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# First Total Synthesis of (−)-AL-2

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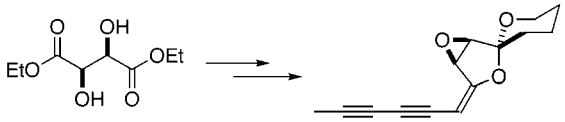
## ABSTRACT




Dietyl L-Tartrate (-)-AL-2

**Treatment of the 3,4-dioxygenated-9-hydroxy-1-nonyn-5-one derivative, derived from diethyl L-tartrate, with a palladium catalyst in methanol under a CO atmosphere effected an intramolecular acetalization and a stereoselective construction of the (*E*)-methoxycarbonylmethylidene functionality resulting in formation of the core framework of the diacetylenic spiroacetal enol ether natural products. Chemical transformations of the 1,6-dioxaspiro[4.5]decane derivative thus formed led to the first total synthesis of (−)-AL-2.**

A wide range of biological and pharmacological activities of the genus *Artemisia* have been reported with more than 10 diacetylenic spiroacetal enol ether derivatives being isolated from this plant family.[1] These diacetylenic spiroacetal enol ethers have a common structural feature, the (2*E*)-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane framework,[1f,2] as exemplified by several related natural products **1**−**4** (Figure 1). 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 $H_2O_2$ production induced by TPA treatment.[1f,3] Thus, it was discovered that AL-1 (**1**) strongly inhibits 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor promotion.[1f,3] The 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**).[1f,3] Despite its unique structural features and promising biological activity, no previous 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 products except for the total synthesis of

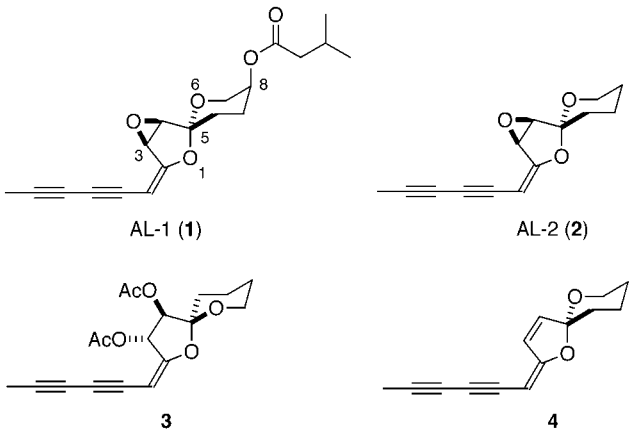



**Figure 1.**

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

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

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

(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-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.5]decane. This numbering system is used for the dioxaspiro compounds in this manuscript.

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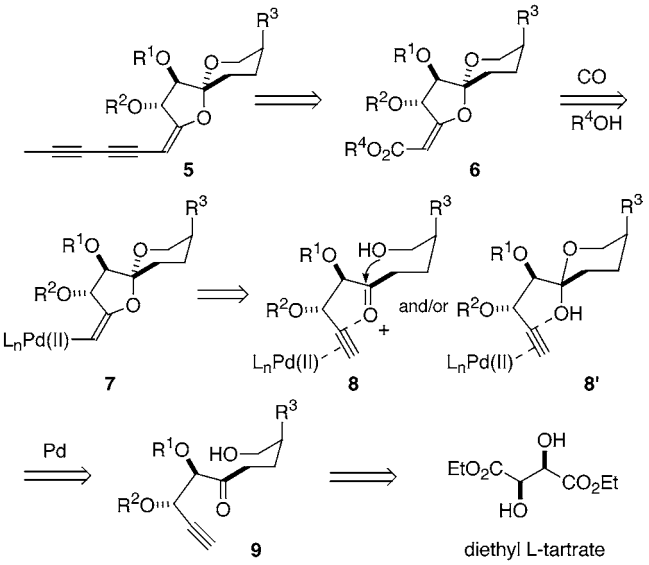
(±)-**4**,[6] the racemic 3,4-deoxygenated analogue of **2**, which did not control the stereochemistry of an enediyne moiety.

As part of our program[7] to design a highly stereocontrolled total synthesis of natural products from commercially available tartaric acid derivatives, we have focused considerable attention on the total synthesis of a series of diacetylenic spiroacetal enol ether natural products. A general retrosynthetic analysis of not only AL-1 (**1**) and AL-2 (**2**) but also of their related natural products is outlined in Scheme 1. We envisioned that the two chiral centers of L-tartrate

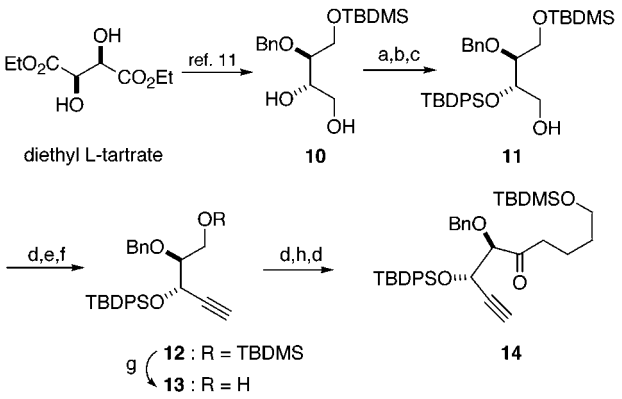
**Scheme 1**




would be incorporated into the C-3 and C-4 positions of the target natural products **5**. Kato and Akita[8] very recently reported the palladium(II)-catalyzed formation of the 2-methoxy-(5*E*)-methoxycarbonylmethylidenetetrahydrofuran framework from the corresponding 1-yne-4-one and 2-yn-5-one derivatives.[9] Thus, the 3,4-dioxygenated-9-hydroxy-1-nonyn-5-one species **9**, prepared from diethyl L-tartrate, 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,[8] which involve (i) palladium(II)-catalyzed formation of the intermediate **8** and/or the hemiacetal species **8′**,[10] (ii) followed by intramolecular capture of the transient oxonium ion species **8** by the terminal hydroxyl group, and/or nucleophilic attack of the hemiacetal hydroxyl group on the activated triple bond of **8′**, and finally (iii) the palladium-mediated carbon monoxide insertion reaction (conversion of **7** into **6**) leading to the 1,6-dioxaspiro[4.5]decane skeleton **6** having an (*E*)-alkoxycarbonylmethylidene moiety. This 1,6-dioxaspiro[4.5] compound **6** would be a useful intermediate for further chemical elaboration resulting in the stereoselective synthesis of various diacetylenic spiroacetal enol ether natural products **5**. This Letter describes our preliminary results regarding (i) the stereocontrolled construction of the (2*E*)-methoxycarbonylmethylidene-3,4-dioxygenated-1,6-dioxaspiro[4.5]decane framework and (ii) its application to the first total synthesis of (−)-AL-2 (**2**).

The required alkyne derivatives **14** possessing suitable functionalities for the palladium-catalyzed ring closure reaction was prepared by conventional means as depicted in Scheme 2. The selective introduction of a pivaloyl group on

**Scheme 2**[a]




[a] Reaction conditions: (a) PivCl, $Et_3N$, $CH_2Cl_2$, −78 °C; (b) TBDPSCl, imidazole, DMF, 50 °C; (c) EtMgBr, $Et_2O$ rt, (76%); (d) Dess−Martin oxidation, $CH_2Cl_2$, 0 °C to room temperature; (e) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C; (f) $^n$BuLi, THF, −78 °C, (72%); (g) PPTS, MeOH, rt, (75%); (h) TBDMSO$(CH_2)_4$MgI, $CH_2Cl_2$, −78 °C, (74%).

the primary alcohol moiety of the known diol **10**, derived from diethyl L-tartrate according to Saito's procedure,[11] was followed by treatment with *tert*-butyldiphenylsilyl (TBDPS) chloride and then ethylmagnesium bromide to afford **11** in 76% yield. Dess−Martin oxidation of **11** gave the corresponding aldehyde, which was subsequently exposed to Corey's conditions (dibromoolefination conditions with carbon tetrabromide and triphenylphosphine and then *n*-butyllithium treatment)[12] to produce the alkyne derivative

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

(6) Bohlmann, F.; Florentz, G. *Chem. Ber.* **1966**, *99*, 990.

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

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

(9) For similar palladium(II)-catalyzed reactions, see: (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *54*, 1845. (b) Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127. (c) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (d) Okumoto, H.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 217. (e) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764 and references therein.

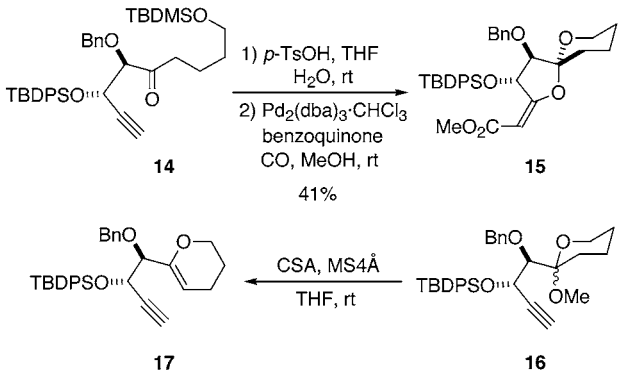
(10) Yamamoto suggested the intermediacy of the hemiacetal species for the palladium(II)-catalyzed formation of oxacycles from the carbon-tethered acetylenic aldehydes on the basis of the $^{13}$C NMR experiments. See ref 9e.

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

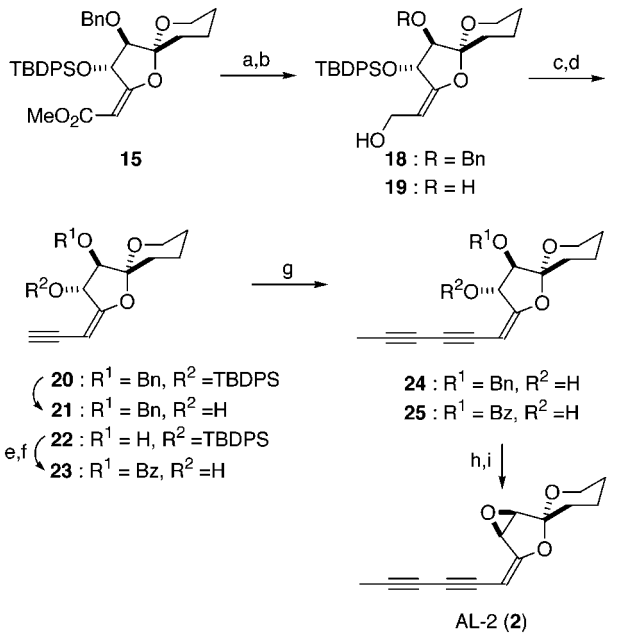
**12** in 72% yield. A selective desilylation of the primary silyl ether of **12** was realized by treatment with pyridinium *p*-toluenesulfonate (PPTS) in methanol to furnish **13** in 75% yield. Transformation of **13** into the required alkyne **14** was accomplished as follows. Oxidation of **13** with Dess−Martin periodinane gave the aldehyde, which was reacted with the functionalized $C_4$-Grignard reagent. The resulting secondary hydroxyl compound was oxidized by Dess−Martin periodinane to provide **14** in 74% yield.

According to the retrosynthetic analysis described in Scheme 1, the crucial transformation of **14** into the (2*E*)-2-(methoxycarbonylmethylidene)-1,6-dioxaspiro[4.5]decane framework was investigated. A selective desilylation of **14** was carried out by *p*-TsOH in THF at room temperature to afford the corresponding primary hydroxyl compound, which was then exposed to catalytic amounts of palladium(II) catalysts in the presence of an oxidizing agent such as benzoquinone under various conditions.[13] However, the isolable product from the reaction mixture was not the desired **15** but the tetrahydropyran derivative **16**,[14] although a trace amount of **15** was sometimes detected. The structure of **16** was confirmed by conversion to **17** under conventional conditions. The preferential formation of **16** over **15** was tentatively rationalized in terms of the Lewis acidic property of the palladium(II) catalyst,[9e] which might have catalyzed intramolecular acetalization prior to activation of the triple bond. After screening several conditions, we finally found that by using a catalytic amount of palladium(0) catalyst and excess amounts of oxidizing reagent, 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 the undesired acetal. Thus, the primary hydroxyl compound, prepared from **14**, was submitted to 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 equiv of benzoquinone in methanol under a carbon monoxide atmosphere at room temperature to produce the desired **15** in 41% yield as the sole product.[15,16] 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 (−)-AL-2 (**2**) were constructed in a stereocontrolled fashion. Therefore, our next efforts focused on the first total synthesis of (−)-AL-2 (**2**). The oxaspiro compound **15** was reduced with diisobutylaluminum hydride (DIBAL-H) to give **18**, which was subsequently transformed into **20** by the standard method.[17] However, introduction of the propyne moiety to the triple-bond terminus of **20** could not be realized, even under various conditions, presumably because of the bulkiness of the silyl protecting group on the $C_3$-hydroxyl moiety. Thus, the hydroxyl congener **21**, prepared from **20** by removal of the TBDPS group on the $C_3$-hydroxyl functionality, underwent a coupling reaction with 1-propynyl iodide in the presence of copper(I) iodide[18] to produce **24**. It turned out that debenzylation of **24** 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 **24** was also found to be ineffective for the debenzylation reaction. On the basis of these unsuccessful preliminary experiments, two considerations became apparent. To complete the transfor-

**Scheme 3**




**Scheme 4**[a]




[a] Reaction conditions: (a) DIBAL-H, $CH_2Cl_2$, −78 °C; (b) LiDBB, THF, −78 °C, (**19**: 72%); (c) $MnO_2$, $CH_2Cl_2$, rt; (d) $TMSCHN_2$, $^nBuLi$, THF, −78 °C, (**22**: 84%); (e) BzCl, pyridine, rt; (f) TBAF, THF, rt, (**23**: 95%); (g) $CH_3C{\equiv}C$-I, CuI, pyrrolidine, rt, (**25**: 60%); (h) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C; (i) $K_2CO_3$, MeOH, rt, (**2**: 79%).

(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(13) Reaction was monitored under various conditions by changing the kinds of palladium(II) catalysts and oxidizing reagents as well as the amounts of catalysts and oxidizing reagents.
(14) Mixture of diastereoisomers was obtained.
(15) Structure of **15** 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 **3**-related (4*R*,5*S*)-compounds, an enhancement between H-4 and H-10 was observed in the NOE experiments.[1f,5c]
(16) Exclusive formation of the (5*R*)-isomer might be tentatively explained by assuming that the reaction proceeds via oxonium intermediate **8**.[8]
(17) Procedure similar to the conversion of **19** into **22** was employed.
(18) Alami, M.; Ferri. F. *Tetrahedron Lett.* **1996**, *37*, 2763.

mation of **15** into the target natural product, (−)-AL-2 (**2**), removal of the bulky silyl protecting group on the $C_3$-hydroxyl moiety prior to the introduction of the terminal propyne moiety was essential, and 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, the first total synthesis of (−)-AL-2 (**2**) was completed as follows. DIBAL-H reduction of **15** was followed by debenzylation with lithium di-*tert*-butylbiphenylide (LiDBB)[19] in THF at −78 °C to furnish the diol **19** in 72% yield. Compound **19** was oxidized with $MnO_2$ to provide the corresponding aldehyde, which was subsequently exposed to lithium trimethylsilyldiazomethylide[20] to afford **22** in 84% yield. Conversion of **22** into **23** was realized by consecutive introduction of a benzoyl group on a $C_4$-hydroxyl group and desilylation under conventional conditions to afford **23** in 95% yield. Construction of the enediyne moiety was achieved by exposure of **23** to 1-propynyl iodide in the presence of copper(I) iodide and pyrrolidine[18] at room temperature to produce **25** in 60% yield. The final phase of this synthesis was the formation of the epoxide. Compound **25** was treated with mesyl chloride and triethylamine to give the $C_3$-mesyloxy derivative, which was then 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 on the basis of their spectral data.

Thus, we achieved the first total synthesis of (−)-AL-2 (**2**) highly stereoselectively from diethyl L-tartrate. (+)-AL-2, ent-**2**, can also be prepared from commercially available D-tartrate according to this newly developed synthetic protocol. On the other hand, the 3,4-epoxy functionality of **2** was shown to be susceptible to nucleophilic ring-opening reaction at the $C_3$-position[2b] with inversion of stereochemistry.[1g] In addition, epimerization of the $C_6$-stereogenic center[1g,2b] was also observed. On the basis of these facts, it can be assumed that the chemical transformation of (−)-**2** and/or (+)-**2** to other related natural products would be feasible. Studies on the total synthesis of similarly related diacetylenic spiroacetal enol ether natural products are now in progress.

**Acknowledgment.** This work was supported in part by a Grant-In-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, to which the authors thanks are due.

**Supporting Information Available:** Experimental procedures for conversion of **10** to (−)-**2** and $^1H$ and $^{13}C$ NMR spectra for **2**, **11**−**15**, **19**, **22**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0300569

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(20) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun*. **1992**, 721.
(21) Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. *Synlett.* **1998**, 35.