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Total Syntheses of Naturally Occurring Diacetylenic Spiroacetal Enol Ethers

Naoki Miyakoshi, Daisuke Aburano, and Chisato Mukai*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

cmukai@kenroku.kanazawa-u.ac.jp

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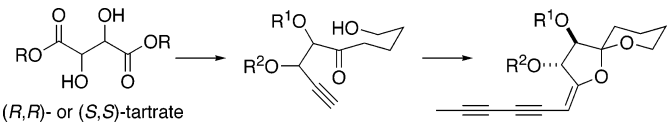

A highly stereoselective method for constructing a (2*E*)-methoxymethylidene-1,6-dioxaspiro[4.5]-decane skeleton has been developed on the basis of the palladium(II)-catalyzed ring-closing reaction of the 3,4-dioxygenated-9-hydroxy-1-nonyn-5-one derivatives as a crucial step. The newly developed procedures could be successfully applied to the first total synthesis of five diacetylenic spiroacetal enol ether natural products starting from commercially available (*R*,*R*)- or (*S*,*S*)-diethyl tartrate.

Introduction

A wide range of biological and pharmacological activities of the genus *Artemisita* have been reported with more than 10 diacetylenic spiroacetal enol ether derivatives being isolated from this plant family.[1] Several related natural products **1**−**6** are depicted in Figure 1. These diacetylenic spiroacetal enol ethers have a common structural feature, namely the (2*E*)-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane framework.[1g,2] The representative diacetylenic spiroacetal enol ether epoxide, the so-called AL-1 (**1**), has been found to be a specific inhibitor of the activation phase in hydrogen peroxide production induced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) treatment.[1h,3] Thus, it was discovered that AL-1 (**1**) strongly inhibits TPA-induced tumor promotion.[1h,3] The simpler 8-deisovaleryloxy congener, the so-called AL-2 (**2**),[4] also showed similar antitumor activities, although they were much weaker than those of AL-1 (**1**).[1h,3] Despite their unique structural features and promising biological activity, no reports[5] have dealt with the total syntheses of AL-1 (**1**) and AL-2 (**2**) or any of the other related diacetylenic spiroacetal enol ether natural

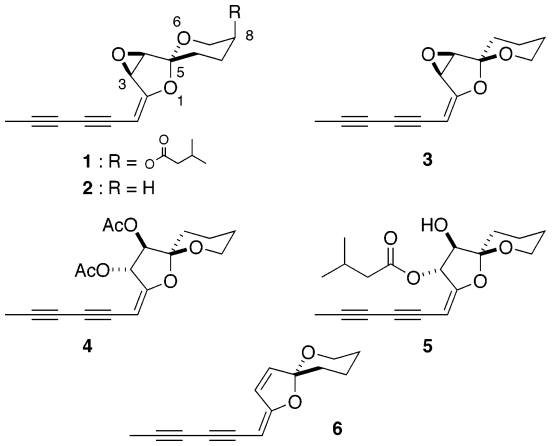

FIGURE 1. Typical diacetylenic spiroacetal enol ethers.

* To whom correspondence should be addressed. Tel: +81-76-234-4411. Fax: +81-76-234-4410.

(1) For examples, see: (a) Bohlmann, F.; Herbst, P.; Arndt, C.; Schönowsky, H.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 3193−3216. (b) Bohlmann, F.; Herbst, P.; Dohrmann, I. *Chem. Ber.* **1963**, *96*, 226−236. (c) Bohlmann, F.; Arndt, C.; Bornowski, H.; Kleine, K.-M.; Herbst, P. *Chem. Ber.* **1964**, *97*, 1179−1192. (d) Bohlmann, F.; Burkhardt, T.; Zdero, C. In *Naturally Occurring Acetylenes*; Academic Press: London, 1973. (e) Bohlmann, F.; Ates, N.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1982**, *21*, 2691−2697. (f) Martínez, V.; Barbera, O.; Sánchez-Parareda, J.; Marco, J. A. *Phytochemistry* **1987**, *26*, 2619−2624. (g) Marco, J. A.; Sanz, J. F.; Jakupovic, J.; Huneck, S. *Tetrahedron* **1990**, *46*, 6931−6938. (h) Nakamura, Y.; Ohto, Y.; Murakami, A.; Jiwajinda, S.; Ohigashi, H. *J. Agric. Food Chem.* **1998**, *46*, 5031−5036.

(2) For structure determination, see: (a) Wurz, G.; Hofer, O.; Sanz-Cervera, J. F.; Marco, J. A. *Ann. Chem.* **1993**, 99−101. (b) Birnecker, W.; Wallnöfer, B.; Hofer, O.; Greger, H. *Tetrahedron* **1988**, *44*, 267−276.

(3) Nakamura, Y.; Kawamoto, N.; Ohto, Y.; Torikai, K.; Murakami, A.; Ohigashi, H. *Cancer Lett.* **1999**, *140*, 37−45.

(4) According to the IUPAC nomenclature system, (−)-AL-2 (**2**) should be described as (−)-(2*E*,3*S*,4*R*,5*R*)-3,4-epoxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane. This numbering system is used for the dioxaspiro compounds in this paper.

(5) For synthetic studies on total synthesis, see: (a) Toshima, H.; Furumoto, Y.; Inamura, S.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 5707−5710. (b) Toshima, H.; Aramaki, H.; Furumoto, Y.; Inamura, S.; Ichihara, A. *Tetrahedron* **1998**, *54*, 5531−5544. (c) Toshima, H.; Aramaki, H.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 3587−3590.

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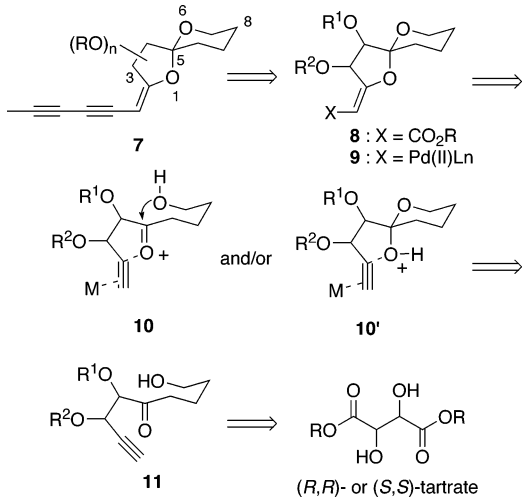
SCHEME 1

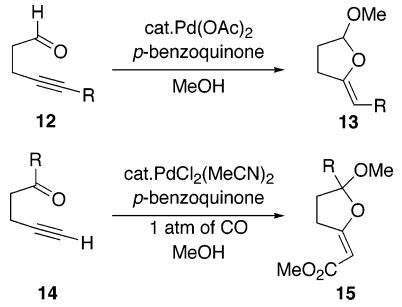


products except for the total synthesis of the structurally simplest (±)-**6**,[6] the racemic 3,4-deoxygenated analogue of AL-2 (**2**), which did not control the stereochemistry of an enediyne moiety.

As part of our program[7] to design a highly stereocontrolled total synthesis of natural products from commercially available tartrate derivatives, we have focused considerable attention on the total synthesis of a series of diacetylenic spiroacetal enol ether natural products. A general retrosynthetic analysis for these natural products **1**−**6** is outlined in Scheme 1. We roughly envisaged that a common basic core skeleton, the (2*E*)-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane **7** for these natural products, might be constructed by the metal-catalyzed acetal formation and spontaneous CO-insertion reaction of the 1-hydroxy-8-nonyn-5-one derivatives **11** with suitable hydroxyl functionalities via intermediates **10** and/or **10′**. The chiral key compound **11** would be derived from (*R*,*R*)- or (*S*,*S*)-diethyl tartrate by conventional means.

Thus, the most significant feature of this synthesis would become transformation of **11** to the 1,6-dioxaspiroacetal frameworks **9** possessing a (2*E*)-alkoxycarbonylmethylidene moiety. In 2002, Yamamoto and coworkers[8] developed a novel palladium-catalyzed ring-closing reaction[9] of 4-yn-1-al derivatives **12** in methanol resulting in the formation of cyclic acetal derivatives **13** with a (*Z*)-alkylidne moiety. On the other hand, Kato and Akita[10] recently reported the palladium-catalyzed formation of oxacycles **15** with (*E*)-methoxycarbonylmethylidene functionality from 4-yn-1-ones derivatives **14** in methanol under an atmosphere of CO (Scheme 2). Thus, the 3,4-dioxygenated-9-hydroxy-1-nonyn-5-one **11** would be expected to undergo a one-pot construction of the core framework of the target natural products under the conditions of Kato and Akita,[10] which involve (i) activation of an alkyne moiety with a palladium(II) catalyst resulting in the formation of the intermediate **10** (M = LnPd(II)) and/or the hemiacetal species **10′** (M = LnPd(II)),[11] (ii) followed by intramolecular capture of the transient oxonium ion species **10** by the terminal hydroxyl group, and/or nucleophilic attack of the hemiacetal hydroxyl group[11] at the activated triple bond of **10′**, and finally (iii) the palladium-mediated carbon monoxide insertion reaction (conversion of **9** to **8**) leading to the 1,6-dioxaspiro[4.5]decane skeleton **8** having an (*E*)-alkoxycarbonylmethylidene moiety. This compound **8** would be a useful as well as common synthetic intermediate for further chemical elaboration resulting in the stereoselective total synthesis of various diacetylenic spiroacetal enol ether natural products. We describe here the first total synthesis of five natural products,[12] (−)-AL-2 (**2**), (+)-5-*epi*-AL-2 (**3**), (−)-**4**, (+)-**5**, and (−)-**6**, from tartrates in a stereocontrolled manner.

SCHEME 2



Results and Discussion

AL-2 (**2**) was chosen as our first target natural product from (*R*,*R*)-diethyl tartrate as a starting material. The required alkynone derivative **20** possessing suitable functionalities for the palladium-catalyzed ring-closing reaction was prepared by conventional means depicted in Scheme 3. The selective introduction of a pivaloyl group on the primary alcohol moiety of the known diol **16**, derived from (*R*,*R*)-diethyl tartrate according to Saito's procedure,[13] was followed by treatment with *tert*-butyldiphenylsilyl (TBDPS) chloride and then EtMgBr to give **17** in 76% yield. Dess−Martin oxidation of **17** afforded the corresponding aldehyde, which was subsequently exposed to trimethylsilyldiazomethane[14] and ^{n}BuLi to provide the alkyne derivative **18** in 72% yield.

(6) (a) Bohlmann, F.; Florentz, G. *Chem. Ber*. **1966**, *99*, 990−994. (b) Gao, Y.; Wu, W.-L.; Ye, B.; Zhou, R.; Wu, Y.-L. *Tetrahedron Lett*. **1996**, *37*, 893−896.

(7) (a) Mukai, C.; Moharram, S. M.; Kataoka, O.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2849−2854. (b) Mukai, C.; Moharram, S. M.; Hanaoka, M. *Tetrahedron Lett.* **1997**, *38*, 2511−2512. (c) Mukai, C.; Moharram, S. M.; Azukizawa, S.; Hanaoka, M. *J. Org. Chem*. **1997**, *62*, 8095−8103. (d) Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875−5880.

(8) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc*. **2002**, *124*, 764−765.

(9) For similar palladium(II)-catalyzed reactions, see: (a) Utimoto, K. *Pure Appl. Chem*. **1983**, *54*, 1845−1852. (b) Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett*. **1987**, *28*, 3127−3130. (c) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816−5819. (d) Okumoto, H.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 217−218.

(10) (a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett*. **2002**, *43*, 4915−4917. (b) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett*. **2002**, *43*, 6587−6590.

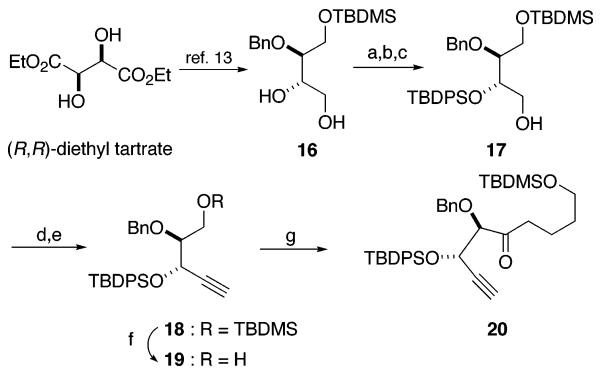
(11) Yamamoto suggested the intermediacy of the hemiacetal species for the palladium(II)-catalyzed formation of oxacycles from the carbon-tethered acetylenic aldehydes on the basis of the ^{13}C NMR experiments. See ref 8.

(12) Part of this work was published as a preliminary communication: Miyakoshi, N.; Mukai, C. *Org. Lett*. **2003**, *5*, 2335−2338.

(13) Saito, S.; Kuroda, A.; Tanaka, K.; Kimura, R. *Synlett* **1996**, 231−233.

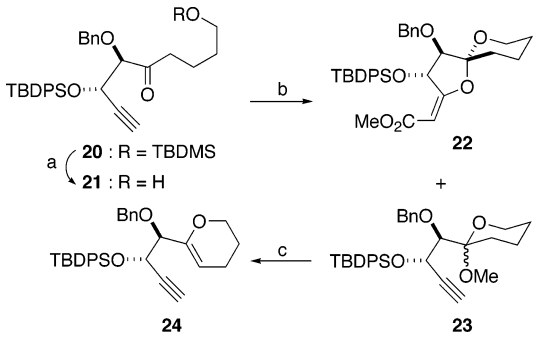
(14) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107−108.

SCHEME 3[a]



[a] Reaction conditions: (a) PivCl, Et_3N, CH_2Cl_2, −78 °C; (b) TBDPSCl, imid, DMF, 50 °C; (c) EtMgBr, Et_2O rt (76%); (d) Dess−Martin oxidation, CH_2Cl_2, 0 °C to rt; (e) $TMSCHN_2$, ^{n}BuLi, THF, −78 °C (72%); (f) PPTS, MeOH, rt (75%); (g) (i) Dess−Martin oxidation, CH_2Cl_2, 0 °C to rt, (ii) $TBDMSO(CH_2)_4MgI$, Et_2O−CH_2Cl_2, −78°C, (iii) Dess−Martin oxidation, CH_2Cl_2, 0 °C to rt (74%).

SCHEME 4[a]



[a] Reaction conditions: (a) *p*-TsOH, THF−H_2O, rt; (b) $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), *p*-benzoquinone (20 equiv), 1 atm of CO, MeOH, rt (41% from **20**); (c) CSA, MS 4Å, THF, rt (59% from **20**).

A selective desilylation of the primary silyl ether of **18** was realized by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol to furnish **19** in 75% yield. Transformation of **19** into the required **20** was accomplished as follows. Oxidation of **19** with Dess−Martin periodinane (DMP) gave the aldehyde, which was reacted with 4-(*tert*-butyldimethylsiloxy)butylmagnesium iodide.[15] The resulting adduct was oxidized by DMP to give the alkynone **20** in 74% yield.

The crucial transformation of **20** into the (2*E*)-2-(methoxycarbonylmethylidene)-1,6-dioxaspiro[4.5]-decane framework was investigated. A selective desilylation of the primary silyl ether of **20** was carried out using *p*-toluenesulfonic acid (*p*-TsOH) in THF at room temperature to afford the corresponding primary alcohol **21** (Scheme 4). According to Kato and Akita's procedure,[10] **21** was exposed to 5 mol % of $PdCl_2(MeCN)_2$ in methanol in the presence of *p*-benzoquinone as an oxidant under an atmosphere of CO to furnish the desired spiroacetal enol ether derivative **22** along with the tetrahydropyran derivative **23**, both in low yields. The ratio of **22** to **23** was inconsistently changed. Therefore, we needed reliable conditions which would consistently provide **22** in a selective manner. Increasing the amounts of $PdCl_2(MeCN)_2$ from 5 to 50 mol % resulted in the exclusive formation of **23**,[16] which was converted into the dihydropyran derivative **24** in 59% overall yield from **20** by acid treatment. 2,6-Dichloroquinone and α-naphthoquinone were used as an oxidant instead of *p*-benzoquinone, but the major product was again the tetrahydropyran derivative **23**. Use of other palladium(II) catalysts such as $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2(C_6H_5CN)_2$ was fruitless for this transformation and provided results similar to those for $PdCl_2(MeCN)_2$ in most cases or no reaction in some cases. The preferential formation of **23** over **22** was tentatively rationalized in terms of the Lewis acidic property of the palladium(II) catalyst,[8] which might have catalyzed acetalization prior to activation of the triple bond. Finally, we found that, by using a catalytic amount of palladium(0) catalyst and excess amounts of *p*-benzoquinone, in which only a minimal amount of the active palladium(II) catalyst would be present in the reaction vessel, we were able to retard the formation of undesired acetal **23**. In fact, The primary hydroxyl compound **21**was submitted to 5 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 20 equiv of *p*-benzoquinone in methanol under a carbon monoxide atmosphere at room temperature to produce the desired **22** in 41% yield as the sole product.[17] No significant improvement of the chemical yield of **22** (ethyl and isopropyl esters instead of the methyl ester) was observed when bulkier alcohols (EtOH and ^{i}PrOH) were used as a solvent. In addition, ^{t}BuOH gave an intractable mixture.

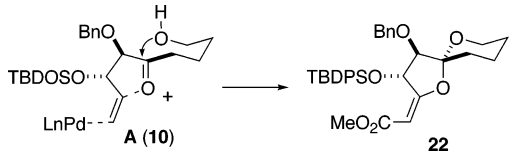


FIGURE 2. Stereoselective formation of **22**.

Exclusive formation of **22**, the (5*R*)-isomer, might be tentatively interpreted by the mechanism proposed by Kato and Akita (Figure 2).[10] Activation of an alkyne moiety with the palladium(II) catalyst would be followed by an attack of the oxygen atom of the carbonyl functionality to produce the transient five-membered oxonium intermediate **A** (**10**). Intramolecular capture of the resulting oxonium ion species by the terminal hydroxyl group would predominantly occur from the face opposite the C_4-benzyloxy functionality to avoid a nonbonding interaction leading to the exclusive construction of **22** with the (5*R*)-stereochemistry. We could now synthesize the (2*E*)-2-(methoxycarbonylmethylidene)-1,6-dioxaspiro-[4.5]decane framework with suitable oxygen functionalities, in which all of the stereogenic centers of the first target natural product, (−)-AL-2 (**2**), were constructed in a stereocontrolled manner.

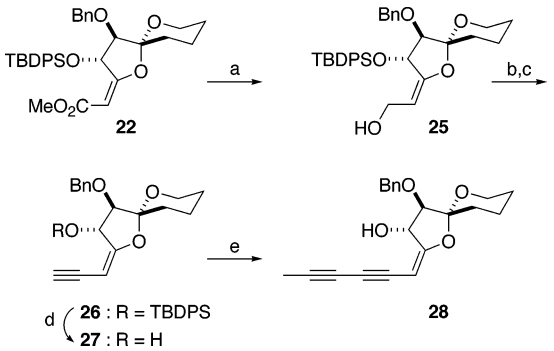
Our next efforts focused on the completion of the first total synthesis of (−)-AL-2 (**2**). The dioxaspiro compound **22** was reduced with diisobutylaluminum hydride (DIBAL-

(15) CH_2Cl_2 was used as a solvent instead of THF or Et_2O. See: Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Wienreb, S. M. *J. Am. Chem. Soc.* **2001**, *123*, 8851−8853.

(16) A mixture of two diastereoisomers was obtained.

(17) The structure of **22** was elucidated by spectral evidence. In particular, NOE experiments revealed no enhancement between the vinylic proton and H-3 or between H-4 and H-10. In the **4**-related (4*R*,5*S*)-compounds, an enhancement between H-4 and H-10 was observed in the NOE experiments.[1g,5]

SCHEME 5[a]

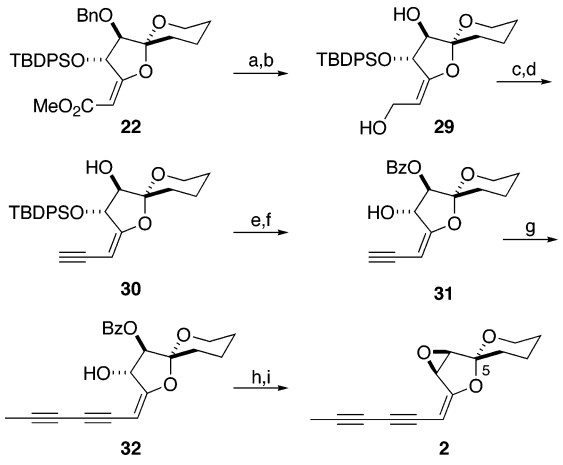


[a] Reaction conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C (92%); (b) MnO_2, CH_2Cl_2, rt; (c) $TMSCHN_2$, ^{n}BuLi, THF, −78 °C (90%); (d) TBAF, THF, rt (94%); (e) 1-propynyl iodide, CuI, pyrrolidine, rt (67%).

H) to give the allyl alcohol derivative **25** in 92% yield, which was subsequently oxidized with manganese dioxide and then treated with trimethylsilyldiazomethane[14] and ^{n}BuLi to afford the enyne derivative **26** in 90% yield (Scheme 5). Introduction of a propyne appendage at the triple bond terminus of **26** under several conditions was unsuccessful, presumably because of the bulkiness of the silyl protecting group on the C_3-hydroxyl moiety. Thus, desilylation of **26** with tetrabutylammonium fluoride (TBAF) furnished the hydroxyl compound **27**, which was exposed to the coupling reaction with 1-propynyl iodide in the presence of copper(I) iodide in pyrrolidine[18] at room temperature to produce the enediyne derivative **28** in 67% yield. The final stage for completing the total synthesis of AL-2 (**2**) was debenzylation and epoxy formation. However, it turned out that debenzylation of **28** under various conditions led to the formation of an intractable mixture, presumably due to the instability of the enediyne moiety. Protection of the C_3-hydroxyl group of **28** was also found to be ineffective for the debenzylation reaction.

On the basis of these unfavorable preliminary results, two considerations became apparent. Namely, (i) to complete the transformation of **22** into the first target natural product, AL-2 (**2**), removal of the bulky silyl group on the C_3-hydroxyl functionality, prior to introduction of the terminal propyne moiety, was essential, and (ii) the benzyl group on the C_4-hydroxyl group had to be changed to a suitable protecting group before constructing the enediyne moiety. With these considerations in mind, DIBAL-H reduction of **22** was followed by debenzylation with lithium di-*tert*-butylbiphenylide (LiDBB)[19] in THF at −78 °C to furnish the diol **29** in 72% yield (Scheme 6). A selective oxidation of the allyl alcohol moiety of **29** with manganese dioxide gave the aldehyde, which was converted into the enyne derivative **30** in 84% yield by the procedure described for the preparation of **26**. Introduction of a benzoyl group on the C_3-hydroxyl group of **30** and desilylation under conventional conditions afforded **31** in 95% yield. According to the procedure developed for conversion of **27** into **28**, the enediyne compound **32** (60%) was easily prepared from the enyne

SCHEME 6[a]



[a] Reaction conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C; (b) LiDBB, THF, −78 °C (72%); (c) MnO_2, CH_2Cl_2, rt; (d) $TMSCHN_2$, ^{n}BuLi, THF, −78 °C (84%); (e) BzCl, pyridine, rt; (f) TBAF, THF, rt (95%); (g) 1-propynyl iodide, CuI, pyrrolidine, rt (60%); (h) MsCl, Et_3N, CH_2Cl_2, rt; (i) K_2CO_3, MeOH, rt (79%).

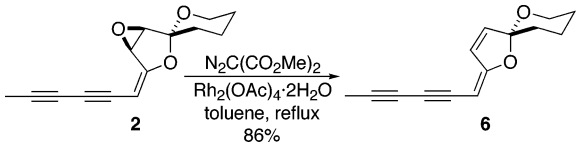
derivative **31**. The final phase of the first total synthesis of AL-2 (**2**) was the formation of the epoxide. Compound **32** was treated with mesyl chloride and triethylamine to give the C_3-mesyloxy derivative, which was subsequently exposed to potassium carbonate in methanol to produce (−)-AL-2 (**2**) in 79% yield. The synthetic (−)-AL-2 (**2**) was identical to the natural compound based on their spectral data.[2b] Thus, we have completed the first total synthesis of (−)-AL-2 (**2**) from commercially available (*R*,*R*)-diethyl tartrate in a stereocontrolled manner.

The specific rotation of the simplest natural product **6**, a 3,4-deoxygenated analogue of AL-2 (**2**), was shown to be $[\alpha]^{20}_D$ ±0,[1b] indicating that either this natural product must be a racemate or that racemization had occurred during its isolation process. As aforementioned, the total synthesis of a racemic **6** has already been reported,[6a,b] but the attempt[20] at preparing it as an optically active form has not been recorded yet. Therefore, our efforts turned to the first synthesis of optically active compound **6** from (−)-AL-2 (**2**). Treatment of **2** with dimethyl diazomalonate in the presence of rhodium(II) acetate $[Rh_2(OAc)_4 \cdot 2H_2O]$[21] in refluxing toluene effected easy deoxygenation of the epoxy functionality to give (−)-**6** in 86% yield, the spectral data of which were identical to those of (±)-**6**.[6a,b] The synthetic (−)-**6** with the (5*R*)-stereochemistry showed its specific rotation, $[\alpha]^{29}_D$ −47.7. Thus, we have accomplished the first synthesis of optically active **6** from (*R*,*R*)-diethyl tartrate via (−)-AL-2 (**2**) (Scheme 7).

Birnecker et al.[2b] reported the following isomerization reaction between AL-2 (**2**) and its C_5-epimer **3** under acidic conditions. As a matter of fact, a solution of AL-2 (**2**) in MeOH-Et_2O (3:1) was allowed to stand in the presence of *p*-TsOH at room temperature for 6 h to give a mixture of **2** and **3** in a ratio of 2.8 to 0.2, whereas a

(18) Alami, M.; Ferri. F. *Tetrahedron Lett.* **1996**, *37*, 2763−2766.
(19) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem*. **1980**, *45*, 1924−1930.
(20) Ohigashi and co-workers reported preparation of compound **6** from naturally occurring AL-2 (**2**) and ***ent*-3** by successive reduction, tosylation, and olefin formation reaction. However, no description concerning to its specific rotation could be available. See ref 1h.
(21) Martin, M. G.; Ganem, B. *Tetrahedron Lett*. **1984**, *25*, 251−254.

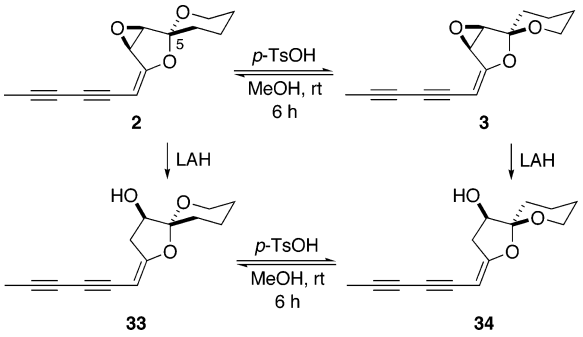
SCHEME 7



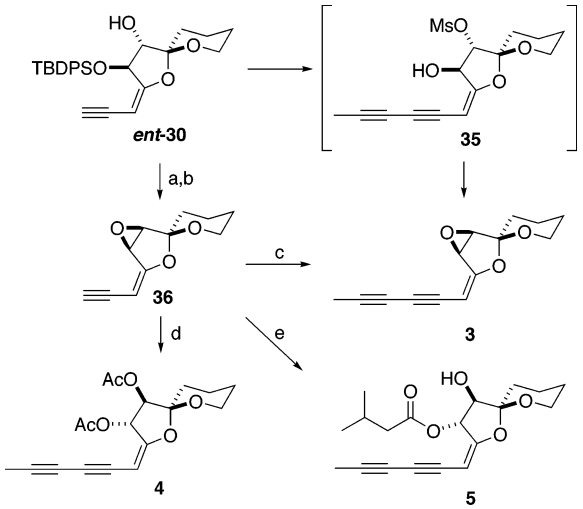
similar mixture of **2** and **3** (1.2:1.8) was obtained when **3** was exposed to the same acidic conditions. Furthermore, the secondary hydroxyl compounds **33** and **34**, derived from **2** and **3**, respectively, also showed a similar equilibration: a mixture of **33** and **34** in a ratio of 2.7 and 0.2 from **33** as well as a mixture of **33** and **34** (1:2) from **34** was obtained.[22] On the basis of these literature precedents, [2b] we expected that acid treatment of AL-2 (**2**) would provide its epimer **3** in a straightforward manner. Thus, AL-2 (**2**) was treated with *p*-TsOH in MeOH-Et_2O at room temperature. However, the desired **3** could not be isolated from the reaction mixture, and an intractable mixture was obtained instead. Several acidic conditions produced by changing the solvent, the acid involving Lewis acids, and the reaction temperature were examined, but no improvement could be accomplished. Therefore, we next searched for an alternative method for the synthesis of C_5-*epi*-AL-2 (**3**) as well as other natural products **4** and **6**, both of which would be derived via compound **3**.

Because our next target natural products, involving not only the C_5-*epi*-AL-2 (**3**) but also 3,4-dioxygenated natural products **4** and **5**, have the (5*S*)-configuration in common, we conceived the utilization of (*S*,*S*)-diethyl tartrate as a starting material by taking advantage of newly developed procedures for the synthesis of (−)-AL-2 (**2**). Thus, ***ent*-30**, derived from (*S*,*S*)-diethyl tartrate according to the aforementioned procedure, was converted into the labile endiyne derivative **35** by successive mesylation, desilylation, and introduction of a propyne moiety. Final epoxy formation of **35** leading to C_5-*epi*-AL-2 (**3**) was examined under various conditions, but only an intractable mixture was obtained presumably due in large part to the instability of the enediyne compound **35**. Our scenario was then modified by constructing an epoxy functionality at an early stage. Thus, ***ent*-30** was converted into the mesylate, which was subsequently treated with TBAF at room temperature to give the labile 4-hydroxyl-3-mesyloxy derivative. No epoxy formation at lower temperature (room temperature) could be realized. Therefore, the resulting reaction mixture in THF in the presence of fluoride anion was directly heated under reflux to afford the desired expoxide **36** in a quantitative yield. Introduction of the terminal propyne residue under the copper(I) iodide-catalyzed conditions as depicted in the preparation of **32** from **31** (Scheme 6) was troublesome due to the formation of considerable amounts of inseparable dimerized products. After searching for several copper-free conditions, the Sonogashira-type conditions[23] were found to be suitable for this transformation. Indeed, **36** was exposed to [(allyl)PdCl]$_2$ and tri(*tert*-butyl)phosphine in DMF[23] at room temperature in the presence of cesium carbonate to produce (+)-**3** in 78% overall yield, which was identical to the natural compound.[2b] The ring-opening reaction of an epoxy functionality of **36** by nucleophiles would be expected to occur at the C_3-position in a highly regioselective manner based on the literature precedents (e.g., conversion of **2** and **3** to **33** and **34** in Scheme 8).[24] Thus, the ring-opening of the epoxy moiety of **36** with cesium acetate[25] was followed by acetylation furnishing the corresponding diacetate, which was subsequently exposed to the coupling conditions with 1-propynyl iodide to provide (−)-**4** in 58% overall yield. Similarly, treatment of **36** with cesium isovalerate in DMF at 80 °C effected the regioselective cleavage of an epoxy group to give the 4-hydroxy-3-isovaleroxy derivative, which was then transformed to the target (+)-**5** in 64% yield (Scheme 9). Both synthetic natural products, **4** and **5**, were identical to the corresponding natural products[2a] based on a comparison of their spectral data.

SCHEME 8



SCHEME 9[a]



[a] Reaction conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C; (b) TBAF, THF, rt to reflux (quant); (c) 1-propynyl iodide, [(allyl)PdCl]$_2$, ^{t}Bu$_3$P, Cs_2CO_3, DMF, rt (78%); (d) (i) AcOH, Cs_2CO_3, DMF, 80 °C, then Ac_2O, DMAP, DMF, 0 °C, (ii) 1-propynyl iodide, [(allyl)PdCl]$_2$, ^{t}Bu$_3$P, Cs_2CO_3, DMF, rt (58%); (e) (i) isovaleric acid, Cs_2CO_3, DMF, 80 °C, (ii) 1-propynyl iodide, [(allyl)PdCl]$_2$, ^{t}Bu$_3$P, Cs_2CO_3, DMF, rt (64%).

(22) Ohigashi and co-workers isolated 1 mg of (+)-**3** when 4.2 mg of (−)-AL-2 (**2**) was exposed to the same acidic conditions. See ref 1h.

(23) Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.: Hughes, D. L. *Org. Lett*. **2003**, *4*, 4191−4194.

(24) An epoxy group of ***ent*-3** was regioselectively cleaved at the C_3-position when treated with 10% hydrochloric acid in methanol. See ref 1h.

(25) (a) Kuntz, H.; Kullmann, R.; Wernig, P.; Zimmer, J. *Tetrahedron Lett*. **1992**, *33*, 1969−1972. (b) Arbelo, D. O.; Prieto, J. A. *Tetrahedron Lett*. **2002**, *43*, 4111−4114.

In summary, we have developed a highly stereoselective method for constructing the (2*E*)-2-methoxymethylidene-1,6-dioxaspiro[4.5]decane skeleton by the palladium (II)-catalyzed ring-closing reaction of the 3,4-dioxygenated-9-hydroxy-1-nonyn-5-one derivatives as a crucial step. By taking advantage of the newly developed procedures, the first total synthesis of five diacetylenic spiroacetal enol ether natural products, AL-2 (**2**), C_5-*epi*-AL-2 (**3**), **4**, **5**, and **6** in a chiral form, has been achieved starting from commercially available (*R*,*R*)- or (*S*,*S*)-diethyl tartrate depending on the configuration of the target molecules.

Experimental Section

(2*S*,3*S*)-3-Benzyloxy-4-(*tert*-butyldimethylsiloxy)-2-(*tert*-butyldiphenylsiloxy)butan-1-ol ((−)-17). A solution of PivCl (1.19 mL, 9.70 mmol) in CH_2Cl_2 (12 mL) was added to a solution of **16** (3.00 g, 9.20 mmol), Et_3N (3.67 mL, 27.6 mmol), and DMAP (0.11 g, 0.92 mmol) in CH_2Cl_2 (80 mL) at −78 °C over a period of 3 h. After being stirred for 16 h at the same temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (1:1) to afford the crude alcohol. To a solution of the crude alcohol and imidazole (1.88 g, 27.6 mmol) in DMF (4.5 mL) was added TBDPSCl (3.56 mL, 13.8 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 42 h, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane-AcOEt (1:1) to afford the crudeTBDPS-protected product. To a solution of the crudeTBDPS-protected product in Et_2O (90 mL) was added EtMgBr in Et_2O (1.00 M, 92.0 mL, 92.0 mmol) at room temperature, and the reaction mixture was stirred for 22 h, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (10:1) afforded (−)-**17** (3.94 g, 76%) as a colorless oil: $[\alpha]^{27}_D$ −18.0 (*c* 1.00, $CHCl_3$); IR 3612 cm^{-1}; ^1H NMR δ 7.68−7.64 (m, 4H), 7.43−7.32 (m, 6H), 7.28−7.16 (m, 5H), 4.51, 4.36 (AB-q, 2H, J = 11.9 Hz), 3.95−3.83 (m, 3H), 3.62−3.57 (m, 2H), 3.49 (m, 1H), 1.06 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 138.5, 135.9, 135.7, 133.7, 133.3, 129.8, 129.2, 127.7, 127.6, 127.4, 81.8, 72.7, 72.6, 63.4, 62.3, 27.0, 19.3, 18.2, −5.4, −5.5; MS *m*/*z* 564 (M^+, 1.1); HRMS calcd for $C_{33}H_{48}O_4Si_2$ 564.3091, found 564.3095.

(3*S*,4*S*)-4-Benzyloxy-5-(*tert*-butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)pent-1-yne ((−)-18). To a solution of (−)-**17** (400 mg, 0.71 mmol) in CH_2Cl_2 (7.0 mL) was added Dess−Martin periodinane (DMP) (470 mg, 1.01 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, poured into a solution of sodium thiosulfate and sodium bicarbonate (1:1), and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The crude aldehyde was used directly for the next reaction. To a solution of $TMSCLi(N_2)$ in THF (2.0 mL), prepared from reaction of $TMSCHN_2$ in hexane (1.50 M, 2.00 mL, 3.00 mmol) and ^{n}BuLi in hexane (1.43 M, 1.50 mL, 2.20 mmol) at −78 °C for 30 min, was added a solution of the crude aldehyde in THF (3.0 mL). The reaction mixture was stirred at −78 °C for 30 min and then allowed to stand at 0 °C for 30 min, quenched by addition of water, and extracted with Et_2O. The extract was washed with water, and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (10:1) afforded (−)-**18** (297 mg, 72%) as a colorless oil: $[\alpha]^{25}_D$ −0.5 (*c* 1.00, $CHCl_3$); IR 3306, 2120 cm^{-1}; ^1H NMR δ 7.74−7.71 (m, 2H), 7.66−7.64 (m, 2H), 7.44−7.30 (m, 6H), 7.27−7.20 (m, 5H), 4.54 (s, 2H), 4.51 (dd, 1H, J = 4.9, 2.0 Hz), 4.06 (dd, 1H, J = 10.7, 2.6 Hz), 3.88 (dd, 1H, J = 10.7, 7.3 Hz), 3.48 (ddd, 1H, J = 7.3, 4.9, 2.6 Hz), 2.27 (d, 1H, J = 2.0 Hz), 1.07 (s, 9H), 0.95 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 138.6, 136.1, 135.8, 133.1, 129.8, 129.7, 128.1, 127.7, 127.6, 127.4, 127.3, 82.3, 82.2, 74.1, 72.9, 63.5, 63.4, 31.6, 26.9, 26.0, 25.9, 22.6, 19.3, 18.2, 14.1, 9.4, −5.3, −5.4; FABMS *m*/*z* 581 (M^+ + 1, 1.1). Anal. Calcd for $C_{34}H_{46}O_3Si_2$: C, 73.07; H, 8.30. Found: C, 72.71, H, 8.57.

(2*S*,3*S*)-2-Benzyloxy-3-(*tert*-butyldiphenylsiloxy)-4-pentyn-1-ol ((−)-19). PPTS (570 mg, 2.27 mmol) was added to a solution of (−)-**18** (1.15 g, 2.06 mmol) in MeOH (10 mL) at room temperature, and the reaction mixture was stirred for 24 h. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed with saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded (−)-**19** (683 mg, 75%) as a colorless oil: $[\alpha]^{27}_D$ −5.7 (*c* 1.00, $CHCl_3$); IR 3587, 3306, 2120 cm^{-1}; ^1H NMR δ 7.75−7.71 (m, 2H), 7.69−7.65 (m, 2H), 7.47−7.33 (m, 6H), 7.27−7.14 (m, 5H), 4.56 (dd, 1H, J = 5.3, 2.0 Hz), 4.47, 4.30 (AB-q, 2H, J = 11.9 Hz), 4.01−3.82 (m, 2H), 3.52−3.47 (m, 1H), 2.37 (d, 1H, J = 1.7 Hz), 1.09 (s, 9H); ^{13}C NMR δ 137.8, 136.1, 135.8, 132.8, 132.6, 130.0, 129.9, 128.4, 128.0, 127.8, 127.8, 127.6, 81.5, 81.0, 75.0, 72.7, 63.7, 61.9, 26.9, 19.2; FABMS *m*/*z* 445 (M^+ + 1, 1.1). Anal. Calcd for $C_{28}H_{32}O_3Si$: C, 75.63; H, 7.25. Found: C, 75.55, H, 7.26.

(3*S*,4*R*)-4-Benzyloxy-9-(*tert*-butyldimethylsiloxy)-3-(*tert*-butyldiphenylsiloxy)-1-nonyn-5-one ((+)-20). According to the procedure described for oxidation of (−)-**17**, (−)-**19** (146 mg, 0.33 mmol) was converted to the corresponding aldehyde. The crude aldehyde was used directly for the next reaction. A solution of Grignard reagent in Et_2O was adjusted as follows: 4-*tert*-butyldimethylsiloxybutyl-1-iodide (2.00 g, 6.37 mmol) in Et_2O (8.0 mL) was added to a suspension of magnesium powder (440 mg, 18.3 mmol) in Et_2O (4.0 mL). The mixture was vigorously stirred at room temperature for 30 min. The Grignard reagent (0.50 M, 1.32 mL, 0.66 mmol), thus prepared, was added to a solution of the crude aldehyde in CH_2Cl_2 (3.0 mL) at −78 °C. After being stirred for 20 min, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to leave the crude alcohol. The crude alcohol was then oxidized by DMP to afford the title compound (102 mg, 74%) as a colorless oil: $[\alpha]^{28}_D$ +33.6 (*c* 1.00, $CHCl_3$); IR 3306, 2122, 1716 cm^{-1}; ^1H NMR δ 7.75−7.66 (m, 4H), 7.43−7.24 (m, 11H), 4.71 (dd, 1H, J = 4.9, 2.4), 4.58, 4.56 (AB-q, 2H, J = 11.7), 3.89 (d, 1H, J = 4.9), 3.57 (t, 2H, J = 6.8), 2.66 (m, 1H), 2.57 (m, 1H), 2.29 (d, 1H, J = 2.4) 1.61−1.45 (m, 4H), 1.04 (s, 9H), 0.88 (s, 9H), 0.03 (s, 6H);^{13}C NMR δ 208.8, 137.3, 136.1, 135.9, 132.9, 132.7, 129.9, 129.7, 128.3, 127.9, 127.9, 127.6, 127.3, 86.7, 81.1, 75.8, 73.4, 64.6, 62.9, 40.0, 32.3, 26.8, 25.9, 19.3, 18.3, −5.3; MS *m*/*z* 628 (M^+ + 1, 1.4). Anal. Calcd for $C_{38}H_{52}O_4Si_2$: C, 72.56; H, 8.33. Found: C, 72.20, H, 8.53.

(2*E*,3*R*,4*R*,5*R*)-4-Benzyloxy-3-(*tert*-butyldiphenylsiloxy)-2-methoxycarbonylmethylidene-1,6-dioxaspiro[4.5]-decane ((−)-22). *p*-TsOH was added to a solution of (+)-**20** (61.0 mg, 0.10 mmol) in a combined solution of THF and H_2O (20:1, 3.0 mL) at room temperature. The reaction mixture was stirred at the same temperature for 4 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (1:1) to afford the crude alcohol. A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mg, 0.002 mmol) in MeOH (3.5 mL) was stirred under a CO atmosphere at room temperature for 30 min, to which a solution of the crude alcohol and benzoquinone (217 mg, 1.94 mmol) in MeOH (1.5 mL) was added. After being stirred for 48 h, MeOH was evaporated off and the residue was taken up in CH_2Cl_2, which was successively washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine, dried, and concentrated

to dryness. Chromatography of the residue with hexane−AcOEt (30:1) afforded (−)-**22** (23.0 mg, 41%) as a colorless oil: $[\alpha]^{26}_D$ −75.0 (*c* 1.00, $CHCl_3$); IR 1707, 1659 cm^{-1}; ^1H NMR δ 7.95−7.93 (m, 2H), 7.69−7.66 (m, 2H), 7.49−7.32 (m, 6H), 7.24−7.19 (m, 3H), 6.97−6.95 (m, 2H), 5.42(s, 1H), 5.39 (s, 1H), 3.98 (m, 1H), 3.77 (m, 1H), 3.70 (s, 2H), 3.61 (s, 1H), 3.31 (s, 3H), 1.95−1.56 (m, 6H), 1.03 (s, 9H); ^{13}C NMR δ 173.6, 167.0, 137.6, 136.6, 136.0, 133.9, 133.3, 129.9, 129.4, 128.1, 127.7, 127.4, 127.2, 127.0, 110.8, 93.7, 86.1, 73.6, 71.0, 62.4, 50.6, 28.7, 26.7, 24.8, 19.4, 19.1; FABMS *m/z* 573 (M^+ + 1, 1.1); FABHRMS calcd for $C_{34}H_{41}O_6Si$ 573.2672, found 573.2640.

(2*E*,3*R*,4*R*,5*R*)-4-Benzyloxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decan-3-ol ((−)-28). CuI (1.0 mg, 0.57 × 10^{-2} mmol) was added to a solution of (+)-**27** (3.3 mg, 0.11 × 10^{-1} mmol) and 1-propynyl iodide (0.20 × 10^{-1} mL, 0.19 mmol) in pyrrolidine (1.0 mL) at room temperature. The reaction mixture was stirred for 1.5 h, diluted with water, and extracted with Et_2O. The extract was washed with water, and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane-AcOEt (7:2) afforded (+)-**28** (2.50 mg, 67%) as a colorless oil: $[\alpha]^{27}_D$ −126.8 (*c* 0.36, $CHCl_3$); IR 3690, 2253, 2142, 1649 cm^{-1}; ^1H NMR δ 7.38−7.25 (m, 5H), 5.17 (br-s, 1H), 4.76 (d, 1H, *J* = 9.8 Hz), 4.73, 4.53 (AB-q, 2H, *J* = 12.0 Hz), 3.91−3.71 (m, 2H), 2.91 (d, 1H, *J* = 9.8 Hz), 2.00 (m, 1H), 1.98 (d, 3H, *J* = 1.0 Hz), 1.75−1.60 (m, 5H); ^{13}C NMR δ 171.5, 137.3, 128.5, 128.0, 127.7, 110.4, 85.7, 83.4, 79.8, 73.6, 71.9, 70.2, 64.9, 62.7, 28.0, 24.7, 18.6, 4.5; FABMS *m/z* 339 (M^+, 9.5); FABHRMS calcd for $C_{21}H_{23}O_4$ 339.1596, found 339.1595.

(2*E*,3*R*,4*R*,5*R*)-3-(*tert*-Butyldiphenylsiloxy)-2-(2-hydroxyethylidene)-1,6-dioxaspiro[4.5]decan-4-ol ((−)-29). According to the procedure described for reduction of (−)-**22**, (−)-**15** (79.0 mg, 0.14 mmol) was converted to the corresponding crude alcohol. A solution of lithium *tert*-butylbiphenylide in THF was prepared as follows: lithium (20.0 mg, 2.85 mmol) was added to a solution of *p,p′*-di-*tert*-butylbiphenyl (620 mg, 2.38 mmol) in THF (14 mL) at room temperature. The mixture was vigorously stirred at room temperature until the dark green radical anion was developed, at which time the reaction mixture was cooled in ice bath. Stirring was continued at 0 °C for 4 h. A solution of LiDBB in THF, thus prepared, was added to a solution of the crude alcohol in THF (3.0 mL) at −78 °C until the reaction mixture turned to deep green. After being stirred for 10 min at −78 °C, the reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane-AcOEt (1:1) afforded (−)-**29** (45.0 mg, 72%) as colorless needles: mp 178.5−179.5 °C (hexane−AcOEt); $[\alpha]^{24}_D$ −71.6 (*c* 0.74, THF); IR 3311, 3177, 1699 cm^{-1}; ^1H NMR δ 7.80−7.74 (4H, m) 7.48−7.41 (m, 6H), 5.25 (dt, 1H, *J* = 1.3, 7.9 Hz), 4.58 (br s, 1H), 4.14−3.68(m, 5H), 1.85−1.60 (m, 6H), 1.06 (s, 9H).; ^{13}C NMR δ 158.5, 136.0, 136.0, 133.3, 132.9, 130.2, 130.0, 128.0, 127.8, 107.3, 102.0, 80.9, 62.2, 58.6, 28.2, 26.8, 24.9, 19.4, 19.0; MS *m/z* 454 (M^+, 0.1); HRMS calcd for $C_{26}H_{34}O_5Si$ 454.2175, found 454.2174.

(2*E*,3*R*,4*R*,5*R*)-4-Benzoyloxy-2-propynylidene-1,6-dioxaspiro[4.5]decan-3-ol ((+)-31). BzCl (0.05 mL, 0.42 mmol) was added to a solution of (−)-**30** (6.20 mg, 0.14 × 10^{-1} mmol) in pyridine (1.5 mL) at room temperature. After being stirred for 20 min, the reaction mixture was quenched by addition of water and extracted with Et_2O, which was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (30:1) to afford the crude benzoate. To a solution of crude benzoxylate in THF (6.0 mL) was added TBAF·*x*H_2O (10.0 mg), and the reaction mixture was stirred for 4 h at room temperature, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (2:1) afforded (+)-**31** (4.10 mg, 95%) as a colorless oil: $[\alpha]^{26}_D$ +38.4 (*c* 0.37, $CHCl_3$); IR 3308, 2108, 1728, 1657 cm^{-1}; ^1H NMR δ 8.03−7.99 (m, 2H), 7.62−7.57 (m, 1H), 7.48−7.42 (m, 2H), 5.30 (s, 1H), 5.22 (m, 1H), 4.80 (d, 1H, *J* = 9.9 Hz), 3.98−3.78 (m, 2H), 3.04−3.01 (m, 2H) 1.85−1.60(m, 6H); ^{13}C NMR δ 169.3, 164.9, 133.6, 129.9, 128.9, 128.6, 109.6, 83.9, 80.3, 79.6, 78.9, 74.5, 62.7, 27.6, 24.4, 18.5; MS *m/z* 314 (M^+, 2.8); HRMS calcd for $C_{18}H_{18}O_5$ 314.1154, found 314.1157.

(2*E*,3*S*,4*R*,5*R*)-3,4-Epoxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane ((−)-AL-2). MsCl (0.87 × 10^{-2} mL, 0.11 mmol) was added to a solution of (+)-**32** (4.00 mg, 0.11 × 10^{-1} mmol) and Et_3N (0.28 × 10^{-1} mL, 0.20 mmol) in CH_2Cl_2 (0.50 mL) at 0 °C. After being stirred for 5 min, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2, which was washed with water and brine, dried, and concentrated to dryness. The crude methanesulfonate was used directly for the next reaction. K_2CO_3 (15.1 mg 0.11 mmol) was added to a solution of the residue in MeOH (1.5 mL), and the reaction mixture was stirred for 1 h. MeOH was evaporated off, and the residue was taken up in AcOEt, which was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (10:1) afforded (−)-**2** (2.1 mg, 79%) as a colorless oil: $[\alpha]^{27}_D$ −26.6 (*c* 0.14 $CHCl_3$) (lit.[2b] $[\alpha]^{20}_D$ −14 (*c* 0.5, $CHCl_3$)); IR 2143, 1655 cm^{-1}; ^1H NMR δ 5.18 (s, 1H), 4.29 (d, 1H, *J* = 2.5 Hz), 3.87 (dt, 1H, *J* = 3.0, 11.2 Hz), 3.80 (d, 1H, *J* = 2.5 Hz), 3.77 (m, 1H), 1.99 (s, 1H), 1.93−1.90 (m, 1H), 1.79−1.58 (m, 5H); ^{13}C NMR δ 164.9, 105.9, 85.9, 79.6, 69.8, 63.2, 60.0, 51.9, 28.8, 24.8, 18.7, 4.6; MS *m/z* 230 (M^+, 13.8); HRMS calcd for $C_{14}H_{14}O_3$ 230.0943, found 230.0945.

(2*E*,5*R*)-2-(2,4-Hexadiynylidene)-1,6-dioxaspiro[4.5]dec-3-ene ((−)-6). A solution of dimethyl diazomalonate (19.0 mg, 0.12 mmol) in toluene (0.5 mL) was added to a mixture of $Rh_2(OAc)_4·2H_2O$ (1.20 mg, 0.24 × 10^{-2} mmol) and **(−)-AL-2** (5.6 mg, 0.24 × 10^{-1} mmol) in toluene (2.0 mL) at room temperature. The reaction mixture was refluxed for 1 h. Toluene was evaporated off, and the residue was chromatographed with hexane−AcOEt (20:1) to afford (−)-**6** (4.5 mg, 86%) as a colorless oil: $[\alpha]^{29}_D$ −47.7 (*c* 0.09 Et_2O) (lit.[1b] $[\alpha]^{20}_D$ 0 (Et_2O)); IR 2190 2150 cm^{-1}; ^1H NMR δ 6.66 (d, 1H, *J* = 5.9 Hz), 6.22 (dd, 1H, *J* = 5.9, 2.0 Hz), 4.97 (br-s, 1H), 3.98 (m, 1H), 3.82 (m, 1H), 1.98 (d, 3H, *J* = 1.0 Hz), 1.95−1.86 (m, 1H), 1.81−1.59 (m, 5H); ^{13}C NMR δ 169.8, 138.4, 125.1, 112.7, 79.8, 79.6, 76.2, 71.6, 65.0, 64.3, 32.5, 24.4, 19.2, 4.7; MS *m/z* 214 (M^+, 9.0); HRMS calcd for $C_{14}H_{14}O_3$ 214.0994, found 214.0991.

(2*E*,3*S*,4*R*,5*S*)-3,4-Epoxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane ((+)-3). To a solution of (+)-**36** (1.7 mg, 0.89 × 10^{-2} mmol), $(allylPdCl)_2$ (1.0 mg, 0.27 × 10^{-2} mmol), $^tBu_3P$ (2.2 mg, 0.11 × 10^{-2} mmol), and Cs_2CO_3 (29.0 mg, 0.89 × 10^{-1} mmol) in DMF (1.5 mL) was added 1-propynyl iodide (14.8 mg, 0.89 × 10^{-1} mmol) at room temperature. After being stirred for 0.5 h, the reaction mixture was quenched by addition of water and extracted with Et_2O, which was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane−AcOEt (5:1) afforded (+)-**3** (1.4 mg, 68%) as a colorless oil: $[\alpha]^{26}_D$ +245.8 (*c* 0.01, $CHCl_3$) (lit.[2b] $[\alpha]^{20}_D$ +259 (*c* 0.5, $CHCl_3$)); IR 2146, 1653 cm^{-1}; ^1H NMR δ 5.14 (q, 1H, *J* = 1.0 Hz), 4.28 (d, 1H, *J* = 3.0 Hz), 3.90−3.87 (m, 2H), 3.79 (d, 1H, *J* = 3.0 Hz), 1.98 (d, 1H, *J* = 1.0 Hz), 1.85−1.60 (m, 6H); ^{13}C NMR δ 163.6, 105.9, 85.4, 79.7, 69.7, 64.7, 58.9, 52.2, 30.7, 24.4, 18.0; MS *m/z* 230 (M^+, 2); HRMS calcd for $C_{14}H_{14}O_5$ 230.0943, found 230.0945.

(2*E*,3*R*,4*R*,5*S*)-3,4-Diacetoxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane ((−)-4). A mixture of Cs_2CO_3 (52.0 mg, 0.16 mmol) and acetic acid (9.6 mg, 0.16 mmol) in DMF (1.0 mL) was heated at 80 °C for 1 h. The reaction mixture was cooled to room temperature, to which a solution of (+)-**36** (3.0 mg, 0.16 × 10^{-1} mmol) in DMF (0.7 mL) was added. The mixture was heated at 80 °C for 3 h. Ac_2O (0.15 × 10^{-1} mL, 0.16 mmol) and DMAP (19.5 mg, 0.16 mmol) were added to the mixture at 0 °C, which was then stirred for 5 min, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad

of silica gel with hexane−AcOEt (5:1) to afford the crude diacetate. The crude diacetate was exposed to the procedure described for cross coupling of (+)-**36** to afford the title compound (3.10 mg, 58%) as a colorless oil: $[\alpha]^{23}_{D}$ −0.9 (*c* 0.05, $CHCl_3$) (lit.[1g] $[\alpha]^{24}_{D}$ −1 (*c* 1.16, $CHCl_3$)); IR 2145, 1745, 1653 cm^{-1}; ^1H NMR δ 6.25 (dd, 1H, *J* = 7.9, 0.7 Hz), 5.17−5.14 (m, 2H), 3.83 (m, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.96 (s, 3H), 1.80−1.60 (m, 6H); ^{13}C NMR δ 170.4, 169.9, 164.1, 104.2, 83.8, 80.3, 78.4, 78.1, 73.1, 68.5, 64.5, 63.1, 30.6, 24.1, 20.9, 20.4, 18.7, 4.7; MS *m/z* 332 (M^+, 30); HRMS calcd for $C_{18}H_{20}O_6$ 332.1260, found 332.1247.

(2*E*,3*R*,4*R*,5*S*)-2-(2,4-Hexadiynylidene)-3-isovaleryloxy-1,6-dioxaspiro[4.5]decan-4-ol ((+)-5). A mixture of Cs_2CO_3 (52.0 mg, 0.16 mmol) and isovarelic acid (16.3 mg, 0.16 mmol) in DMF (1.0 mL) was heated at 80°C for 1 h. The reaction mixture was cooled to room temperature, to which a solution of (+)-**36** (3.0 mg, 0.16×10^{-1} mmol) in DMF (0.7 mL) was added. The mixture was heated at 80 °C for 3 h, quenched by addition of water, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (5:1) to afford the crude isovalerate. The crude isovalerate was exposed to the procedure described for cross-coupling of (+)-**36** to afford the title compound (3.60 mg, 68%) as a colorless oil: $[\alpha]^{24}_{D}$ +68.3 (*c* 0.04, $CHCl_3$) (lit.[1g] $[\alpha]^{24}_{D}$ +68 (*c* 2.28, $CHCl_3$)); IR 2145, 1745, 1653 cm^{-1}; ^1H NMR δ 5.99 (dd, 1H, *J* = 7.3, 2.3 Hz), 5.11 (br-s, 1H), 3.86−3.82 (m, 2H), 2.40 (dd, 1H, *J* = 15.6, 6.8 Hz), 2.31 (dd, 1H, *J* = 15.6, 7.3 Hz), 2.19 (m, 1H), 1.95 (br-s, 3H), 1.90−1.60 (m, 6H), 1.01 (d, 3H, *J* = 6.6 Hz), 1.00 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR δ 172.7, 164.6, 104.0, 83.4, 80.0, 79.7, 78.0, 76.0, 68.7, 64.6, 63.1, 42.7, 30.0, 25.4, 24.3, 22.6, 22.5, 18.6, 4.6; MS *m/z* 332 (M^+, 21); HRMS calcd for $C_{18}H_{20}O_6$ 332.1624, found 332.1622.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds (−)-**2**, (+)-**3**, (−)-**4**, (+)-**5**, (−)-**6**, (−)-**17**, (−)-**22**, (+)-**24**, (−)-**27**, (−)-**28**, (−)-**29**, (−)-**30**, (+)-**31**, (+)-**32**, and (+)-**36**; preparation and characterization data for compounds (+)-**24**, (−)-**25**, (−)-**26**, (−)-**27**, (−)-**30**, (+)-**32**, and (+)-**36**; characterization data for compounds (+)-**17**, (+)-**18**, (+)-**19**, (−)-**20**, (+)-**22**, (+)-**29**, and (+)-**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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