A Concise Route to the Key Intermediate of (+)-Vernolepin Using A Bicyclo[3.2.1]octane Chiral Building Block

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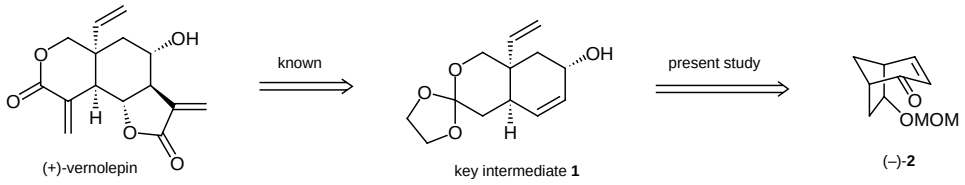
Abstract: An enantioselective route to the key intermediate leading to (+)-vernolepin, an antitumor sesquiterpene, isolated from *Vernonia hymenolepis*, has been developed starting from the chiral building block having a bicyclo[3.2.1]octane framework accessible by either enzymatic or catalytic kinetic resolution.

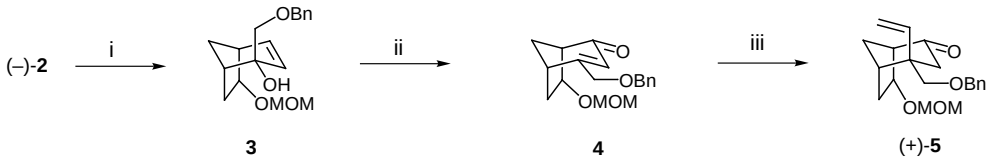
Key words: chiral building block, convex-face stereoselection, (+)-vernolepin precursor, antitumor sesquiterpene, bicyclo[3.2.1]octenone

(+)-Vernolepin, a sesquiterpene isolated from the Ethiopian plant *Vernonia hymenolepis*,[1] has been the subject of intense synthetic investigation owing to its potent antitumor activity and unique structure. Since the total syntheses by Grieco's group[2] and Danishefsky's group[3] in 1976, several syntheses of vernolepin have been reported.[4,5] However, included among them was only one synthesis, by Shibasaki's group,[5] which allowed the enantioselective construction of the natural product by employing an asymmetric Heck reaction as the key step. We have recently developed an efficient method for the preparation the enantiopure enone **2** having a bicyclo[3.2.1]octane framework in both enantiomeric forms by employing either the enzymatic[6] or the catalytic[7] kinetic resolution method. The enone **2** exhibits inherent convex-face selectivity owing to its sterically biased framework to allow diastereocontrolled modification which led to enantio- and diastereocontrolled construction of the diterpene (+)-ferruginol,[6] the A-ring[8] and the C/D-ring[7] moieties of vitamin D, and the analgesic alkaloid (-)-morphine.[9] Utilizing this chiral building block (–)-**2**, we attempted the enantioselective construction of the bicyclic orthoester **1**,[4d] the racemate of which has been transformed into racemic vernolepin,[3,4d] to develop a more efficient enantioselective route to enantiopure (+)-vernolepin as well as to demonstrate the versatility of our chiral building block **2**. We wish to report here the successful enantioselective construction of the key intermediate **1** starting from the enantiopure enone (–)-**2** (Scheme 1).

The synthesis began with the reaction of the enone (–)-**2** with the carbanion generated in situ from benzyloxymethyltributylstannane and butyllithium.[10,11] The reaction proceeded diastereoselectively from the convex-face to give the tertiary allyl alcohol **3**, $[\alpha]_D^{23}$ –161.2 (*c* 1.1, $CHCl_3$), which was oxidized with pyridinium chlorochromate (PCC)[11] to afford the β-substituted enone **4**, $[\alpha]_D^{22}$ +54.8 (*c* 1.0, $CHCl_3$). On 1,4-addition with the vinyl cuprate reagent, prepared in situ, in THF containing hexamethylphosphoric triamide (HMPA),[12] the enone **4** furnished selectively the ketone **5**, $[\alpha]_D^{24}$ +105.0 (*c* 1.0, $CHCl_3$), having a quaternary stereogenic center. The overall yield of the ketone **5** from the chiral building block (–)-**1** was 66% in three steps (Scheme 2).



Scheme 1



Scheme 2 *Reagents and conditions*: i) Bu_3SnCH_2OBn, BuLi, THF, –78 °C (95%). ii) PCC, CH_2Cl_2 (75%). iii) vinyl-MgCl, CuBr·Me_2S, HMPA, TMS-Cl, THF, –78 °C, then TBAF (92%).

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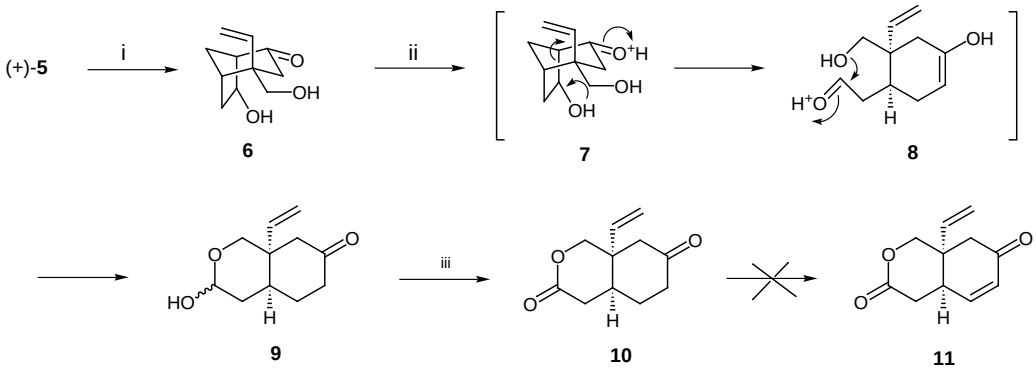
Utilizing the ketone **5** thus obtained we first attempted to transform it into the bicyclic keto-lactone **10** the racemate of which has been prepared by Heathcock's group[13] employing a completely different approach. Although the Heathcock group did not report its conversion into racemic vernolepin,[14] it seemed to us the most suitable precursor for the key intermediate **1** since there is very little difference between the keto-lactone **10** and our target molecule **1**: namely, introduction of a double bond and stereoselective reduction of the ketone functionality.

Thus, the ketone **5** was first exposed to boron tribromide to give the crystalline keto-diol **6**, mp 141–143 °C, $[\alpha]_D^{23}$ +131.5 (*c* 0.9, $CHCl_3$), by concurrent removal of the benzyl and MOM-protecting groups. Refluxing the keto-diol **6** with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in 50% aqueous dioxane initiated the retro-aldolization, followed by hemiacetalization to give rise to the bicyclic keto-hemiacetal mixture **9** presumably through the transient intermediates **7** and **8.** On Fetizon oxidation,[15] the hemiacetal mixture **9** afforded the optically active Heathcock lactone **10**, mp 104–106 °C, $[\alpha]_D^{23}$+11.3 (*c* 0.8, $CHCl_3$), as a single crystalline product. The overall yield of the lactone **10** from the ketone **5** was 64%.

However, we were unable to introduce the double bond at the requisite position of the keto-lactone **10** even using a variety of conditions including the selenide,[16] the sulfide,[17] the Saegusa,[18] and the IBX[19] methods, respectively. Discrimination of the two carbonyl functionalities of the lactone **10** was also found to be difficult since both behaved as ketone functionalities under borohydride reduction and ketalization conditions. We now understand why the Heathcock group did not report the synthesis of racemic vernolepin from the racemic keto-lactone (±)-**10** even though they had obtained it in a hundred-gram quantity and referred[13] to it as 'an attractive intermediate' (Scheme 3).

We, therefore, turned our attention to the introduction of the requisite double bond at an earlier stage before forming the *cis*-decalin framework which, we believed, was hindering the introduction of the double bond. Thus, the ketone **5** was treated with hydrochloric acid in THF to remove the MOM-protecting group to give the secondary alcohol **12**, $[\alpha]_D^{24}$+110.9 (*c* 1.0, $CHCl_3$), leaving the benzyl protecting group intact. Oxidation of the alcohol **12** with PCC gave the 1,3-diketone **13**, $[\alpha]_D^{27}$+279.7 (*c* 1.2, $CHCl_3$). When the diketone **13** was exposed to sodium methoxide in methanol a facile and clean reaction took place immediately to furnish the cyclohexanone **15**, $[\alpha]_D^{27}$ –4.9 (*c* 1.0, $CHCl_3$), in nearly quantitative yield as the single product. The observed remarkable regioselective retro-Dieckmann cleavage may be due to the steric congestion of the cyclohexanone moiety compared to the cyclopentanone moiety, which forced the methoxide attack on the cyclopentanone carbonyl to form a single transient intermediate **14**, which collapsed to give the cyclohexanone **15** exclusively. We have observed the opposite situation in which exclusive cleavage occurred with the cyclohexanone moiety to furnish the cyclopentanone derivative in the synthesis of the C/D-ring system of the vitamin D derivative.[6] Upon exposure to iodoxybenzoic acid (IBX)[19] in toluene containing DMSO and a catalytic amount of *p*-TsOH at 65 °C, the cyclohexanone **15** afforded the cyclohexenone **16**, $[\alpha]_D^{28}$ –97.8 (*c* 1.1, $CHCl_3$), cleanly in satisfactory yield. Although we could not find the optimal conditions to induce diastereoselective reduction, reduction of the enone**16** with sodium borohydride-cerium (III) chloride at –78 °C afforded a readily separable 3.8:1 mixture of the desired α-alcohol **17**, $[\alpha]_D^{24}$ –97.8 (*c* 1.0, $CHCl_3$), and the undesired β-epimer **18**, $[\alpha]_D^{24}$ –47.5 (c 1.0, $CHCl_3$), the latter of which reverted to the enone **16** in 85% yield upon oxidation and could be recycled. Having installed the requisite cyclohexenol moiety, the benzyl protecting group was next removed using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[20] Since direct treatment induced oxidation of the allylic alcohol moiety, the major alcohol **17** was first transformed into the trifluoroacetate **19**, $[\alpha]_D^{25}$ –88.8 (*c* 1.2, $CHCl_3$), under standard conditions. On stirring with DDQ in 1,2-ethylene dichloride containing a small amount of water at 50 °C, the monocyclic ester **19** furnished the lactone **20**, $[\alpha]_D^{25}$ –102.9 (*c* 1.0, $CHCl_3$), by spontaneous debenzylation and lactonization under these conditions presumably



Scheme 3 *Reagents and conditions*: i) BBr_3, CH_2Cl_2, –78 °C (92%). ii) *p*-TsOH (cat.), 50% aq Dioxane, reflux (79%). iii) Fetizon oxidation (88%).

via the hydroxy-ester**.** Transformation of the lactone **20** into the orthoester **21** was readily carried out under the same conditions as those reported in the Danishefsky synthesis.[3,4d] Finally, the ester **21** was treated with potassium carbonate to give the target molecule, the key intermediate **1**, $[\alpha]_D^{27}$ –157.6 (*c* 1.1, $CHCl_3$), of (+)-vernolepin by removal of the trifluoroacetyl moiety. The overall yield of the key intermediate (-)-**1** from the ketone (+)-**5** was 22% in nine steps, and, thus, 15% in twelve steps from the chiral building block (–)-**2**. Since the route to racemic vernolepin from the racemic **1** employing the Danishefsky synthesis[3] has been established,[4d] the present acquisition of the optically active key intermediate (–)-**1** constitutes a formal synthesis of (+)-vernolepin (Scheme 4).

In summary, we have found a new utilization for the chiral building block we developed by converting it enantioselectively into the key intermediate of the sesquiterpene (+)-vernolepin. The present example demonstrates not only the potential of the chiral building block owing to its inherent stereochemical and chemical nature, but also shows a facile entry into the physiologically and structurally interesting natural product.

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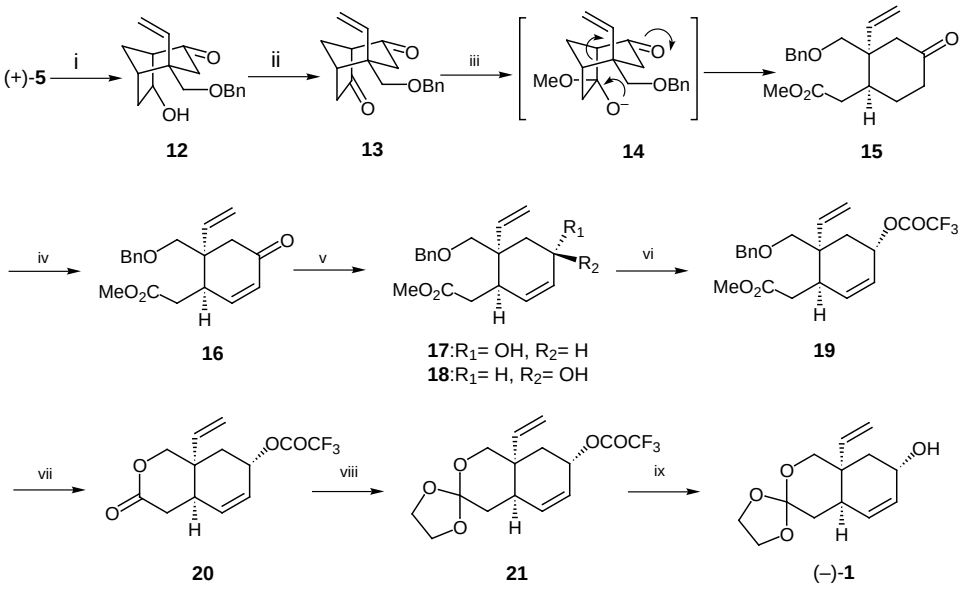

Scheme 4 *Reagents and conditions*: i) concd HCl–THF (1:4) (90%). ii) PCC, CH_2Cl_2 (84%). iii) NaOMe, MeOH, 0 °C (99%). iv) IBX, *p*-TsOH (cat.), DMSO, toluene, 65 °C (78%). v) $NaBH_4$–$CeCl_3$–$7H_2O$, –78 °C (**17**: 65% and **18**: 17%). vi) $(CF_3CO)_2O$, pyridine, THF (100%). vii) DDQ, $(CH_2Cl)_2$, H_2O (cat.) (77%). viii) $(CH_2OH)_2$, *p*-TsOH (cat.), Dowex-50W-X8, $MgSO_4$, benzene, reflux. ix) K_2CO_3, MeOH (75%, 2 steps).

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