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Asymmetric synthesis of the 2,2,3-trisubstituted cyclopentanone, D-ring fragment of 9,11-secosterols

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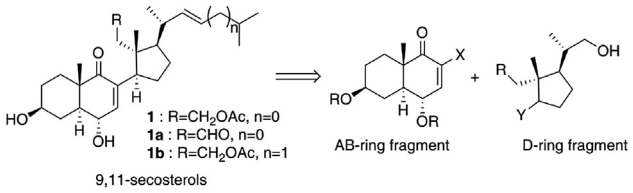
ABSTRACT

As a part of our studies on the total synthesis of 9,11-secosterols, the possibility of creating a substituted and functionalized D-ring fragment with three consecutive stereocentres, one of which was quaternary, was studied. The simple starting compound 2-methyl-cyclopent-2-ene-1-one was subjected to asymmetric 1,4-addition with (*S*,*S*)-crotyl phosphonamide and alkylation with methyl bromoacetate, resulting in a 2,2,3-substituted cyclopentanone in high diastereoselectivity. The covalently bonded chiral auxiliary was removed using oxidative methods. As a result, a stable D-ring fragment was obtained. The relative configuration of the substituents on the cyclopentane ring was assigned by comparison of the experimental with the quantum chemically calculated $^{1}H-^{1}H$ and $^{1}H-^{13}C$ *J*-coupling constants.

1. Introduction

Substituted cyclopentane fragments are found in several natural products, for example, in 9,11-secosterol,[1] vitamin D,[2] (+)-α-cuparenone,[3–5] 11-deoxy-PGF$_{1\alpha}$,[6] (−)-khusimone,[7] (−)-seco-daphnipylline,[8] and (−)-methyl jasmonate,[9,10] and in their synthetic intermediates. There are examples in the literature of the stereocontrolled construction of the cyclopentane derivatives by using various chiral auxiliaries, including *N*-acyl pyrrolidine,[8] vinylic[9] and allylic sulfoxides,[10] and phosphonamides,[11] or by using such heterobimetallic catalysts as ALB[6] based on the asymmetric Michael-type addition to unsaturated cyclopentanes. There are also examples where a polysubstituted cyclopentane derivative was constructed via cyclization of an acyclic intermediate[3,4] or via ring expansion from a cyclopropane.[5,12] However, many presented examples deal with racemic compounds only.

We have been engaged in the synthesis of 9,11-secosterol **1** (Scheme 1) and its analogues **1a** and **1b**, which were isolated from White Sea soft coral *Gersemia fruticosa*,[1] and exhibited strong antiproliferative and cytotoxic activity.[1,13,14] Our strategy for the total synthesis of secosterol **1** and its analogues **1a** and **1b** was based on a separate synthesis of the AB-ring and D-ring, and on the coupling of these two fragments (Scheme 1). The synthesis of the AB-ring fragment precursor has been described by our group previously.[15]



Scheme 1. The retrosynthetic analysis of 9,11-secosterols.

The main challenge of the approach is the synthesis of a highly functionalized D-ring fragment, demanding construction of three contiguous stereocentres with high stereoselectivity. In the present work, we describe a one-pot method, using a stereoselective 1,4-addition and subsequent alkylation reactions, starting with 2-methylcyclopent-2-ene-1-one **2**.

2. Results and discussion

We considered several possibilities for achieving an efficient synthesis of a D-ring carbon skeleton of 9,11-secosterols. These attempts are outlined in Scheme 2. The desymmetrization of

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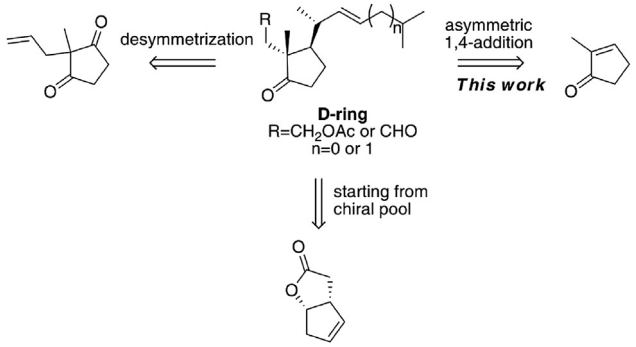
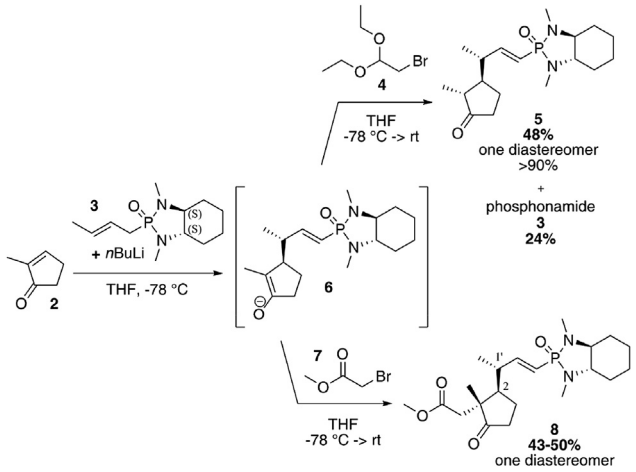
prochiral 2-methyl-2-propenylcyclopentane-1,3-dione by asymmetric reduction with a stoichiometric amount of CBS catalyst gave the corresponding hydroxyketone in only 25% ee.[16] Furthermore, desymmetrization of the same diketone via Horner–Wadsworth–Emmons olefination, which would eventually lead to the side-chain of the D-ring, afforded the cleavage of the cyclopentane ring instead of the expected monoolefination.[17] Oxidation of the double bond of enantiomerically pure (−)-Grieco lactone led to a mixture of regioisomers with poor selectivity.[18] Finally, the construction of the D-ring fragment by an asymmetric 1,4-addition to 2-methylcyclopent-2-ene-1-one was envisioned.



Scheme 2. Our approaches to the synthesis of a D-ring fragment.

According to the literature, a method of synthesizing substituted cyclic ketones bearing up to three contiguous stereocentres has been developed by Hanessian et al.[11] This approach consists of a 1,4-addition of allylic phosphonamide anions to a five- or six-membered cyclic α,β-unsaturated carbonyl compound and the trapping of the formed enolates with a proton or a simple carbon electrophile. We applied that approach to build up the secosterol D-ring fragment.

Chiral phosphorus oxychloride was synthesized from (*S*,*S*)-dimethyl-1,2-diaminocyclohexane according to the literature procedures[11,19–23] in four steps, with 60% total yield. This was added to a 4-carbon crotonic unit to afford (*S*,*S*)-crotyl phosphonamide **3** (Scheme 3). Then, a tandem alkylation of 2-methylcyclopent-2-ene-1-one **2** with enantiomerically pure phosphonamide **3**, followed by alkylation with an appropriate functionalized electrophile was studied. The first step of the tandem alkylation with (*S*,*S*)-crotyl phosphonamide proceeded smoothly with high yield. The second step, the alkylation of enolate **6**, demanded a good electrophile: with 2-bromoacetaldehyde diethyl acetal **4** no reaction occurred and only monoalkylated product **5** was isolated. By using methyl bromoacetate **7**, the alkylation afforded cyclopentanone **8** in exceptionally high enantio- and diastereoselectivity.



Scheme 3. Asymmetric 1,4-addition–enolate alkylation.

The diastereoselectivity of the two simultaneously formed stereocentres at carbons 2 and 1′ was controlled by the chiral auxillary in the first Michael addition step. The following alkylation of the intermediate **6** with ethyl bromoacetate **7** also occurred stereoselectively in *anti*-manner, affording cyclopentanone **8** in ~50% isolated total yield for three subsequent reactions. In all cases, ~25% of unreacted starting phosphonamide **3** was also recovered.

The diastereoselectivity of the asymmetric tandem 1,4-addition–alkylation reaction was very high. ^{31}P NMR spectroscopic analysis of product **8** confirmed that only a single stereoisomer, giving a singlet at 32.60 ppm, was formed (Fig. 1), indicating the high purity of the isolated product **8**. The small peaks in the range 32–33 ppm do not necessarily belong to the diastereomers of the product **8**, but may belong to the other by-products. In any case, the extraordinary stereoselectivity of the subsequent alkylation reactions led selectively to one diastereomer only out of a possible eight stereoisomers.

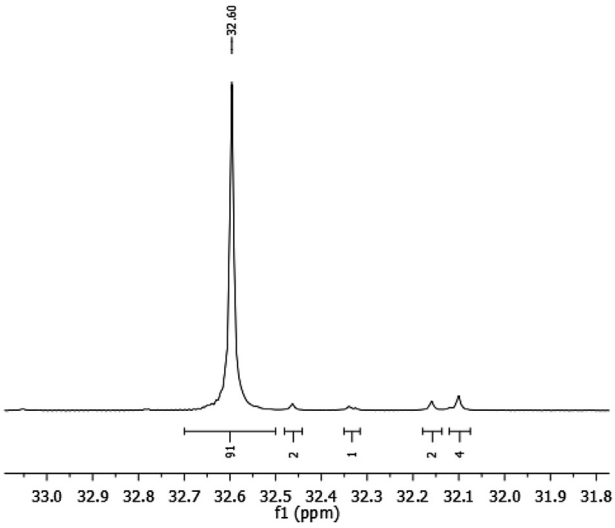


Fig. 1. ^{31}P NMR spectrum of 2,2,3-substituted cyclopentanone **8**.

The chiral phosphonamide auxiliary was covalently bonded to the cyclopentane fragment via a double bond. The auxiliary can be removed by oxidative cleavage of the double bond. From the point of view of the synthesis of the D-ring, oxidation leading to carbonyl compounds is preferable. First, alkenes can be cleaved by direct ozonolysis, affording carbonyl compounds. Another widely used possibility for auxiliary removal is to convert the double bond to a diol with potassium permanganate,[24] osmium tetroxide[25] or I_2/Ag-salts[26,27] and oxidize the vicinal glycol C–C bond. The diols can also be obtained by the hydrolysis of alkene oxides. In the present work, we studied two methods of removing the chiral auxiliary: dihydroxylation with subsequent oxidation, and ozonolysis (Scheme 4).

Dihydroxylation of the intermediate **8** with immobilized Os-catalyst FibreCat®3003 in the biphasic solvent system *t*-BuOH/H_2O (3:1) at an elevated temperature of 60 °C, applying *N*-methylmorpholine *N*-oxide (NMO) as a co-oxidant, did not give any oxidation product after 24 h. Instead, the hydrolysis product of phosphonamide **8** was detected in the ^{31}P NMR spectrum (at 18.39 ppm). We expected that dihydroxylation with a pure OsO_4