

Total Syntheses of Naturally Occurring Diacetylenic Spiroacetal Enol Ethers

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A highly stereoselective method for constructing a (2E)-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 (2E)-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-13acetate (TPA) treatment.^{1h,3} Thus, it was discovered that AL-1 (1) strongly inhibits TPA-induced tumor promo-



FIGURE 1. Typical diacetylenic spiroacetal enol ethers.

tion.^{1h,3} The simpler 8-deisovaleryloxy congener, the socalled 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 reports⁵ 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

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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.; Artes, 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 (–)-(2E,3S,4R,5R)-3,4-epoxy-2-(2,4-hexadi-ynylidene)-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.

SCHEME 1



products except for the total synthesis of the structurally simplest (\pm) -**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 program⁷ 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 (2E)-2-(2,4-hexadivnylidene)-1,6-dioxaspiro[4.5]decane 7 for these natural products, might be constructed by the metal-catalyzed acetal formation and spontaneous COinsertion 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 coworkers⁸ developed a novel palladium-catalyzed ringclosing reaction⁹ 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 Akita¹⁰ recently reported the palladium-catalyzed formation of oxacycles **15** with (*E*)-methoxycarbonylmeth-





ylidene functionality from 4-yn-1-ones derivatives14 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 group¹¹ 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.

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 trimethylsilyldiazomethane¹⁴ and "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 $^{13}\mathrm{C}$ 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.



^{*a*} Reaction conditions: (a) PivCl, Et₃N, CH₂Cl₂, -78 °C; (b) TBDPSCl, imid, DMF, 50 °C; (c) EtMgBr, Et₂O rt (76%); (d) Dess–Martin oxidation, CH₂Cl₂, 0 °C to rt; (e) TMSCHN₂, ^{*n*}BuLi, THF, -78 °C (72%); (f) PPTS, MeOH, rt (75%); (g) (i) Dess–Martin oxidation, CH₂Cl₂, 0 °C to rt, (ii) TBDMSO(CH₂)₄MgI, Et₂O–CH₂Cl₂, -78°C, (iii) Dess–Martin oxidation, CH₂Cl₂, 0 °C to rt (74%).

SCHEME 4^a



 a Reaction conditions: (a) p-TsOH, THF $-H_2O$, rt; (b) Pd₂(dba)₃· CHCl₃ (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 (2E)-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 PdCl₂(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





FIGURE 2. Stereoselective formation of 22.

selective manner. Increasing the amounts of PdCl₂- $(MeCN)_2$ 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 PdCl₂(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 Pd₂(dba)₃. CHCl₃ 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 ⁱPrOH) were used as a solvent. In addition, 'BuOH gave an intractable mixture.

Exclusive formation of 22, the (5R)-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 C₄-benzyloxy functionality to avoid a nonbonding interaction leading to the exclusive construction of 22 with the (5R)-stereochemistry. We could now synthesize the (2E)-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 disobutylaluminum hydride (DIBAL-

⁽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 (4R,5S)-compounds, an enhancement between H-4 and H-10 was observed in the NOE experiments.^{1g,5}

SCHEME 5^a BnO TBDPSO TBDPSO а b.c MeO₂C нó 25 22 BnC Bn(BO HO 26 : R = TBDPS 28 27 : R = H

 a Reaction conditions: (a) DIBAL-H, CH₂Cl₂, -78 °C (92%); (b) MnO₂, CH₂Cl₂, rt; (c) TMSCHN₂, 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 trimethylsilyldiazomethane¹⁴ and ⁿBuLi to afford the envne 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 silvl protecting group on the C₃-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 pyrrolidine¹⁸ 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 C₃-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 silvl group on the C₃-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 enedivne 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 desilvlation 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 envne



 a Reaction conditions: (a) DIBAL-H, CH₂Cl₂, -78 °C; (b) LiDBB, THF, -78 °C (72%); (c) MnO₂, CH₂Cl₂, rt; (d) TMSCHN₂, 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, Et₃N, CH₂Cl₂, rt; (i) K₂CO₃, 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 C₃-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 $[\alpha]^{20}_{D} \pm 0$ ^{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 attempt²⁰ 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 (\pm) -6.^{6a,b} The synthetic (-)-6 with the (5R)-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 C₅-epimer 3 under acidic conditions. As a matter of fact, a solution of AL-2 (2) in MeOH-Et₂O (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-Et₂O 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 (5S)-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-hvdroxyl-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 conditions²³ were found to be suitable for this transformation. Indeed, 36 was exposed to [(allyl)PdCl]₂ and tri-(tert-butyl)phosphine in DMF²³ at room temperature in



SCHEME 9^a



 a Reaction conditions: (a) MsCl, Et₃N, CH₂Cl₂, 0 °C; (b) TBAF, THF, rt to reflux (quant); (c) 1-propynyl iodide, [(allyl)PdCl]₂, 'Bu₃P, Cs₂CO₃, DMF, rt (78%); (d) (i) AcOH, Cs₂CO₃, DMF, 80 °C, then Ac₂O, DMAP, DMF, 0 °C, (ii) 1-propynyl iodide, [(allyl)PdCl]₂, 'Bu₃P, Cs₂CO₃, DMF, rt (58%); (e) (i) isovaleric acid, Cs₂CO₃, DMF, 80 °C, (ii) 1-propynyl iodide, [(allyl)PdCl]₂, 'Bu₃P, Cs₂CO₃, DMF, rt (64%).

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 C₃-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 acetate²⁵ 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-3isovaleroxy 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.

⁽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.:

⁽²⁵⁾ Sohem, A.; Albaneze-waker, 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 (2E)-2-methoxymethylidene-1,6-dioxaspiro[4.5]decane skeleton by the palladium (II)-catalyzed ring-closing reaction of the 3,4dioxygenated-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), C₅-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

(2S,3S)-3-Benzyloxy-4-(tert-butyldimethylsiloxy)-2-(tertbutyldiphenylsiloxy)butan-1-ol ((-)-17). A solution of PivCl (1.19 mL, 9.70 mmol) in CH₂Cl₂ (12 mL) was added to a solution of 16 (3.00 g, 9.20 mmol), Et₃N (3.67 mL, 27.6 mmol), and DMAP (0.11 g, 0.92 mmol) in CH₂Cl₂ (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 CH₂Cl₂. 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 Et₂O. 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 crudeT-BDPS-protected product in Et₂O (90 mL) was added EtMgBr in Et₂O (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 Et₂O. 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 $-18.0 (c \ 1.00, \text{CHCl}_3); \text{IR } 3612 \text{ cm}^{-1}; {}^{1}\text{H} \text{ NMR } \delta 7.68 - 7.64 (m,)$ 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); $^{13}\mathrm{C}$ 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 C₃₃H₄₈O₄Si₂ 564.3091, found 564.3095.

(3S,4S)-4-Benzyloxy-5-(tert-butyldimethylsiloxy)-3-(tertbutyldiphenylsiloxy)pent-1-yne ((-)-18). To a solution of (-)-17 (400 mg, 0.71 mmol) in CH₂Cl₂ (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 Et₂O. 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(N2) in THF (2.0 mL), prepared from reaction of TMSCHN₂ in hexane (1.50 M, 2.00 mL, 3.00 mmol) and "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 Et₂O. 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: $[\alpha]^{25}_{D} = -0.5 (c \ 1.00, \text{CHCl}_{3}); \text{ IR } 3306, 2120 \text{ cm}^{-1};$ 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 (dd, 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 $\rm C_{34}H_{46}O_3Si_2$: C, 73.07; H, 8.30. Found: C, 72.71, H, 8.57.

(2S,3S)-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 NaHCO₃, 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, CHCl₃); 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); ¹³C 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 C₂₈H₃₂O₃Si: C, 75.63; H, 7.25. Found: C, 75.55, H, 7.26.

(3S,4R)-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 Et₂O was adjusted as follows: 4-tert-butyldimethylsiloxybutyl-1-iodide (2.00 g, 6.37 mmol) in Et₂O (8.0 mL) was added to a suspension of magnesium powder (440 mg, 18.3 mmol) in Et₂O (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 CH₂Cl₂ (3.0 mL) at -78 °C. After being stirred for 20 min, the reaction mixture was quenched by addition of saturated aqueous NH₄-Cl and extracted with Et₂O. 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, CHCl₃); 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);¹³C 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, $-5.3;\,\mathrm{MS}\;m\!/\!z$ 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.

(2E,3R,4R,5R)-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 H₂O (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 NaHCO₃, and extracted with Et₂O. 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 Pd₂(dba)₃·CHCl₃ (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 CH₂Cl₂, which was successively washed with saturated aqueous Na₂S₂O₃, saturated aqueous NaHCO₃, 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: $[\alpha]^{26}_{\rm D}$ –75.0 (*c* 1.00, CHCl₃); 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); ¹³C NMR δ 173.6, 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); FAB-HRMS calcd for C₃₄H₄₁O₆Si 573.2672, found 573.2640.

(2E,3R,4R,5R)-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 \times 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 Et₂O. 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 (brs, 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); ¹³C 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 C₂₁H₂₃O₄ 339.1596, found 339.1595.

(2E,3R,4R,5R)-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).; ¹³C 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 C₂₆H₃₄O₅Si 454.2175, found 454.2174.

(2E,3R,4R,5R)-4-Benzoyloxy-2-propynylidene-1,6dioxaspiro[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 Et₂O, 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· xH_2O (10.0 mg), and the reaction mixture was stirred for 4 h at room temperature, quenched by addition of water, and extracted with Et₂O. 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: $[\alpha]^{26}_{D} + 38.4 (c \ 0.37, \text{CHCl}_3);$ 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); ¹³C 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 C₁₈H₁₈O₅ 314.1154, found 314.1157.

(2E,3S,4R,5R)-3,4-Epoxy-2-(2,4-hexadiynylidene)-1,6dioxaspiro[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 \times 10^{-1} mmol) and Et₃N (0.28 imes 10^{-1} mL, 0.20 mmol) in CH₂Cl₂ (0.50 mL) at 0 °C. After being stirred for 5 min, the reaction mixture was quenched by addition of water and extracted with CH₂Cl₂, which was washed with water and brine, dried, and concentrated to dryness. The crude methanesulfonate was used directly for the next reaction. K₂CO₃ (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 CHCl₃) (lit.^{2b} [α]²⁰_D -14 (c 0.5, CHCl₃)); 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); $^{13}\mathrm{C}$ 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 C₁₄H₁₄O₃ 230.0943, found 230.0945.

(2E,5R)-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 Rh₂-(OAc)₄·2H₂O (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 Et₂O) (lit.^{1b} $[\alpha]^{20}_D$ (0 (Et₂O)); 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); ¹³C 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 C₁₄H₁₄O₃ 214.0994, found 214.0991.

(2E,3S,4R,5S)-3,4-Epoxy-2-(2,4-hexadiynylidene)-1,6dioxaspiro[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), $^t\mathrm{Bu}_3\mathrm{P}$ (2.2 mg, 0.11 imes 10⁻² mmol), and $\mathrm{Cs_2CO_3}$ (29.0 mg, 0.89 \times 10⁻¹ mmol) in DMF (1.5 mL) was added 1-propynyl iodide $(14.8 \text{ mg}, 0.89 \times 10^{-1} \text{ mmol})$ at room temperature. After being stirred for 0.5 h, the reaction mixture was quenched by addition of water and extracted with Et₂O, 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, CHCl₃) (lit.^{2b} [α]²⁰_D +259 (c 0.5, CHCl₃)); 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); ¹³C 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 C₁₄H₁₄O₅ 230.0943, found 230.0945.

(2E,3R,4R,5S)-3,4-Diacetoxy-2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane ((-)-4). A mixture of Cs₂CO₃ (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. Ac₂O (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 Et₂O. 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); ¹³C 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 *mlz* 332 (M⁺, 30); HRMS calcd for C₁₈H₂₀O₆ 332.1260, found 332.1247.

(2E,3R,4R,5S)-2-(2,4-Hexadiynylidene)-3-isovaleryloxy-1,6-dioxaspiro[4.5]decan-4-ol ((+)-5). A mixture of Cs₂CO₃ (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 Et₂O. 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: $[\alpha]^{24}_{\rm D}$ +68.3 (*c* 0.04, CHCl₃) (lit.^{1g}
$$\begin{split} & [\alpha]^{24}{}_{\rm D} + 68~(c~2.28,~{\rm CHCl}_3));~{\rm IR}~2145,~1745,~1653~{\rm cm}^{-1};~^{1}{\rm H}~{\rm NMR}\\ & \delta~5.99~({\rm dd},~1{\rm H},~J=7.3,~2.3~{\rm Hz}),~5.11~({\rm br-s},~1{\rm H}),~3.86-3.82~({\rm m},~2{\rm H}),~2.40~({\rm dd},~1{\rm H},~J=15.6,~6.8~{\rm Hz}),~2.31~({\rm dd},~1{\rm H},~J=15.6,~7.3~{\rm Hz}),~2.19~({\rm m},~1{\rm H}),~1.95~({\rm br-s},~3{\rm H}),~1.90-1.60~({\rm m},~6{\rm H}),~1.01~({\rm d},~3{\rm H},~J=6.6~{\rm Hz}),~1.00~({\rm d},~3{\rm H},~J=6.6~{\rm Hz});~^{13}{\rm C}~{\rm NMR}~\delta~172.7,~164.6,~104.0,~83.4,~80.0,~79.7,~78.0,~76.0,~68.7,~64.6,~63.1,~42.7,~30.0,~25.4,~24.3,~22.6,~22.5,~18.6,~4.6;~{\rm MS}~m/z~332~({\rm M}^+,~21);~{\rm HRMS}~{\rm calcd}~{\rm for}~{\rm C}_{18}{\rm H}_{20}{\rm O}_{6}~332.1624,~{\rm found}~332.1622. \end{split}$$

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Supporting Information Available: ¹H and ¹³C 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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