.3, 143.2, 113.0, 109.6, 85.8, 51.3, 38.6, 33.3, 26.5, 25.7, 17.7; HRMS (EI) calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1167.

(2*S,4a*R**)-2-(Prop-1-en-2-yl)-4a-(prop-2-ynyl)-3,4,4a,5-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (19a).** Colorless oil: IR (neat) ν 1697 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$) δ 5.45 (s, 1H), 5.10 (s, 1H), 5.00 (s, 1H), 4.38 (dd, 1H, J = 12.0, 2.5 Hz), 2.72 (dd, 1H, J = 17.0, 2.0 Hz), 2.66 (d, 1H, J = 18.0 Hz), 2.39−2.34 (m, 2H), 2.25 (d, 1H, J = 18.0 Hz), 2.08 (t, 1H, J = 2.0 Hz), 2.03−1.94 (m, 1H), 1.84 (s, 3H), 1.82−1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 191.9, 142.9, 113.1, 111.2, 85.9, 79.3, 72.0, 48.6, 41.5, 30.5, 27.8, 25.4, 17.8; HRMS (EI) calcd for $C_{14}H_{16}O_2$ (M^+) 216.1150, found 216.1175.

(2*S,4a*S**)-2-(Prop-1-en-2-yl)-4a-(prop-2-ynyl)-4,4a,5,6-tetrahydro-2*H*-chromen-7(3*H*)-one (20a).** Colorless amorphous solid: IR (neat) ν 1649 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 5.53 (s, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.27 (dd, 1H, J = 11.7, 3.0 Hz), 2.73 (dt, 1H, J = 17.7, 2.1 Hz), 2.57−2.41 (m, 3H), 2.33 (dt, 1H, J =

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13.8, 3.0 Hz), 2.25 (ddd, 1H, J = 13.5, 5.1, 1.8 Hz), 1.80 (s, 3H), 1.78−1.67 (m, 2H), 1.54 (ddt, 1H, J = 13.8, 4.2, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 179.8, 143.8, 113.1, 111.0, 84.3, 79.5, 72.4, 36.4, 33.9, 32.5, 31.7, 25.3, 24.0, 18.3; HRMS (EI) calcd for $C_{15}H_{18}O_2$ (M^+) 230.1307, found 230.1301.

(2*S,4a*S**)-4a-(2-Bromoallyl)-2-(prop-1-en-2-yl)-3,4,4a,5-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (21a).** Colorless amorphous solid: IR (neat) ν 1686 cm^{-1}; ^{1}H NMR (500 MHz $CDCl_3$) δ 5.67 (s, 1H), 5.64 (s, 1H), 5.48 (s, 1H), 5.12(s, 1H), 5.01(s, 1H), 4.39 (dd, 1H, J = 12.2, 3.5 Hz), 2.98 (d, 1H, J = 15.5 Hz), 2.94 (d, 1H, J = 17.5 Hz), 2.64 (d, 1H, J = 15.5 Hz), 2.31 (dt, 1H, J = 13.0, 3.0 Hz), 2.25 (d, 1H, J = 17.5 Hz), 2.09−2.00 (m, 1H), 1.86 (s, 3H), 1.83−1.72 (m, 2H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.9, 192.8, 143.0, 127.8, 122.2, 113.1, 112.2, 85.8, 48.4, 46.9, 42.1, 31.0, 25.7, 17.9; HRMS (EI) calcd for $C_{14}H_{17}{}^{79}BrO_2$ (M^+) 296.0412, found 296.0418.

(2*S,4a*R**)-4a-Benzyl-2-(prop-1-en-2-yl)-3,4,4a,5-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (22a).** Colorless amorphous solid: IR (neat) ν 1703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.09 (m, 5H), 5.36 (s, 1H), 5.17 (s, 1H), 5.05 (brs, 1H), 4.44 (dd, 1H, J = 12.0, 2.7 Hz), 2.98 (d, 1H, J = 13.5 Hz), 2.91 (d, 1H, J = 13.5 Hz), 2.62 (d, 1H, J = 17.4 Hz), 2.35−2.20 (m, 1H), 2.15−2.09 (m, 1H), 2.11 (d, 1H, J = 17.4 Hz), 1.99 (s, 3H), 1.88−1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 192.9, 143.2, 136.2, 130.3, 128.3, 127.0, 113.1, 112.1, 85.9, 47.8, 43.1, 42.4, 32.0, 25.8, 17.9; HRMS (EI) calcd for $C_{18}H_{20}O_2$ (M^+) 268.1463, found 268.1471.

(2*S,4a*S**)-4a-Benzyl-2-(prop-1-en-2-yl)-4,4a,5,6-tetrahydro-2*H*-chromen-7(3*H*)-one (23a).** Pale yellow amorphous solid: IR (neat) ν 1626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5H), 5.62 (s, 1H), 5.12 (s, 1H), 5.00 (s, 1H), 4.30 (dd, 1H, J = 12.0, 2.4 Hz), 3.07 (d, 1H, J = 14.1 Hz), 2.96 (d, 1H, J = 14.1 Hz), 2.62−2.51 (m, 1H), 2.43−2.31 (m, 1H), 2.29−2.17 (m, 1H), 1.94−1.88 (m, 1H), 1.86 (s, 3H), 1.82−1.74 (m, 1H), 1.67- 1.56 (m, 2H), 1.47−1.36 (m, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 181.4, 143.6, 136.3, 130.2, 128.4, 127.0, 112.5, 111.0, 83.9, 38.8, 37.6, 33.9, 31.9, 31.4, 25.3, 18.0; HRMS (EI) calcd for $C_{19}H_{22}O_2$ (M^+) 282.1620, found 282.1619.

(2*S,4a*S**)-4a-(2-Bromoallyl)-2-isopropyl-4,4a,5,6-tetrahydro-2*H*-chromen-7(3*H*)-one (26a).** Colorless amorphous solid: IR (neat) ν 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, 1H, J = 1.8 Hz), 5.66 (d, 1H, J = 1.8 Hz), 5.50 (s, 1H), 3.61 (ddd, 1H, J = 12.0, 6.0, 3.3 Hz), 2.94 (d, 1H, J = 15.3 Hz), 2.77 (d, 1H, J = 15.3 Hz), 2.63−2.51 (m, 1H), 2.43−2.24 (m, 3H), 2.00−1.84 (m, 2H), 1.74−1.62 (m, 2H), 1.51−1.41 (m, 1H), 1.01 (d, 3H, J = 6.9 Hz), 0.97 (d, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 180.8, 127.2, 122.3, 110.3, 85.8, 42.7, 37.5, 33.8, 32.8, 31.7, 31.0, 22.6, 17.8, 17.7; HRMS (EI) calcd for $C_{15}H_{21}{}^{79}BrO_2$ (M^+) 312.0752, found 312.0754.

(2*S,4a*S**)-4a-Benzyl-2-isopropyl-4,4a,5,6-tetrahydro-2*H*-chromen-7(3*H*)-one (28a).** Colorless amorphous solid: IR (neat) ν 1657 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.15 (m, 5H), 5.56 (s, 1H), 3.60 (ddd, 1H, J = 12.4, 6.0, 3.2 Hz), 3.02 (d, 1H, J = 14.0 Hz), 2.93 (d, 1H, J = 14.0 Hz), 2.59−2.50 (m, 1H), 2.40−2.35 (m, 1H), 2.14−2.03 (m, 1H), 1.99−1.77 (m, 3H), 1.70−1.61 (m, 2H), 1.37−1.29 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.8 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 182.1, 136.4, 130.2, 128.4, 126.9, 110.3, 85.9, 38.8, 37.8, 33.9, 32.9, 31.9, 31.3, 22.6, 17.9, 17.8; HRMS (EI) calcd for $C_{19}H_{24}O_2$ (M^+) 284.1776, found 284.1778.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of the ^{1}H/^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Selected reviews for the stereoselective construction of the quaternary carbon center: (a) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623. (b) Shimizu, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5998−6000. (c) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207−1222. (d) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295−7306. (e) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583−1614. (f) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488−5508. (g) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873−888. (h) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *36*, 5969−5994. (i) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J.* **2007**, *2*, 1476−1491. (j) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Ley, S. V., Foreword; John Wiley & Sons: New York, 2006. (k) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369−396. (l) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473−1482. (m) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943−11948. (n) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (o) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (p) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

(2) Selected instances of alkylative stereoselective quaternization of enolates having a chiral auxiliary: (a) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231−13233. (b) Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146−1148. (c) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569. (d) Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591−4594. (e) Schultz, A. G.; Sundararaman, P.; Macielag, M.; Lavieri, F. P.; Welch, M. *Tetrahedron Lett.* **1985**, *26*, 4575−4578. (f) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828−7841. (g) Abe, T.; Suzuki, T.; Sekiguchi, K.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2003**, *44*, 9303−9305. (h) Manthorpe, J. M.; Gleason, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2091−2092. (i) Manthorpe, J. M.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2338−2341. (j) Boeckman, R. K. Jr.; Boehmler, D. J.; Musselman, R. A. *Org. Lett.* **2001**, *3*, 3777−3780.

(3) Yoshimistu, T.; Nojima, S.; Hashimoto, M.; Tanaka, T. *Org. Lett.* **2011**, *13*, 3698−3701.

(4) For the pioneering work on the 1,4-chiral induction of δ-hydroxyl acyclic esters in which a tertiary stereocenter α to the ester carbonyl group is successfully created by δ-hydroxyl directed alkylation or aldolization, see: Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc., Jpn.* **1987**, *60*, 1457−1464.

(5) For a recent report on the remote 1,4-stereoinduction via tandem Reformatsky/Claisen condensation, see: Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 17393−17395.

(6) Copies of ^{1}H and ^{13}C NMR spectra of the regioisomers are provided in the Supporting Information.

(7) For determination of stereochemistry of compounds **26** and **28**, see Table 3.