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First total synthesis of strongylodiol A†

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Abstract—A new cytotoxic long-chain acetylenic alcohol (*R*)-strongylodiol A, originally isolated from an Okinawan marine sponge of the genus *Strongylophora*, has been synthesized for the first time using commercially available 1,10-decanediol. The key step of this process involves the selective introduction of the (*R*)-configuration at C-6 which was achieved by β-elimination of epoxychlorides.

1. Introduction

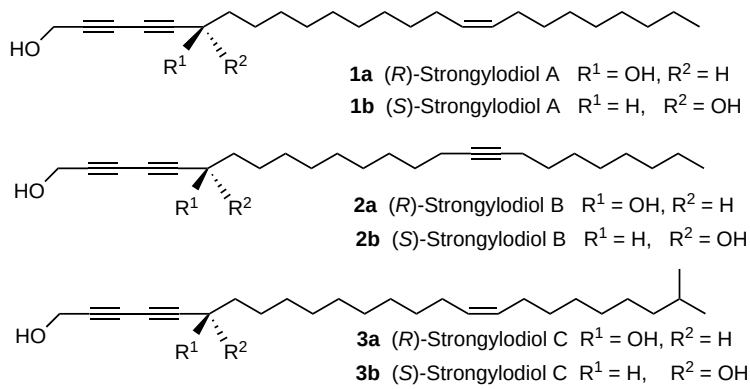
A new class of cytotoxic long-chain acetylenic alcohols, strongylodiols A–G, has been isolated recently by Iguchi et al.,[1] from an Okinawan marine sponge of the genus, *Strongylophora* (class Demospongiae, order Haplosclerida, family Petrosiidae). Based on absolute stereochemistry determinations, these acetylenic alcohols were found to comprise different enantiomeric mixtures. Interestingly, strongylodiols A–D exhibit potent cytotoxic activity against human T lymphocyte leukemia (MOLT–4) cells.

Extending our research program to the synthesis of biologically active natural products, we herein describe a short and efficient route for the first total synthesis of (*R*)-strongylodiol A.

2. Results and discussion

The key intermediate was the chiral carbinol **12**, which was easily synthesized using our earlier approach[2] from chiral 2,3-epoxychlorides obtained from 2,3-epoxyalcohols which in turn are easily synthesized by the Sharpless asymmetric epoxidation of an *E*-allyl alcohol.

Accordingly, 1,10-decanediol was monobrominated and the free hydroxyl functionality protected as its THP ether which was coupled with propargyl alcohol using $LiNH_2$ in liquid ammonia to afford an acetylenic alcohol.[3] The resulting alcohol was reduced with LAH in refluxing THF to furnish the *E*-allyl alcohol **4**.[4] The free hydroxyl group of **4** was protected as its MOM ether and the THP ether was selectively cleaved to give the alcohol **6** which was oxidized to aldehyde **7** employ-



Keywords: strongylodiol; chiral carbinol; 2,3-epoxychloride; Cadiot–Chodkiewiez cross coupling.

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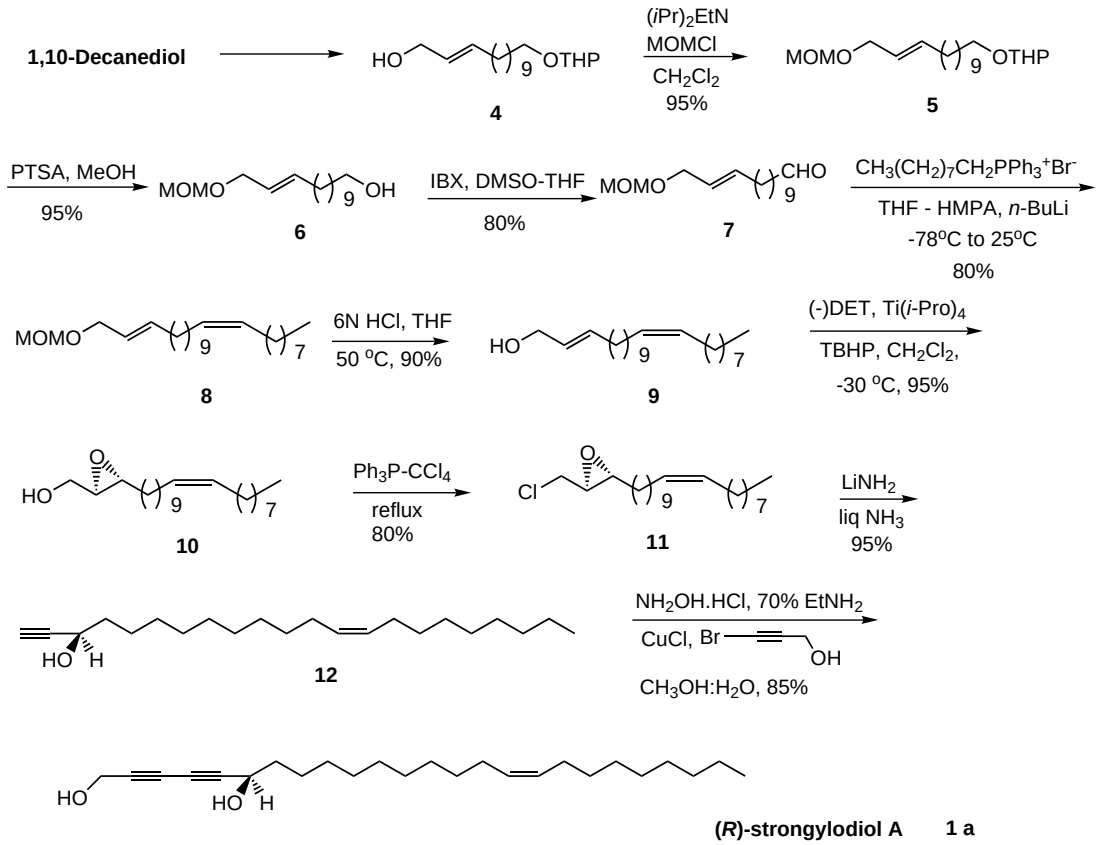

Scheme 1. Total synthesis of (*R*)-strongylodiol A

ing IBX in DMSO. Aldehyde **7** was subjected to a Wittig olefination with nonyltriphenylphosphonium bromide in THF–HMPA and *n*-butyllithium at −78°C to give the *Z*-olefin **8**. This generated the *Z*-stereochemistry at C-16 and C-17 of strongylodiol A.

The MOM ether protective group was cleaved to generate the *E*-allyl alcohol **9**, which was subjected to a Sharpless asymmetric epoxidation[5] to yield epoxide **10**. Epoxy alcohol **10** was converted to the chiral epoxychloride **11**, using CCl_4–Ph_3P at reflux temperature. 2,3-Epoxychloride **11** was subjected to our reaction conditions[2] to give the chiral carbinol, **12**. Our approach afforded this carbinol **12**, exclusively as a single isomer in an excellent yield (95%).[†]

The final step was the Cadiot–Chodkiewiez cross coupling[6] of **12** with 3-bromo-2-propyne-1-ol to give (*R*)-strongylodiol A. The physical and spectroscopic data (MS, ^1H and ^{13}C NMR, IR and optical rotation) were found to be identical in all respects with those reported for the natural (*R*)-strongylodiol A.[7] The synthesis of other strongylodiols using this novel approach is in progress in our laboratory and we will shortly be communicating a full account of our work in this area.

In summary, this paper describes a short and efficient approach for the synthesis of strongylodiol A using a simple synthetic sequence and easily available starting materials. Besides its novelty and efficiency, this method provides a useful entry to strongylodiols (Scheme 1).

[†] All new compounds in this paper were satisfactorily characterized by ^1H and ^{13}C NMR, IR and FAB MS spectra.

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7. Spectroscopic data for selected compounds:
Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$, J in Hz, TMS internal standard) δ 0.88 (t, 3H, $J=6.66$), 1.25–1.35 (m, 24H), 1.43 (m, 2H), 1.7 (m, 2H), 2.00 (m, 4H), 2.41 (m, 1H), 4.34 (t, 1H, $J=6.8$), 5.34 (m, 2H); m/z (FAB) 320 (M^+); ν_{max} (neat/cm^{-1}): 1651, 2120, 3310; $[\alpha]_D^{25}$ −10.1 (c 0.5, $CHCl_3$).
(b) Optical rotation for (*R*)-strongylodiol A (**1a**): $[\alpha]_D^{25}=-7.3$ ($c=1$, $CHCl_3$) [lit. $[\alpha]_D^{22}=-7.2$ ($c=1.11$, $CHCl_3$)].[1]