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Two-Directional Elaboration of Hydroxyacetone under Thermodynamically Controlled Conditions: Allylation or 2-Propynylation and Aldol Reaction

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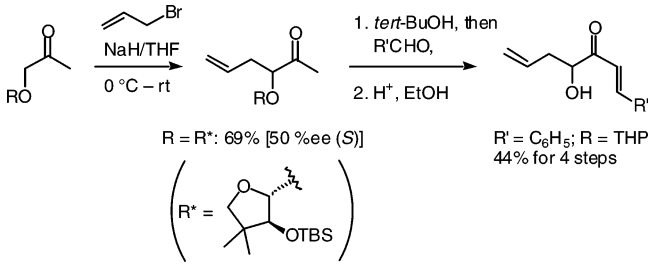

Enolate generated from *O*-(tetrahydropyran-2-yl)hydroxyacetone under thermodynamically controlled conditions (1.3 equiv of NaH, THF, 0 °C to rt) was allylated at the carbon bearing the protected hydroxy group with very high regioselectively. When *tert*-BuOH, equivalent to the excessive portion of initially added NaH, was introduced into the mixture followed by addition of aldehyde, aldol reaction took place on the methyl group to give 1-substituted 4-hydroxy-(1*E*),6-heptadien-3-one in acceptable yields after acidic treatment of the mixture for dehydration and deprotection. Introducing a chiral auxiliary protecting group into hydroxyacetone led to asymmetric allylation though stereoselectivity was around 50 % ee. Thus, the hidden aspect of the chemoselective nature of protected hydroxyacetone-derived enolate generated under thermodynamically controlled conditions has opened a new avenue for two-directional elaboration of hydroxyacetone that should be potentially useful in organic synthesis.

Introduction

Since domino processes deserve consideration in terms of synthetic efficiency, environmental benignity, or, more importantly, reaction processing, a great deal of efforts have been paid for developing such processes.[1] In accordance with this issue, we have been involved in developing domino processes such as Michael addition and Claisen reactions leading to a variety of cyclohexane-1,3-dione derivatives.[2] In this transformation employing equilibrated enolates produced from unsymmetrical simple ketones (*tert*-BuOK, THF, 0 °C to rt) we recognized that the more substituted enolates served as a Michael donor attacking α,β-unsaturated esters as illustrated in Scheme 1 for isopropyl methyl ketone as a representative case. Additionally, in separate experiments the less substituted enolate reacted with aldehydes or esters again in a highly regioselective manner to give α,β-unsaturated ketone or 1,3-diketone (Scheme 1).[2]

Since then we have been intrigued by the potential of regioselective functionalization of simple unsymmetrical ketones as an efficient synthetic method under thermodynamically controlled conditions. Eventually, we found that hydroxyacetone can lead to ketones bearing 1-hydroxy-3-butenyl (or 3-butynyl) segments in one side and 2-substituted ethenyl segments in the other via sequential allylation (or propargylation) and aldol condensation[3] as illustrated in Scheme 2. We also found that these processes could be performed as one-pot transformations if so desired and the former processes as asymmetric allylations.

(1) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCE: Weinheim, Germany, 2000; pp 39−64. See also: Pellissier, H. *Tetrahedron* **2006**, *62*, 1619−1665 and 2143−2173.

(2) (a) Ishikawa, T.; Kadoya, R.; Arai, M.; Takahashi, H.; Kaishi, Y.; Mizuta, T.; Yoshikai, K.; Saito, S. *J. Org. Chem.* **2001**, *66*, 8000−8009. See also: Ishikawa, T.; Miyahara, T.; Asakura, M.; Higuchi, S.; Miyauchi, Y.; Saito, S. *Org. Lett.* **2005**, *7*, 1211−121. We succeeded in achieving domino processes leading to benzofurans from cyclohexane-1,3-diones in one pot in which 13 elementary processes were operating.

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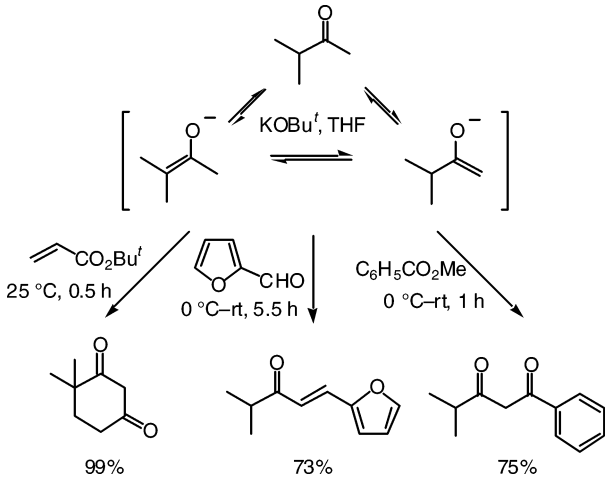
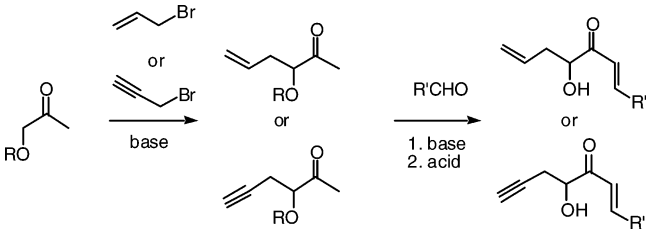
SCHEME 1. Observed Chemoselective Aspect of Ketone Enolate Generated under Thermodynamically Controlled Conditions



SCHEME 2



Four representative strategies have been available for synthesizing hydroxyacetone derivatives which involve direct oxidations of enolates or enol ethers,[4] reactions of enamines or enolates with nitroso compounds,[5] aldol reactions of hydroxyacetones,[6] and traditional acyloin ester condensation.[7] However, by inspection of the literature pertinent to this field it turned out that regioselective allylation (or propargylation) of prototype hydroxyacetones under thermodynamically controlled conditions has no precedence. Here we will disclose the first example of regioselective allylation (or propargylation) of the hydroxyacetone enolates on the oxygen-centered carbon followed by aldol reaction on the methyl carbon under thermodynamically controlled conditions.

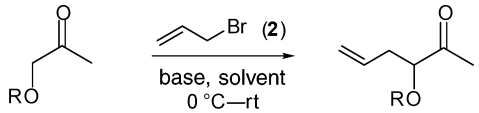
(3) Since domino reactions are defined as processes of making two or more bonds in which the subsequent reactions take place at the functionalities obtained in the former step, the processes presented in this work are not necessarily the domino processes. For the definition of the domino processes, see ref 1.

(4) For review, see: Jones, A. B. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, Chapter 2.3.

(5) For review, see: Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995−2997.

(6) For recent examples, see: (a) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R.; Barbas, C. F., III *J. Am. Chem. Soc.* **1998**, *120*, 2768−2779. (b) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. *Chem. Eur. J.* **1998**, *4*, 881−885. (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. (d) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467. (e) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368. (f) Tang, Z.; Yang, Z.-H.; Cun, L.-Z.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285−2287. Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331−3333. For reviews, see: (g) Hassner, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 2.4. (h) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.

TABLE 1. Preliminary Experiments for Allylation of 1a



1a: R = THP
1b: Bn
1c: TBS

3a: R = THP
3b: R = Bn

entry	**1**	allyl−Br equiv	base (equiv)	solvent	product: yield %[a]
1	1a	1.2	NaH (1.1)	THF	**3a**: 35 (50)
2	1a	1.2	NaH (1.1)	THF/DMF[b]	**3a**: 12
3	1a	1.5	NaH (1.1)	THF/DMSO[b]	**3a**: 37
4	1a	2.0	NaH (1.3)	THF	**3a**: 52 (62)
5	1a	2.0	*t*-BuOK (1.3)	THF	**3a**: 61
6[c]	1a	2.0	LDA (1.1)	THF	
7	1b	2.0	NaH (1.3)	THF	**3b**: 53
8	1c	2.0	NaH (1.3)	THF	

[a] For isolated products, yields in parentheses are corrected for recovered **1a**. [b] 1:1 ratio. [c] LDA was prepared at −78 °C: alkylation was conducted at 0 °C to rt.

Results and Discussion

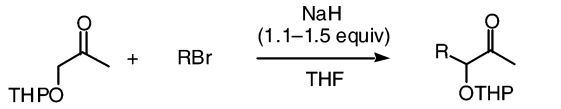
Two-Directional Elaboration of Hydroxyacetone. Alkylation of enolates generated from simple dissymmetric ketones under thermodynamically controlled conditions is difficult to control in terms of the regiochemistry of the alkylation when the ketones bear methyl and methylene groups or methylene groups at both sides of the carbonyl group. Furthermore, these carbons can be dialkylated if alkylating agent and base are employed in an excessive amount. Hydroxyacetone (**1a**) is not an exceptional molecule in that context, and we thought that **1a** may fall into such a category. Contrary to this negative assumption, however, the unexpected allylation of *O*-(tetrahydropyran-2-yl)hydroxyacetone (**1a**) was realized in a preliminary experiment as shown in Table 1 (entry 1). Thus, treatment of a mixture of **1a** and allyl bromide (**2a**, 1.2 equiv) in THF with sodium hydride (NaH, 1.1 equiv) at 0 °C to rt furnished *O*-(tetrahydropyran-2-yl)-2-oxo-5-hexen-3-ol (**3a**) in 35% yield (50%, corrected for recovered **1a**, entry 1) although accompanied by highly polar, unidentifiable byproducts. Closer inspection paying strong attention to finding the regioisomeric allylation product was in vain. These results clearly indicated for the first time that the allylation reaction of this class proceeded at the carbon bearing the protected hydroxy group with very high regioselectivity (>99%).

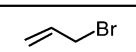
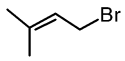
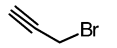
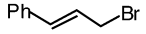
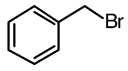
When the amounts of both bases (NaH) and allyl bromide were increased (1.3 and 2.0 equiv, respectively), a much better yield as 52% (62% corrected for recovered **1a**, entry 4) resulted, although undesired polyalkylation or formation of regioisomers was expected. Alkoxide base such as potassium *tert*-butoxide (*tert*-BuOK, 1.3 equiv) led to almost the same yield of **3a** (entry 5).

Although a possible Williamson process between the base and reactive allyl bromide employed in a 1.3:2.0 ratio was considered to be unavoidable, the desired allylation indeed

(7) (a) Freund, A. *Justus Liebigs Ann. Chem.* **1861**, *118*, 33−34. (b) McElvain, *Org. React.* **1948**, *4*, 256−268. (c) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259−403. (d) Finley, K. T. *Chem. Rev.* **1964**, *64*, 573−589. (e) Rühlmann, K. *Synthesis* **1971**, 236−253. (f) Cram, D. J.; Antar, M. F. *J. Am. Chem. Soc.* **1958**, *80*, 3109−3114. (g) Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433−4434. (h) Sauvage, J.-P. *Acc. Chem. Res.* **1990**, *23*, 319−327.

TABLE 2. Regioselective Allylation and Propargylation of (2-Tetrahydropyranyl)oxyacetone



entry	RBr: **2** (equiv)	NaH equiv.	Time (h)	**3**: yield% (conv)
1	 : **2a** (2.0)	1.3	15	**3a** 62% (84%)
2	 : **2b** (1.2)	1.1	12	**4** 67% (96%)
3	 : **2c** (1.2)	1.2	12	**5** 62% (82%)
4	 : **2d** (1.2)	1.1	12	**6** 64% (86%)
5	 : **2e** (2.5)	1.5	17	**7** 66% (81%)

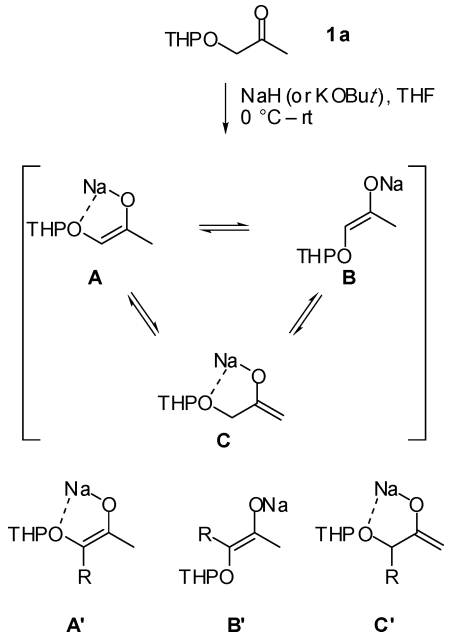
proceeded. No significant improvement in chemical yields was attained when changing solvent (THF) to mixed solvent systems such as THF−DMF (entry 2) or THF−DMSO (entry 3) and protecting group to a benzyl group (**1b**, entry 7). It should be mentioned that the reaction was deteriorated to only result in decomposition of **1c** and formation of highly polar unidentifiable mixtures for LDA as a base (entry 6).[8] Such was also the case for a TBDMS protecting group (**1c**, entry 8).[9] On the basis of these preliminary results we decided to use the NaH/THF system for allylation of protected hydroxyacetone in this work.

In Table 2 are summarized the results for allylations of **1a** with other allylic bromides plus benzyl bromide and 2-propynyl bromide (NaH in THF, 0 °C to rt). Almost the same level of chemical yields as that for the prototype allylic bromide (entry 1) resulted for those electrophiles. Very careful diagnosis of the products (**3a**, **4**−**7**) by means of NMR spectroscopy in terms of the site of carbon−carbon bond formation revealed that an extremely high level of regioselectivity was again achieved.

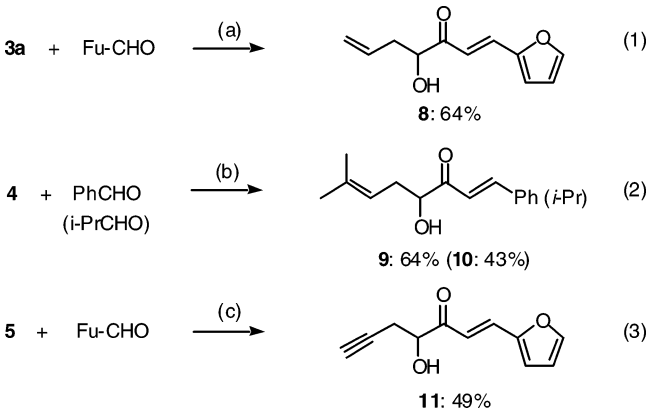
Since the protected hydroxyacetone **1a** is considered to surely lead to thermodynamically controlled enolates under the given reaction conditions (NaH or *tert*-BuOK, THF, 0 °C to rt), the cause of the observed regiochemical outcome should be ascribed to the intrinsic reactivity difference between the two types of enolates **A** (or **B**) and **C** (Scheme 3) toward electrophiles. In addition to this interesting aspects of the reaction, **3a** provided the additional significant result that only type-**C'** enolates react with furfural on treatment of **3a** with *tert*-BuOK (20 mol %) in THF in the presence of the aldehyde (1.5 equiv) to give **8** in 64% yield after acidic treatment with complete reverse regioselectivity (Scheme 4). Acyloins **4** or **5** also gave aldol condensation products **9**−**11** exclusively on treatment with base in the presence of aldehydes such as benzaldehyde, 2-methylpropanal, or furfural (Scheme 4). These facts clearly indicate the generality of the regioselective aldol reaction of this class taking place on less substituted acyloin enolate even if the enolate is equilibrated with the more substituted one.

The two processes indicated in Table 1 and Scheme 4 can be conducted in one pot. For instance, after treating **1a** in THF with NaH (1.3 equiv) in the presence of prenyl bromide (1.2 equiv) (18 h, rt), *tert*-BuOH (0.3 equiv, corresponding to the excessive portion of NaH employed initially) was added to the mixture followed by addition of benzaldehyde (2.0 equiv), and the resulting mixture was stirred at rt for 13 h. Then 2 N HCl (aqueous solution, 2 equiv) was added to the mixture for dehydration and deprotection (rt, 12 h) to give **9** in 44% yield based on **1a**. Since the whole process consists of four individual

SCHEME 3



SCHEME 4[a]

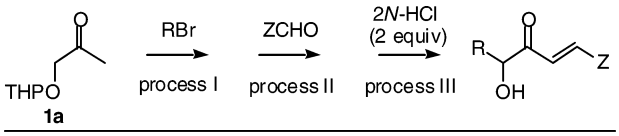


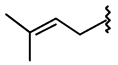
[a] Conditions: (a) (1) *tert*-BuOK (20 mol %), THF, 0 °C, 5 min, then Fu-CHO (1.5 equiv), 0 °C, 1 h, (2) TsOH (0.1 equiv), EtOH, rt, 5 h. (b) (1) *tert*-BuOK (20 mol %), THF, 0 °C, 5 min, then PhCHO or *i*-PrCHO (1.5 equiv), 0 °C, 1.5 h, (2) TsOH (0.1 equiv), EtOH, rt, 5 h. (c) (1) *tert*-BuOK (20 mol %), THF, 0 °C, 5 min, then Fu-CHO (1.5 equiv), 0 °C, 1.5 h, (2) TsOH (0.1 equiv), EtOH, rt, 17 h.

(8) It was reported that when LDA was employed for generating chiral enolates from *N*-(benzyloxyacetyl)- or *N*-(*tert*-butyldimethylsilyloxyacetyl)-oxazolidinone followed by addition of neryl bromide, no alkylation proceeded at all for the TBDMS-protection case and only 20% yield of alkylated product was obtained for the benzyl-protection case. However, when other chiral auxiliary such as (−)-ephedrine-derived imidazolidinone was employed, its *N*-(benzyloxyacetyl) derivative led to 49% yield of alkylated product (LDA, neryl bromide), see: Cardillo, G.; Orena, M.; Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501−1508.

(9) As indicated in ref 8, Evans substrate such as *N*-(*tert*-butyldimethylsilyloxyacetyl)oxazolidinone did not lead to any alkylation product at all (LDA, neryl bromide, THF). Our observation for **1c** similar to that previous case may be ascribed to the same cause, which is not completely clear at present. We must await future systematic studies for elucidating the exact nature of the hydroxyacetone enolates concerned.

TABLE 3. One-Pot Two-Directional Elaboraton of 1a



entry	R:	time (h): process I	II	III	Z:	yield%
1[a]		18	13	12	Ph	**9** 44%
2[b]		18	16	20		**12** 33%
3[c]		18	15	12	Ph	**13** 40%
4[d]		16	6	14	Ph	**14** 32%

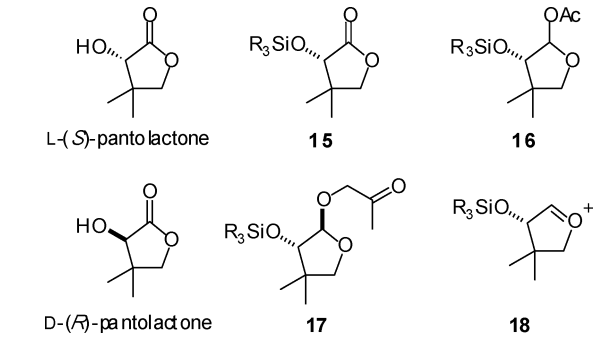
[a] RBr (1.2 equiv), NaH (1.3 equiv), THF, *t*-BuOH (0.6 equiv), ZCHO (2.0 equiv). [b] RBr (2.0 equiv), NaH (1.3 equiv), THF, *t*-BuOH (0.3 equiv), ZCHO (2.0 equiv). [c] RBr (2.0 equiv), NaH (1.3 equiv), THF, *t*-BuOH (0.3 equiv), ZCHO (2.0 equiv). [d] RBr (1.2 equiv), NaH (1.2 equiv), THF, *t*-BuOH (0.2 equiv), ZCHO (2.0 equiv).

reactions such as allylation, aldol reaction, dehydration, and deprotection, the average chemical yield for each step can be estimated to be ca. 82%. Other results pertinent to this two-directional elaboration of **1a** in one pot are summarized in Table 3. The one-pot process required much longer for the aldol reaction (6−16 h, Table 3), whereas 1−1.5 h was enough for the separate experiments (Scheme 4). This is probably because most of the generated *tert*-BuONa by addition of *tert*-BuOH can be used as a nucleophile in Williamson ether synthesis with unchanged halides during process II.

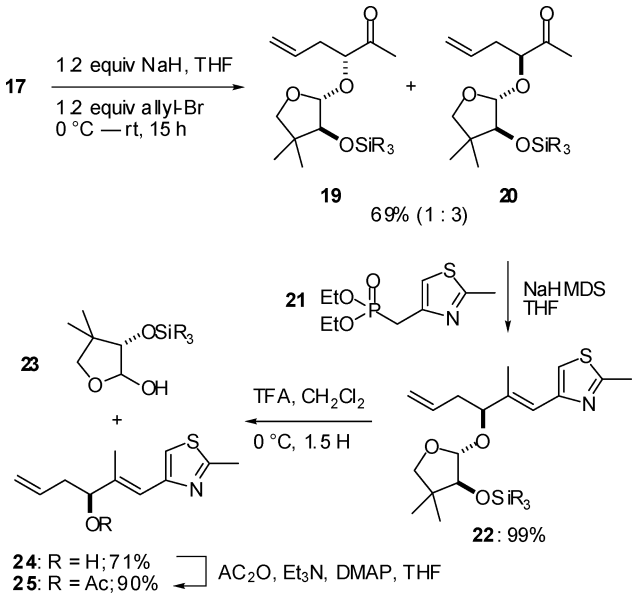
Thus, two-directional chain synthesis of simple acyloins such as **1a** has been realized by means of unveiled chemoselective nature of acyloin-based enolates generated under thermodynamically controlled conditions. It may make sense that generation of enolates under kinetically controlled conditions including amide bases at −78 °C is not necessarily needed when we contemplate bringing about aldol reaction at terminal methyl groups of acyloin derivatives. This outcome is quite consistent with the previous results outlined in Scheme 1.

Asymmetric Allylation: Preliminary Results. The regioselective construction of allylated acyloin frameworks shown so far is concerned with introduction of oxygen-centered stereogenic carbons. To realize asymmetric allylation reactions of prototype acyloin, replacement of the THP protecting group in **1a** with an appropriate chiral auxiliary capable of performing its easy introduction and recycling may be desirable. This idea led us to develop pantolactone-based acetal-type chiral auxiliary as depicted in Chart 1. Each enantiomer of pantolactone is commercially available, and the (*S*)-isomer, for example, was converted to **16** (63% in three steps) by DIBAL-H reduction (toluene, −78 °C) after protecting the hydroxy group with a *tert*-butyldiphenylsilyl group (TBDPSCl, imidazole, THF, **15**) followed by acetylation (Ac_2O, Et_3N, DMAP, THF). A mixture of **16** and hydroxyacetone in CH_2Cl_2 in the presence of Lewis acid such as BF_3•OEt_2 (−50 °C, 1 h to 0 °C, 3 h) exclusively gave substrate **17** (72%) ready for examining asymmetric allylation. Nucleophilic attack of hydroxyacetone biased by the neighboring TBDPSO-centered stereogenic center may probably take place from the convex face of intermediate **18** produced through Lewis-acid-promoted deacetoxylation.

CHART 1



SCHEME 5



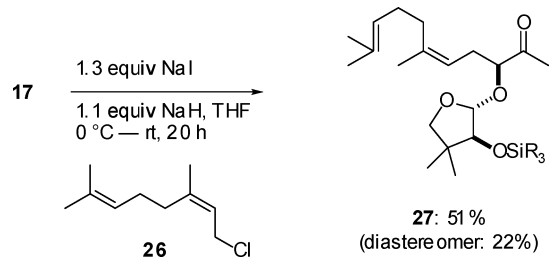
In Scheme 5 is summarized the reaction of **17** with allyl bromide under the reaction conditions developed in this work (2.0 equiv of NaH, THF, 2.0 equiv of CH_2═$CHCH_2Br$, 0 °C to rt) to give a mixture of diastereoisomers (**19** and **20**, 69% in a ratio of 1:3), which were able to be separated by column chromatography over silica gel. In order to confirm absolute configurations for newly developed stereogenic centers, the major component **20** was correlated with known derivatives **24** or **25**. Wadsworth−Emmons reaction of **20** with diethyl thiazolylmethylphosphonate **21**[10] (NaHDMS, THF) gave the (*E*)-trisubstituted olefin derivative (**22**) in quantitative yield (99%), which was treated with trifluoroacetic acid in CH_2Cl_2 at 0 °C for 1.5 h to afford **24** (71%) with $[\alpha]_D$ −18.6 (*c* 1.0) together with recovered chiral auxiliary (**23**, 33%)[11] for recycling: the

(10) Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996**, *2*, 1477−1482.

(11) Acid-promoted dehydrative dimerization of liberated **23** took place under the given reaction conditions (CF_3CO_2H, CH_2Cl_2, 0 °C) to give bis-[(2*S*,3*S*)-3-*tert*-butyldiphenylsiloxy-4,4-dimethyl]oxolan-2-yl ether. We are now trying to convert this dimer (hemiacetal anhydride) to **23**.

(12) (a) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974−7991. (b) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073−10092. (c) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523−524. (d) Schinzer, D.; Bauer, A.; Böhm, O. M.; Limherg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483−2491. (e) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529−2547.

SCHEME 6



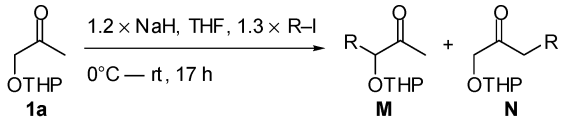
sign of the optical rotation of **24** was the same as that reported for **24**.[12] Routine acetylation of **24** gave the corresponding acetate (**25**, 90%) exhibiting $[\alpha]_D$ −41.8 (*c* 1.1), which is fully consistent with that reported.[12b]

The asymmetric allylation developed here was applied to reaction of **17** with neryl chloride (**26**),[13] which is shown in Scheme 6. The reaction resulted in nearly the same level of chemical yield (73%) and diastereoselectivity (2.3:1) as that for prototype allylation (Scheme 5). Separation of the major isomer (**27**) by silica gel column chromatography was also successful in this case, which is a useful synthetic block in the total synthesis of epothilone families.[13]

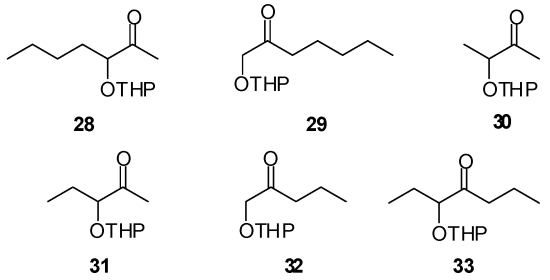
Alkylation: Preliminary Results. The feasibility of alkylations under the reaction conditions used for the allylations of **1a** should be examined because it would be of benefit to organic synthesis. Although we attempted alkylation using bromoalkanes, more reactive iodomethane, iodoethane, and 1-iodobutane were needed for expected alkylation to be realized [1.2 equiv of NaH, 1.3 equiv of iodoalkane, THF (32 mL/g **1a**), 0 °C to rt, 17 h]. Contrary to the case of allylations, alkylations resulted in formation of regioisomers except for methylation and polyalkylation in every case examined. In addition, separations of these products by column chromatography over silica gel were successful only partly, and hence, usually structure determinations were forced to be done for such mixtures. The results are shown in Table 4.

Separation of product mixtures obtained from entry 1 by column chromatography over silica gel afforded, apart from unchanged **1a** (14%), three parts **X**, **Y**, and **Z** in order of decreasing polarity. **X** (14 wt % based on the total weight of the products mixture) was an inseparable mixture and estimated to contain at least three polyalkylated products judging from the presence of three NMR signals for protons attached to the THP-based acetal carbon as well as the increasing amounts of methylene protons (9 × CH_2) and teminal methyl protons (2 × CH_3).[14] On the contrary, NMR analysis for **Y** unambiguously indicated that **Y** is a single diastereoisomer of **28** produced via

TABLE 4. Alkylations of 1a with Iodoalkanes[a]



entry	R–I	rec. **1a** %	**M** yield/% (dr)[b]	**N** yield%[b]
1	R = C_4H_9	14	**28**: 18 (1.2 : 1)[c]	**29**: 5%
2	R = CH_3	7	**30**: 60 (1.2 : 1)[d]	—
3	R = C_2H_5	11	**31**: 27 (1.1 : 1)[e]	**32**: 2%



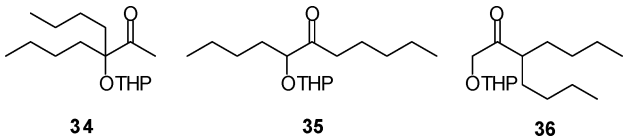
[a] Conditions: 1.2 equiv of NaH, 1.3 equiv of iodoalkane, THF (32 mL/g **1a**), 0 °C to rt, 17 h. For entries 1 and 2, polyalkylation products were isolated as the least polar fractions in chromatographic separation: 2.5% and 6% yield, respectively. For entry 3, polyalkylation products (**33**) were detected in a very small amount (>1%). [b] Corrected for recovered **1a**. [c] Minor diastereomer could be separated, major diastereomer and **29** were obtained as a mixture, and their ratio was determined by NMR. [d] Diastereoisomers were difficult to separate. [e] Diastereoisomeric mixture (**31**), **32**, and **33** were difficult to separate; yields and diastereoisomeric ratio were determined by NMR.

alkylation at the more substituted carbon of **1a** (8% yield corrected for recovered **1a**). Since the NMR spectra of **Z** exhibited both an AB quartet due to THPO-attached methylene group and a sharp singlet due to an acyl methyl group, **Z** was determined to be a mixture of another diastereoisomer of **28** (10% yield corrected for recovered **1a**) and constitutional isomer **29** (5% yield corrected for recovered **1a)** produced via alkylation at the methyl carbon of **1a**. Thus, the regioselectivity for monobutylation of **1a** was 3.6:1 in preference of alkylation proceeding at the more substituted site of **1a** though the chemical yield was unacceptable (18%).

In contrast to those disappointing results for butylation, alkylation using iodomethane (entry 2) provided more hopeful results: **30** as a diastereoisomeric mixture (1.2:1) produced from alkylation at the more substituted carbon of **1a** was obtained in 60% yield (corrected for recovered **1a**)[15] as a monomethylation product. Although a mixture of less polar polyalkylation products was separable (6% yield, corrected for recovered **1a**),[16]

(13) For synthesis of the epothilone D segment from neryl halide, see: Scheid, G.; Ruijter, E.; Konarzycka-Bessler, M.; Bornscheuer, U. T.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **2004**, *15*, 2861−2869.

(14) Even very careful flash column chromatography was not successful for separation of the mixture. In addition to NMR information described in the text, other significant NMR signals were observed indicating the presence of acyl CH_3 (singlet), O═C−CH_2R (triplet), or THPO−CH_2 (AB quartet) for **X**, which tentatively led us to conclude that **X** contains polyalkylated products such as **34**, **35**, or **36**, though a final decision must await further reliable structural analyses. On the basis of these considerations, the yield of the polyalkylated products was calculated to be 2.5%.



(15) Because of the higher volatility of **30**, significant loss of products during evaporative workup was unavoidable. Accordingly, the yield indicated in the text was determined by NMR for a sample containing EtOAc stemmed from column chromatographic separation.

(16) Structures of difficult to separate polyalkylation products (three components) were estimated to be **37** (two diastereoisomers) and **38** on the basis of NMR analysis of the mixture. Chemical yield was calculated based on these structures.

no signal for the AB quartet due to THPO-based acetal proton was observed by NMR diagnosis, and accordingly, only polyalkylation[16] of the initial alkylation products **30** was troublesome; thus, highly regioselective methylation indeed proceeded under the same reaction conditions as those for the allylations of **1a**. Ethylation (entry 3), much less reactive than the methylation, afforded a mixture of **31** (two diastereoisomers), regioisomeric **32** (29%, 14:1), and very small amount of **33** (>1%).

Regioselectivity. The results listed in Table 4 clearly suggest that the regioselectivity of alkylation may be correlated to the reactivity of each alkylation: the more reactive the alkylation becomes, the higher the regioselectivity results in terms of a ratio of alkylation at a THPO-centered carbon to that at a methyl carbon. Since the reactivity of this class (S_N2) should be partly controlled by steric reason of iodoalkanes (electrophiles), we must estimate the stability difference between more substituted enolate (**A** or **B**) and less substituted enolate (**C**) shown in Scheme 3 in order to evaluate the transition-state energy difference between the alkylation at a THPO-centered carbon and that at a methyl carbon of **1a**. Future systematic studies including calculations for energy levels of components involved in alkylation pathways as well as allylation pathways need to be performed.

Concluding Remarks

The present stage for the asymmetric allylation of protected hydroxy acetone (**17**), though novel, seems to be short of the modern level of stereoselectivity requirement. A breakthrough in this context is now one of our major concerns. Nevertheless, the thermodynamically controlled enolates generated from protected hydroxyacetones have proven useful for two-directional carbon chain elongation involving allylation on the oxygen-centered carbon and aldol condensation on the methyl carbon. This shows the hidden potential of acyloins in synthetic organic chemistry. With respect to α-oxygen carbanions of other types developed so far, almost all of them have additional stabilization systems such as allylic or benzylic conjugation, electron-withdrawing cyano conjugation (protected cyanohydrins), α-silicon effect (α,*β*-epoxyalkylsilanes), or phosphorus conjugation.[17] Furthermore, it should be noted that no regiochemical issue exists for these cases. Therefore, the acyloin chemistry developed here would provide a conceptually novel bias or clue about synthetic planning of carbon chains involving an acyloin unit which may serve as an efficient strategy in synthesizing targeting molecules for natural[18] or unnatural products.

(17) For a review on alkylations of heteroatom-stabilized carbanions other than acyloins, see: Cheshire, D. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.4. In this series of outstanding comprehensive surveys, no description of the alkylation or allylation of acyloins is presented, see also: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789−6791 in which regioselective alkylation of 2-butanone-based 3-PhS-substituted *N*,*N*-dimethylhydrazone under thermodynamically controlled conditions [KH, *tert*-BuOK (0.03 equiv), THF, reflux, then iodoalkane, 0 °C to rt) is described.

(18) The acyloin framework is a key structural unit of many natural products, and chiral α-hydroxy ketones (acyloins) are versatile synthetic intermediates for diversified bioactive compounds, see: (a) Bel-Rhlid, R.; Fauve, A.; Veschambre, H. *J. Org. Chem.* **1989**, *54*, 3221−3223. (b) Awano, K.; Yanai, T.; Watanabe, I.; Takagi, Y.; Kitahara, T.; Mori, K. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 1251−1254. (c) Shi, X.; Leal, W. S.; Meinwald, J. *Bioorg. Med. Chem.* **1996**, *4*, 297−303 (d) Scheid, G.; Huit, W.; Ruijter, E.; Orru, R. V. A.; Henke, E.; Bornscheuer, U.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2004**, 1063−1074.

Experimental Section

General Procedure for Allylation or 2-Propynylation. The following procedure for the synthesis of **3a** is representative. To a solution of ketone **1a** (77 mg, 0.49 mmol) in THF (4 mL) was added NaH (2.5 mg, 60% in oil, 0.63 mmol, 1.3 equiv), and the mixture was stirred at 0 °C for 5 min followed by addition of allyl bromide (0.082 mL, 0.97 mmol, 2 equiv) at 0 °C. The reaction was stirred at room temperature for 15 h and quenched by addition of a saturated aqueous solution of NH_4Cl (1 mL) and water at 0 °C. The mixture was extracted with ethyl acetate−hexane mixed solvent (1:1). The combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **3a** as a mixture of two diastereoisomers (1.2:1) [50 mg, 0.25 mmol, 52% (62%: corrected for unchanged **1a**)] and **1a** (12 mg, 16% recovered). **3a**: IR (neat): 2942, 1716 cm^{-1}. ^1H NMR δ 1.46−1.90 (m, ring-$(CH_2)_3$, 6H), 2.13 and 2.21 (s for each, C*H*$_3$C═O, 3H), 2.39 and 2.46 (ddt for each, J = 7.2, 6.3, 1.0 Hz, ═C−C*H*H and ═C−CH*H*, 2H), 3.37−3.53 (m, ring-C*H*H−O, 1H), 3.77−3.90 (m, ring-CH*H*−O, 1H), 3.95 and 4.22 (t for each, J = 6.3 Hz, C*H*−OTHP, 1H), 4.54 and 4.55 (dd for each, J = 6.1, 2.8 Hz and 6.7, 3.7 Hz, ring-O−C*H*−O, 1H), 5.03−5.16 (m, H_2C═, 2H), 5.74 and 5.83 (ddt for each, J = 17.0, 10.2, 7.1 Hz, ═C*H*−, 1H). ^{13}C NMR δ (19.1, 20.3), (25.2, 25.3), (26.3, 26.4), (30.5, 30.7), (36.1, 36.9), (62.4, 63.9), (80.7, 82.7), (97.7, 100.1), (117.9, 118.0), (132.9, 133.1), (210.0, 210.4). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.78; H, 9.02. Exact mass, *m*/*z* 198.125112 (calcd for $C_{11}H_{18}O_3$ *m*/*z* 198.12560).

General Procedure for Aldol Condensation Followed by Deprotection. The following procedure for the synthesis of **9** is representative.

To a solution of **4** (0.24 g, 1.0 mmol) in THF (10 mL) was added *tert*-BuOK (0.022 g, 0.20 mmol) at 0 °C. After stirring at 0 °C for 5 min, benzaldehyde (0.15 mL, 1.5 mmol) was added to the mixture at 0 °C. The reaction was stirred at 0 °C for 1.5 h and quenched by addition of water at 0 °C. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography on silica gel to provide an enone (0.233 g, 0.74 mmol, 74%). To a solution of this enone in EtOH (7 mL) was added TsOH (0.014 g, 0.074 mmol) at 0 °C. The reaction was stirred at room temperature for 5 h and quenched by addition of NEt_3 (0.021 mL, 0.15 mmol) and water. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **9** (0.15 g, 0.64 mmol, 64% from **4**): ^1H NMR δ 1.61 (s, *trans*-C*H*$_3$C═, 3H), 1.71 (d, J = 1.3 Hz, *cis*-C*H*$_3$C═, 3H), 2.43 (m, ═C−C*H*H, 1H), 2.60 (m, ═C−CH*H*, 1H), 3.61 (bd, J = 5.5 Hz, OH, 1H), 4.51 (bq, J = 5.5 Hz, C*H*−OH, 1H), 5.18 (tq, J = 7.3, 1.3, ═C*H*, 1H), 6.88 (d, J = 15.9 Hz, O═C−C*H*═, 1H), 7.34−7.43 (m, 3H), 7.53−7.62 (m, 2H), 7.74 (d, J = 15.9 Hz, O═C−C═CH, 1H). ^{13}C NMR δ 18.0, 25.8, 33.3, 75.1, 118.1, 120.7, 128.2, 128.5, 129.0, 129.9, 131.0, 134.1, 135.5, 144.4, 200.4. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; O, 13.89. Found: C, 78.01; H, 7.79. Exact mass, *m*/*z* 230.13108 (calcd for $C_{15}H_{18}O_2$ *m*/*z* 230.13068).

General Procedure for One-Pot Chemoselective Transformation of 1a. The following procedure for the synthesis of **9** is representative.

To a solution of ketone **1a** (100 mg, 0.66 mmol) in THF (3 mL) was added NaH (3.4 mg 60% in oil, 0.85 mmol, 1.3 equiv) at 0 °C. After stirring at 0 °C for 5 min, prenyl bromide (0.092 mL, 0.79 mmol, 1.2 equiv) was added to the mixture at 0 °C. The reaction was stirred at room temperature for 18 h, *tert*-BuOH (0.04 mL, 0.39 mmol, 0.6 equiv) and benzaldehyde (0.15 mL, 1.31 mmol, 2.0 equiv) were added to the reaction mixture at 0 °C, and the resulting mixture was stirred at room temperature for 13 h, followed by addition of 2 N HCl (aqueous solution 0.65 mL, 2.0 equiv),

stirring being continued at room temperature for 12 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ and water at 0 °C. The mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated by a rotary evaporator to give an oil, which was purified by column chromatography to provide **9**.

*1-[(2R,3S)-3-tert-Butyldiphenylsiloxy-4,4-dimethyloxolan-2-yloxyl-propan-2-one (**17**).* To a solution of **16** (17.9 g, 43.4 mmol) and hydroxyacetone (3.6 mL, 52.1 mmol) in CH_2Cl_2 (200 mL) was slowly added $BF_3{\cdot}OEt_2$ (1.10 mL, 8.68 mmol) at −78 °C. The mixture was stirred at −78 to −10 °C for 4.5 h and quenched by addition of Et_3N (1.20 mL, 8.68 mmol) at −10 °C, and to the thus-obtained mixture were added CH_2Cl_2 and water. The aqueous solution was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **17** (13.5 g, 73%); $[\alpha]^{17}_D$ +18.4 (*c* 1.00, $CHCl_3$). IR (film): 2960, 2858, 1722 cm^{-1}. ^1H NMR δ 0.92 (s, 3H), 1.11 (s, 9H), 1.18 (s, 3H), 1.94 (s, 3H), 3.45 and 3.87 (ABq, J = 16.5 Hz, ring-CH_2O, 2H), 3.63 (s, O═C−CH_2, 2H), 3.98 (d, J = 2.5 Hz, ring-CH−OSi, 1H), 4.78 (d, J = 2.5 Hz, ring-OCH(O), 1H), 7.30−7.50 (m, Ar−H, 6H), 7.65−7.71 (m, Ar−H, 4H). ^{13}C NMR δ 19.3, 20.7, 23.3, 26.5, 26.9, 42.6, 73.4, 78.8, 84.9, 110.1, 127.4, 127.6, 129.7, 129.8, 133.1, 133.7, 135.9, 135.9, 206.8.

*(3S)-3-[(2R,3S)-3-tert-Butyldiphenylsiloxy-4,4-dimethyloxolan-2-yl]oxy-5-hexen-2-one (**20**).* To a solution of **17** (0.834 g, 1.95 mmol) in THF (12 mL) was added NaH (0.094 g, 60%, 2.34 mmol), and the mixture was stirred at 0 °C for 5 min followed by addition of allyl bromide (0.20 mL, 2.34 mmol) at 0 °C. The reaction was stirred at room temperature for 15 h and quenched by addition of a saturated aqueous solution of NH_4Cl (1 mL) and water at 0 °C. The mixture was extracted with ethyl acetate−hexane mixed solvent (1:1), and the combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provided **19** (0.15 g, 0.33 mmol, 17%) and **20** (0.47 g, 1.01 mmol, 52%). Data of **20** (major isomer): $[\alpha]^{20}_D$ +7.5 (*c* 1.0, $CHCl_3$). IR (film): 2931, 2858, 1716, 1427 cm^{-1}. ^1H NMR δ 0.88 (s, 3H), 1.11 (s, 9H), 1.12 (s, 3H), 2.04 (s, 3H), 2.10 (tt, =C−CH_2, J = 6.6, 1.1 Hz, 2H), 3.57 and 3.61 (ABq, J = 8.3 Hz, ring-OCH_2, 2H), 3.57 (t, J = 6.6 Hz, CH-OR*, 1H), 3.95 (d, J = 2.5 Hz, ring-CHOSi, 1H), 4.92 (d, J = 2.5 Hz, ring-OCH(O), 1H), 4.95−5.02 (m, CH_2═C, 2H), 5.58−5.75 (m, ═CH−, 1H), 7.34−7.48 (m, 6H), 7.63−7.75 (m, 4H). ^{13}C NMR δ 19.6, 21.0, 23.5, 26.0, 27.2, 36.1, 43.0, 78.9, 83.7, 85.3, 110.4, 117.5, 127.3, 127.4, 129.5, 129.6, 132.3, 132.9, 133.6, 135.6, 209.3. Data of **19** (minor isomer): $[\alpha]^{22}_D$ +26.3 (*c* 1.00, $CHCl_3$). ^1H NMR δ 0.90 (s, 3H), 1.10 (s, 9H), 1.13 (s, 3H), 1.76 (s, 3H), 2.30−2.43 (m, 2H), 3.68 and 3.64 (ABq, J = 8.5 Hz, 2H), 3.76 (t, J = 5.8 Hz, 1H), 3.96 (d, J = 1.8 Hz, 1H), 4.94 (d, J = 1.8 Hz, 1H), 4.96−5.04 (m, 2H), 5.58−5.74 (m, 1H), 7.32−7.49 (m, 6H), 7.62−7.74 (m, 4H). ^{13}C NMR δ 19.7, 21.5, 24.2, 26.4, 27.2, 37.2, 42.5, 79.3, 82.2, 85.2, 109.7, 117.5, 127.4, 127.5, 129.6, 129.7, 132.8, 133.0, 133.5, 135.6, 135.8, 208.8.

*(3S)-3-[(2R,3S)-3-tert-Butyldiphenylsiloxy-4,4-dimethyloxolan-2-yloxy]-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)hexa-(1E,5)-diene (**22**).* To a solution of **21** (0.505 g, 2.03 mmol) in THF (2 mL) was added NaHMDS (2.0 mL, 1.0 M, 2.0 mmol) at −78 °C, and the mixture was stirred at −78 °C for 30 min followed by addition of a solution of **20** (0.379 g, 0.812 mmol) in THF (3.5 mL) at −78 °C. The reaction was stirred at room temperature for 15 h and quenched by addition of water at 0 °C. The mixture was extracted with ethyl acetate−hexane mixed solvent (1:1). The combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **22** (0.455 g, 0.809 mmol, 99%); $[\alpha]^{25}_D$ +5.3 (c 1.0, $CHCl_3$). IR (neat): 2931, 2858, 1427 cm^{-1}. ^1H NMR δ 0.88 (s, 3H), 1.11 (s, 3H), 1.12 (s, 9H), 1.90 (s, 3H), 2.10 (t, J = 7.1 Hz, 2H), 2.69 (s, 3H), 3.54−3.62 (m, 3H), 3.94 (d, J = 1.9 Hz, 1H), 4.85−4.91 (m, 2H), 4.94 (d, J = 2.2 Hz, 1H), 5.38−5.53 (m, 1H), 6.32 (s, 1H), 6.90 (s, 1H), 7.36−7.48 (m, 6H), 7.67−7.77 (m, 4H). ^{13}C NMR δ 14.0, 19.1, 19.4, 21.0, 23.7, 27.0, 37.6, 42.3, 78.6, 84.4, 85.8, 109.5, 115.2, 116.4, 120.1, 127.5, 127.6, 129.6, 129.7, 133.3, 134.1, 134.4, 135.9, 136.1, 140.2, 152.9, 164.0.

*(3S)-2-Methyl-1-(2-methyl-1,3-thiazol-4-yl)-(1E,5)-hexadien-3-ol (**24**).* To a solution of **22** (54 mg, 0.097 mmol) in CH_2Cl_2 (4.4 mL) was added trifluoroacetic acid (0.44 mL) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h and quenched by addition of a saturated aqueous solution of $NaHCO_3$ at 0 °C. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **24** (14.5 mg, 0.069 mmol, 71%) and **23** (11.7 mg, 0.032 mmol, 33%). **24**: $[\alpha]^{17}_D$ −18.6 (*c* 1.00, $CHCl_3$) (Lit.[13] $[\alpha]^{22}_D$ −20.2 (*c* 1.0, $CHCl_3$). IR (neat): 3350, 2945, 1643 cm^{-1}. ^1H NMR δ 2.01 (d, J = 1.4 Hz, CH_3C═, 3H), 2.30−2.47 (m, ═C−CH_2, 2H), 2.61 (b, OH, 1H), 2.68 (s, N═C−CH_3, 3H), 4.19 (b three lines, CH−O, 1H), 5.06−5.17 (m, 2H), 5.81 (ddt, J = 17.1, 10.1, 7.1 Hz, C═CH−C, 1H), 6.53 (bs, MeC═CH, 1H), 6.91 (s, ring-C═CH−S, 1H). ^{13}C NMR δ 14.3, 19.1, 40.0, 76.4, 115.4, 117.7, 118.9, 134.6, 141.5, 152.7, 164.5.

*(1S)-[(1E)-Methyl-2-(2-methyl-1,3-thiazol-4-yl)ethynyl]-3-butenyl Acetate (**25**).* To a solution of **24** (17.1 mg, 0.081 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (0.030 mL, 0.20 mmol), Ac_2O (0.015 mL, 0.15 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (2.1 mg, 0.016 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h and quenched by addition of water at 0 °C. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography over silica gel to provide **25** (18.6 mg, 96%); $[\alpha]^{20}_D$ −41.8 (*c* 1.10, $CHCl_3$) (Lit.[13b] $[\alpha]_D$ −40.0 (*c* 7.3, $CHCl_3$). IR (film): 2944, 1740 cm^{-1}. ^1H NMR δ 2.07 (s, CH_3C= + CH_3CO, 6H), 2.48 (t, J = 6.9 Hz, ═C−CH_2−C−OAc, 2H), 2.70 (s, N═C−CH_3, 3H), 5.05 (ddt, J = 10.1, 1.9, 1.1 Hz, *cis*-HHC═CH−C, 1H), 5.10 (ddd, J = 17.1, 3.3, 1.4 Hz, *trans*-HHC═CH−C, 1H), 5.32 (t, J = 6.9 Hz, CH−OAc, 1H), 6.51 (bs, MeC═CH, 1H), 6.94 (s, ring-C═CH−S, 1H). ^{13}C NMR δ 14.8, 19.2, 21.2, 37.6, 78.1, 116.2, 117.7, 120.7, 133.4, 137.2, 152.5, 164.6, 170.1.

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Supporting Information Available: Representative experimental procedures, physical properties, and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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