Total Synthesis of A-Nor B-Aromatic OSW-1 Aglycon: A Highly Effective Approach to Optically Active *trans*-4,5-Benzhydrindane

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A new enantioselective approach to the *trans*-4,5-benzhydrindane skeleton by intramolecular cycloaddition of *o*-quinodimethane, generated by thermolysis of a benzocyclobutene derivative, is described. Using this method, the synthesis of the A-nor B-aromatic aglycon of OSW-1, a potent antitumor saponin, was accomplished.

Introduction

There has been great interest in A-nor B-aromatic steroidal compounds as they have tremendous importance as a potential precursor of various physiologically important steroids.[1] In addition, they have been reported to exhibit a remarkable hormonal and anti-hormonal activity,[2] and to have modulatory actions at $GABA_A$ receptors as neurosteroid analogues.[3] For the synthesis of these compounds, the development of a method to construct the *trans*-4,5-benzhydrindane skeleton (**1**; Figure 1)[4] as an enantiopure form is a critical and essential task. However, a truly effective approach for this purpose has not been reported so far, although several efforts have been made, including ours.[5] In the course of our search for new candidate structures having anticancer properties, we have taken notice of the potent antitumor saponin OSW-1 (**2**; Figure 1), which was isolated from the bulbs of *Ornithogalum saundersiae* by Sashida et al. and found to possess a cholestane aglycon and a disaccharide moiety.[6] This natural product has been paid a great deal of attention because of its exceptionally potent activity (more potent than mitomycin C, camptothecin, taxol, etc.)[7] and the similarity of its cytotoxicity profile to that of cephalostatins, indicating the same mechanism of action.[8] Although some synthetic studies of OSW-1, including a total synthesis, have been reported so far,[8,9] the structure-activity relationship has not been established for its clinical use. In this context, we decided to synthesize an A-nor B-aromatic analogue of OSW-1 as a potential candidate for a new anti-tumor agent. For the synthesis of this compound, *trans*-4,5-benzhydrindane (**1**) could be a reasonable precursor, which prompted us to explore a new enantioselective method for the synthesis of the compound. In this paper, we wish to report a highly effective approach to optically active *trans*-4,5-benzhydrindane using a diastereoselective Grignard addition and *o*-quinodimethane chemistry, and its use for the synthesis of the aglycon (**3**; Figure 1) of the target OSW-1 analogue.

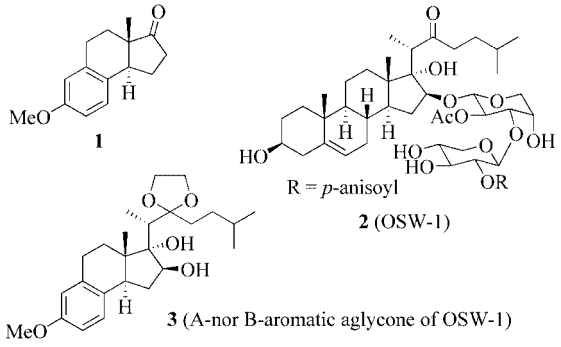

Figure 1. Structures of *trans*-4,5-benzhydrindane skeleton (**1**), OSW-1 (**2**), and our target aglycon (**3**)

Results and Discussion

Our synthetic strategy for the target molecule **1** is outlined in Scheme 1, and involves a thermal intramolecular cycloaddition of benzocyclobutene derivative (**5**) to give *trans*-4,5-benzhydrindane (**4**)[1] — known as a promising method to achieve *trans*-stereochemistry — as a key step. We expected that the enantioselectivity would be regulated under the influence of a bulky 2,2-dimethyl-1,3-dioxolane substructure. Formation of this intermediate **5** was envisioned via 1,2-asymmetric induction of a ketone **6**, a regioselective oxirane-opening reaction of **7**, and a Sharpless asymmetric epoxidation of allyl alcohol **8**.

To prepare the allyl alcohol **8**, benzocyclobutene derivative **9**[10] was converted into alcohol **10** in three steps in a 67% overall yield, according to the reported procedure.[11]

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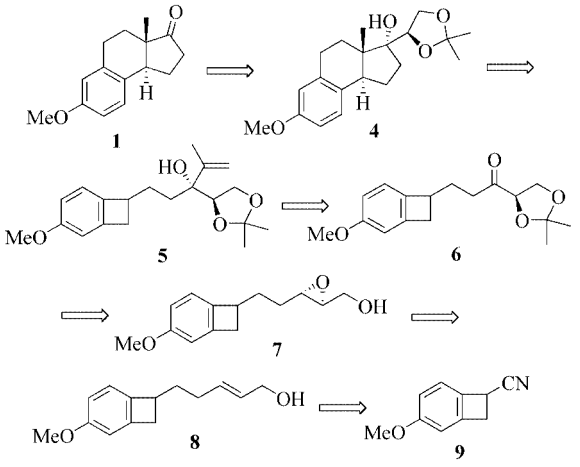
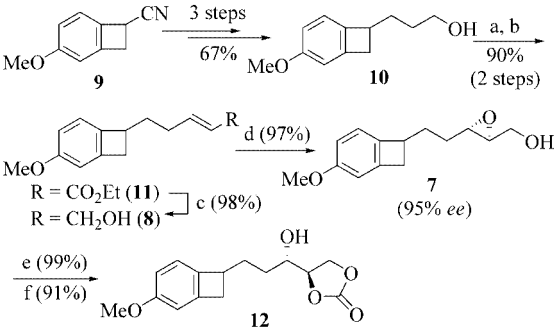


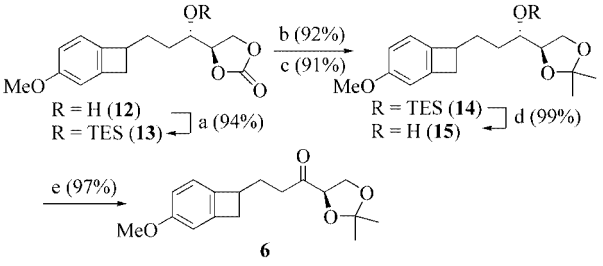
Scheme 1. Retrosynthesis of **1**

Swern oxidation of **10** and Horner−Wadsworth−Emmons reaction of the resulting aldehyde proceeded smoothly to afford the conjugated ester **11**, which was subjected to DIBAL reduction to provide the desired allyl alcohol **8** in high yields. Sharpless asymmetric epoxidation[12] of **8** using (+)-diethyl tartrate resulted in the formation of an optically active epoxide **7**[13] in excellent chemical (97%) and optical (95% *ee*) yields.[14] To achieve a regioselective oxirane ring opening we adopted Roush's protocol,[15] in which five-membered cyclic carbonates are formed via carbamates. The epoxy-alcohol **7** was treated with phenyl isocyanate followed by $BF_3{\cdot}OEt_2$ and dilute sulfuric acid to afford a cyclic carbonate **12** selectively.[16] The six-membered cyclic isomer could not be detected (Scheme 2).



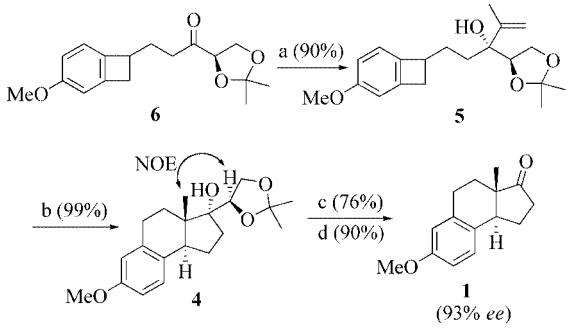
Scheme 2. Reagents and conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (b) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF; (c) DIBAL, Et_2O; (d) TBHP, (+)-diethyl tartrate, $Ti(O\mathit{i}Pr)_4$, CH_2Cl_2; (e) PhNCO, pyridine, CH_2Cl_2; (f) $BF_3{\cdot}OEt_2$, then 0.5 M H_2SO_4

Although we prepared a ketone by Swern oxidation of **12** as a potential substrate for Grignard addition leading to an analogous compound of **5**, this reaction resulted in an inseparable mixture of several products, even at −78 °C, probably due to the sensitivity of the carbonate moiety in the presence of the Grignard reagent. With this result in hand, the carbonate **12** was converted into its acetonide **15**, which was then oxidized to the corresponding ketone **6** with a high efficiency, as shown in Scheme 3.



Scheme 3. Reagents and conditions: (a) TESCl, imidazole, DMF; (b) DIBAL, Et_2O; (c) $MeOC(=CH_2)Me$, PPTS, CH_2Cl_2; (d) TBAF, THF; (e) TPAP, NMO, MS4A, CH_2Cl_2

A high diastereoselectivity was realized in the Grignard addition reaction of the ketone **6** using 2-propenylmagnesium bromide at −78 °C (diastereomeric ratio 19:1) to give the alcohol **5** in 90% yield (Scheme 4).[17] As a simplified model of our substrate **6**, 2,3-*O*-isopropylideneglyceraldehyde has been extensively studied on its stereochemical course toward various nucleophiles,[18] and the facial preference has been reported to be controlled in general by Cram's β-chelation or the Felkin−Anh model, leading to an *anti* configuration[19] in low or moderate selectivity. On the other hand, only a few studies describing the stereoselectivity of the nucleophilic addition to the corresponding ketones have been reported. In this case, the products having a *syn* configuration were formed predominantly, and the selectivity was explained based on Cram's α-chelation model.[20] This explanation agrees with our result, although further investigation is necessary for a complete elucidation of this high diastereoselectivity.



Scheme 4. Reagents and conditions: (a) $Me(CH_2{=})CMgBr$, THF (*dr* = 19:1); (b) *o*-dichlorobenzene, reflux; (c) *p*-TsOH, MeOH; (d) HIO_4, THF/H_2O (1:1)

The cyclobutene derivative **5** was subjected to a thermal ring opening, followed by intramolecular cycloaddition in refluxing *o*-dichlorobenzene to bring about a highly effective construction of the *trans*-4,5-benzhydrindane skeleton **4** in a stereoselective manner.[21] An almost quantitative yield was achieved and a small amount (< 8%) of stereoisomer[22] could be removed after the transformation of the products to the triol form by treatment with *p*-TsOH. Our supposition for rationalizing the observed selectivity is that the cycloaddition proceeds via an exo transition state (TS-1) in which the steric repulsion arising from the bulky cyclic

acetal moiety is lower than in TS-2 (Figure 2).[23] Finally, compound **4** was subjected to oxidative cleavage to afford our target molecule **1** in 90% yield. The structure and absolute configuration were determined unambiguously by comparison with authentic spectral and specific rotation data.[5b] The enantiomeric purity was largely conserved through the manipulations (93% *ee*, estimated by HPLC analysis). Thus, the development of a new efficient synthetic route to *trans*-4,5-benzhydrindane (**1**), which is recognized as a versatile synthetic intermediate, was accomplished.

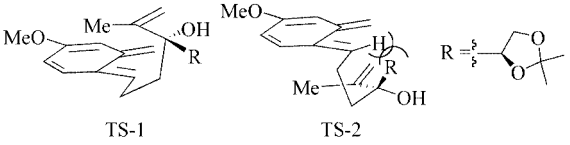
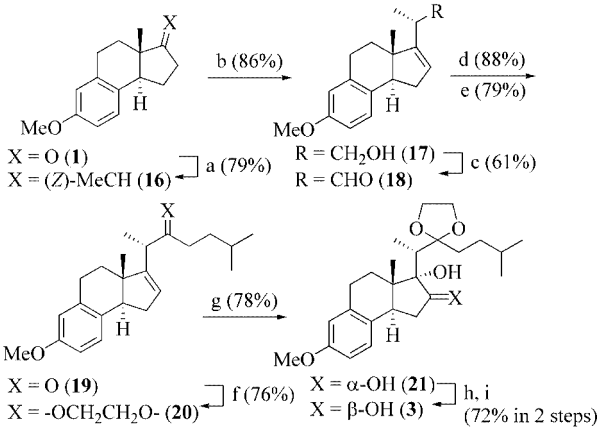


Figure 2. Plausible transition state model of the intramolecular Diels−Alder reaction

With the optically active A-nor steroidal ketone in hand, we turned our attention toward the synthesis of the A-nor aglycon (**3**) of OSW-1. Wittig olefination of **1** gave a (*Z*)-ethylidene derivative **16** exclusively, and a subsequent ene reaction using paraformaldehyde and dimethylaluminum chloride proceeded in high yield and high stereoselectivity. The alcohol **17** thus obtained was oxidized with PDC to afford an aldehyde **18**, which was successively subjected to Grignard addition, PDC oxidation, and ketalization, providing a compound (**20**) containing a suitable alkyl side-chain. The required *trans*-dihydroxylation was achieved in three steps. Thus, dihydroxylation of **20** with osmium tetroxide took place on the α-face preferentially and Swern oxidation of the resulting secondary hydroxyl group gave a ketone, which was reduced with sodium borohydride in the presence of cerium(III) chloride to afford *trans vic*-diol **3**. In this way, our target aglycon **3** was prepared in nine steps and a 12.3% overall yield from the optically active *trans*-4,5-benzhydrindane (**1**; Scheme 5).[24]



Scheme 5. Reagents and conditions: (a) $Ph_3P{=}CHMe$, THF; (b) $(CH_2O)_n$, Me_2AlCl, CH_2Cl_2; (c) PDC, MS4A, CH_2Cl_2; (d) $Me_2CH(CH_2)_2MgBr$, THF; (e) PDC, MS4A, CH_2Cl_2; (f) ethylene glycol, $HC(OEt)_3$, *p*-TsOH, CH_2Cl_2; (g) OsO_4, pyridine, Et_2O; (h) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (i) $NaBH_4$, $CeCl_3$, THF

Conclusion

In summary, we developed a new efficient method to construct the *trans*-4,5-benzhydrindane skeleton enantioselectively, and applied it to synthesize a biologically important OSW-1 analogue. Preparation and installation of the disaccharide moiety and biological evaluation of the final OSW-1 analogue are now in progress. These results and further synthetic use of the *trans*-4,5-benzhydrindane for various A-nor steroidal compounds will be reported in due course.

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[13] Two isomers of **7** (as well as **5, 6**, and **12−15**) originating from a chiral center on the cyclobutene ring could not be distinguished in the ^1H NMR spectra.
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[16] The five-membered cyclic carbonate structure was determined based on the 2D NMR spectroscopic data.
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[19] The term *anti* or *syn* used here means a relative configuration between the α-oxy group and the hydroxyl group resulting from the addition reaction when an introduced carbon chain is extended.
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[21] The relative configuration between the angular methyl group and hydroxyl group in compound **4** was determined by a NOE experiment (indicated in Scheme 4), and based on the absolute

configuration of the angular methyl group in compound **1**; the stereostructure of the Grignard adduct **5** was also determined.
[22] The structure of the isomer has not yet been confirmed.
[23] The other two possible transition states (endo transition state), which lead to *cis*-fused cycloadducts, have a considerable steric repulsion between the aromatic ring and the alkyl chain.
[24] Satisfactory spectroscopic data for all new compounds were obtained. Experimental details and all characterization data are available as Supporting Information.(see also footnote on the first page of this article).

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