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Graphical Abstract

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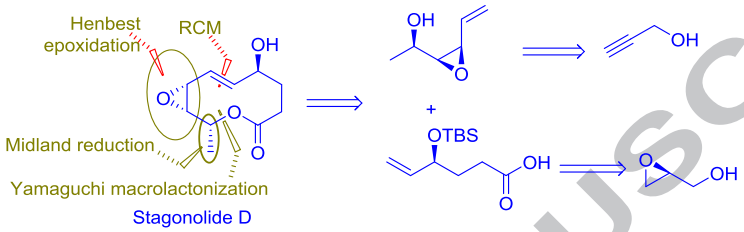

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First stereoselective total synthesis and reconfirmation of absolute structure of nonenolide (-)-stagonolide D

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ABSTRACT

The first stereoselective total synthesis of nonenolide (-)-stagonolide D has been accomplished. Midland Alpine borane reduction to install hydroxyl group at C4, Henbest epoxidation to introduce epoxide stereoselectively between C7-C8, Yamaguchi esterification and Olefin metathesis reaction are the key steps involved in the total synthesis.

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1. Introduction

During the last decade, there has been significant interest for the 10-membered macrolides due to their impressive biological properties.[1] The scarcity of the natural products coupled with complexity provided by them attracts a notable challenge for synthetic chemists. In 2007, a new nonenolide stagonolide A was isolated from fungus *Stagonospora Cirsii*,[2] a pathogen of Cirsium arvense that causes necrotic lesions on leaves and found to display herbicidal activity. In 2008, Evidente et al reported the isolation of five new nonenolides, which have been named as stagonolide B-F respectively from fungus *Stagonospora cirsii*.[3] These compounds were found to display strong inhibitory activity on root growth in seedlings of *C. Arvense* and some other *Asteraceae* species. Stagonolide F was found to display antibacterial, antifungal and cytotoxic properties.[4] Stagonolides have an allylic system in the ring, a double bond with *trans* geometry, and an alkyl group at C9 position. Our own interest in this class of molecules in the synthetic perspective made us to accomplish the total synthesis of stagonolide A, B and G in a concise manner.[5] In continuation to our work on the total synthesis of macrolides,[6] we have targeted stagonolide D, structurally unique among others with an epoxy appendage at C7 and C8 for the total synthesis. Though couple of groups has already taken initiatives in accomplishing the total synthesis of natural stagonolide D, either the data of the final product was in disagreement with the natural product data or the efforts ended up in the structural revision of the product.[7] This feature has also prompted us to take up the initiative for the total synthesis of natural product stagonolide D, and reconfirmation of the absolute structure.

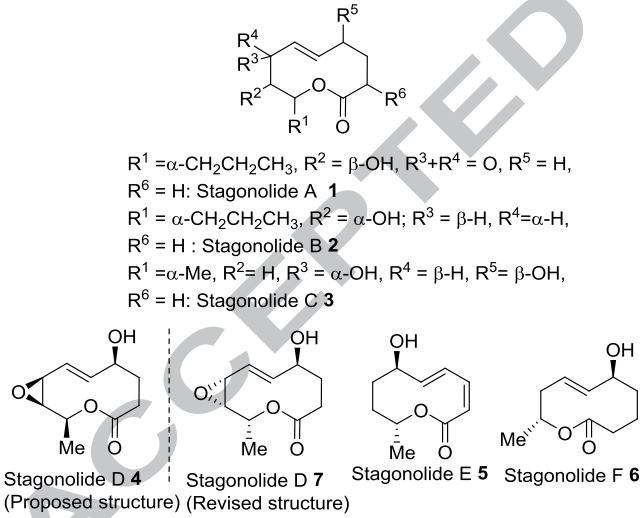
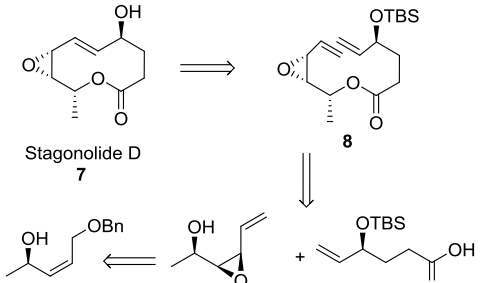


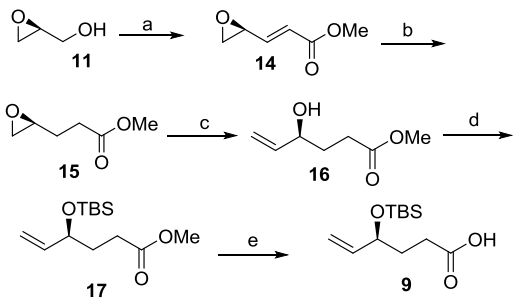
Figure 1. Structures of stagonolides A-F.

Our retrosynthetic analysis of stagonolide D is based on the convergent approach starting from acid **9** and alcohol **10**, which are coupled through an esterification reaction to yield the *α*, *ω*-diene **8**. The diolefin **8** can be subjected to RCM reaction to provide the 10-membered skeleton that, on desilylation provides the target molecule stagonolide D (Scheme 1). While the acid **9** can be synthesized from readily available *R*-glycidol **11,** the epoxy alcohol **10** can be accessible from allyl alcohol **12**, which in turn can be easily synthesized from commercially available propargylic alcohol **13** in a five-step sequence.



Scheme 1. Retrosynthetic analysis of stagonolide D **(7)**

The synthesis of acid fragment **9** commenced from the readily available *R*-glycidol **11**, which was converted to the corresponding α,β-unsaturated ester **14** through oxidation to aldehyde with BAIB, TEMPO followed by 2C-Wittig reaction with methyl-2-(triphenylphosphoranylidene)acetate in an overall yield of 85% yield.[8] Double bond reduction was smoothly achieved with phenylsilane in the presence of $[CuH(PPh_3)]_6$ as catalyst to afford **15** in 90% yield.[9] Compound **15** was subjected to an epoxide ring opening reaction with TMSI and n-BuLi under Corey-Chaykovsky conditions to yield alcohol **16**.[10] The allylic alcohol **16** was protected as the corresponding silyl ether **17** with TBSCl and imidazole and subsequently the ester functionality was hydrolyzed to acid **9** with of LiOH in 94% yield.[11]



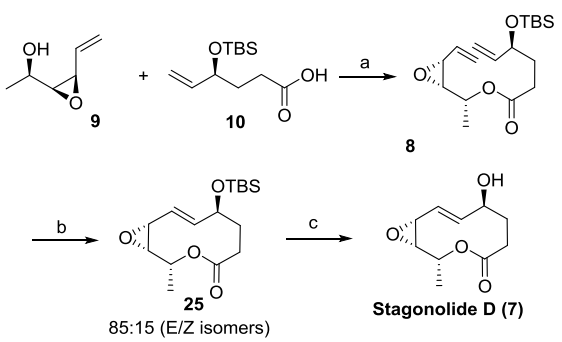
Scheme 2 Reagents and conditions: (a) (i) BAIB/TEMPO, CH_2Cl_2, 0 °C–rt, 1 h and, (ii) methyl 2-(triphenylphosphoranylidene)acetate, rt, 3 h, 85% over two steps; (b) $[CuHP(PPh_3)]_6$, $PhSiH_3$, THF, 0 °C–rt , 2 h, 90%; (c) TMSI, n-BuLi, THF, -20 °C–rt, 3 h, 82%. (d) TBSCl, imidazole, CH_2Cl_2, 0 °C–rt, 3 h, 95%; (e) LiOH, THF:H_2O (3:1), 4 h, 94%.

The other key fragment alcohol **10** was synthesized from commercially available propargyl alcohol **13** which was protected as the corresponding benzyl ether. Treatment of acetaldehyde with lithium acetylide (generated in situ by treating *O*-benzylated propargyl alcohol with lithium diisopropylamide, LDA) afforded alcohol **18** in 88% yield.[12] PCC oxidation of **18** in CH_2Cl_2 resulted in ynone **19** in 91% yield. The carbonyl functionality in **19** was subjected to chiral reduction employing *R*-alpine borane to afford chiral alcohol **20** in 88% yield with >80% ee.[13] Compound **20** upon hydrogenation[14] reaction under Lindlars conditions afforded cis–alkene **12** which was subjected to diastereoselective alcohol directed epoxidation (Henbest epoxidation) reaction with mCPBA to afford mixture of easily separable diastereomers in 9:1 ratio.[15] The hydroxyl group in **21** (major compound) was protected as the corresponding TBS ether **22** and treated with Pd/C (10 mol%) in EtOAc to obtain

debenzylated alcohol **23**. The alcohol **23** upon oxidation followed by one carbon Wittig olefination reaction with PPh_3CH_3Br and KO^{t}Bu yielded **24** in 78% yield over two steps. Treatment of **24** with HF.Py in THF afforded **10** in 95% yield.

Scheme 3. Reagents and conditions: (a) Benzyl bromide, NaH, THF, 0 ^{o}C–rt, 6 h, 98%; (b) LDA, CH_3CHO, THF, 0 ^{o}C, 6 h, 88%; (c) PCC, Celite, CH_2Cl_2, rt, 4 h, 91%; (d) Alpine borane® (0.5M, THF, 2 equiv.), THF, 0 ^{o}C, 1 h, 88%; (e) Pd/$BaSO_4$/quinoline, EtOAc, 0 ^{o}C, 20 h, 82%; (f) mCPBA, CH_2Cl_2, 0 ^{o}C–rt, 12 h, 74%; (g) TBSCl, imidazole, CH_2Cl_2, 0 ^{o}C–rt, 3 h, 96%; (h) Pd/C, EtOAc, 4 h, 95% (i) (i) DMP, CH_2Cl_2 , 0 ^{o}C–rt, 3 h and (ii) PPh_3CH_3Br, KO^{t}Bu, THF, -10 ^{o}C, 2 h, 78% over two steps; (j) HF-Py., THF, 0 ^{o}C–rt, 4 h, 95%.

With the two key intermediates acid **9** and alcohol **10** in hand, we proceeded further for coupling them together under Yamaguchi conditions to provide ester **8,** the precursor for RCM reaction in 80% yield.[16] The diolefin **8** was subjected to meathesis reaction using Grubbs' 2nd generation catalyst[17] in CH_2Cl_2 under reflux condition to afford the inseparable mixture of diastereoisomers (*E*/*Z* = 85:15) in 60% yield. Finally, exposure of **25** to HF.Py followed by coloumn chromatography provided stagonolide D in 95% yield. *E*-geometry of the product was confirmed by the ^{1}H NMR analysis, where in the coupling constant for olefinic proton was found to be *J*H5, H6 = 17 Hz. In the ^{1}H NMR spectra of the synthesized product, the signals corresponding to the minor conformer were also observed, however, the chemical shifts of ^{13}C NMR spectra were indistinguishable.[7b] The chemical shifts and coupling constants of major conformational isomer was in good agreement with that of the data of natural product.[3a, 18] The specific rotation of synthetic stagonolide [-79.7 (*c* 0.2, $CHCl_3$)] was in good agreement with that of the naturally occurring stagonolide D {Ref.[3a] [−82.0 (*c* 0.2, $CHCl_3$)]}, thus conforming the abosolute structure as **7** for the natural stagonolide D.



Scheme 4: Reagents and conditions: (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP, THF, toluene, 0 ^{o}C, 8 h, 80%; (b) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 24 h, 60% (E/Z = 85:15) ; (c) HF-Py., THF, 0 ^{o}C – rt, 4 h, 95%.

In conclusion, the first total synthesis of stagonolide D has been achieved in 8 shortest steps with an overall yield of 21.2% from glycidol or in 13 longest linear steps with an overall yield of 10.7% starting from propargylic alcohol. The key reactions involved in the strategy were Midland alpine borane reduction, Henbest epoxidation and Grubbs cyclization. Application of this strategy for preparing other analogues towards investigation for biological activity is under progress.

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18. Analytical data of **7**: $[\alpha]_D^{25}$ = -79.7 (*c* 0.2, $CHCl_3$); {Lit.[3a] $[\alpha]_D^{25}$ = −82 (*c* 0.51, $CHCl_3$)}; IR ν_{max}: 3435, 1730, 1643, 1090 cm^{-1}; ^1H NMR (500MHz, $CDCl_3$): δ 5.66 (dd, *J* = 17.0, 4.9 Hz, 1H), 5.54 (dd, *J* = 16.3, 8.4 Hz, 1H), 5.35 (dq, *J* = 6.7, 2.6 Hz, 1H), 4.15 (ddd, *J* = 8.4, 6.7, 4.3 Hz, 1H), 3.66 (dd, *J* = 5.0, 4.0 Hz, 1H), 3.06 (dd, *J* = 4.3, 2.8 Hz, 1H), 2.30 (ddd, *J* = 13.8,7.8, 2.7 Hz, 1H), 2.13 (dd, *J* = 13.1, 11.6 Hz, 1H), 2.06 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.02 (ddd, *J* = 13.7, 11.0, 4.3 Hz, 1H), 1.39 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 134.1, 128.2, 75.2, 65.7, 58.2, 55.4, 35.0, 31.2, 16.2.; HRMS (m/z) calcd for $C_{10}H_{14}O_4Na$ $[M+Na]^+$ 215.1043 found 215.1040.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at doi:.

Highlights

Justification for publication

This manuscript provides the first total synthesis of stagonolide D, a unique compound in the family of stagonolides with an epoxide moiety.

Earlier attempts for the total synthesis of this molecule (stagonolide D) resulted in product whose data was in disagreement with the data of the natural product or ended up with the revision of the structure.

The strategy followed by us is a convergent approach utilizing coupling (an esterification reaction) and ring closing metathesis reaction to get the basic 10-membered scaffold.

Midland Alpine borane reduction and Henbest epoxidation reactions have been employed as other key reactions in the total synthesis to get the chiral centers.

The total synthesis was achieved in 8 shortest steps starting from known compound R-glycidol.

By maneuvering the reagents, the other isomers can be easily synthesized and the synthesis is practically amenable for large scale reactions.