

Establishing the Absolute Configuration of the Asbestinins: Enantioselective Total Synthesis of 11-Acetoxy-4-deoxyasbestinin D

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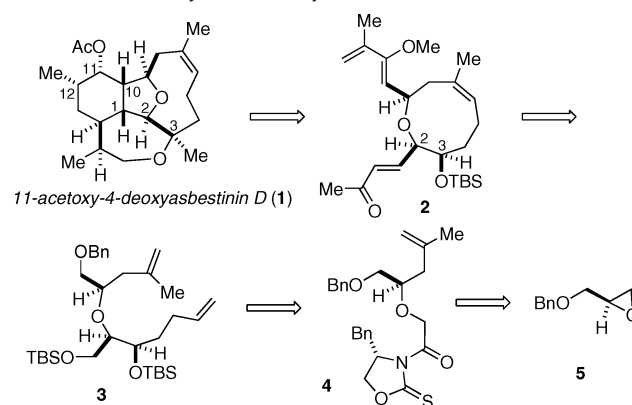
Interest in the synthesis of C-2–C-11 cyclized cembranoids has intensified over the past decade, due to their fascinating molecular topology and interesting biological properties.¹ Various approaches to the syntheses of the cladiellins and briarellins have been implemented;² however, none of the asbestinins have been prepared by total synthesis, leaving some doubt regarding their absolute configuration and biosynthetic origin.^{1b,3} In 1990, Rodríguez and co-workers isolated 11-acetoxy-4-deoxyasbestinin D (**1**) from *Briareum asbestinum*, making note of its particular cytotoxicity against CHO–K1 cells (ED₅₀ = 4.82 μg/mL) and strong antimicrobial activity against *Klebsiella pneumoniae*.³ The tetracyclic framework of 11-acetoxy-4-deoxyasbestinin D includes nine contiguous stereocenters and a fully substituted tetrahydrofuran, rendering it a formidable and intriguing target for chemical synthesis.

We recently reported a successful strategy for the synthesis of members of the eunicellin class of cembranoids involving the construction of the oxonene ring through ring-closing metathesis,^{4–6} followed by stereoselective formation of the hydroisobenzofuran via an intramolecular Diels–Alder cycloaddition.^{2k} The total synthesis of 11-acetoxy-4-deoxyasbestinin D (**1**) was undertaken with the intent of validating the intramolecular Diels–Alder approach for the synthesis of the asbestinins.⁷ Our synthetic plan hinged on an asymmetric glycolate aldol reaction of oxazolidinethione **4** to assemble the diene **3**, a precursor of the oxonene **2** (Scheme 1). This report describes the first total synthesis of an asbestinin verifying the absolute configuration of the subclass.

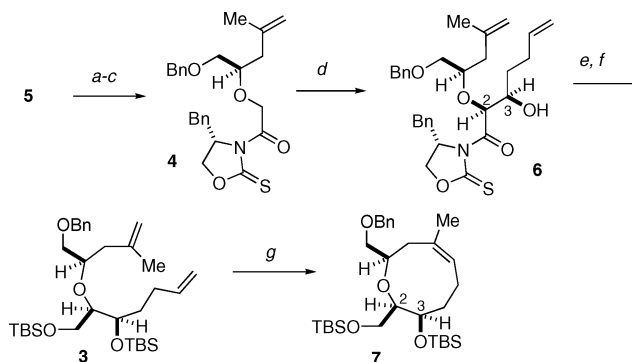
The synthesis of the oxonene core began with the addition of isoprenylmagnesium bromide to (*R*)-benzyl glycidyl ether (**5**) to afford a secondary alcohol,⁸ which was O-alkylated with sodium bromoacetate (Scheme 2). The resultant glycolic acid was coupled with (*S*)-4-benzylloxazolidinethione to deliver thioimide **4**. Addition of 4-pentenal⁹ to the chlorotitanium enolate of thioimide **4** in the presence of NMP^{5c,7} gave *syn*-aldol adduct **6** in good yield and diastereoselectivity (70%, >95:5 dr).¹⁰ Reductive removal of the chiral auxiliary and protection of the diol afforded diene **3**. As anticipated, on the basis of previous successful metathesis reactions to form medium ring ethers,^{4–6} treatment of diene **3** with the Grubbs catalyst¹¹ led to facile formation of oxonene **7** (99% yield).

With the oxonene **7** in hand, efforts focused on construction of the required Diels–Alder precursor. To this end, the benzyl ether was reductively cleaved, and the resultant alcohol was oxidized to the aldehyde under Swern conditions (Scheme 3).¹² The aldehyde was subjected to successive Wittig reactions, first using phosphorane **8**,¹³ then methylene triphenylphosphorane to yield the requisite diene **9**. Selective deprotection of the primary TBS ether was carefully carried out in the presence of the labile enol ether.¹⁴ Oxidation¹² of the alcohol provided an aldehyde, which was treated with phosphorane **10**¹⁵ at elevated temperature. After the Wittig reaction, a spontaneous Diels–Alder cycloaddition ensued through the more favorable *exo* transition state, providing adduct **11** in 80% yield as a single diastereomer. Earlier work in related systems had dem-

Scheme 1. Retrosynthetic Analysis of **1**



Scheme 2. Synthesis of the Oxonene Ring^a

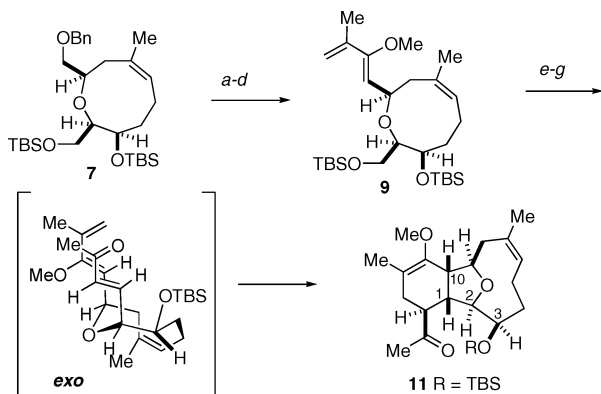


^a Conditions: (a) CH₂=C(CH₃)MgBr, CuI, THF, –40 °C, 99%; (b) NaH, BrCH₂CO₂H, THF, DMF, 95%; (c) (*S*)-benzyl-1,3-oxazolidine-2-thione, DCC, DMAP, CH₂Cl₂, 86%; (d) TiCl₄, *i*-Pr₂NEt, NMP, 4-pentenal, CH₂Cl₂, –78 °C, 70%; (e) LiBH₄, MeOH, Et₂O, 0 °C, 95%; (f) TBSCl, imidazole, DMAP, DMF, 50 °C, 87%; (g) Cl₂(Cy₃P)(IMes)Ru=CHPh, CH₂Cl₂, 40 °C, 99%.

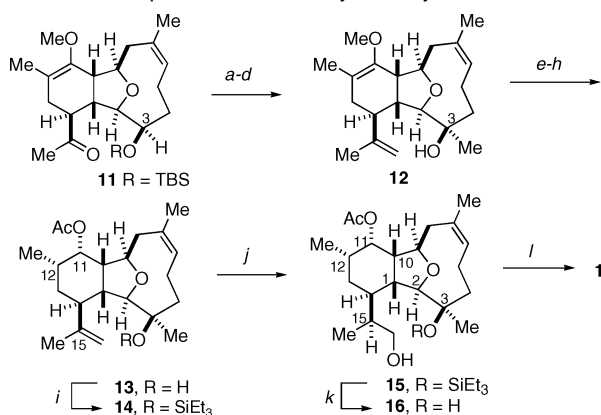
onstrated the importance of both the C-3 configuration and the C-3 hydroxyl protecting group in controlling the diastereoselectivity of the Diels–Alder reaction.^{2k,16}

Ketone **11** was converted to an alkene to introduce a handle to establish the C-15 stereocenter (Scheme 4). Deprotection and oxidation¹⁷ of the C-3 secondary alcohol followed by addition of methylmagnesium chloride to the resultant ketone provided the tertiary alcohol **12** in excellent yield as a single isomer.

With the required tricyclic core in place, refunctionalization of the cyclohexane ring was undertaken. Acidic hydrolysis of the enol ether yielded the α -methyl ketone (10:1 dr); however, ¹H NMR analysis (COSY, nOeSY) indicated the undesired isomer was the major product. This problem was easily corrected by base-catalyzed equilibration to the desired isomer to provide 84% of the desired ketone after two recycles. Reduction of the ketone with *L*-Selectride yielded the secondary alcohol as a single diastereomer, which was esterified to give acetate **13**.

Scheme 3. Intramolecular Diels–Alder Cycloaddition^a

^a Conditions: (a) Na, NH₃, THF, -78 °C, 86%; (b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to 0 °C, 94%; (c) Ph₃P=C(OMe)C(O)Me (**8**), PhCH₃, 110 °C, 84%; (d) Ph₃PCH₂Br, *t*-BuOK, THF, 0 °C, 87%; (e) NH₄F, MeOH, 79%; (f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to 0 °C, 93%; (g) Ph₃P=CHC(O)Me (**10**), PhCH₃, 110 °C, 80%.

Scheme 4. Completion of 11-Acetoxy-4-deoxyasbestinin D^a

^a Conditions: (a) Ph₃PCH₂Br, KO-*t*-Bu, THF, 85%; (b) *n*-Bu₄NF, THF, 95%; (c) Dess–Martin periodinane, pyridine, CH₂Cl₂, 98%; (d) MeMgCl, THF, 0 °C, 98%; (e) HCl, CHCl₃, 96%, 10:1 dr; (f) NaH, MeOH, 99%, 1:1.2 dr; (g) L-Selectride, THF, -78 °C, 94%; (h) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 99%; (i) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 80%; (j) (+)-Ipc₂BH, THF, NaOH, H₂O₂; (k) *n*-Bu₄NF, THF, 64% (two steps); (l) Tf₂O, 2,6-lutidine, CHCl₃, 0 to 25 °C, 66%.

The final stage of the synthesis required introduction of the C-15 stereocenter and formation of the oxapane. The regioselective and stereoselective hydroboration of the 1,1-disubstituted olefin of diene **13** proved to be a challenge. Regioselective hydroboration occurred in high yield with 9-BBN, but the reaction was not stereoselective.¹⁸ It was speculated that increasing the steric bulk at C-3 could impede addition from the undesired face of the alkene, improving the diastereoselection. Accordingly, the C-3 hydroxyl was protected as triethylsilyl ether **14**, but only moderate improvement in the diastereoselectivity (2:1 dr) was observed. Fortunately, the use of (+)-diisopinocampheylborane delivered the desired alcohol **15** as a single isomer after oxidative workup.^{19,20} The triethylsilyl ether was subsequently cleaved to deliver the diol **16** in 64% yield over two steps. Taking advantage of the conditions employed by Overman in the syntheses of briarellins E and F,²¹ the diol **16** was treated with triflic anhydride and 2,6-lutidine to deliver 11-acetoxy-4-deoxyasbestinin D (**1**) in 66% yield. Spectroscopic data for synthetic **1** matched the reported data for the natural product in all regards.³ Of particular note, the specific rotation of synthetic **1** and a purified sample of natural **1** were identical ($[\alpha]_D^{26}$; CHCl₃; = -15) when measured under the same conditions.

In summary, a highly stereoselective synthesis of 11-acetoxy-4-deoxyasbestinin D has been completed in 26 linear steps, hinging

on a selective glycolate aldol addition to establish the C-2 stereocenter, a ring-closing metathesis reaction to complete the oxonene, and an intramolecular Diels–Alder cycloaddition to establish the relative configuration at C-1, C-10, and C-14. This initial total synthesis of an asbestinin also serves to confirm the absolute configuration of this family of natural products.

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Supporting Information Available: Experimental procedures, as well as ¹H and ¹³C NMR spectra for all new compounds, and synthetic 11-acetoxy-4-deoxyasbestinin D. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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