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Enantioselective Total Synthesis of RQN-18690A (18-Deoxyherboxidiene)

Yasunobu Matsumoto,*[,†,‡] Kazuhiro Hibino,[§] Masahiro Yonaga,[†,‡] Hideaki Kakeya,[∥,⊥] and Yujiro Hayashi*[,#]

[†]Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]Discovery Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan

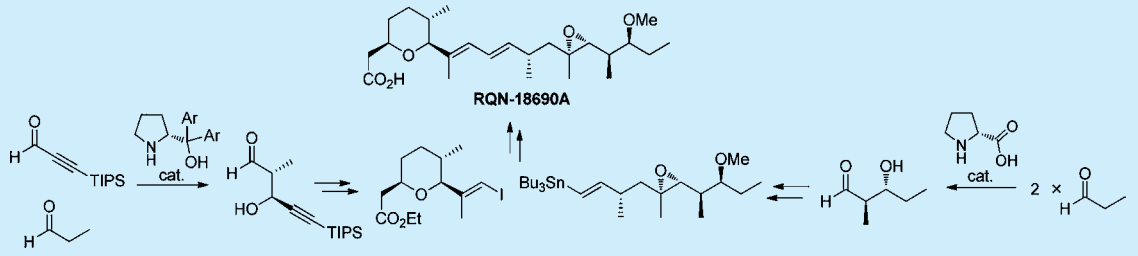
[§]Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka Shinjuku-ku, Tokyo 162-8601, Japan

[∥]Department of System Chemotherapy and Molecular Sciences, Division of Bioinformatics and Chemical Genomics, Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

[⊥]Chemical Biology Research Group, RIKEN Center for Sustainable Resource Science, Wako, Saitama 351-0198, Japan

[#]Department of Chemistry, Graduate School of Science, Tohoku University, 6-3 Aramaki-Aza Aoba, Aoba-ku, Sendai 980-8578, Japan

Supporting Information



ABSTRACT: The first total synthesis of RQN-18690A (18-deoxyherboxidiene) and the determination of its absolute stereochemical configuration are described. The synthesis features an organocatalytic aldol reaction for the first step, 1,4- and 1,2-dual reductions of α,β-unsaturated δ-lactone followed by a domino reaction in a one-pot operation, and diastereoselective epoxidation with kinetic resolution.

RQN-18690A, 18-deoxyherboxidiene (**1**, Figure 1), is produced by the actinomycete *Streptomyces* sp. QN18690 and was isolated as a promising angiogenesis inhibitor.[1] RQN-18690A (**1**) targets SF3b in the spliceosome, which is responsible for pre-mRNA splicing. For the past few years, several natural products have been reported to inhibit pre-mRNA splicing. For example, herboxidiene (**2**) binds to spliceosome-associated protein (SAP) 155, a subunit of SF3b, in the splicesome,[2] and Spliceostatin A, a methylated derivative of FR901464, interacts with SAP 130 or SAP155.[1,3] Pladienolide binds to SAP 130, and its analog E7107 has been evaluated in clinical trials for the treatment of various cancers.[4] Thus, by binding to the SF3b subunit of the spliceosome, these natural products have revealed a novel mechanism of action that has attracted considerable attention.

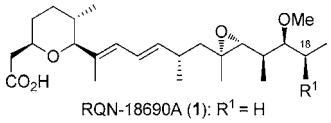


Figure 1. Structure of RQN-18690A (**1**) and herboxidiene (**2**).

RQN-18690A (**1**) has an effect on the spliceosome similar to that of Spliceostatin A and may, therefore, have potential as a novel anticancer agent. RQN-18690A (**1**) possesses several synthetically challenging structural features, including a trisubstituted tetrahydropyran core, a conjugated diene moiety, and a side chain containing five stereocenters. Its relative stereochemistry has been assigned by examining its physicochemical properties and via extensive NMR analysis; however, its absolute stereochemistry had not been determined. Moreover, the data also revealed that the chemical structure of RQN-18690A is an analog of herboxidiene (**2**), except that it lacks the C18 hydroxy group. While various approaches to synthesis of herboxidiene (**2**) have been reported owing to its challenging chemical structure and characteristic biological activities,[5] there is no synthetic effort for RQN-18690A (**1**). In this paper, the first total stereocontrolled synthesis of RQN-18690A (**1**) and its absolute stereochemical assignment were accomplished via an asymmetric direct aldol reaction catalyzed by a diarylprolinol derivative or proline as the key reaction.

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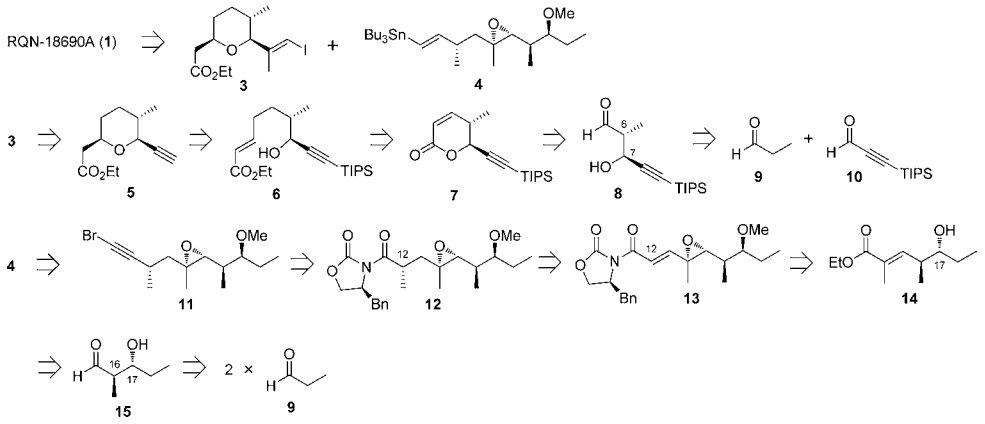
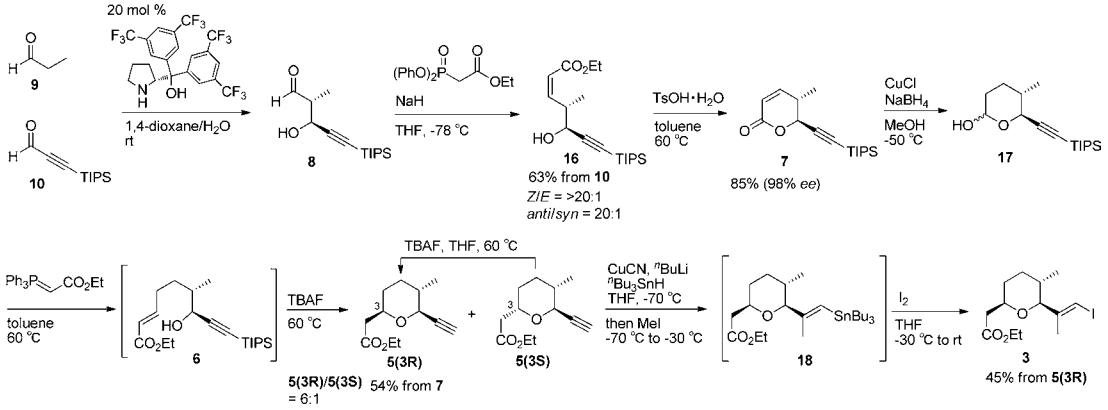
Scheme 1. Retrosynthetic Analysis of RQN-18690A (1)



Scheme 2. Synthesis of Vinyl Iodide 3



Our retrosynthetic analysis is shown in Scheme 1. The *E,E* diene moiety of RQN-18690A (**1**) could be assembled through the Stille coupling reaction to attach the vinyl iodide **3** and vinyl stannane **4** at a late stage.[6] The vinyl iodide **3** would be transformed from terminal alkyne **5**. The trisubstituted tetrahydropyran moiety would be constructed via reduction of *α,β*-unsaturated lactone **7**, a Wittig reaction, and an intramolecular *oxa*-Michael reaction of the corresponding hydroxy *α,β*-unsaturated ester **6**. Then, *α,β*-unsaturated lactone **7** would be prepared from aldehyde **8** by the *cis*-selective Horner–Wadsworth–Emmons reaction, followed by lactonization. To construct the C6 and C7 stereocenter of aldehyde **8**, a cross-aldol reaction of propanal (**9**) and (triisopropylsilyl)-propynal (**10**) catalyzed by a diarylprolinol derivative would be employed, as recently reported.[7] The vinyl stannane **4** would be delivered from alkynyl bromide **11**, which can be obtained by the transformation of oxazolidinone **12**. The stereocenter at C12 of oxazolidinone **12** would be constructed via asymmetric methylation using the Evans oxazolidinone auxiliary of **13**. The optically active methyl ether **13** would be synthesized with the inversion of the hydroxyl group of ester **14** via a Mitsunobu reaction, followed by methyl etherification. The stereochemistry of the chiral epoxide would be controlled by a metal catalyst-directed epoxidation by the use of the C17 chiral hydroxyl group of ester **14**. Ester **14** would be prepared from aldehyde **15** via a Wittig reaction, in which the consecutive chiral centers C16 and C17 would be constructed by an asymmetric direct self-aldol reaction of propanal (**9**).

The synthesis of vinyl iodide **3** was initiated with the asymmetric cross aldol reaction followed by a Horner–Wadsworth–Emmons reaction[8] (Scheme 2). Therefore, 1.5 equiv of propanal (**9**) and (triisopropylsilyl)propynal (**10**) treated with 20 mol % of trifluoromethyl-substituted diarylprolinol and 3 equiv of water in 1,4-dioxane gave aldol product **8**, which was directly treated with Ando's reagent[9] via a Horner–Wadsworth–Emmons reaction to afford *Z*-*α,β*-unsaturated ester **16** at a 63% yield with excellent *Z*-selectivity (*Z*/*E* = >20:1) and excellent *anti* selectivity (*anti*/*syn* = 20:1). Next, the intramolecular lactonization of ester **16** under acidic conditions proceeded smoothly to provide *α,β*-unsaturated *δ*-lactone **7**, which showed sufficiently high optical purity, as determined by HPLC analysis of the chiral phase (98% ee). Next, 1,4- and 1,2- double reductions of *α,β*-unsaturated *δ*-lactone **7** using CuCl–$NaBH_4$ in a MeOH system efficiently afforded the corresponding saturated *δ*-lactol **17**.[10] The reduction of *α,β*-unsaturated *δ*-lactone **7** to lactol **17** via successive 1,4- and 1,2-reduction in a single pot is a clear synthetic advantage. To obtain the trisubstituted tetrahydropyran core, we evaluated an intramolecular *oxa*-Michael reaction after the Wittig reaction. Lactol **17** was treated with a Wittig reagent in toluene at 60 °C for 6 h, affording the hydroxy *α,β*-unsaturated ester **6**.

Without isolation, addition of TBAF to the same pot, followed by heating the reaction mixture at 60 °C for 0.5 h, gave a mixture of the desired tetrahydropyran **5(3R)** and **5(3S)** isomers (**5(3R)**:**5(3S)** = 6:1). Purification by column chromatography afforded a pure **5(3R)** isomer at a 48% yield and the **5(3S)** isomer at an 8% yield from **7**. When the reaction of the isolated hydroxyl ester **6** and TBAF was performed at room temperature, a mixture of **5(3R)** and **5(3S)** (**5(3R)**:**5**-

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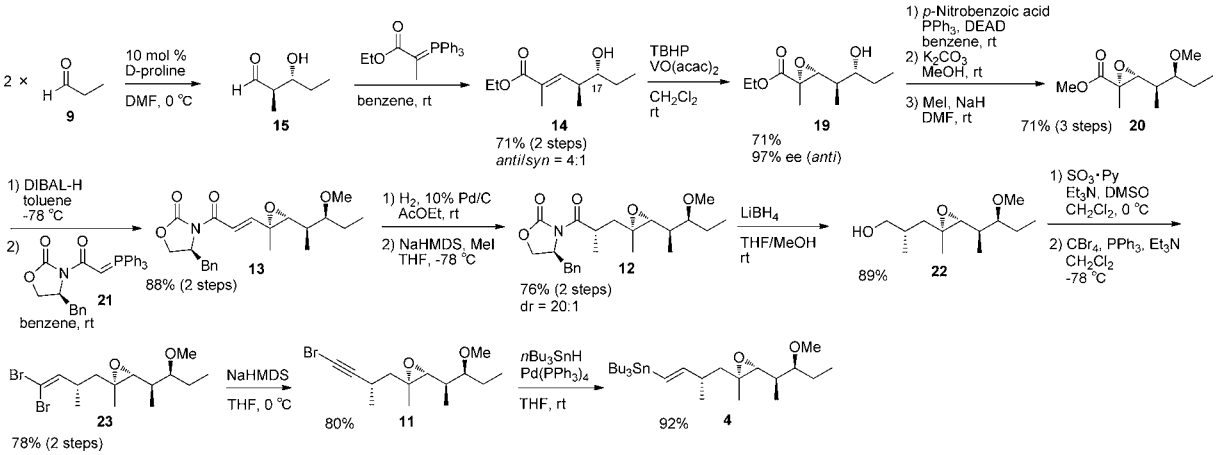
Scheme 3. Synthesis of Vinyl Stannane 4

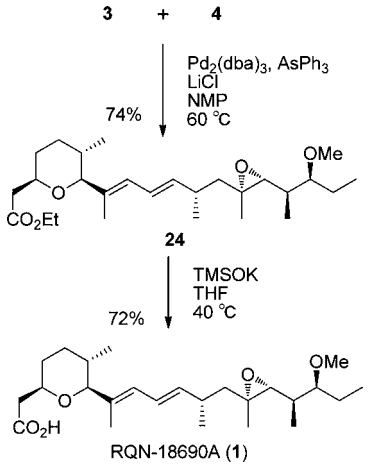


(**3S**) = 1:2) was obtained at an 80% yield, whereas at 60 °C the mixture (**5(3R)**:**5(3S)** = 6:1) was obtained at a 70% yield. These results indicate that there is an equilibration between **5(3R)** and **5(3S)** and that **5(3R)** is thermodynamically more stable.[11] It should be noted that four sequential reactions proceeded in this one-pot transformation[12] from **7** to **5**: a Wittig reaction, an intramolecular *oxa*-Michael reaction, deprotection of the TIPS group, and isomerization from **5(3R)** to **5(3S)**. When isomer **5(3S)**, which was obtained via the first column chromatography, was treated with TBAF at 60 °C for 0.5 h in THF, **5(3R)** was obtained at a 74% yield after isomerization. Thus, lactone **7** was converted into the desired tetrahydropyran **5(3R)** at a 54% overall yield by use of this recycling method. Finally, the terminal alkyne of **5(3R)** was led to vinyl iodide **3** as a coupling precursor. Thus, addition of (tributylstannyl)butylcuprate reagent[13] (n-$Bu_3SnCu(n$-Bu)-$CNLi_2$) to alkyne **5(3R)**, followed by trapping of the intermediate alkenylcuprate *in situ* with MeI, afforded vinylstannane **18**, which was converted to vinyl iodide **3** with I_2 in a one-pot operation with a 45% yield.

The synthesis of side chain unit **4** is shown in Scheme 3. The α,β-unsaturated ester **14** was obtained by a D-proline-catalyzed, asymmetric self-aldol reaction of propanal (**9**),[14] followed by a Wittig reaction. The desired *anti*-isomer **14** was obtained as the major product (*anti*/*syn* = 4:1) with high enantioselectivity (97% ee). The mixture of *anti* and *syn* isomers was used directly in the next step. C17 hydroxyl-directed epoxidation of **14** proceeded in the presence of a catalytic amount of $VO(acac)_2$ only from the *anti*-isomer **14** to afford epoxide **19** as a single diastereomer with the recovery of the *syn*-isomer **14**, because of the efficient kinetic resolution.[15] The unreacted *syn*-isomer of **14** could be separated by use of column chromatography. A Mitsunobu reaction[16] followed by solvolysis with K_2CO_3/MeOH afforded an inverted secondary alcohol, which was treated with NaH/MeI to provide methyl ether **20**. After reduction of the ester group of **20**[17] to aldehyde, a Wittig reaction with phosphorus ylide **21** delivered olefin **13**. Hydrogenation of **13** followed by highly diastereoselective alkylation of the chiral imide enolate with MeI afforded the desired compound **12** (dr = 20:1).[18] Reduction of **12** with $LiBH_4$ gave the corresponding alcohol **22**. The Parikh–Doering oxidation[19] of alcohol **22**, followed by a Corey–Fuchs dibromo-olefination[20] in the presence Et_3N to avoid a side reaction,[21] produced dibromoethylene derivative **23**. Base-induced elimination of hydrogen bromide from **23** gave bromoalkyne **11**. Finally, hydrostannylation of **11** with n-Bu_3SnH in the presence of a catalytic amount of $Pd(PPh_3)_4$ provided *E*-vinylstannane **4** in a stereoselective manner.[22]

With key intermediates **3** and **4** in hand, we constructed the *E*,*E* diene moiety by use of a Stille coupling reaction (Scheme 4). The palladium-catalyzed Stille coupling of **3** and **4**

Scheme 4. Total Synthesis of RQN-18690A (1)



proceeded with LiCl in the presence of $Pd_2(dba)_3$ and $AsPh_3$ in NMP at 60 °C for 10 min, providing *E*,*E* diene **24** in a 74% yield.[23] Finally, treatment of **24** with TMSOK[24] gave RQN-18690A (**1**). The spectroscopic data and specific rotation of the synthetic substance were in accord with those reported for natural RQN-18690A, thereby establishing its absolute stereochemistry.

In summary, the first asymmetric total synthesis of RQN-18690A (**1**) has been achieved, and its absolute configuration has been determined. The longest linear path was 17 steps with an overall yield of 6.5%. There are several noteworthy features in the present synthesis: an organocatalytic aldol reaction for the first step, 1,4- and 1,2- dual reductions of α,β-unsaturated δ-lactone **7** followed by a subsequent domino reaction in a one-pot operation, and diastereoselective epoxidation with kinetic resolution. The present synthesis could be used in the synthesis of structural variants of RQN-18690A.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01524.

Experimental procedures, characterization data of new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: y7-matsumoto@hhc.eisai.co.jp.
*E-mail: yhayashi@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

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