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First total syntheses of bicyclic marine sesquiterpenoids drechslerines A and B

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ABSTRACT

The first total syntheses of the bicyclic sesquiterpenoids drechslerines A (**1**) and B (**2**), which were isolated from the algicolous fungus *Drechslera dematioidea* in the marine red alga *Liagora viscida*, has been accomplished starting from (*S*)-carvone (**13**) via three palladium-catalyzed reactions, namely, diastereoselective allylation, conjugate reduction, and carbon monoxide insertion, as the key reactions.

1. Introduction

Marine organisms produce a large number of structurally interesting and biologically unique natural products.[1] Several polycyclic sesquiterpenoids were recently isolated from the algicolous fungus *Drechslera dematioidea* of leaf mold of the red algae *Liagora viscida*.[2] Among them were nor-sesquiterpenoids drechslerines A (**1**) and C (**3**), and sesquiterpenoids drechslerines B (**2**), D (**4**), E (**5**), F (**6**), and G (**7**). These compounds have the same carbon framework as helminthosporal (**8**) isolated from the terrestrial fungus, having a unique bicyclo[3.2.1]octane framework with an isopropyl group in common. However, the absolute stereochemistries of drechslerines have not been fully discussed.[2] Synthetic studies of sesquiterpenoids with the bicyclo[3.2.1]octane core have already been conducted: first, in the total synthesis of helminthosporal (**8**)[3] by Corey and Nozoe in 1965,[3a] and subsequently by other groups in the total synthesis of sativene (**9**),[4] which has an antipodal core of helminthosporal (**8**). Since then, synthetic studies in this area have been interrupted over two decades because new natural products have not been isolated. In the course of our synthetic study of bridged carbocyclic compounds,[4f,5] we re-visited the synthesis of the functionalized bicyclo[3.2.1]octane core and describe here the first total syntheses of drechslerines A (**1**) and B (**2**), thereby establishing their absolute stereochemistries.

2. Results and discussions

2.1. Synthesis of common intermediate 10

The retrosynthetic plan is outlined in Scheme 1. Enol triflate **10** was envisaged as an advanced common intermediate in the syntheses of drechslerines A (**1**) and B (**2**) by palladium-catalyzed conjugate reduction, and carbon monoxide insertion, respectively, which could be derived from bicyclic keto alcohol **11** via Wittig olefination. The keto alcohol **11** in turn could be obtained by regio- and diastereo-controlled allylation of optically active (*S*)-carvone (**13**), followed by an intramolecular aldol reaction. Carvone (**13**) is a classic but still useful chiral building block in the total synthesis of natural products.

The (*S*)-enantiomer of carvone (**13**) was chosen as the starting material. Reduction of the enone moiety of **13** with zinc in potassium hydroxide solution[6] and subsequent reduction of the isopropenyl group with platinum under hydrogen atmosphere led to tetrahydrocarvone (**14**) in 75% overall yield, although laborious workup to remove zinc circumvented large-scale preparation. On the other hand, hydrogenation of **13** with palladium on carbon resulted in partial isomerization to carvacrol along with partial epimerization of the isopropyl group, which was identified later by (*S*)-MTPA ester **23** (Fig. 2). These features made the hydrogenation protocols less attractive. Fortunately, the hydrogenation issue was solved by catalytic medium-pressure hydrogenation with rhodium on alumina to afford a diastereomeric mixture of tetrahydrocarvone (**14**) in 96%

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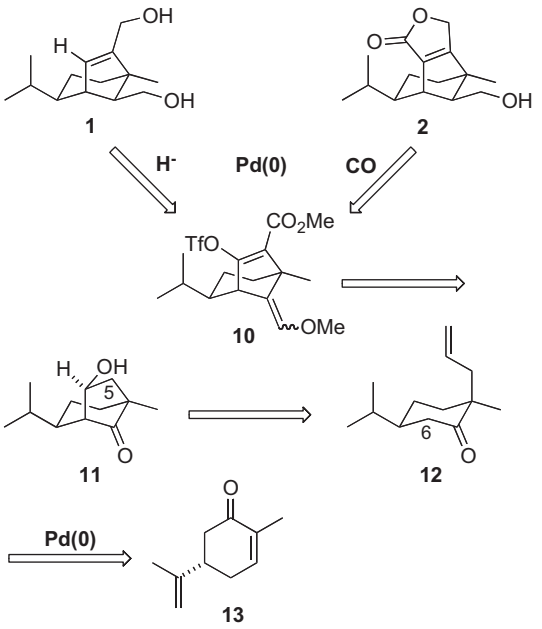


Scheme 1. Synthetic plan of drechslerines A (**1**) and B (**2**).

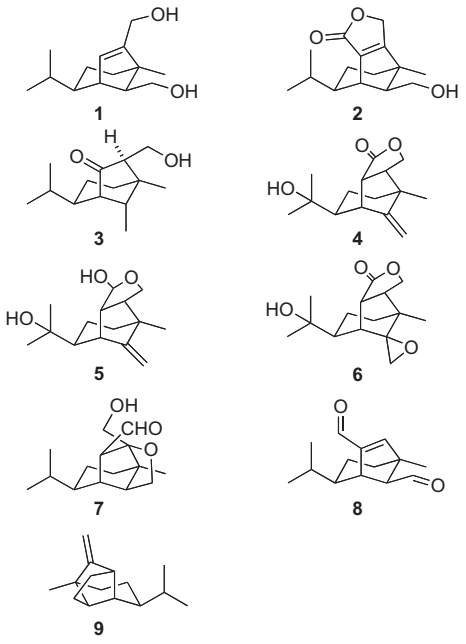


Fig. 1. Drechslerines A (**1**) and B (**2**) and their congeners.

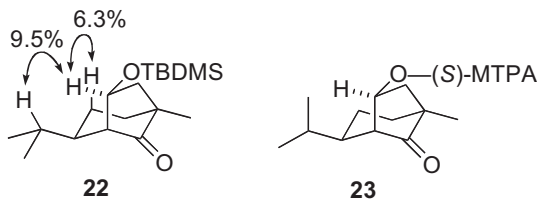
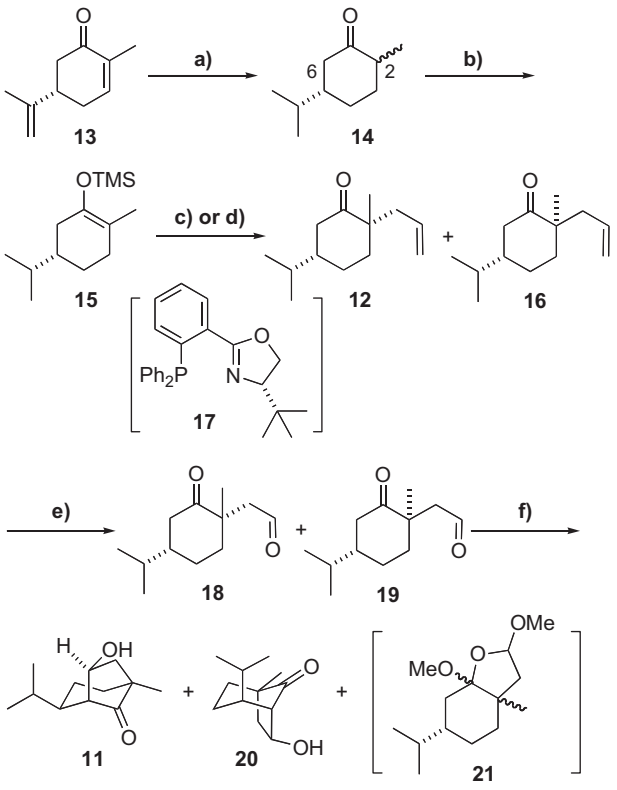


Fig. 2. Determination of the relative stereochemistry and enantiomeric excess of the intramolecular aldol product **11**.

yield. Moreover, the catalyst could be re-used without loss of catalytic activity (Scheme 2).

The control of regio- and diastereoselectivity in the alkylation of a monocyclic carbonyl compound is not an easy task due to



Scheme 2. Reagents and conditions: (a) H_2 (4 MPa), Rh/Al_2O_3 (0.1 mol %), EtOH, rt, 3.5 h, 96%. (b) TMSCl, NaI, Et_3N, MeCN, rt, 4 h, 99%. (c) MeLi, DME, −40 °C then allyliodide, THF, −50 °C, 22 h, 97% (**12**/**16**=3.4:1). (d) TBAT, $Pd_2(dba)_3$, **17**, THF, allyl carbonate, 78%, (**12**/**16**=55:1). (e) O_3, CH_2Cl_2, then Et_3N, −78 °C, 3 h, quant. (f) KOH, EtOH, 50 °C, 13 h, 80%, recrystallization.

flexibility and the lack of steric constraints in a monocyclic ring. In the total synthesis of helminthosporal (**8**) by Corey and Nozoe,[3a] the stereoselectivity in the introduction of the side chain at C-2 of the tetrahydrocarvone derivative was 60% de. Although Mori et al. in their synthesis of (+)-sorokinianin already reported the synthesis of the 5-hydroxy isomer of **11** by allylation at C-6 of tetrahydrocarvone (**14**) followed by ozonolysis and intramolecular aldol reaction, an undesired diastereomer also appeared in 26% yield, even under thermodynamically forced reaction conditions.[7] On the basis of these results, we anticipated that the allyl group could be initially introduced to the thermodynamically stable enolate of tetrahydrocarvone **14** from the same side of the isopropyl group by kinetically controlled axial alkylation. Then, thermodynamically stable tetrasubstituted silylenol ether **15** was prepared quantitatively by treatment with chlorotrimethylsilane in the presence of sodium iodide and triethylamine. Silylenol ether **15** was cleaved with methyllithium in dimethoxymethane (DME) at −40 °C to give the regioselective enolate. After fine tuning a variety of reaction conditions, the chemical yield and diastereoselectivity of allylation was optimized when allyliodide was employed and the reaction mixture was allowed to stand at −50 °C for 22 h. Fortunately, the desired 2*S*-isomer **12** predominated in 78% de as an inseparable mixture with 2*R*-isomer **16**, in which the ratio of diastereomers was estimated by the tertiary methyl peaks in NMR. The stereochemistry of the major 2*S*-isomer **12** was determined by NOE measurement of silyl ether **22** after several subsequent transformations (Fig. 2). A reversal of diastereoselectivity was observed when hexamethylphosphoric triamide was added. Allylation proceeded very slowly in diethyl ether.

The issue regarding diastereoselective allylation was solved via palladium-catalyzed diastereoselective Tsuji allylation developed by Behenna and Stoltz.[8] In the presence of a catalytic amount of