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A new strategy for the synthesis of substituted dihydropyrones and tetrahydropyrones via palladium-catalyzed coupling of thioesters

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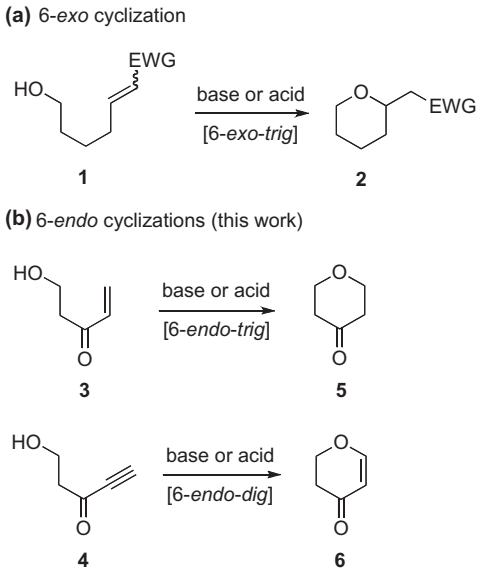
ABSTRACT

In this paper, we describe a new strategy for the synthesis of substituted dihydropyrones and tetrahydropyrones. By exploiting palladium-catalyzed coupling of thioesters with terminal alkynes or alkenylboronic acids, a variety of β-hydroxy ynones or enones, respectively, could be prepared in an efficient manner under mild conditions. AgOTf-promoted intramolecular oxa-conjugate cyclization of β-hydroxy ynones provided 2,6-substituted dihydropyrones in excellent yields. On the other hand, acid-catalyzed cyclization of β-hydroxy enones caused racemization of the product 2,6-substituted tetrahydropyrones due to its reversible nature. Eventually, stereoselective hydrogenation of substituted dihydropyrones was found to be a solid and efficient approach for the synthesis of 2,6-*cis*-substituted tetrahydropyrone derivatives.

1. Introduction

Due to their abundant presence in a plethora of naturally occurring biologically active substances, substituted tetrahydropyrans have been for a long time important synthetic targets and provide excellent opportunities for the synthetic community to develop new chemistry. Although less frequently encountered in the structure of natural substances, substituted dihydropyrans represent valuable synthetic precursors for tetrahydropyran derivatives via transformation of the double bond. Consequently, a number of methodologies for the synthesis of substituted tetrahydropyrans and dihydropyrans are currently available and have been reviewed elsewhere.[1]

One of the renowned methods for the stereoselective synthesis of substituted tetrahydropyran derivatives is an intramolecular oxa-conjugate cyclization[2] (Scheme 1a). This reaction has been most commonly applied to hydroxy enones and enoates under basic conditions to deliver 2,6-*cis*- or 2,6-*trans*-substituted tetrahydropyran derivatives via 6-*exo*-*trig* ring closure (generally represented by the transformation of **1** into **2**).[3] It has also been reported that acid-catalyzed intramolecular oxa-conjugate cyclization of hydroxy enones provides substituted tetrahydropyrans.[4] The stereochemical outcome depends on the local structure of the substrates and the reaction conditions (i.e., kinetic vs thermodynamic).[5] Importantly, a recent biosynthetic study on the bryostatins has suggested that the tetrahydropyran ring of this family of natural products would be formed via intramolecular oxa-conjugate cyclization of an intermediary α,β-unsaturated thioester on a polyketide synthase, and it has been proposed that 'pyran synthase' would be responsible for the cyclization.[6] Thus, intramolecular oxa-conjugate



Scheme 1. Synthesis of substituted tetrahydropyrans and dihydropyrans via intramolecular oxa-conjugate cyclization.

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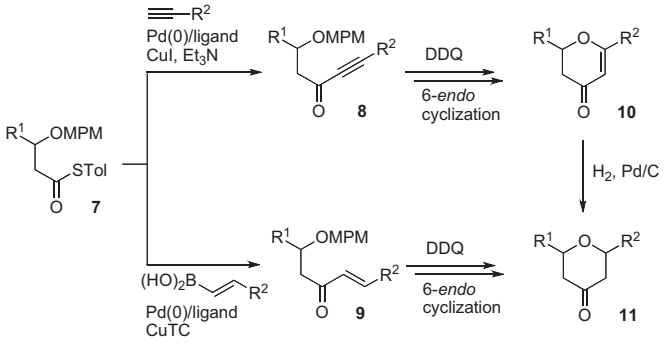
cyclization may represent a 'biomimetic' strategy for the synthesis of tetrahydropyran derivatives.[7] With this in mind, we have implemented intramolecular oxa-conjugate cyclization in our recent total syntheses of (+)-neopeltolide,[8] (−)-aspergillides A and B,[9] (−)-exiguolide,[10] and (±)-centrolobine.[11]

In contrast, there are only limited reports on the intramolecular oxa-conjugate cyclization of β-hydroxy enones **3** or ynones **4** via 6-*endo* closure to provide the respective substituted tetrahydropyrones **5** or dihydropyrones **6**,[12,13] although these products are potentially useful for the synthesis of tetrahydropyran-containing natural products (Scheme 1b). One plausible reason for this may be the difficulty in the synthesis of acid and base sensitive β-hydroxy enones and ynones. In recent years, β-hydroxy enones have been synthesized via elongation of simple enones via aldol coupling[14] or olefin cross-metathesis,[15] but multistep synthetic transformations would be necessary for the preparation of the substrates utilized in these approaches. On the other hand, it is well accepted that β-hydroxy ynones could be prepared by means of anion coupling of carbonyl compounds and terminal alkynes. However, the coupling might be problematic when enolizable carbonyl compounds were used as the substrate.[16]

Herein, we describe in detail a new strategy for the synthesis of substituted dihydropyrones and tetrahydropyrones via palladium-catalyzed reactions of thioesters.[17–19] We envisioned that palladium-catalyzed coupling of thioesters **7** with terminal alkynes would provide β-alkoxy ynones **8** (Scheme 2, Tol=*p*-tolyl). Subsequent intramolecular oxa-conjugate cyclization would afford 2,6-substituted dihydropyrones **10**. A similar strategy involving palladium-catalyzed coupling of thioesters **7** with alkenylboronic acids would be applicable to the synthesis of 2,6-substituted tetrahydropyrones **11** via β-alkoxy enones **9**. Meanwhile, we envisaged that hydrogenation of 2,6-substituted dihydropyrones **10** would also afford the corresponding tetrahydropyrones **11**.



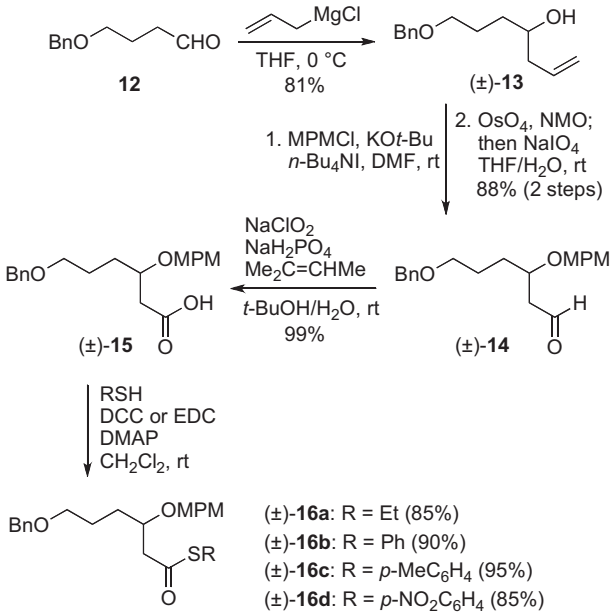
Scheme 2. Synthesis of substituted dihydropyrones and tetrahydropyrones via palladium-catalyzed coupling of thioesters and intramolecular oxa-conjugate cyclization. Tol=*p*-tolyl.

2. Results and discussion

2.1. Synthesis of β-alkoxy ynones via palladium-catalyzed coupling of thioesters with terminal alkynes

We first investigated the synthesis of β-alkoxy ynones as a precursor to substituted dihydropyrones. Because of their lability under acidic or basic conditions, we planned to prepare β-alkoxy ynones via palladium-catalyzed coupling of thioesters and terminal alkynes, which has already been reported by Fukuyama et al.[20]

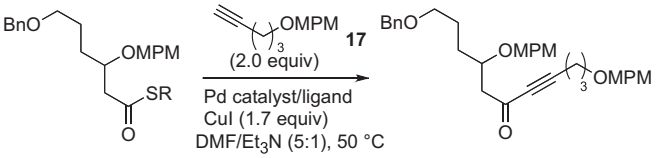
The preparation of thioesters (±)-**16a**–**d**, illustrated in Scheme 3, started with allylation of 4-(benzyloxy)butylaldehyde (**12**) to give homoallylic alcohol (±)-**13**.[21] After protection of the hydroxy group as its MPM ether, the double bond was oxidatively cleaved (OsO_4, NMO; then $NaIO_4$) to provide aldehyde (±)-**14**. $NaClO_2$ oxidation of (±)-**14** led to the corresponding carboxylic acid (±)-**15**. Finally, coupling with an appropriate thiol using DCC/DMAP or EDC/DMAP afforded thioesters (±)-**16a**–**d**.



Scheme 3. Preparation of thioesters (±)-**16a**–**d**.

Initially, we attempted coupling of *S*-ethyl thioester (±)-**16a** with terminal alkyne **17** under the conditions reported by Fukuyama et al.,[20] giving ynone (±)-**18**, albeit in 39% yield (Table 1, entry 1). The reaction proceeded only slowly and prolonged reaction time was necessary for complete consumption of (±)-**16a**, during which time 1,4-addition of ethanethiol to the product ynone (±)-**18** was observed as a side reaction and lowered the product yield. We also observed competitive homocoupling of terminal alkyne **17** under these conditions. To overcome these problems, we examined various reaction parameters, including bases (*i*-Pr_2NEt, 2,6-lutidine), additives (CuTC,[22] CuDPP[23]), and solvents (CH_3CN, THF, 1,4-dioxane), but all of these attempts turned out to be fruitless. However, we were delighted to find that *S*-aryl thioesters (±)-**16b**–**d** displayed much higher reactivity than (±)-**16a** under the Fukuyama conditions (entries 2–4). Especially, coupling of *S*-(*p*-tolyl)thioester (±)-**16c** with terminal alkyne **17** was complete within 4 h to give ynone

Table 1
Screening of the reaction conditions



(±)-**16a**: R = Et
(±)-**16b**: R = Ph
(±)-**16c**: R = *p*-MeC_6H_4
(±)-**16d**: R = *p*-$NO_2C_6H_4$

(±)-**18**

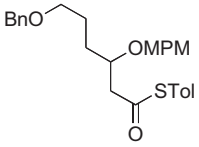
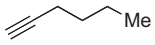
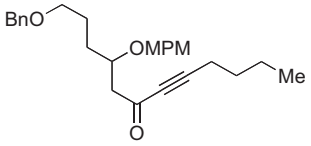
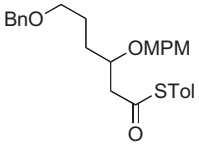
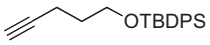
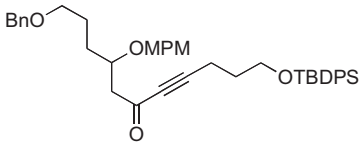
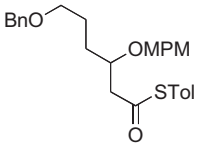
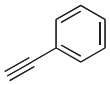
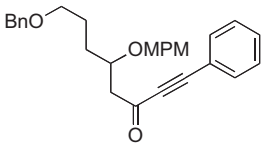
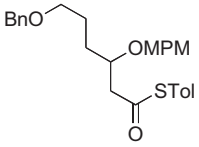
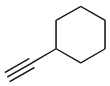
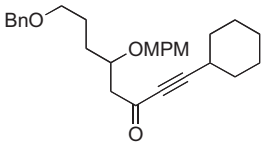
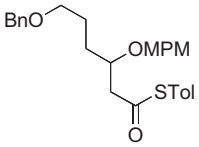
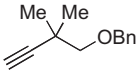
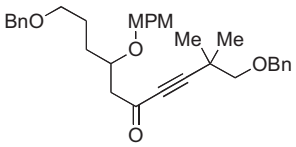
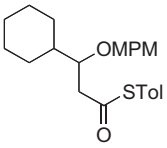
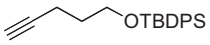
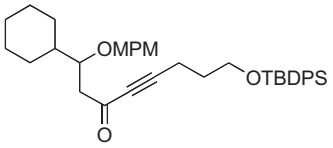
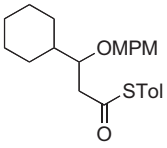
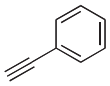
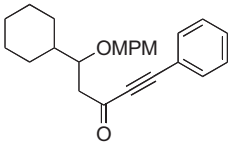
Entry	Thioester	Pd catalyst, ligand	Yield (%)
1	(±)-**16a**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol %), (2-furyl)$_3$P (25 mol %)	39
2	(±)-**16b**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol %), (2-furyl)$_3$P (25 mol %)	70
3	(±)-**16c**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol %), (2-furyl)$_3$P (25 mol %)	73
4	(±)-**16d**	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol %), (2-furyl)$_3$P (25 mol %)	65
5	(±)-**16c**	$Pd_2(dba)_3\cdot CHCl_3$ (5 mol %), (2-furyl)$_3$P (40 mol %)	77
6[a]	(±)-**16c**	$Pd_2(dba)_3\cdot CHCl_3$ (5 mol %), (2-furyl)$_3$P (40 mol %)	80

[a] Reaction performed at room temperature.

(±)-**18** in 73% yield (entry 3). Examination of several catalyst systems ($PdCl_2(dppf)\cdot CH_2Cl_2$/$Ph_3As$, $Pd_2(dba)_3$/(2-furyl)$_3$P, $Pd_2(dba)_3\cdot CHCl_3$/(2-furyl)$_3$P) revealed that $Pd_2(dba)_3\cdot CHCl_3$ was the optimal source of palladium (entry 5). In addition, we were able to isolate (±)-**18** in 80% yield when the reaction was performed at room temperature, although longer reaction time (22 h) was necessary in this case (entry 6).

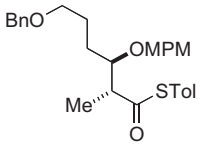
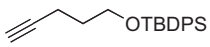
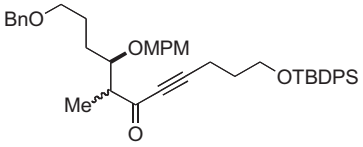
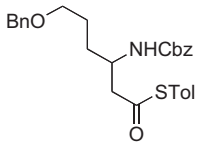
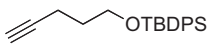
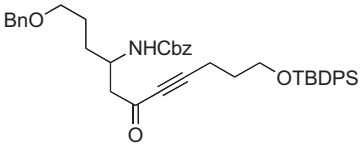
Encouraged by the optimization study, we next investigated the synthesis of a series of β-alkoxy ynones, as summarized in Table 2. Various combinations of thioesters[24] and terminal alkynes were tolerated under the optimized conditions (5 mol % of $Pd_2(dba)_3\cdot CHCl_3$, 40 mol % of (2-furyl)$_3$P, 1.7 equiv of CuI, DMF/Et_3N (5:1), 50 °C) to deliver β-alkoxy ynones in good yields (73–93%). In the case of (−)-**20**, however, we isolated β-alkoxy ynone (−)-**34** as an inseparable 1.3:1 mixture of diastereomers, indicating that a significant degree of epimerization of the stereogenic center next to the carbonyl group occurred under the reaction conditions (entry 8). The palladium-catalyzed coupling of β-[(benzyloxycarbonyl) amino]thioester (±)-**21** with alkyne **23** also proceeded cleanly to afford ynone (±)-**35** in high yield (entry 9).

Table 2
Application to a variety of substrates[a]

Entry	Thioester	Alkyne	Product (Yield %)
1[b]	 (±)-**16c**	 **22**	 (±)-**27** (80%)
2[c]	 (±)-**16c**	 **23**	 (±)-**28** (80%)
3[b]	 (±)-**16c**	 **24**	 (±)-**29** (82%)
4[b]	 (±)-**16c**	 **25**	 (±)-**30** (75%)
5[c]	 (±)-**16c**	 **26**	 (±)-**31** (82%)
6[c]	 (±)-**19**	 **23**	 (±)-**32** (80%)
7[b]	 (±)-**19**	 **24**	 (±)-**33** (73%)

(*continued on next page*)

Table 2 (*continued*)

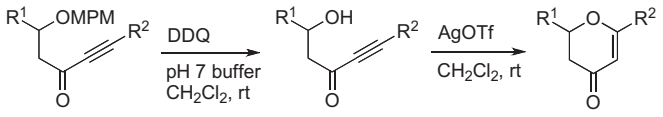
Entry	Thioester	Alkyne	Product (Yield %)
8[c]	 (–)-**20**	 **23**	 (–)-**34** (83%, dr 1.3:1)
9[c]	 (±)-**21**	 **23**	 (±)-**35** (93%)

[a] All reactions were performed using $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), $(2\text{-furyl})_3P$ (40 mol %), and CuI (1.7 equiv) in DMF/Et_3N (5:1) at 50 °C.
[b] Alkyne (2.0 equiv) was used.
[c] Alkyne (1.5 equiv) was used.

2.2. Synthesis of substituted dihydropyrones via intramolecular oxa-conjugate cyclization

With a facile access to a series of β-alkoxy ynones established, we put our efforts on their intramolecular oxa-conjugate cyclization to synthesize dihydropyrone derivatives. Toward this end, deprotection of the MPM group in β-alkoxy ynones **27**–**34** was carried out using DDQ (pH 7 buffer/CH_2Cl_2, room temperature) to give the corresponding β-hydroxy ynones in good yields without incident (Table 3). Treatment of the resultant β-hydroxy ynones with AgOTf in CH_2Cl_2 at room temperature[12c,d] furnished the respective dihydropyrones in excellent yields (Table 3). This reaction could be performed under either catalytic or stoichiometric conditions without affecting the product yield (see entry 2), but the latter conditions proceeded more rapidly. On the other hand, CSA, TMSOTf or KO*t*-Bu were completely ineffective for the cyclization and caused

Table 3
Deprotection and 6-*endo* cyclization



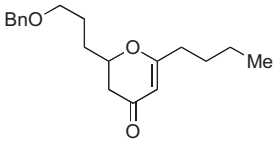
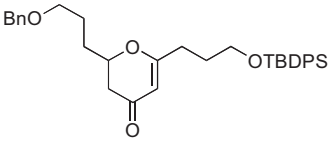
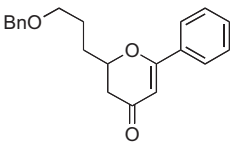
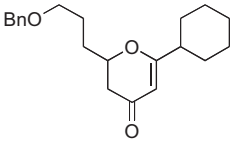
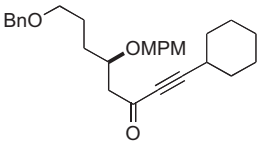
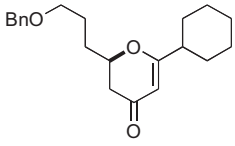
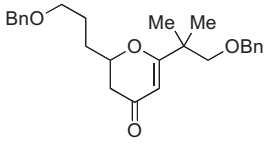
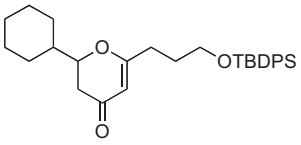
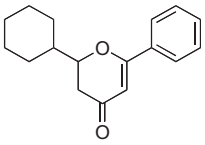
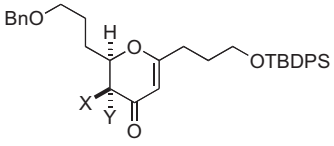
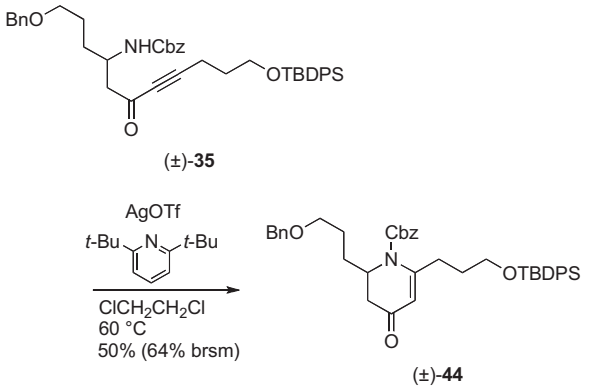
Entry	Ynone	Product	Yield step 1 (%)	Yield step 2 (%)
1	(±)-**27**	 (±)-**36**	85	96[a]
2	(±)-**28**	 (±)-**37**	92	98[a] 98[b]
3	(±)-**29**	 (±)-**38**	90	97[a]
4	(±)-**30**	 (±)-**39**	100	100[a]

Table 3 (*continued*)

Entry	Ynone	Product	Yield step 1 (%)	Yield step 2 (%)
5	 (+)-**30**	 (+)-**39** (98%ee)	94	100[a]
6	(±)-**31**	 (±)-**40**	96	98[a]
7	(±)-**32**	 (±)-**41**	88	98[b]
8	(±)-**33**	 (±)-**42**	88	94[a]
9	(−)-**34**	 (+)-**43a**: X = H, Y = Me (+)-**43b**: X = Me, Y = H [(+)-**43a**:(+)-**43b** = 1.3:1]	96	100[a]

[a] Cyclization was performed using 1.1 equiv of AgOTf.
[b] Cyclization was performed using 0.1 equiv of AgOTf.

material decomposition. Notably, our strategy enabled the synthesis of optically active dihydropyrone (+)-**39** (entry 5). The enantiomeric excess of (+)-**39** was determined to be 98% ee on the basis of chiral HPLC analysis, which matched that of the starting material (i.e., (−)-**16c**[25]). Furthermore, the cyclization could also be applied to β-[(benzyloxycarbonyl)amino]ynone (±)-**35** to give *N*-Cbz protected dihydropyridin-4-one (±)-**44**, albeit in 50% yield (64% yield based on recovered starting material) (Scheme 4).



Scheme 4. Synthesis of 2,6-disubstituted dihydropyridin-4-one (±)-**44**.

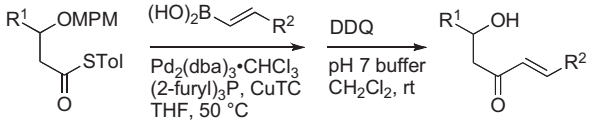
2.3. Synthesis of β-hydroxy enones via palladium-catalyzed coupling of *S*-(*p*-tolyl)thioesters with alkenylboronic acids

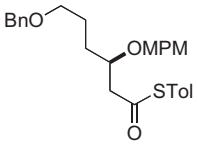
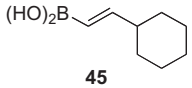
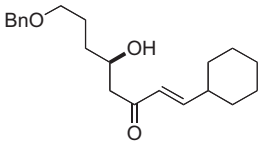
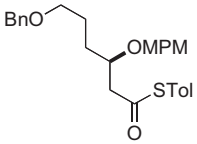
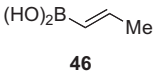
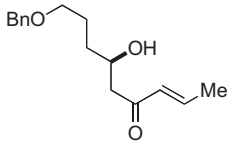
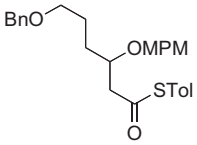
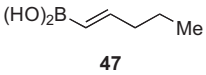
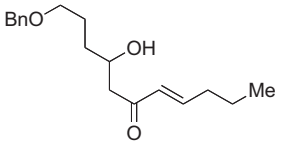
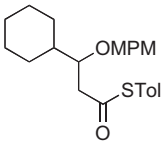
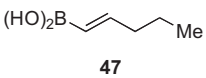
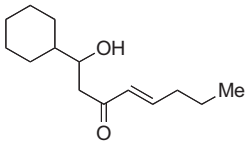
We envisioned that β-hydroxy enones would be accessible in an efficient manner via palladium-catalyzed coupling of *S*-(*p*-tolyl) thioesters with alkenylboronic acids, the reaction originally discovered by Liebeskind and Srogl.[26] In the event, we were pleased to find that the coupling reaction of *S*-(*p*-tolyl)thioesters and alkenylboronic acids proceeded smoothly under the influence of $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), $(2\text{-furyl})_3P$ (40 mol %), and CuTC (1.5 equiv) in THF at 50 °C (Table 4).[27] After removal of the MPM group, the desired β-hydroxy enones were isolated in good overall yields from the respective thioesters.

2.4. Synthesis of substituted tetrahydropyrones via intramolecular oxa-conjugate cyclization

Having synthesized a series of β-hydroxy enones, we turned our attention to the construction of substituted tetrahydropyrone derivatives. We chose optically active β-hydroxy enone (−)-**48** (97% ee, determined by chiral HPLC analysis) as a model substrate to investigate its ring closure under various conditions (Table 5). We quickly recognized that the desired cyclization could not be

Table 4
Synthesis of β-hydroxy enones[a]



Entry	Thioester	Boronic acid	Product (Yield %)
1	 (–)-**16c**	 **45**	 (–)-**48** (71%)
2	 (–)-**16c**	 **46**	 (–)-**49** (66%)
3	 (±)-**16c**	 **47**	 (±)-**50** (53%)
4	 (±)-**19**	 **47**	 (±)-**51** (64%)

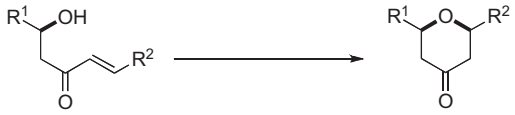
[a] All coupling reactions were performed using alkenylboronic acid (1.1 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), (2-furyl)$_3$P (40 mol %), and CuTC (1.5 equiv) in THF at 50 °C.

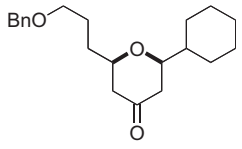
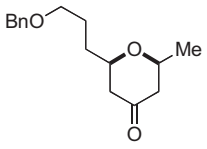
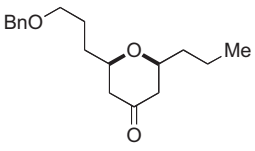
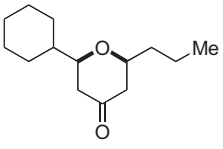
achieved under basic conditions; exposure of (−)-**48** to a strong base such as KO*t*-Bu or NaH gave only a complex mixture of unidentified products (entries 1 and 2). Treatment of (−)-**48** with CSA in CH_2Cl_2 at room temperature resulted in dehydration and did not give tetrahydropyrone (+)-**52** at all (entry 3). In contrast, trifluoromethanesulfonic acid (TfOH) promoted the cyclization of (−)-**48** to give (+)-**52** in 92% yield with moderate diastereoselectivity (*cis*/*trans*=7:1) (entry 4). In line with the previous observation by Gouverneur et al.,[12b] (−)-**48** cyclized cleanly upon exposure to Amberlyst® 15 to afford tetrahydropyrone (+)-**52** in 95% yield (*cis*/*trans*=3:1) (entry 5). AgOTf also facilitated the cyclization smoothly to afford tetrahydropyrone (+)-**52** in 94% yield as a 6:1 mixture of *cis*/*trans* isomers (entry 6). Prompted by this result, we examined the use of several Lewis acids, such as $BF_3 \cdot OEt_2$, TMSOTf, and $[Pd(MeCN)_4](BF_4)_2$, and found that all of these Lewis acids facilitated the cyclization of (−)-**48** to deliver (+)-**52** in moderate to good yields, although the diastereoselectivity depended on Lewis acid used and varied significantly, ranging from 3:1 to >20:1 (entries 7–9). We also examined AgOTf-promoted cyclization of β-hydroxy enones (−)-**49**, (±)-**50**, and (±)-**51**, which afforded tetrahydropyrones (+)-**53**, (±)-**54**, and (±)-**55**, respectively, with moderate to good diastereoselectivity (entries 10–12). The relative stereochemistry of each product was established on the basis of an NOE experiment or $^3J_{H,H}$ analysis. For example, the major isomer of (+)-**52** was assigned to be 2,6-*cis* isomer since an NOE enhancement was observed between the two axial oxymethine protons flanking the cyclic ether oxygen (Fig. 1). On the other hand, the minor isomer of (+)-**52** was assigned to be 2,6-*trans* isomer on the basis of the diagnostic $^3J_{H,H}$ values as shown. The relative stereochemistry of **53**–**55** was assigned in a similar manner.

At this stage, we thought that the observed deviations in diastereoselectivity would be, at least in part, ascribed to isomerization of the thermodynamically less favored 2,6-*trans* isomer to the more favored 2,6-*cis* isomer via a ring-opening/cyclization sequence. This possibility was easily confirmed by treatment of tetrahydropyrone (+)-**52** (*cis*/*trans*=ca. 3:1) with TMSOTf (CH_2Cl_2, room temperature), which gave (+)-**52** as a single stereoisomer (*cis*/*trans* >20:1). Thus, TMSOTf was found to promote not only cyclization of (−)-**48** but also thermodynamic equilibration of a kinetically formed mixture of 2,6-*cis* and 2,6-*trans* isomers. However, these results suggested that a serious problem would arise when enantiomerically pure β-hydroxy enones were used as substrates. On the basis of the ring-opening/cyclization mechanism, racemization of the stereogenic center of the cyclization precursor would occur as the reaction proceeds and result in a loss of enantiomeric purity of the product (Scheme 5).[12c]

To ascertain the above racemization problem, we assessed the optical purity of the products (+)-**52** and (+)-**53** by chiral HPLC (Table 5). Not surprisingly, the use of TMSOTf as a Lewis acid resulted in complete racemization (0% ee, entry 8), and a partial racemization was observed for the product synthesized by the reaction with TfOH, Amberlyst® 15, AgOTf or $BF_3 \cdot OEt_2$ (entries 4–7). In contrast, cyclization of (−)-**48** with $[Pd(MeCN)_4](BF_4)_2$ delivered (+)-**52** in 95% ee, albeit in moderate yield (entry 9).

Table 5
Intramolecular oxa-conjugate cyclization of β-hydroxy enones



Entry	β-Hydroxy enone	Reagents and conditions	Product	Yield (%)	dr[a]	ee (%)[b]
1	(−)-**48**	KO*t*-Bu, THF, 0 °C	 (+)-**52**	0	N/A	N/A
2	(−)-**48**	NaH, THF, rt	(+)-**52**	0	N/A	N/A
3	(−)-**48**	CSA, CH_2Cl_2, rt	(+)-**52**	0	N/A	N/A
4	(−)-**48**	TfOH, CH_2Cl_2, 0 °C to rt	(+)-**52**	92	7:1	79
5	(−)-**48**	Amberlyst® 15, CH_2Cl_2, rt	(+)-**52**	95	3:1	81
6	(−)-**48**	AgOTf, CH_2Cl_2, rt	(+)-**52**	94	6:1	81
7	(−)-**48**	BF_3•OEt_2, CH_2Cl_2, rt	(+)-**52**	80	3:1	86
8	(−)-**48**	TMSOTf, CH_2Cl_2, 0 °C to rt	(+)-**52**	51	>20:1	0
9	(−)-**48**	$[Pd(MeCN)_4](BF_4)_2$, CH_2Cl_2, rt	(+)-**52**	54	3:1	95
10	(−)-**49**	AgOTf, CH_2Cl_2, rt	 (+)-**53**	89	3:1	92
11	(±)-**50**	AgOTf, CH_2Cl_2, rt	 (±)-**54**	87	10:1	N/A
12	(±)-**51**	AgOTf, CH_2Cl_2, rt	 (±)-**55**	100	3:1	N/A

[a] Diastereomer ratio was determined by 600 MHz ^{1}H NMR analysis of a purified mixture of *cis*/*trans* isomers.
[b] Enantiomeric excess (ee) of 2,6-*cis* isomers was determined by chiral HPLC analysis.

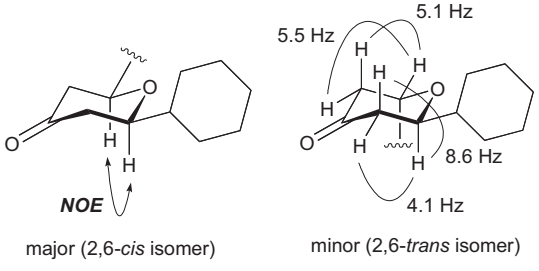
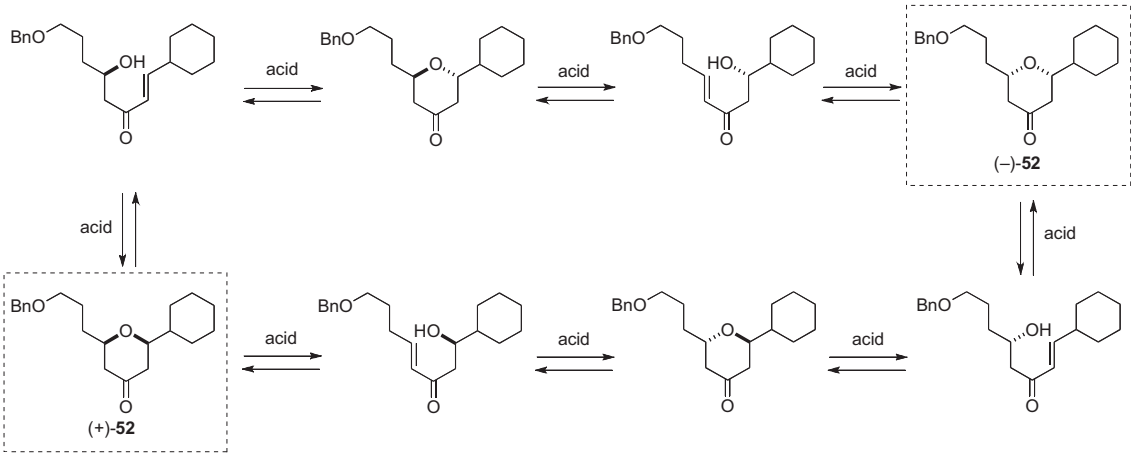


Fig. 1. Stereochemical assignment of the cyclization product (+)-**52**.

The optical purity of (+)-**53** was determined to be 92% ee, indicating that only a slight racemization occurred in this case (entry 10).

2.5. Synthesis of substituted tetrahydropyrones via stereoselecive hydrogenation of dihydropyrones

Although intramolecular oxa-conjugate cyclization of β-hydroxy enones **48**–**51** could afford 2,6-substituted tetrahydropyrone derivatives **52**–**55** in good yields, the racemization problem of this process makes it synthetically incompetent. Accordingly, as summarized in Table 6, we investigated the synthesis of 2,6-*cis*-



Scheme 5. Racemization via ring-opening/cyclization mechanism.

substituted tetrahydropyrones from the corresponding dihydropyrones via hydrogenation (H_2, Pd/C, Et_3N, EtOAc or EtOH, room temperature) and found it feasible.[28] Thus, a series of tetrahydropyrones (+)-**52**, (±)-**56**–(±)-**60** could be synthesized in good to excellent yields. Importantly, hydrogenation of (+)-**39** proceeded to give (+)-**52** without any loss of its optical purity (98% ee by chiral HPLC analysis). The relative stereochemistry of each product was established on the basis of an NOE enhancement observed between the two oxymethine protons flanking the oxygen. Thus, stereoselective hydrogenation of 2,6-substituted dihydropyrones serves as a solid and efficient method for the synthesis of 2,6-*cis*-substituted tetrahydropyrones.

3. Conclusion

We have shown that β-hydroxy ynones and enones could be synthesized in an efficient manner by means of palladium-catalyzed coupling of *S*-(*p*-tolyl)thioesters. Intramolecular oxa-conjugate cyclization of β-hydroxy ynones could be achieved by treatment with AgOTf to provide substituted dihydropyrone derivatives in high yields. On the other hand, several Brønsted and Lewis acids were found to facilitate intramolecular oxa-conjugate cyclization of β-hydroxy enones. However, as a result of the reversible nature of the cyclization, racemization of the product was observed under these conditions. Finally, we found that stereoselective hydrogenation of substituted dihydropyrones represents a solid and efficient approach for the synthesis of 2,6-*cis*-substituted tetrahydropyrone derivatives.

4. Experimental

4.1. General remarks

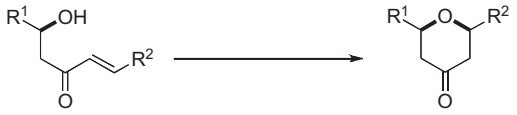
All reactions sensitive to moisture and/or air were carried out under an atmosphere of argon in dry, freshly distilled solvents under anhydrous conditions using oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2) was purchased from Kanto Chemical Co. Inc. and used directly without further drying. Anhydrous tetrahydrofuran and toluene were purchased from Wako Pure Chemical Industries, Ltd. and further purified by a Glass Contour solvent purification system under an atmosphere of argon immediately prior to use. Diisopropylethylamine, triethylamine, 2,6-lutidine, and acetonitrile (CH_3CN) were distilled from calcium hydride under an atmosphere of argon. *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from magnesium sulfate under reduced pressure. All other chemicals were purchased at the highest commercial grade and used directly. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} plates (0.25-mm thickness). Flash column chromatography was carried out using Kanto chemical silica gel 60 N (40–100 mesh, spherical, neutral) or Fuji Silysia silica gel BW-300 (200–400 mesh). Optical rotations were recorded on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM ECA-600 or a Varian Unity INOVA 500 spectrometer, and chemical shift values are reported in parts per million (δ) downfield from tetramethylsilane with reference to internal solvent [^1H NMR, $CHCl_3$ (7.24), C_6HD_5 (7.15); ^{13}C NMR, $CDCl_3$ (77.0), C_6D_6 (128.0)] unless otherwise noted. Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations were used to designate the multiplicities: s=singlet; d=doublet; t=triplet; m=multiplet; br=broad. EI and FAB mass spectra were recorded on a JEOL JMS-700 spectrometer and ESI-TOF mass spectra were measured on a Bruker microTOFfocus spectrometer.

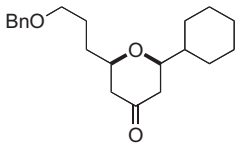
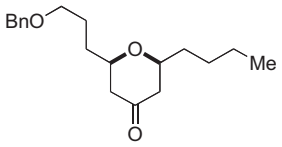
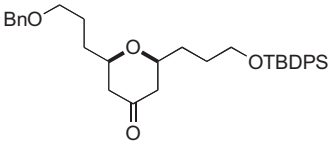
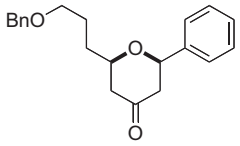
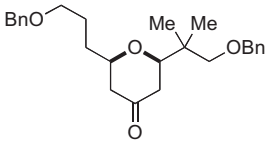
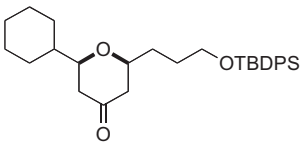
4.2. Synthesis of thioesters (±)-16a–d

*4.2.1. 7-Benzyloxy-1-heptene-4-ol (±)-**13**.* To a solution of 4-(benzyloxy)butylaldehyde (1.25 g, 7.01 mmol) in THF (25 mL) cooled to 0 °C was added allylmagnesium chloride (2.0 M solution in THF, 4.21 mL, 8.42 mmol), and the resultant solution was stirred at 0 °C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution. The resultant mixture was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–20% EtOAc/hexanes) gave the known *title compound* (±)-**13**[21] (1.25 g, 81%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 3H), 7.28–7.23 (m, 2H), 5.82 (m, 1H), 5.12–5.08 (m, 2H), 4.50 (s, 2H), 3.63 (m, 1H), 3.50 (t, *J*=6.0 Hz, 2H), 2.36 (br s, 1H), 2.28–2.14 (m, 2H), 1.78–1.60 (m, 3H), 1.48 (m, 1H).

*4.2.2. 6-Benzyloxy-3-(4-methoxybenzyloxy)-1-hexanal (±)-**14**.* To a solution of homoallylic alcohol (±)-**13** (1.24 g, 5.63 mmol) in DMF (28 mL) cooled to 0 °C was added KO*t*-Bu (1.26 g, 11.3 mmol). After being stirred at 0 °C for 10 min, MPMCl (1.14 mL, 8.44 mmol), and *n*-Bu_4NI (0.42 g, 1.13 mmol) were added to the solution at 0 °C. The resultant mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C. The resultant mixture was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and

Table 6
Stereoselective hydrogenation of 2,6-substituted dihydropyrones



Entry	Dihydropyrone	Product (Yield %)
1[a]	(+)-**39**	 (+)-**52** (91%, 98% ee)
4[b]	(±)-**36**	 (±)-**56** (95%)
3[a]	(±)-**37**	 (±)-**57** (100%)
5[b]	(±)-**38**	 (±)-**58** (52%)
2[a]	(±)-**40**	 (±)-**59** (96%)
6[a]	(±)-**41**	 (±)-**60** (96%)

[a] Performed in EtOAc at room temperature.
[b] Performed in EtOH at room temperature.

concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5% EtOAc/hexanes) gave an MPM ether (1.92 g), which was contaminated with some impurities and used in the next reaction without further purification.

To a solution of the above MPM ether (1.92 g) in THF/H_2O (1:1, v/v, 28 mL) were added NMO (4.8 M solution in H_2O, 3.52 mL, 16.9 mmol) and OsO_4 (1.0 g in 100 mL of *t*-BuOH, 7.2 mL, 0.28 mmol), and the resultant solution was stirred at room temperature overnight. To this solution was added $NaIO_4$ (1.81 g, 8.46 mmol), and the resultant suspension was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and washed successively with H_2O, saturated aqueous Na_2SO_3 solution, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–20% EtOAc/hexanes) gave the *title compound* (±)-**14** (1.70 g, 88% for the two steps) as a pale yellow oil: IR (film) 2937, 2856, 1717, 1513, 1247, 1031 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.75 (ddd, *J*=9.6, 2.4, 1.7 Hz, 1H), 7.33–7.20 (m, 7H), 6.84 (ddd, *J*=8.9, 2.8, 2.0 Hz, 2H), 4.47 (s, 2H), 4.45 (d, *J*=11.0 Hz, 1H), 4.42 (d, *J*=11.0 Hz, 1H), 3.94 (m, 1H), 3.78 (s, 3H), 3.47–3.45 (m, 2H), 2.25 (ddd, *J*=16.5, 7.2, 2.4 Hz, 1H), 2.53 (ddd, *J*=16.5, 4.8, 1.7 Hz, 1H), 1.73–1.65 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.5, 159.2, 138.4, 130.2, 129.3 (2C),

128.3 (2C), 127.6 (2C), 127.5, 113.8 (2C), 73.6, 72.9, 70.8, 70.0, 55.2, 48.2, 30.9, 25.3; HRMS (ESI) calcd for $C_{21}H_{26}O_4Na$ [$(M+Na)^+$] 365.1723, found 365.1732.

*4.2.3. 6-Benzyloxy-3-(4-methoxybenzyloxy)-1-hexanoic acid (±)-**15**.* To a solution of aldehyde (±)-**14** (1.61 g, 4.70 mmol), 2-methyl-2-butene (2.49 mL, 23.5 mmol), and NaH_2PO_4 (0.62 g, 5.17 mmol) in *t*-BuOH/H_2O (4:1, v/v, 25 mL) cooled to 0 °C was added $NaClO_2$ (1.49 g, 16.5 mmol), and the resultant mixture was stirred at room temperature for 50 min. The reaction mixture was diluted with H_2O, cooled to 0 °C, and acidified with 0.5 M aqueous HCl. The resultant mixture was extracted with EtOAc, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc/hexanes) gave the *title compound* (±)-**15** (1.66 g, 99%) as a colorless oil: IR (film) 2935, 2861, 1708, 1513, 1247, 1033 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4H), 7.27 (m, 1H), 7.24–7.21 (m, 2H), 6.84 (ddd, *J*=8.9, 2.8, 2.0 Hz, 2H), 4.49 (d, *J*=11.3 Hz, 1H), 4.48 (s, 2H), 4.46 (d, *J*=11.3 Hz, 1H), 3.88 (m, 1H), 3.77 (s, 3H), 3.47–3.44 (m, 2H), 2.62 (dd, *J*=15.4, 7.2 Hz, 1H), 2.52 (dd, *J*=15.4, 5.5 Hz, 1H), 1.72–1.65 (m, 4H) (one proton missing due to H/D exchange); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.8, 159.2, 138.4, 130.1, 129.5 (2C), 128.3 (2C), 127.6 (2C), 127.5, 113.8 (2C), 75.0, 72.8, 71.2, 70.0, 55.2, 39.4, 30.8, 25.3; HRMS (ESI) calcd for $C_{21}H_{25}O_5$ [$(M-H)^-$] 357.1707, found 357.1698.

*4.2.4. S-Ethyl 6-benzyloxy-3-(4-methoxybenzyloxy)-1-hexanethioate (±)-**16a**.* To a solution of carboxylic acid (±)-**15** (1.02 g, 2.85 mmol), DMAP (17.4 mg, 0.14 mmol), and ethanethiol (0.85 mL, 11 mmol) in CH_2Cl_2 (29 mL) cooled to 0 °C was added EDC·HCl (0.82 g, 4.3 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc, washed successively with saturated aqueous NH_4Cl solution, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (0–10% EtOAc/hexanes) gave the *title compound* (±)-**16a** (0.97 g, 85%) as a yellow oil: IR (film) 2931, 2858, 1682, 1613, 1513, 1454, 1301, 1173, 1097, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36–7.34 (m, 5H), 7.25 (d, *J*=8.2 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.50 (d, *J*=11.0 Hz, 1H), 4.49 (s, 2H), 4.42 (d, *J*=11.0 Hz, 1H), 3.93 (m, 1H), 3.78 (s, 3H), 3.46–3.44 (m, 2H), 2.94–2.86 (m, 3H), 2.67 (dd, *J*=14.8, 5.5 Hz, 1H), 1.78–1.63 (m, 4H), 1.26 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5, 159.0, 138.5, 130.3, 129.3 (2C), 128.2 (2C), 127.5 (2C), 127.4, 113.6 (2C), 75.5, 72.7, 71.2, 70.0, 55.1, 49.0, 31.1, 25.4, 23.3, 14.6; HRMS (ESI) calcd for $C_{23}H_{30}O_4SNa$ [$(M+Na)^+$] 425.1757, found 425.1760.

*4.2.5. S-Phenyl 6-benzyloxy-3-(4-methoxybenzyloxy)-1-hexanethioate (±)-**16b**.* To a solution of carboxylic acid (±)-**15** (0.56 g, 1.56 mmol), DMAP (9.5 mg, 0.078 mmol), and benzenethiol (0.190 mL, 1.87 mmol) in CH_2Cl_2 (15.6 mL) cooled to 0 °C was added DCC (0.39 g, 1.87 mmol), and the resultant mixture was stirred at room temperature for 1 h. Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc/hexanes) gave the *title compound* (±)-**16b** (0.63 g, 90%) as a colorless oil: IR (film) 2934, 2857, 1702, 1513, 1247, 1096 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40–7.33 (m, 5H) (s, 5H), 7.39–7.36 (m, 5H), 7.30 (d, *J*=8.9 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 4.54 (d, *J*=11.0 Hz, 1H), 4.52 (s, 2H), 4.48 (d, *J*=11.0 Hz, 1H), 4.01 (m, 1H), 3.80 (s, 3H), 3.51–3.47 (m, 2H), 3.01 (dd, *J*=15.1, 7.2 Hz, 1H), 2.81 (dd, *J*=15.1, 5.2 Hz, 1H), 1.80–1.70 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.4, 159.1, 138.4, 134.3 (2C), 130.3, 129.3 (2C), 129.2, 129.1 (2C), 128.2 (2C), 128.1, 127.5 (2C), 127.4, 113.6 (2C), 75.5, 72.3, 71.4, 69.9, 55.1, 48.6, 31.1, 25.3; HRMS (ESI) calcd for $C_{27}H_{30}O_4SNa$ [$(M+Na)^+$] 473.1757, found 473.1774.

*4.2.6. S-(4-Methylphenyl) 6-benzyloxy-3-(4-methoxybenzyloxy)-1-hexanethioate (±)-**16c**.* Using the procedure described for (±)-**16b**, carboxylic acid **15** (1.46 g, 4.07 mmol) was reacted with *p*-toluenethiol (0.61 g, 4.9 mmol), DCC (1.01 g, 4.89 mmol), and DMAP (24.9 mg, 0.20 mmol) in CH_2Cl_2 (21 mL) to give the *title compound* (±)-**16c** (1.80 g, 95%); IR (film) 2932, 2863, 1698, 1512, 1247, 1033 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.20 (m, 12H), 6.84 (d, *J*=9.0 Hz, 2H), 4.49 (d, *J*=10.8 Hz, 1H), 4.47 (s, 2H), 4.42 (d, *J*=10.8 Hz, 1H), 3.94 (m, 1H), 3.78 (s, 3H), 3.47–3.41 (m, 2H), 2.95 (dd, *J*=14.4, 7.2 Hz, 1H), 2.74 (dd, *J*=14.4, 5.4 Hz, 1H), 2.36 (s, 3H), 1.74–1.65 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 159.2, 139.7, 138.5, 134.4 (2C), 130.4, 130.0 (2C), 129.4 (2C), 128.3 (2C), 127.6 (2C), 127.5, 124.2, 113.7 (2C), 75.6, 72.8, 71.5, 70.1, 55.2, 48.6, 31.2, 25.5, 21.3; HRMS (ESI) calcd for $C_{28}H_{32}O_4SNa$ [$(M+Na)^+$] 487.1914, found 487.1915.

*4.2.7. S-(4-Nitrophenyl) 6-benzyloxy-3-(4-methoxybenzyloxy)-1-hexanethioate (±)-**16d**.* Using the procedure described for (±)-**16b**, carboxylic acid **15** (0.51 g, 1.4 mmol) was reacted with *p*-nitrobenzenethiol (0.26 g, 1.7 mmol), DCC (0.35 g, 1.7 mmol), and DMAP (8.7 mg, 0.071 mmol) in CH_2Cl_2 (14 mL) to give the *title compound* (±)-**16d** (0.60 g, 85%) as a pale yellow oil: IR (film) 2935, 2857, 1710, 1517, 1343, 1248, 1092, 1033, 852 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, *J*=8.9 Hz, 2H), 7.54 (ddd, *J*=8.9, 2.4, 2.4 Hz, 2H), 7.36–7.31 (m, 5H), 7.25 (d, *J*=7.6 Hz, 2H), 6.87 (d, *J*=8.3 Hz, 2H), 4.51 (s, 2H), 4.49 (s, 2H), 4.00 (m, 1H), 3.79 (s, 3H), 3.49 (t, *J*=5.9 Hz, 2H), 3.00 (dd, *J*=14.8, 7.3 Hz, 1H), 2.84 (dd, *J*=14.8, 4.9 Hz, 1H), 1.78–1.68 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.2, 159.1, 147.9, 138.3, 136.1, 134.4 (2C), 130.0, 129.3 (2C), 128.2 (2C), 127.5 (2C), 124.3, 123.7 (2C), 113.6 (2C), 75.4, 72.7, 71.3, 69.8, 55.1, 48.9, 30.9, 25.2; HRMS (ESI) calcd for $C_{27}H_{29}NO_6SNa$ [$(M+Na)^+$] 518.1608, found 518.1597.

4.3. General procedure for the palladium-catalyzed coupling of thioesters and terminal alkynes

General procedure (**GP-1**): To a mixture of $Pd_2(dba)_3\cdot CHCl_3$ (13.2 mg, 0.0128 mmol), CuI (82.7 mg, 0.434 mmol), and $(2\text{-furyl})_3P$ (23.7 mg, 0.102 mmol) in degassed DMF (1.1 mL) was added a solution of thioester (±)-**16c** (118.7 mg, 0.255 mmol) in degassed DMF (1.1 mL), 1-hexyne (0.059 mL, 0.51 mmol), and Et_3N (0.430 mL). The resultant mixture was stirred at 50 °C for 4.4 h. After being cooled to room temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (30 mL). The organic layer was washed with brine (20 mL×2), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5–10% EtOAc/hexanes) gave ynone (±)-**27** (86.7 mg, 80%) as a yellow oil.

*4.3.1. 1-Benzyloxy-4-(4-methoxybenzyloxy)-7-dodecyn-6-one (±)-**27**.* IR (film) 2930, 2210, 1670, 1513, 1455, 1247, 1095, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 7.21 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=8.5 Hz, 2H), 4.47–4.37 (m, 4H), 4.00 (m, 1H), 3.77 (s, 3H), 3.44 (t, *J*=5.0 Hz, 2H), 2.86 (dd, *J*=15.5, 7.5 Hz, 1H), 2.63 (dd, *J*=15.5, 4.5 Hz, 1H), 2.36–2.29 (m, 2H), 1.74–1.60 (m, 4H), 1.58–1.50 (m, 2H), 1.49–1.36 (m, 2H), 0.89 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 159.1, 138.4, 130.4, 129.3 (2C), 128.3 (2C), 127.5 (2C), 127.4, 113.6 (2C), 94.9, 81.2, 74.7, 72.8, 71.1, 70.1, 55.2, 50.6, 31.0, 29.6, 25.4, 21.9, 18.6, 13.4; HRMS (ESI) calcd for $C_{27}H_{34}O_4Na$ [$(M+Na)^+$] 445.2349, found 445.2365.

*4.3.2. 1-Benzyloxy-4,11-bis(4-methoxybenzyloxy)-7-undecyn-6-one (±)-**18**.* According to **GP-1**, thioester (±)-**16c** (65.6 mg, 0.141 mmol) was reacted with alkyne **17** (57.7 mg, 0.282 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (7.3 mg, 0.0071 mmol), $(2\text{-furyl})_3P$ (13.1 mg, 0.0565 mmol), and CuI (45.6 mg, 0.240 mmol) in DMF/Et_3N (5:1, v/v, 0.70 mL) to give the title compound (±)-**18** (58.8 mg, 77%) as a yellow oil: IR (film) 2857, 2210, 1670, 1612, 1512, 1246, 1172, 1100, 1033,

819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 7.23–7.21 (m, 4H), 6.86 (d, J=9.0 Hz, 2H), 6.84 (d, J=8.5 Hz, 2H), 4.48 (s, 2H), 4.44 (d, J=9.5 Hz, 2H), 4.41 (s, 2H), 4.01 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.49 (t, J=5.5 Hz, 2H), 3.45 (t, J= 5.5 Hz, 2H), 2.85 (dd, J=15.5, 7.5 Hz, 1H), 2.62 (dd, J=15.5, 5.0 Hz, 1H), 2.45 (t, J=6.5 Hz, 2H), 1.85–1.80 (m, 2H), 1.75–1.62 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 186.0, 159.2, 159.1, 138.5, 130.4, 130.2, 129.4 (2C), 129.2 (2C), 128.3 (2C), 127.6 (2C), 127.5 (2C), 113.8 (2C), 113.7 (2C), 94.2, 81.3, 74.7, 72.8, 72.6, 71.1, 70.1, 68.0, 55.2, 50.6, 31.0, 27.9, 25.4, 15.9; HRMS (ESI) calcd for $C_{34}H_{40}O_6Na$ [$(M+Na)^+$] 567.2717, found 567.2716.

*4.3.3. 1-Benzyloxy-11-(tert-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-7-undecyn-6-one (±)-**28**.* According to **GP-1**, thioester (±)-**16c** (411 mg, 0.885 mmol) was reacted with alkyne **23** (428 mg, 1.33 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (46.0 mg, 0.0442 mmol), (2-furyl)$_3$P (82.0 mg, 0.354 mmol), and CuI (286 mg, 1.50 mmol) in DMF/Et_3N (5:1, v/v, 8.8 mL) to give the *title compound* (±)-**28** (385 mg, 80%) as a yellow oil: IR (film) 2857, 2211, 1671, 1513, 1428, 1247, 1109, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.62 (m, 4H), 7.40–7.30 (m, 11H), 7.20 (d, J=8.5 Hz, 2H), 6.81 (d, J=8.0 Hz, 2H), 4.46 (s, 2H), 4.45–4.36 (m, 2H), 3.98 (m, 1H), 3.75 (s, 3H), 3.69 (t, J=5.5 Hz, 2H), 3.43–3.42 (m, 2H), 2.83 (dd, J=15.5, 7.5 Hz, 1H), 2.59 (dd, J=15.5, 5.0 Hz, 1H), 2.49 (t, J=6.5 Hz, 2H), 1.79–1.74 (m, 2H), 1.70–1.62 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.0, 159.1, 138.5, 135.5, 135.5 (4C), 133.5, 130.4, 129.7 (2C), 129.4 (2C), 128.3 (2C), 128.3, 127.7 (4C), 127.6 (2C), 113.7 (2C), 94.4, 81.2, 74.6, 72.8, 71.1, 70.1, 62.0, 55.2, 50.5, 31.0, 30.6, 26.8 (3C), 25.4, 19.2, 15.6; HRMS (ESI) calcd for $C_{42}H_{50}O_5SiNa$ [$(M+Na)^+$] 685.3320, found 685.3342.

*4.3.4. 8-Benzyloxy-5-(4-methoxybenzyloxy)-1-phenyl-1-octyn-3-one (±)-**29**.* According to **GP-1**, thioester (±)-**16c** (132.8 mg, 0.286 mmol) was reacted with ethynylbenzene (0.063 mL, 0.57 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (14.8 mg, 0.0143 mmol), (2-furyl)$_3$P (26.5 mg, 0.114 mmol), and CuI (92.5 mg, 0.486 mmol) in DMF/Et_3N (5:1, v/v, 2.9 mL) to give the *title compound* (±)-**29** (103.6 mg, 82%) as a yellow oil: IR (film); 2856, 2202, 1665, 1612, 1512, 1454, 1246, 1070, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.25 (m, 10H), 7.23 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.0 Hz, 2H), 4.48 (dd, J=12.0, 11.5 Hz, 2H), 4.47 (s, 2H), 4.10–4.07 (m, 1H), 3.74 (s, 3H), 3.47–3.46 (m, 2H), 2.98 (dd, J=7.5, 7.0 Hz, 1H), 2.76 (dd, J=5.5, 5.0 Hz, 1H), 1.76–1.66 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.9, 159.0, 138.4, 133.0, 130.7, 130.2 (2C), 129.5, 129.4, 128.6, 128.5, 128.3, 127.5, 127.4, 119.7, 113.6 (4C), 91.2, 88.1, 74.6, 72.8, 71.1, 70.0, 55.1, 50.5, 30.9, 25.4; HRMS (ESI) calcd for $C_{29}H_{30}O_4Na$ [$(M+Na)^+$] 465.2036, found 465.2037.

*4.3.5. 8-Benzyloxy-1-cyclohexyl-5-(4-methoxybenzyloxy)oct-1-yn-3-one (±)-**30**.* According to **GP-1**, thioester (±)-**16c** (145.1 mg, 0.312 mmol) was reacted with cyclohexylacetylene (0.080 mL, 0.63 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (16.2 mg, 0.0156 mmol), (2-furyl)$_3$P (29.0 mg, 0.125 mmol), and CuI (101 mg, 0.531 mmol) in DMF/Et_3N (5:1, v/v, 3.2 mL) to give the *title compound* (±)-**30** (104.4 mg, 75%) as a yellow oil: IR (film) 2931, 2854, 2205, 1670, 1613, 1513, 1451, 1247, 1172, 1096, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.30 (m, 5H), 7.22 (d, J=8.0 Hz, 2H), 6.83 (d, J=8.0 Hz, 2H), 4.47 (s, 2H), 4.46–4.42 (m, 2H), 4.02 (m, 1H), 3.77 (s, 3H), 3.44 (t, J=5.0 Hz, 2H), 2.86 (dd, J=15.5, 7.0 Hz, 1H), 2.63 (dd, J=15.5, 5.0 Hz, 1H), 2.50 (m, 1H), 1.78 (br s, 2H), 1.74–1.64 (m, 6H), 1.48–1.41 (m, 3H), 1.30–1.23 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 159.0, 138.4, 130.3, 129.3 (2C), 128.2 (2C), 127.5 (2C), 127.4, 113.6 (2C), 98.4, 81.0, 74.7, 72.7, 71.0, 70.0, 65.7, 55.1, 50.6, 31.4, 30.9, 29.0, 25.49, 25.42, 24.5, 15.2; HRMS (ESI) calcd for $C_{29}H_{36}O_4Na$ [$(M+Na)^+$] 471.2506, found 471.2494.

*4.3.6. 1,10-Bis(benzyloxy)-7-(4-methoxybenzyloxy)-2,2-dimethyldec-3-yn-5-one (±)-**31**.* According to **GP-1**, thioester (±)-**16c** (1.01 g, 2.17 mmol) was reacted with alkyne **26** (0.61 g, 3.26 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (99.5 mg, 0.109 mmol), (2-furyl)$_3$P (0.20 g, 0.87 mmol), and CuI (0.70 g, 3.70 mmol) in DMF/Et_3N (5:1, v/v, 22 mL) to give the *title compound* (±)-**31** (0.94 g, 82%) as a yellow oil: IR (film) 2858, 2361, 2208, 1671, 1612, 1513, 1454, 1360, 1247, 1173, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 7.21 (d, J=9.0 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 4.55 (s, 2H), 4.47 (s, 2H), 4.46–4.41 (m, 2H), 4.00 (m, 1H), 3.76 (s, 3H), 3.43 (t, J=5.0 Hz, 2H), 3.32 (s, 2H), 2.86 (dd, J=15.5, 7.5 Hz, 1H), 2.63 (dd, J=15.5, 5.5 Hz, 1H), 1.72–1.63 (m, 4H), 1.25 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.1, 159.1, 138.5, 138.1, 130.5, 129.4 (2C), 128.4 (2C), 128.3 (2C), 127.6 (2C), 127.5, 127.4 (2C), 113.7 (2C), 109.7, 99.4, 80.8, 77.3, 74.8, 73.3, 72.9, 71.2, 70.1, 55.2, 50.7, 32.9, 31.0, 25.5, 25.2 (2C); HRMS (ESI) calcd for $C_{34}H_{40}O_5Na$ [$(M+Na)^+$] 551.2768, found 551.2755.

*4.3.7. 8-(tert-Butyldiphenylsilyloxy)-1-cyclohexyl-1-(4-methoxybenzyloxy)oct-4-yn-3-one (±)-**32**.* According to **GP-1**, thioester (±)-**19** (155.1 mg, 0.374 mmol) was reacted with alkyne **23** (181.0 mg, 0.561 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (19.4 mg, 0.0187 mmol), (2-furyl)$_3$P (34.7 mg, 0.150 mmol), and CuI (121.1 mg, 0.636 mmol) in DMF/Et_3N (5:1, v/v, 3.7 mL) to give the *title compound* (±)-**32** (177.8 mg, 80%) as a yellow oil: IR (film) 2928, 2854, 2361, 1671, 1612, 1513, 1247, 1109 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J=6.6 Hz, 4H), 7.32–7.26 (m, 6H), 7.13 (d, J=8.4 Hz, 2H), 6.73 (d, J=8.4 Hz, 2H), 4.35 (q, J=14.5 Hz, 2H), 3.72 (m, 1H), 3.64 (s, 3H), 3.62 (t, J=5.4 Hz, 2H), 2.68 (dd, J=15.6, 7.8 Hz, 1H), 2.53 (dd, J=15.6, 4.2 Hz, 1H), 2.41 (t, J=7.8 Hz, 2H), 1.70–1.63 (m, 5H), 1.57 (m, 1H), 1.50–1.43 (m, 2H), 1.16–0.99 (m, 3H), 0.96 (s, 9H), 0.93–0.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.6, 159.0, 135.4 (4C), 133.4, 130.6, 129.6 (2C), 129.3 (2C), 128.2, 127.6 (4C), 113.6 (2C), 94.2, 81.3, 79.2, 71.9, 62.0, 55.1, 48.0, 41.7, 30.6, 28.6, 28.5, 26.8 (3C), 26.5, 26.2 (2C), 19.1, 15.5; HRMS (ESI) calcd for $C_{38}H_{48}O_4SiNa$ [$(M+Na)^+$] 619.3214, found 619.3235.

*4.3.8. 1-Cyclohexyl-1-(4-methoxybenzyloxy)-5-phenyl-4-pentyn-3-one (±)-**33**.* According to **GP-1**, thioester (±)-**19** (138.1 mg, 0.333 mmol) was reacted with ethynylbenzene (0.073 mL, 0.67 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (17.2 mg, 0.0167 mmol), (2-furyl)$_3$P (30.9 mg, 0.133 mmol), and CuI (107.9 mg, 0.566 mmol) in DMF/Et_3N (5:1, v/v, 3.3 mL) to give the *title compound* (±)-**33** (91.0 mg, 73%) as a yellow oil: IR (film) 2926, 2852, 1668, 1512, 1247, 1070, 821 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53–7.52 (m, 2H), 7.43 (m, 1H), 7.37–7.35 (m, 2H), 7.25 (d, J=9.6 Hz, 2H), 6.81 (d, J=8.4 Hz, 2H), 4.50 (dd, J=15.6, 7.8 Hz, 1H), 3.91 (m, 1H), 3.73 (m, 1H), 2.93 (dd, J=15.6, 7.8 Hz, 4H), 2.79 (dd, J=15.6, 4.2 Hz, 1H), 1.83–1.61 (m, 6H), 1.27–1.01 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.6, 159.0, 132.9 (2C), 130.6, 130.5, 129.3 (2C), 128.5 (2C), 119.8, 113.6 (2C), 91.0, 88.2, 79.3, 71.9, 55.1, 48.0, 41.6, 28.7, 28.4, 26.4, 26.2, 26.1; HRMS (ESI) calcd for $C_{25}H_{28}O_3Na$ [$(M+Na)^+$] 399.1931, found 399.1941.

*4.3.9. (4R,5S)-1-Benzyloxy-11-(tert-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-5-methyl-7-undecyn-6-one and (4R,5R)-1-benzyloxy-11-(tert-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-5-methyl-7-undecyn-6-one (−)-**34**.* According to **GP-1**, thioester (−)-**20** (156.2 mg, 0.326 mmol) was reacted with alkyne **23** (157.8 mg, 0.490 mmol) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (16.9 mg, 0.0163 mmol), (2-furyl)$_3$P (30.3 mg, 0.131 mmol), and CuI (106.2 mg, 0.555 mmol) in DMF/Et_3N (5:1, v/v, 3.3 mL) to give the *title compounds* **34** (184.0 mg, 83%) as an inseparable 1.3:1 mixture of diastereomers: $[\alpha]_D^{30}$ −4.6 (*c* 1.00, $CHCl_3$); IR (film) 2932, 2857, 2209, 1671, 1612, 1513, 1455, 1428, 1360, 1301, 1247, 1175, 1109 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.73–7.71 (m, 4H), 7.32–7.30 (m, 6H), 7.23–7.11 (m, 5H), 7.11–7.09 (m, 2H), 6.79–6.75 (m, 2H), 4.43 (q, J=4.8 Hz, 2H), 4.31 (d, J=9.6 Hz, 2H), 4.09 (m, 0.43H), 4.01 (m, 0.57H), 3.55 (q, J=4.2 Hz, 2H), 3.28 (d, J=3.0 Hz, 3H), 3.27–3.25 (m, 2H), 2.98 (m, 0.57H), 2.64 (m, 0.43H), 2.19–2.16 (m, 2H), 1.84–1.78 (m, 2H), 1.66–1.57 (m, 2H), 1.51–1.46 (m, 2H), 1.29 (d, J=7.2 Hz, 1.3H), 1.13

(s, 9H), 1.12 (d, J=7.2 Hz, 1.7H); ^{13}C NMR (150 MHz, C_6D_6) δ 189.2, 188.9, 159.6, 159.6, 139.4, 139.4, 135.9 (4C), 133.9 (2C), 131.2, 131.1, 130.1 (2C), 129.6, 129.5, 128.5 (4C), 128.5, 128.3, 128.1 (2C), 127.71, 127.69, 127.6, 127.5, 113.9 (2C), 93.7, 93.5, 81.5, 81.4, 79.3, 79.1, 72.9, 72.9, 71.9, 71.3, 70.4, 70.3, 62.2, 54.7, 52.5, 51.7, 30.9, 27.0 (3C), 26.4, 25.7, 19.4, 15.50, 15.49, 11.2, 10.6; HRMS (ESI) calcd for $C_{43}H_{52}O_5SiNa$ [(M+Na)$^+$] 699.3476, found 699.3484.

*4.3.10. 1-Benzyloxy-4-(benzyloxycarbonylamino)-11-(tert-butyldiphenylsilyloxy)-7-undecyn-6-one (±)-**35**.* According to **GP-1**, thioester (±)-**21** (51.1 mg, 0.107 mmol) was reacted with alkyne **23** (51.8 mg, 0.160 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (5.5 mg, 0.0054 mmol), (2-furyl)$_3$P (9.9 mg, 0.043 mmol), and CuI (34.6 mg, 0.182 mmol) in DMF/Et_3N (5:1, v/v, 1.1 mL) to give the *title compound* (±)-**35** (67.0 mg, 93%) as a yellow oil: IR (film) 3325, 3068, 2930, 2856, 2366, 2210, 1720, 1669, 1508, 1427, 1233, 1108, 1026, 823 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.42–7.25 (m, 16H), 5.15 (d, J=9.0 Hz, 1H), 5.05 (s, 2H), 4.46 (s, 2H), 4.01 (m, 1H), 3.69 (t, J=6.0 Hz, 2H), 3.45 (s, 2H), 2.78 (dd, J=17.4, 5.4 Hz, 1H), 2.71 (dd, J=16.8, 5.4 Hz, 1H), 2.49 (t, J=7.2 Hz, 2H), 1.80–1.75 (m, 2H), 1.67–1.58 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.8, 155.7, 138.3, 136.5, 135.5 (4C), 133.5 (2C), 129.7 (2C), 128.5 (2C), 128.3 (2C), 128.0 (2C), 127.9 (2C), 127.7 (4C), 127.6 (2C), 94.9, 81.0, 72.9, 69.7, 66.6, 62.0, 49.6, 47.9, 31.1, 30.5, 26.8 (3C), 26.4, 19.2, 15.6; HRMS (ESI) calcd for $C_{42}H_{49}NO_5SiNa$ [(M+Na)$^+$] 698.3272, found 698.3275.

4.4. General procedure for the deprotection and 6-*endo-dig* cyclization of β-alkoxy ynones

Step 1: *Deprotection of MPM group*. General procedure (**GP-2**): To a solution of β-alkoxy ynone (±)-**27** (79.4 mg, 0.188 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 1.9 mL) cooled to 0 °C was added DDQ (48.4 mg, 0.207 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The whole mixture was filtered through a pad of Celite, and the filtrate was extracted with EtOAc (40 mL). The organic layer was washed with brine (30 mL×2), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10–30% EtOAc/hexanes) gave a β-hydroxy ynone (48.5 mg, 85%) as a pale yellow oil: IR (film): 3427, 2930, 2862, 2210, 1669, 1455, 1362, 1160, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H), 4.49 (s, 2H), 4.12 (m, 1H), 3.49 (t, J=6.5 Hz, 2H), 3.06 (br s, 1H), 2.69 (d, J=6.0 Hz, 2H), 2.35 (t, J=7.5 Hz, 2H), 1.79–1.67 (m, 2H), 1.63–1.49 (m, 4H), 1.45–1.37 (m, 2H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.5, 138.2, 128.4 (2C), 127.6 (2C), 127.5, 95.5, 81.0, 72.9, 70.1, 67.3, 52.3, 33.5, 29.6, 25.9, 21.9, 18.6, 13.4; HRMS (ESI) calcd for $C_{19}H_{26}O_3Na$ [(M+Na)$^+$] 325.1774, found 325.1770.

Step 2: *AgOTf-mediated* 6-*endo-dig cyclization*. General procedure (**GP-3**): To a solution of the above β-hydroxy ynone (38.0 mg, 0.126 mmol) in CH_2Cl_2 (12.6 mL) was added AgOTf (35.5 mg, 0.138 mmol), and the resultant mixture was stirred at room temperature for 3.2 h under exclusion of light. The reaction mixture was diluted with EtOAc (40 mL) and washed with brine (30 mL×2). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (30% EtOAc/hexanes) gave dihydropyrone (±)-**36** (36.5 mg, 96%) as a yellow oil.

*4.4.1. 6-(3-Benzyloxypropyl)-2-butyl-5,6-dihydro-4H-pyran-4-one (±)-**36**.* IR (film) 2955, 1666, 1604, 1398, 1099, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H), 5.29 (s, 1H), 4.49 (s, 2H), 4.31 (m, 1H), 3.50 (t, J=5.0 Hz, 2H), 2.43–2.30 (m, 2H), 2.25–2.15 (m, 2H), 1.87–1.68 (m, 4H), 1.53–1.46 (m, 2H), 1.35–1.28 (m, 2H), 0.89 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 177.9, 138.3, 128.4 (2C), 127.6 (2C), 104.1, 104.0, 78.9, 73.0, 69.6, 41.0, 34.5, 31.3, 28.4, 25.3, 22.1, 13.7; HRMS (ESI) calcd for $C_{19}H_{27}O_3$ [(M+H)$^+$] 303.1955, found 303.1965.

*4.4.2. 6-(3-Benzyloxypropyl)-2-[3-(tert-butyldiphenylsilyloxy)propyl]-5,6-dihydro-4H-pyran-4-one (±)-**37**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**28** (302 mg, 0.456 mmol) with DDQ (117 mg, 0.501 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 4.6 mL) gave a β-hydroxy ynone (228.8 mg, 92%) as a yellow oil: IR (film) 3443, 2930, 2857, 2212, 1670, 1428, 1361, 1159, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.42–7.30 (m, 11H), 4.49 (s, 2H), 4.09 (m, 1H), 3.98 (m, 1H), 3.71 (t, J=5.5 Hz, 2H), 3.49 (t, J=6.0 Hz, 2H), 2.65 (d, J=5.5 Hz, 2H), 2.51 (t, J=7.0 Hz, 2H), 1.81–1.75 (m, 2H), 1.74–1.64 (m, 2H), 1.60–1.45 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4, 138.2, 135.4 (4C), 133.5, 129.7 (2C), 128.4 (2C), 128.3, 127.7 (4C), 127.6 (2C), 127.6, 94.9, 81.0, 73.0, 70.1, 67.3, 62.0, 52.3, 33.5, 30.5, 26.8 (3C), 25.9, 19.2, 15.6; HRMS (ESI) calcd for $C_{34}H_{42}O_4SiNa$ [(M+Na)$^+$] 565.2745, found 565.2724.

According to **GP-3**, the above β-hydroxy ynone (85.1 mg, 0.157 mmol) was reacted with AgOTf (4.0 mg, 0.0016 mmol) in CH_2Cl_2 (1.6 mL) to give the *title compound* (±)-**37** (83.9 mg, 98%) as a yellow oil: IR (film) 2857, 1667, 1605, 1428, 1398, 1108, 822 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.61 (m, 4H), 7.42–7.29 (m, 11H), 5.29 (s, 1H), 4.48 (s, 2H), 4.27 (m, 1H), 3.64 (t, J=6.0 Hz, 2H), 3.51–3.46 (m, 2H), 2.37–2.30 (m, 4H), 1.86–1.65 (m, 6H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 177.3, 138.3, 135.5 (2C), 135.5 (2C), 133.6 (2C), 129.6 (2C), 128.4 (2C), 127.64 (3C), 127.59 (2C), 104.1 (2C), 78.9, 77.2, 73.0, 69.6, 62.6, 62.6, 41.0, 31.3, 31.2, 29.2, 26.8 (3C), 25.2, 19.2; HRMS (ESI) calcd for $C_{34}H_{43}O_4Si$ [(M+H)$^+$] 543.2925, found 543.2922.

*4.4.3. 6-(3-Benzyloxypropyl)-2-phenyl-5,6-dihydro-4H-pyran-4-one (±)-**38**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**29** (140.1 mg, 0.317 mmol) with DDQ (81.5 mg, 0.348 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 3.3 mL) gave a β-hydroxy ynone (92.4 mg, 90%) as a yellow oil: IR (film); 3422, 2924, 2857, 2203, 1489, 1454, 1286, 1095, 1026 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.37 (m, 1H), 7.31–7.25 (m, 5H), 7.20–7.17 (m, 2H), 4.43 (s, 2H), 4.14 (m, 1H), 3.44 (t, J=5.4 Hz, 2H), 3.08 (br s, 1H), 2.77 (d, J=6.6 Hz, 2H), 1.74–1.62 (m, 2H), 1.61–1.48 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.2, 138.1, 133.1 (2C), 130.9, 128.6 (2C), 128.4 (2C), 127.7 (2C), 127.6, 119.7, 91.6, 87.9, 73.0, 70.1, 67.4, 52.4, 33.7, 25.9; HRMS (ESI) calcd for $C_{21}H_{22}O_3Na$ [(M+Na)$^+$] 345.1461, found 345.1470.

According to **GP-3**, the above β-hydroxy ynone (50.0 mg, 0.155 mmol) was reacted with AgOTf (43.8 mg, 0.171 mmol) in CH_2Cl_2 (16 mL) to give the *title compound* (±)-**38** (48.5 mg, 97%) as an orange oil: IR (film) 2857, 1660, 1594, 1570, 1492, 1449, 1385, 1338, 1294, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71(d, J=7.5 Hz, 2H), 7.33–7.31 (m, 8H), 5.99 (s, 1H), 4.54 (m, 1H), 4.52 (s, 2H), 3.58–3.50 (m, 2H), 2.59–2.46 (m, 2H), 2.04–1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 170.1, 138.2, 131.6, 128.6 (2C), 128.4 (2C), 128.3 (2C), 127.6 (2C), 126.5 (2C), 102.0, 79.3, 73.0, 69.6, 41.4, 31.4, 25.5; HRMS (ESI) calcd for $C_{21}H_{23}O_3$ [(M+H)$^+$] 323.1642, found 323.1631.

*4.4.4. 6-(3-Benzyloxypropyl)-2-cyclohexyl-5,6-dihydro-4H-pyran-4-one (±)-**39**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**30** (83.2 mg, 0.185 mmol) with DDQ (47.7 mg, 0.204 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 1.9 mL) gave a β-hydroxy ynone (60.5 mg, 100%) as an orange oil: IR (film) 3432, 2930, 2854, 2363, 2205, 1667, 1450, 1362, 1160, 1099 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 5H), 4.49 (s, 2H), 4.13 (m, 1H), 3.50 (t, J=5.5 Hz, 2H), 3.05 (br s, 1H), 2.70 (d, J=6.0 Hz, 2H), 2.53 (m, 1H), 1.82–1.79 (m, 2H), 1.77–1.67 (m, 4H), 1.63–1.45 (m, 4H), 1.31–1.22 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.6, 138.2, 128.3 (2C), 127.6 (2C), 127.5, 98.9, 80.8, 72.9, 70.1, 67.3, 52.4, 41.2, 38.8, 33.4, 31.4, 29.0, 25.8, 25.5, 24.5; HRMS (ESI) calcd for $C_{21}H_{28}O_3Na$ [(M+Na)$^+$] 351.1931, found 351.1938.

According to **GP-3**, the above β-hydroxy ynone (52.7 mg, 0.160 mmol) was reacted with AgOTf (45.3 mg, 0.0176 mmol) in CH_2Cl_2 (16 mL) to give the *title compound* (±)-**39** (52.6 mg, 100%) as a yellow oil: IR (film) 2929, 2854, 1666, 1599, 1451, 1396, 1338, 1243, 1099, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (m, 5H), 5.27 (s, 1H), 4.50 (s, 2H), 4.29 (m, 1H), 3.51–3.49 (m, 2H), 2.42–2.31 (m, 2H), 2.09 (m, 1H), 1.88–1.66 (m, 9H), 1.30–1.14 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 181.3, 138.2, 128.3 (2C), 128.2, 127.6 (2C), 102.0, 78.8, 72.9, 69.6, 41.2, 41.1, 31.2, 30.0, 29.8, 25.8, 25.71, 25.69, 25.3; HRMS (ESI) calcd for $C_{21}H_{29}O_3$ [$(M+H)^+$] 329.2111, found 329.2101.

*4.4.5. 2-(2-Benzyloxy-1,1-dimethylethyl)-6-(3-benzyloxypropyl)-5,6-dihydro-4H-pyran-4-one (±)-**40**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**31** (0.86 g, 1.63 mmol) with DDQ (0.42 g, 1.79 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 16 mL) gave a β-hydroxy ynone (0.64 g, 96%) as a yellow oil: IR (film) 3444, 2858, 2360, 2208, 1669, 1454, 1361, 1295, 1099, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 4.57 (s, 2H), 4.49 (s, 2H), 4.11 (m, 1H), 3.50–3.47 (m, 2H), 3.33 (s, 2H), 3.11 (d, *J*=3.5 Hz, 1H), 2.69 (d, *J*=6.0 Hz, 1H), 1.78–1.64 (m, 2H), 1.61–1.49 (m, 2H), 1.26 (s, 6H), one proton missing due to H/D exchange; ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.5, 138.2, 138.0, 128.4 (4C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 99.9, 80.6, 73.3, 73.0, 70.1, 67.3, 52.4, 33.5, 32.9, 25.9, 25.1 (2C), −3.4; HRMS (ESI) calcd for $C_{26}H_{32}O_4Na$ [$(M+Na)^+$] 431.2193, found 431.2200.

According to **GP-3**, the above β-hydroxy ynone (47.6 mg, 0.117 mmol) was reacted with AgOTf (32.9 mg, 0.128 mmol) in CH_2Cl_2 (12 mL) to give the *title compound* (±)-**40** (46.5 mg, 98%) as a yellow oil: IR (film) 2857, 1495, 1478, 1454, 1383, 1360, 1291, 1242, 1208, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 10H), 5.44 (s, 1H), 4.46 (s, 4H), 4.25 (m, 1H), 3.50–3.43 (m, 2H), 3.37–3.33 (m, 2H), 2.42–2.31 (m, 2H), 1.84–1.63 (m, 4H), 1.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 181.3, 138.2 (2C), 128.3 (2C), 128.2 (2C), 127.6 (2C), 127.4 (2C), 127.3 (2C), 102.9, 78.9, 76.4, 73.1, 72.9, 69.5, 41.2, 41.1, 31.2, 25.3, 22.92, 22.88; HRMS (ESI) calcd for $C_{26}H_{33}O_4$ [$(M+H)^+$] 409.2373, found 409.2360.

*4.4.6. 2-[3-(tert-Butyldiphenylsilyloxy)propyl]-6-cyclohexyl-5,6-dihydro-4H-pyran-4-one (±)-**41**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**32** (177.3 mg, 0.290 mmol) with DDQ (74.7 mg, 0.319 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 2.9 mL) gave a β-hydroxy ynone (122.1 mg, 88%) as a yellow oil: IR (film) 3481, 2927, 2854, 2212, 1670, 1427, 1109, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.43–7.35 (m, 6H), 3.85 (m, 1H), 3.71 (t, *J*=5.5 Hz, 2H), 2.71–2.59 (m, 2H), 2.52 (t, *J*=6.5 Hz, 2H), 1.82–1.73 (m, 3H), 1.66–1.56 (m, 5H), 1.35–1.10 (m, 5H), 1.03 (s, 9H), one proton missing due to H/D exchange; ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 135.5 (5C), 133.5, 129.7 (2C), 127.7 (4C), 94.9, 81.1, 71.6, 62.0, 49.5, 42.9, 30.5, 28.8, 28.1, 26.8 (3C), 26.4, 26.1, 26.0, 19.1, 15.6; HRMS (ESI) calcd for $C_{30}H_{40}O_3SiNa$ [$(M+Na)^+$] 499.2639, found 499.2632.

According to **GP-3**, the above β-hydroxy ynone (42.1 mg, 0.0883 mmol) was reacted with AgOTf (2.3 mg, 0.00088 mmol) in CH_2Cl_2 (1.5 mL) to give the *title compound* (±)-**41** (41.1 mg, 98%) as a pale yellow oil: IR (film) 2928, 2855, 1669, 1607, 1109, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63–7.62 (m, 4H), 7.42–7.35 (m, 6H), 5.29 (s, 1H), 4.00 (m, 1H), 3.67–3.61 (m, 2H), 2.42–2.26 (m, 4H), 1.86–1.58 (m, 9H), 1.28–1.18 (m, 4H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 177.7, 135.5 (2C), 135.4 (2C), 133.6, 129.6 (2C), 127.6 (4C), 104.0 (2C), 83.2, 62.6, 41.4, 38.2, 31.2, 29.2, 28.2, 28.1, 26.8 (3C), 26.2, 25.8, 25.7, 19.2; HRMS (ESI) calcd for $C_{30}H_{41}O_3Si$ [$(M+H)^+$] 477.2819, found 477.2809.

*4.4.7. 6-Cyclohexyl-1-phenyl-5,6-dihydro-4H-pyran-4-one (±)-**42**.* According to **GP-2**, treatment of β-alkoxy ynone (±)-**33** (86.5 mg, 0.230 mmol) with DDQ (59.1 mg, 0.253 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 2.2 mL) gave a β-hydroxy ynone (51.6 mg, 88%) as a yellow oil: IR (film) 3446, 2924, 2852, 2203, 1665, 1488, 1444, 1284, 1086 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55–7.54 (m, 2H), 7.43 (m, 1H), 7.37–7.34 (m, 2H), 3.95 (m, 1H), 2.86 (m, 1H), 2.80 (dd, *J*=17.4, 9.6 Hz, 1H), 2.64 (br s, 1H), 1.86 (d, *J*=12.6 Hz, 1H), 1.77–1.74 (m, 2H), 1.69–1.64 (m, 2H), 1.40 (m, 1H), 1.26–0.98 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.9, 133.0 (2C), 130.8, 128.6 (2C), 119.6, 91.5, 87.9, 71.6, 49.6, 43.0, 28.8, 28.1, 26.3, 26.1, 26.0; HRMS (ESI) calcd for $C_{17}H_{20}O_2Na$ [$(M+Na)^+$] 279.1356, found 279.1357.

According to **GP-3**, the above β-hydroxy ynone (27.7 mg, 0.108 mmol) was reacted with AgOTf (30.5 mg, 0.119 mmol) in CH_2Cl_2 (11 mL) to give the *title compound* (±)-**42** (26.0 mg, 94%) as a yellow oil: IR (film) 2927, 2853, 1664, 1595, 1571, 1492, 1449, 1386, 1337, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.0 Hz, 2H), 7.48–7.40 (m, 3H), 5.98 (s, 1H), 4.28 (m, 1H), 2.58 (dd, *J*=15.5, 7.5 Hz, 1H), 2.46 (dd, *J*=15.5, 4.0 Hz, 1H), 2.06 (d, *J*=12.0 Hz, 1H), 1.84–1.66 (m, 5H), 1.34–1.14 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 170.3, 132.8, 128.6 (2C), 126.4 (2C), 101.8 (2C), 83.5, 41.6, 38.7, 28.4, 28.4, 26.2, 25.8, 25.7; HRMS (ESI) calcd for $C_{17}H_{21}O_2$ [$(M+H)^+$] 257.1536, found 257.1542.

*4.4.8. (5R,6R)-6-(3-Benzyloxypropyl)-2-[3-(tert-butyldiphenylsilyloxy) propyl]-5-methyl-5,6-dihydro-4H-pyran-4-one (+)-**43a** and (5S,6R)-6-(3-benzyloxypropyl)-2-[3-(tert-butyldiphenylsilyloxy)propyl]-5-methyl-5,6-dihydro-4H-pyran-4-one (+)-**43b**.* According to **GP-2**, treatment of (−)-**34** (70.9 mg, 0.105 mmol) with DDQ (27.2 mg, 0.115 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 1.1 mL) gave a β-hydroxy ynone (56.0 mg, 96%) as a colorless oil: $[\alpha]_D^{30}$ −1.2 (*c* 1.00, $CHCl_3$); IR (film) 3446, 3069, 2931, 2857, 2210, 1668, 1428, 1184, 1109, 970 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.73–7.71 (m, 4H), 7.29–7.24 (m, 5H), 7.19–7.17 (m, 5H), 7.09 (m, 1H), 4.28 (s, 2H), 4.10 (m, 0.43H), 3.90 (m, 0.57H), 3.54 (q, *J*=6.0 Hz, 2H), 3.28–3.24 (m, 2H), 2.80 (br s, 0.57H), 2.67–2.62 (m, 0.57H), 2.56 (br s, 0.43H), 2.44 (m, 0.43H), 2.17–2.14 (m, 2H), 1.78–1.70 (m, 2H), 1.66–1.51 (m, 2H), 1.50–1.38 (m, 2H), 1.30 (d, *J*=7.2 Hz, 1.3H), 1.13 (s, 9H), 1.11 (d, *J*=7.2 Hz, 1.7H); ^{13}C NMR (150 MHz, C_6D_6) δ 190.5, 139.1, 135.9 (4C), 133.9 (2C), 130.1, 130.1, 128.6, 128.5 (2C), 128.1 (4C), 127.8, 127.7, 127.6, 94.0, 94.0, 81.4, 81.3, 73.0, 72.6, 71.1, 70.4, 70.4, 62.2, 54.9, 54.1, 32.3, 31.5, 30.79, 30.76, 27.0 (3C), 26.9, 26.4, 19.4, 15.47, 15.46, 13.0, 10.4; HRMS (ESI) calcd for $C_{35}H_{44}O_4SiNa$ [$(M+Na)^+$] 579.2901, found 579.2892.

According to **GP-3**, the above β-hydroxy ynone (16.2 mg, 0.0291 mmol) was reacted with AgOTf (8.2 mg, 0.032 mmol) in CH_2Cl_2 (2.9 mL) to give the *title compounds* (+)-**43a** (8.8 mg, 54%) and (+)-**43b** (7.4 mg, 46%). Data for **(+)-43a**: $[\alpha]_D^{29}$ +47.0 (*c* 0.81, $CHCl_3$); IR (film) 3069, 2930, 2857, 2357, 1668, 1606, 1455, 1428, 1355, 1248, 1109, 963, 822 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.74–7.73 (m, 4H), 7.29–7.22 (m, 5H), 7.20–7.16 (m, 5H), 7.10 (m, 1H), 5.38 (s, 1H), 4.27 (s, 2H), 3.88 (m, 1H), 3.52 (t, *J*=6.0 Hz, 2H), 3.20–3.14 (m, 2H), 2.12 (m, 1H), 2.08 (t, *J*=8.4 Hz, 2H), 1.69–1.53 (m, 4H), 1.40–1.23 (m, 2H), 1.15 (s, 9H), 0.91 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 195.7, 174.8, 139.2, 135.9 (4C), 135.9 (2C), 134.0 (2C), 130.0 (2C), 128.6, 128.3, 128.1 (2C), 127.9, 127.7, 127.7, 103.4, 81.7, 73.0, 69.7, 63.0, 43.2, 31.0, 29.6, 27.3, 27.0 (3C), 26.1, 19.4, 9.6; HRMS (ESI) calcd for $C_{35}H_{45}O_4Si$ [$(M+H)^+$] 557.3082, found 557.3101.

Data for (+)-**43b**: $[\alpha]_D^{28}$ +59.1 (*c* 1.00, $CHCl_3$); IR (film) 2930, 2857, 2361, 1671, 1613, 1428, 1393, 1213, 1109, 964 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.75–7.73 (m, 4H), 7.30–7.23 (m, 5H), 7.20–7.16 (m, 5H), 7.10 (m, 1H), 5.40 (s, 1H), 4.30 (s, 2H), 3.61 (m, 1H), 3.56–3.52 (m, 2H), 3.24–3.20 (m, 2H), 2.10–2.07 (m, 2H), 2.04 (m, 1H), 1.73–1.69 (m, 2H), 1.65–1.58 (m, 2H), 1.58–1.46 (m, 2H), 1.17 (s, 9H), 1.00 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 193.4, 174.5, 139.2, 135.9 (4C), 134.0 (2C), 130.0 (2C), 128.6, 128.5, 128.1 (4C), 127.9, 127.7 (2C), 103.8, 83.6, 73.0, 69.8, 63.0, 43.3, 31.1, 29.6, 29.4, 27.0 (3C), 25.3, 19.4, 10.6; HRMS (ESI) calcd for $C_{35}H_{45}O_4Si$ [$(M+H)^+$] 557.3082, found 557.3086.

4.4.9. 1-Benzyloxycarbonyl-6-(3-benzyloxypropyl)-2-[3-(tert-butyldiphenylsilyloxy)propyl]-5,6-dihydro-1H-pyridin-4-one

(±)-***44***. According to **GP-3**, treatment of (±)-**35** (12.9 mg, 0.0191 mmol) with AgOTf (5.4 mg, 0.021 mmol) and 2,6-di-*tert*-butylpyridine (1.0 M solution in 1,2-dichloroethane, 0.286 mL, 0.286 mmol) in 1,2-dichloroethane (1.9 mL) at 60 °C gave the *title compound* (±)-**44** (6.5 mg, 50%) along with recovered (±)-**35** (2.8 mg, 22%). Data for (±)-**44**: IR (film) 2929, 2856, 1718, 1668, 1594, 1455, 1427, 1402, 1320, 1232, 1169 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.44–7.26 (m, 16H), 5.45 (s, 1H), 5.17 (d, J=2.4 Hz, 2H), 4.76 (m, 1H), 4.40 (d, J=3.6 Hz, 2H), 3.58–3.51 (m, 2H), 3.38–3.32 (m, 2H), 3.05 (m, 1H), 2.78 (dd, J=17.4, 6.0 Hz, 1H), 2.51 (m, 1H), 2.32 (d, J=16.8 Hz, 1H), 1.77 (m, 1H), 1.69–1.48 (m, 5H), 1.04 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.6, 158.0, 153.3, 138.3, 135.5 (2C), 135.4 (2C), 135.0, 133.6, 129.7 (2C), 128.7 (2C), 128.4 (2C), 128.3 (4C), 127.68 (2C), 127.67 (2C), 127.57, 127.56 (2C), 113.0, 72.9, 69.5, 68.7, 62.7, 56.1, 41.3, 32.4, 31.0, 27.0, 26.8 (3C), 26.5, 19.2; HRMS (ESI) calcd for $C_{42}H_{50}NO_5Si$ [$(M+H)^+$] 676.3453, found 676.3466.

4.5. Synthesis of optically active dihydropyrone derivative (+)-39

*4.5.1. (5R)-8-Benzyloxy-1-cyclohexyl-5-(4-methoxybenzyloxy)oct-1-yn-3-one (+)-**30***. According to **GP-1**, thioester (−)-**16c** (240.8 mg, 0.518 mmol) was reacted with cyclohexylacetylene (0.140 mL, 1.04 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (26.8 mg, 0.0259 mmol), (2-furyl)$_3$P (48.1 mg, 0.207 mmol), and CuI (167.8 mg, 0.881 mmol) in DMF/Et_3N (5:1, v/v, 6 mL) to give the *title compound* (+)-**30** (145.2 mg, 62%) as a brown oil: $[\alpha]_D^{23}$ +2.0 (*c* 1.00, $CHCl_3$). Other data identical to racemic compound.

*4.5.2. (6R)-6-(3-Benzyloxypropyl)-2-cyclohexyl-5,6-dihydro-4H-pyran-4-one (+)-**39***. According to **GP-2**, ynone (+)-**30** (100.9 mg, 0.220 mmol) was treated with DDQ (57.9 mg, 0.250 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 2.2 mL) to give a β-hydroxy ynone (68.1 mg, 94%). According to **GP-3**, the β-hydroxy ynone thus obtained (24.8 mg, 0.0755 mmol) was reacted with AgOTf (21.4 mg, 0.0831 mmol) in CH_2Cl_2 (1.5 mL) to give the *title compound* (+)-**39** (24.8 mg, 100%). $[\alpha]_D^{23}$ +86.8 (*c* 1.00, $CHCl_3$). Other data identical to racemic compound.

4.6. General procedure for the palladium-catalyzed coupling of thioesters and alkenylboronic acids and subsequent deprotection

Step 1: *Palladium-catalyzed coupling of thioesters with alkenylboronic acids*. General procedure (**GP-4**): A mixture of thioester (−)-**16c** (790.1 mg, 1.701 mmol), alkenylboronic acid **45** (290.2 mg, 1.884 mmol), $Pd_2(dba)_3\cdot CHCl_3$ (88.8 mg, 0.0858 mmol), (2-furyl)$_3$P (158.9 mg, 0.6844 mmol), and CuTC (509.6 mg, 2.672 mmol) in THF (10 mL) was stirred at 50 °C for 4 h. After being cooled to room temperature, the reaction mixture was diluted with diethyl ether (10 mL), washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL×2), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (5 to 11% EtOAc/hexanes) gave a β-alkoxy enone (544.9 mg), which was contaminated with some impurities and used in the next reaction without further purification.

Step 2: *Deprotection of MPM group*. General procedure (**GP-5**): To a solution of the above β-alkoxy enone (544.9 mg) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 11 mL) cooled to 0 °C was added DDQ (314.0 mg, 1.342 mmol), and the resultant mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) at 0 °C. The resultant mixture was extracted with EtOAc (30 mL), and the organic layer was washed with brine (20 mL×2), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (8–20% EtOAc/hexanes) gave β-hydroxy enone (−)-**48** (399.6 mg, 71% for the two steps) as a yellow oil.

*4.6.1. (2E,5R)-8-Benzyloxy-1-cyclohexyl-5-hydroxy-1-octen-3-one (−)-**48***. $[\alpha]_D^{25}$ −26.0 (*c* 1.00, $CHCl_3$); IR (film) 3483, 2925, 2851, 1659, 1098, 735, 697 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.30 (d, J=7.3 Hz, 2H), 7.19–7.16 (m, 2H), 7.09 (m, 1H), 6.57 (dd, J=16.1, 6.8 Hz, 1H), 5.89 (d, J=16.1 Hz, 1H), 4.32 (d, J=16.2 Hz, 1H), 4.29 (d, J=16.2 Hz, 1H), 4.10 (m, 1H), 3.36–3.32 (m, 2H), 2.40 (dd, J=17.2, 8.6 Hz, 1H), 2.31 (dd, J=17.2, 3.1 Hz, 1H), 1.83 (m, 1H), 1.75–1.68 (m, 2H), 1.56–1.47 (m, 7H), 1.08–0.96 (m, 3H), 0.89–0.83 (m, 2H), one proton missing due to H/D exchange; ^{13}C NMR (150 MHz, C_6D_6) δ 200.5, 152.3, 139.4, 128.6, 128.5 (2C), 127.8 (2C), 127.6, 72.9, 70.5, 67.7, 46.8, 40.6, 34.0, 31.8 (2C), 26.4, 26.1, 25.9 (2C); HRMS (ESI) calcd for $C_{21}H_{30}O_3Na$ [$(M+Na)^+$] 353.2087, found 353.2084.

*4.6.2. (2E,6R)-9-Benzyloxy-6-hydroxy-2-nonen-4-one (−)-**49***. According to **GP-4**, thioester (−)-**16c** (306.6 mg, 0.660 mmol) was reacted with alkenylboronic acid **46** (62.4 mg, 0.726 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (34.2 mg, 0.0330 mmol), (2-furyl)$_3$P (60.4 mg, 0.260 mmol), and CuTC (188.8 mg, 0.990 mmol) in THF (6.6 mL) to give an enone (166.0 mg). According to **GP-5**, this material was treated with DDQ (108.0 mg, 0.461 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 4 mL) to give the title compound (−)-**49** (115.6 mg, 66% for the two steps) as a yellow oil: $[\alpha]_D^{25}$ −27.4 (*c* 1.00, $CHCl_3$); IR (film) 3444, 2916, 2856, 1661, 1099, 970 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.30 (d, J=7.6 Hz, 2H), 7.19–7.16 (m, 2H), 7.09 (m, 1H), 6.35 (dq, J=15.8, 6.9 Hz, 1H), 5.80 (d, J=15.8 Hz, 1H), 4.30 (s, 2H), 4.07 (m, 1H), 3.35–3.31 (m, 2H), 2.32 (dd, J=17.2, 8.9 Hz, 1H), 2.23 (dd, J=17.2, 3.1 Hz, 1H), 1.81 (m, 1H), 1.70 (m, 1H), 1.70 (m, 1H), 1.56–1.50 (m, 2H), 1.29 (d, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 200.0, 142.6, 139.3, 132.4, 128.5 (2C), 127.8 (2C), 127.6, 73.0, 70.4, 67.7, 46.5, 34.0, 26.4, 17.7; HRMS (ESI) calcd for $C_{16}H_{22}O_3Na$ [$(M+Na)^+$] 285.1461, found 285.1457.

*4.6.3. (7E)-1-Benzyloxy-4-hydroxy-7-undecen-6-one (±)-**50***. According to **GP-4**, thioester (±)-**16c** (485.6 mg, 1.05 mmol) was reacted with alkenylboronic acid **47** (131.0 mg, 1.15 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (54.1 mg, 0.0523 mmol), (2-furyl)$_3$P (97.1 mg, 0.418 mmol), and CuTC (299.0 mg, 1.57 mmol) in THF (8.0 mL) gave an enone (298.2 mg). According to **GP-5**, this material was treated with DDQ (187.0 mg, 0.80 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 7.7 mL) to give the *title compound* (±)-**50** (168.4 mg, 55% for the two steps) as a pale yellow oil: IR (film) 3446, 3029, 2930, 2868, 1660, 1624, 1454, 1361, 1181, 1098, 977 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 7.30 (d, J=7.6 Hz, 2H), 7.21–7.17 (m, 2H), 7.09 (t, J=7.3 Hz, 1H), 6.50 (m, 1H), 5.87 (d, J=15.8 Hz, 1H), 4.31 (s, 2H), 4.09 (m, 1H), 3.77 (s, 3H), 3.49 (br s, 1H), 3.37–3.30 (m, 2H), 2.40 (dd, J=17.2, 8.9 Hz, 1H), 2.28 (dd, J=17.2, 3.1 Hz, 1H), 1.82 (m, 1H), 1.59–1.48 (m, 2H), 1.16–1.10 (m, 2H), 0.69 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 200.1, 147.3, 139.4, 131.1, 128.5 (2C), 128.3, 127.7 (2C), 72.9, 70.5, 67.7, 46.7, 34.4, 34.0, 26.4, 21.4, 13.7; HRMS (ESI) calcd for $C_{18}H_{26}O_3Na$ [$(M+Na)^+$] 313.1774, found 313.1762.

*4.6.4. (4E)-1-Cyclohexyl-1-hydroxy-4-octen-3-one (±)-**51***. According to **GP-4**, thioester (±)-**19** (188.1 mg, 0.454 mmol) was reacted with alkenylboronic acid **47** (56.9 mg, 0.499 mmol) in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (23.5 mg, 0.0227 mmol), (2-furyl)$_3$P (42.1 mg, 0.181 mmol), and CuTC (129.8 mg, 0.68 mmol) in THF (2.5 mL) gave an enone (115.2 mg). According to **GP-5**, this material was treated with DDQ (86.1 mg, 0.368 mmol) in CH_2Cl_2/pH 7 buffer (10:1, v/v, 3.3 mL) to give the *title compound* (±)-**51** (58.5 mg, 64% for the two steps) as a pale yellow oil: IR (film) 3475, 2926, 2852, 1660, 1625, 1449, 1309, 1187, 1085, 1041, 977 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.59 (dt, J=15.8, 6.8 Hz, 1H), 5.92 (d, J=15.8 Hz, 1H), 3.86 (m, 1H), 3.36 (br s, 1H), 2.45 (dd, J=16.8, 9.2 Hz, 1H), 2.37 (dd, J=16.8, 2.8 Hz, 1H), 1.90 (m, 1H), 1.79–1.67 (m, 4H), 1.63–1.57 (m, 2H), 1.29 (m, 1H),

1.19–1.04 (m, 7H), 0.71 (t, J=7.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 200.7, 147.2, 131.1, 71.8, 43.9, 43.6, 34.4, 29.4, 28.4, 26.9, 26.7, 26.6, 21.4, 13.7; HRMS (ESI) calcd for $C_{14}H_{24}O_2Na$ [(M+Na)$^+$] 247.1669, found 247.1667.

4.7. General procedure for 6-*endo-trig* cyclization of β-hydroxy enones

General procedure (**GP-6**): To a solution of β-hydroxy enone (−)-**48** (26.9 mg, 81.4 μmol) in CH_2Cl_2 (1.6 mL) was added AgOTf (23.7 mg, 92.2 μmol), and the resultant mixture was stirred at room temperature for 13 h under exclusion of light. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL×2). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (6–10% EtOAc/hexanes) gave tetrahydropyrone (+)-**52** (25.2 mg, 94%) as a yellow oil. The optical purity of the synthesized material was determined to be 81% ee by chiral HPLC analysis [column: CHIRALPAK AD-H (4.6×250 mm); eluent: 0.7% *i*-PrOH/*n*-hexane; flow rate: 1.0 mL/min; column temperature: 30.0 °C; major peak: t_1=19.0 min; minor peak: t_2=21.3 min].

*4.7.1. (2R,6R)-6-(3-Benzyloxy)-2-cyclohexyltetrahydro-4H-pyran-4-one (+)-**52**.* $[\alpha]_D^{24}$ +3.6 (*c* 1.00, $CHCl_3$); IR (film) 2925, 2851, 1716, 736, 697 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.29–7.28 (m, 2H), 7.20–7.15 (m, 2H), 7.10 (t, J=7.2 Hz, 1H), 4.33 (d, J=12.7 Hz, 1H), 4.30 (d, J=12.7 Hz, 1H), 3.27–3.24 (m, 2H), 3.14 (m, 1H), 2.91 (ddd, J=11.7, 6.2, 2.4 Hz, 1H), 2.20–2.13 (m, 2H), 1.91–1.82 (m, 2H), 1.73 (m, 1H), 1.65–1.53 (m, 5H), 1.42–1.22 (m, 4H), 1.11–1.04 (m, 3H), 0.91–0.80 (m, 2H); ^{13}C NMR (150 MHz, C_6D_6) δ 205.6, 139.3, 128.5 (2C), 127.7 (2C), 127.6, 81.0, 76.7, 73.0, 70.1, 48.2, 45.2, 43.3, 33.4, 28.7, 28.6, 26.8, 26.3 (2C), 26.2; HRMS (ESI) calcd for $C_{21}H_{30}O_3Na$ [(M+Na)$^+$] 353.2087, found 353.2078.

*4.7.2. (2R,6S)-2-(3-Benzyloxypropyl)-6-methyltetrahydro-4H-pyran-4-one (+)-**53**.* According to **GP-6**, treatment of β-hydroxy enone (−)-**49** (26.5 mg, 0.101 mmol) with AgOTf (28.5 mg, 0.111 mmol) in CH_2Cl_2 (2 mL) gave the title compound (+)-**53** (23.7 mg, 89%) as a 3:1 mixture of *cis*/*trans* isomers. Data for the major 2,6-*cis* isomer: $[\alpha]_D^{24}$ +0.72 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2856, 1719, 1094, 736, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 4.49 (d, J=12.6 Hz, 1H), 4.47 (d, J=12.6 Hz, 1H), 3.67 (m, 1H), 3.55 (m, 1H), 3.51–3.45 (m, 2H), 2.35–2.31 (m, 2H), 2.21 (dd, J=12.0, 3.0 Hz, 1H), 2.18 (dd, J=12.0, 3.0 Hz, 1H), 1.81–1.59 (m, 4H), 1.29 (d, J=6.0 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 207.5, 138.4, 128.3 (2C), 127.6 (2C), 127.5, 76.7, 73.1, 72.9, 69.9, 49.4, 47.5, 33.1, 25.7, 22.0; HRMS (ESI) calcd for $C_{16}H_{22}O_3Na$ [(M+Na)$^+$] 285.1461, found 285.1462. The optical purity of this material was determined to be 92% ee by chiral HPLC analysis [column: CHIRALCEL OD-H (4.6×250 mm); eluent: 1.0% *i*-PrOH/*n*-hexane; flow rate: 1.0 mL/min; column temperature: 30.0 °C; major peak: t_1=41.3 min; minor peak: t_2=50.9 min].

*4.7.3. (2R′,6S′)-2-(3-Benzyloxypropyl)-6-propyltetrahydro-4H-pyran-4-one (±)-**54**.* According to **GP-6**, treatment of β-hydroxy enone (±)-**50** (79.6 mg, 0.274 mmol) with AgOTf (14.1 mg, 0.0548 mmol) in CH_2Cl_2 (5.5 mL) gave the *title compound* (±)-**54** (68.7 mg, 87%) as a 10:1 mixture of *cis*/*trans* isomers. Data for the major product (2,6-*cis* isomer): IR (film) 3029, 2957, 2931, 2855, 2358, 1718, 1455, 1361, 1326, 1259, 1098 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6) δ 7.27 (d, J=7.9 Hz, 2H), 7.18 (t, J=7.6 Hz, 2H), 7.09 (t, J=7.2 Hz, 1H), 4.31 (s, 2H), 3.28–3.23 (m, 2H), 3.14–3.07 (m, 2H), 2.13–2.08 (m, 2H), 1.83–1.78 (m, 2H), 1.71 (m, 1H), 1.58–1.47 (m, 2H), 1.41–1.30 (m, 3H), 1.18 (m, 1H), 1.09 (m, 1H), 0.78 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 205.2, 139.3, 128.5 (2C), 128.3, 127.7 (2C), 127.6, 76.7, 76.6, 72.9, 70.1, 48.0, 38.7, 33.4, 26.1, 18.8, 14.1; HRMS (ESI) calcd for $C_{18}H_{26}O_3Na$ [(M+Na)$^+$] 313.1774, found 313.1770.

*4.7.4. (2S′,6S′)-2-Cyclohexyl-6-propyltetrahydro-4H-pyran-4-one (±)-**55**.* According to **GP-6**, treatment of β-hydroxy enone (±)-**51** (22.0 mg, 0.0981 mmol) with AgOTf (5.0 mg, 0.020 mmol) in CH_2Cl_2 (2.0 mL) gave the *title compound* (±)-**55** (22.0 mg, 100%) as a 3:1 mixture of *cis*/*trans* isomers. Data for the major product (2,6-*cis* isomer): IR (film) 2926, 2853, 1719, 1450, 1324, 1270, 1159, 1064, 845 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.47 (m, 1H), 3.23 (ddd, J=6.8, 2.4, 2.4 Hz, 1H), 2.35 (dd, J=14.0, 2.1 Hz, 1H), 2.31 (dd, J=14.0, 2.1 Hz, 1H), 2.23–2.15 (m, 2H), 1.96 (dd, J=13.0, 1.7 Hz, 1H), 1.66–1.58 (m, 4H), 1.53–1.30 (m, 4H), 1.25–1.08 (m, 4H), 0.97 (dt, J=8.9, 2.1 Hz, 2H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.6, 81.2, 75.7, 72.3, 48.3, 45.4, 43.2, 38.5, 28.9, 28.4, 26.4, 26.0, 18.7, 13.9; HRMS (ESI) calcd for $C_{14}H_{24}O_2Na$ [(M+Na)$^+$] 247.1669, found 247.1672.

4.8. General procedure for stereoselective hydrogenation of dihydropyrones

General procedure (**GP-7**): To a solution of dihydropyrone (+)-**39** (5.8 mg, 17.7 μmol) and Et_3N (11.6 μL) in EtOAc (0.708 μL) was added 10% Pd/C (4.7 mg), and the resultant mixture was stirred at room temperature for 14.5 h under an atmosphere of hydrogen (balloon). After completion of the reaction, the whole mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10% EtOAc/hexanes) gave tetrahydropyrone (+)-**52** (5.3 mg, 91%) as a yellow oil. The optical purity was determined to be 98% ee by chiral HPLC analysis [column: CHIRALPAK AD-H (4.6×250 mm); eluent: 0.7% *i*-PrOH/*n*-hexane; flow rate: 1.0 mL/min; column temperature: 30.0 °C; major peak: t_1=19.0 min; minor peak: t_2=21.3 min]. $[\alpha]_D^{23}$ +3.7 (*c* 0.53, $CHCl_3$). Other data identical to the compound prepared above (see Section 4.7.1).

*4.8.1. (2R′,6S′)-2-(3-Benzyloxypropyl)-6-butyltetrahydro-4H-pyran-4-one (±)-**56**.* According to **GP-7**, dihydropyrone (±)-**36** (7.2 mg, 0.024 mmol) was hydrogenated over 10% Pd/C (2.9 mg) in the presence of Et_3N (0.007 mL) in EtOH (0.48 mL) to give the *title compound* (±)-**56** (6.9 mg, 95%) as a colorless oil: IR (film) 2930, 2856, 1716, 1101, 739, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.30 (m, 4H), 7.26 (m, 1H), 4.50 (d, J=12.0 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 3.54–3.45 (m, 4H), 2.35–2.31 (m, 2H), 2.22–2.16 (m, 2H), 1.18 (m, 1H), 1.71–1.59 (m, 4H), 1.50–1.40 (m, 2H), 1.34–1.26 (m, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 138.4, 128.4 (2C), 127.63 (2C), 127.56, 77.0, 76.7, 72.9, 69.9, 48.0 (2C), 36.1, 33.1, 27.5, 25.8, 22.5, 14.0; HRMS (ESI) calcd for $C_{19}H_{28}O_3Na$ [(M+Na)$^+$] 327.1931, found 327.1931.

*4.8.2. (2R′,6S′)-2-(3-Benzyloxypropyl)-6-[3-(tert-butyldiphenylsilyloxy)propyl]tetrahydro-4H-pyran-4-one (±)-**57**.* According to **GP-7**, dihydropyrone (±)-**37** (3.0 mg, 0.0055 mmol) was hydrogenated over 10% Pd/C (2.4 mg) in the presence of Et_3N (0.006 mL) in EtOAc (0.55 mL) to give the *title compound* (±)-**57** (3.0 mg, 100%) as a colorless oil: IR (film): 2927, 2856, 1717, 1111, 701 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.64–7.62 (m, 3H), 7.41–7.25 (m, 11H), 4.48 (d, J=12.0 Hz, 1H), 4.46 (d, J=12.0 Hz, 1H), 3.66–3.64 (m, 2H), 3.48–3.43 (m, 4H), 2.33–2.29 (m, 2H), 2.20–2.15 (m, 2H), 1.78–1.57 (m, 8H), 1.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 135.5 (4C), 134.8 (2C), 133.9, 129.6 (2C), 128.4 (2C), 127.7, 127.63 (5C), 127.56, 76.7, 76.6, 72.9, 69.9, 63.4, 47.98, 47.95, 33.1, 32.7, 28.4, 26.9 (3C), 26.5, 25.8; HRMS (ESI) calcd for $C_{34}H_{44}O_4SiNa$ [(M+Na)$^+$] 567.2901, found 567.2918.

*4.8.3. (2R′,6R′)-2-(3-Benzyloxypropyl)-6-phenyltetrahydro-4H-pyran-4-one (±)-**58**.* According to **GP-7**, dihydropyrone (±)-**38** (4.4 mg, 0.014 mmol) was hydrogenated over 10% Pd/C (3.5 mg) in the presence of Et_3N (0.009 mL) in EtOH (0.55 mL) to give the *title compound* (±)-**58** (2.3 mg, 52%) as a colorless oil: IR (film) 2923, 1715, 1456, 945, 748, 548 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (m, 1H), 7.40–7.25 (m, 9H), 4.60 (dd, J=11.4, 3.0 Hz, 1H), 4.48 (d, J=12.0 Hz, 1H), 4.47 (d, J=12.0 Hz,

1H), 3.76 (m, 1H), 3.51–3.48 (m, 2H), 2.62 (dd, *J*=14.4, 3.0 Hz, 1H), 2.52 (dd, *J*=14.4, 12.0 Hz, 1H), 2.45 (dd, *J*=14.4, 2.4 Hz, 1H), 2.36 (dd, *J*=14.4, 11.4 Hz, 1H), 1.87–1.78 (m, 2H), 1.77–1.70 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 134.8, 128.6 (2C), 128.4 (2C), 127.9, 127.7, 127.64 (2C), 127.57, 125.6 (2C), 78.5, 77.0, 72.9, 69.9, 49.5, 47.7, 33.1, 25.6; HRMS (ESI) calcd for $C_{21}H_{24}O_3Na$ [$(M+Na)^+$] 347.1618, found 347.1619.

*4.8.4. (2R′,6R′)-2-(2-Benzyloxy-1,1-dimethylethyl)-6-(3-benzyloxypropyl)tetrahydro-4H-pyran-4-one (±)-**59**.* According to **GP-7**, dihydropyrone (±)-**40** (40.4 mg, 0.099 mmol) was hydrogenated over 10% Pd/C (8.1 mg) in the presence of Et_3N (0.020 mL) in EtOAc (1.0 mL) to give the *title compound* (±)-**59** (39.0 mg, 96%) as a colorless oil: IR (film) 2960, 2855, 1717, 1099, 737, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.23 (m, 10H), 4.48 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=15.0 Hz, 1H), 4.44 (d, *J*=15.0 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 3.53–3.44 (m, 4H), 3.33 (d, *J*=9.0 Hz, 1H), 3.19 (d, *J*=8.4 Hz, 1H), 2.32–2.30 (m, 3H), 2.16 (dd, *J*=13.8, 11.4 Hz, 1H), 1.79 (m, 1H), 1.66–1.57 (m, 3H), 0.95 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 208.8, 138.6, 138.4, 128.4 (2C), 128.3 (2C), 127.63 (2C), 127.55, 125.4, 127.3 (2C), 80.1, 76.5, 76.4, 73.2, 72.9, 69.9, 45.0, 42.5, 38.6, 33.0, 25.7, 21.0, 20.2; HRMS (ESI) calcd for $C_{26}H_{34}O_4Na$ [$(M+Na)^+$] 433.2349, found 433.2348.

*4.8.5. (2S′,6S′)-2-[3-(tert-Butyldiphenylsilyloxy)propyl]-6-cyclohexyltetrahydro-4H-pyran-4-one (±)-**60**.* According to **GP-7**, dihydropyrone (±)-**41** (8.1 mg, 0.017 mmol) was hydrogenated over 10% Pd/C (6.5 mg) in the presence of Et_3N (0.016 mL) in EtOAc (0.60 mL) to give the *title compound* (±)-**60** (7.8 mg, 96%) as a colorless oil: IR (film) 2929, 2855, 1715, 1111, 706 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64–7.63 (m, 4H), 7.42–7.34 (m, 6H), 3.68–3.65 (m, 2H), 3.43 (m, 1H), 3.17 (ddd, *J*=11.4, 6.6, 2.4 Hz, 1H), 2.36–2.82 (m, 2H), 2.19 (dd, *J*=11.4, 3.6 Hz, 1H), 2.16 (dd, *J*=11.4, 3.6 Hz, 1H), 1.93 (m, 1H), 1.76–1.58 (m, 8H), 1.42 (m, 1H), 1.23–1.08 (m, 3H), 1.03 (s, 9H), 0.99–0.90 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 135.5 (4C), 133.9 (2C), 129.6 (2C), 127.6 (4C), 81.1, 76.6, 63.4, 48.2, 45.4, 43.2, 32.7, 28.8, 28.4 (2C), 26.9 (3C), 26.4, 26.0, 25.9, 19.2; HRMS (ESI) calcd for $C_{30}H_{42}O_3Na$ [$(M+Na)^+$] 501.2795, found 501.2793.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.114.

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