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Studies directed toward the preparation of key intermediates for the synthesis of trisporic acids and cassiol*

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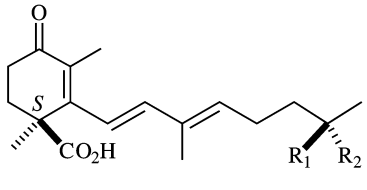
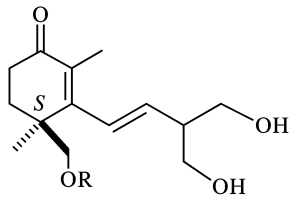
Abstract: An enantioselective synthesis and resolution of the key White intermediate (**3**) for the synthesis of trisporic acids are described. Attempts to develop a synthetic route toward the antiulcerogenic compound cassiol (**2**) by an olefination reaction of **3** and an alternative sequence involving a Michael addition followed by an aldol condensation of an open substrate, are also reported.

The trisporic acids (**1a**, **1b**, **1c**), a group of fungal pheromones [1], and cassioside (**2a**), a potent antiulcerogenic agent isolated from *Cinnamomum cassia* [2], constitute a small family of natural products derived from β-carotene.

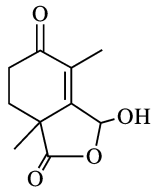
Several synthetic routes directed to specific members of the group of trisporic acids have been reported. More recently, however, White *et al.* [3] described a general convergent approach to the synthesis of **1a**, **1b**, and several related products, via a Wittig reaction of lactol **3** with an appropriate phosphorane.



1a, R_1=R_2=H
1b, R_1=R_2=O
1c, R_1=OH,R_2=H



2a, R=β-D-glucose
2b, R=H



3

The structural features and pharmacological activity of (+)-cassiol (**2b**), exhibiting a more potent antiulcer activity than cassioside (**2a**) itself, have also aroused the interest of synthetic organic chemists and several valuable contributions to its synthesis have appeared in the literature in recent years [4].

In view of our interest in the application of the Michael addition-aldol condensation sequence for the preparation of key intermediates toward the synthesis of natural products [5], we decided to study the enantioselective synthesis of **3** by reaction of a suitable Michael donor and ethyl vinyl ketone. The availability of **3** having *S* configuration at the quaternary carbon stereocenter would eventually allow the preparation of **1a** and/or **1b** with the natural configuration [6] and, furthermore, the coupling of (*S*)-**3** with an appropriate phosphorane would lead to (+)-cassiol (**2b**).

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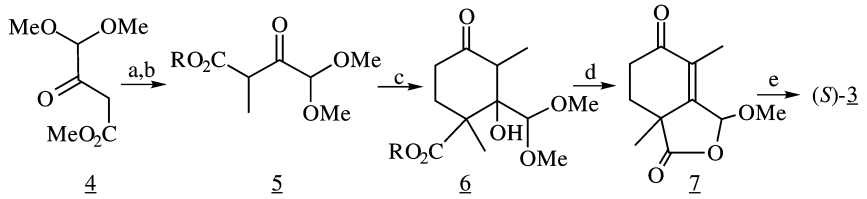
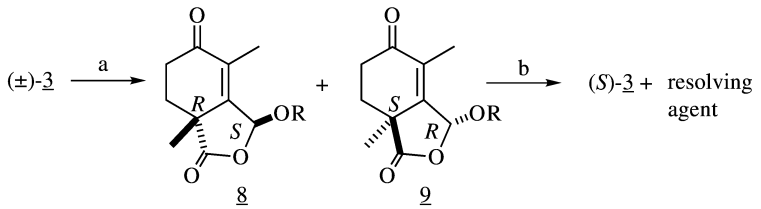
Starting with the β-keto ester **4** and using *endo*-2-β-naphthyl-*endo*-3-borneol as chiral auxiliary we prepared the crystalline aldol **6** in approximately 20% overall yield. An X-ray analysis of **6** showed that the absolute configuration of the three chiral centers generated in the sequence are 2*S*, 3*R*, and 4*S*, respectively. The dehydration of **6** occurred with elimination of the chiral auxiliary as a mixture of alkenes and simultaneous formation of **7** as a 3.5:1 mixture of diastereoisomers (3*R*,8*S*) and (3*S*,8*S*) respectively, in 62% yield, upon hydrolysis (*S*)-3 was obtained [7].



R=*endo*-2-β-naphthyl-*endo*-3-borneol

Reagents and conditions: a)*endo*-2-β-naphthyl-*endo*-3-borneol, DMAP, molecular sieves, PhMe, reflux; b) MeI, TlEtO; c) Ethyl vinylketone, K_2CO_3, MeOH, -25^{0}C; d) $CuSO_4$, SiO_2, PhH, reflux; e) HCl, THF, H_2O, reflux

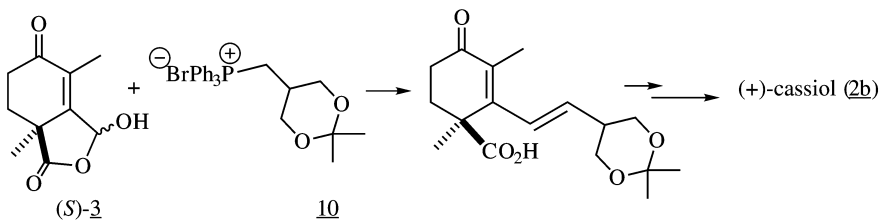
In order to have a more direct access to optically active **3**, we studied the resolution of its readily available racemic modification through the preparation of diastreoisometic acetals by reaction with a chiral alcohol. We found that the acid-catalyzed treatment of (±)-3 with *exo*-2-α-naphthyl-*exo*-3-borneol afforded a mixture of only two diastereosiomeric acetals readily separable by column chromatography in very good yield. Based on an exhaustive ^{1}H NMR analysis of both naphthyl borneol acetals and chemical correlation with known bicyclic lactones, we determined that the absolute configuration of the less and more polar diastereoisomeric acetals are 3*S*,8*R* (**8**) and 3*R*,8*S* (**9**) respectively. The X-ray analysis of **9** unequivocally confirmed this configurational assignment. Finally, the acidic hydrolisis of **9** afforded (*S*)-**3** in good yield with simultaneous recovering of the resolving agent [7].



R= *exo*-2-α-naphthy-*exo*-3-borneol

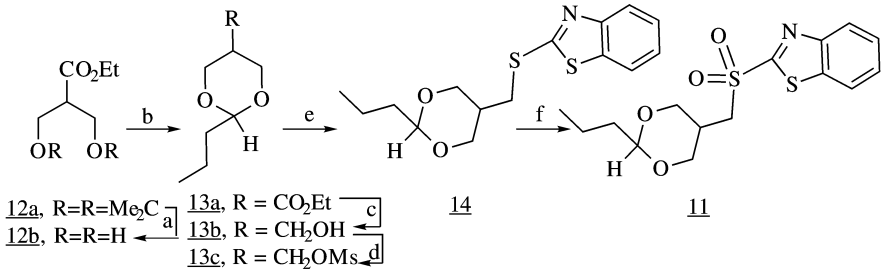
Reagents and conditions: a)*exo*-2-α-naphthy-*exo*-3-borneol, p-TsOH, PhH, reflux; b) 6N HCl, dioxane, reflux, 100%

With (*S*)-**3** in hand, we studied its transformation into (+)-cassiol (**2b**) following an approach involving its olefination with the phosphonium bromide **10**.



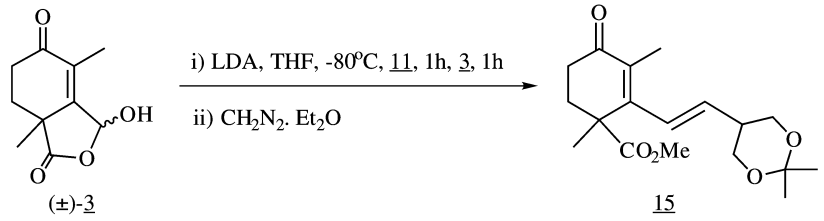
All our attempts to prepare **10** were unsuccessful. The treatment of the corresponding bromide with triphenylphosphine under the usual conditions led to extensive cleavage of the protecting group. The same result was obtained using a variety of hydroxyl protecting groups and under several reaction

conditions. In view of these difficulties we decided to apply the one-pot olefination reaction recently reported by S. Julia *et al.* [8]. The 2-benzothiazolylsulfone **11** that was selected as the most adequate reaction partner was prepared as shown below starting with the ester **12a**, its coupling reaction with (±)-3 was then carefully analyzed.



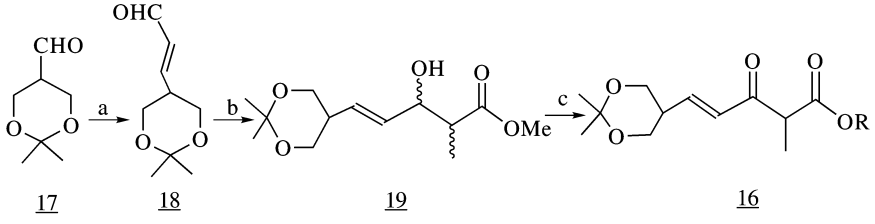
Reagents and conditions: a) 6N HCl, MeOH, rt; b) $CH_3(CH_2)_2CHO$, TsOH, hexane, reflux; c) $LiALH_4$, Et_2O, rt; d) MsCl, Et_3N, 0°C; e) 2-mercaptobenzothiazole, KOH, EtOH, rt; f) ammonium molybdate, H_2O_2 , 0°C to rt.

We have found that under the conditions described by S. Julia *et al.*, the *trans*-alkene **15** was isolated by column chromatography of the crude reaction mixture after its treatment with excess of diazomethane, in only 18% yield. The ^1H and ^{13}C NMR spectral data are in excellent agreement with the proposed structure and stereochemistry for **15**.



A careful analysis of the reaction mixture allowed us the identification of starting material and products of side reactions that suggested a low reactivity of the carbonyl group of **3** under these conditions. All our attempts to improve the yield of **15** were unsuccessful [9].

In view of the results described above, we decided to study an alternative sequence towards cassiol (**2b**), involving also a Michael addition followed by an aldol condensation of the β-keto ester **16**, carrying the side chain present in **2b**, and ethyl vinyl ketone. Interestingly, this approach, if successful, could be potentially useful for the development of an enantioselective synthesis to **2b**. The preparation of **16** was carried out in good overall yield as shown below.

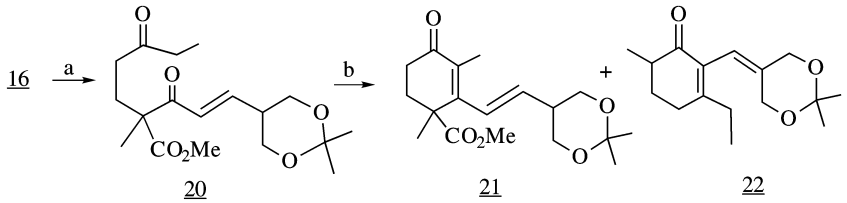


Reagents and conditions: a) (triphenylphosphoranylidene)acetaldehyde, PhH, reflux; b) methyl propionate, THF, LDA, -78°C ; c) PDC, CH_2Cl_2, RT, 24h

The addition of **16** to ethyl vinyl ketone occurred smoothly to yield **20**, and several attempts were carried out to induce the aldol condensation to **21**. Finally, we found that the treatment of **20** with 4%

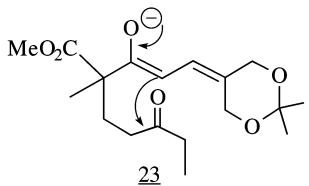
aqueous potassium hydroxide in refluxing methanol afforded a mixture of **21** (10%) and **22** (60%). The ^{1}H and ^{13}C NMR spectral data are in excellent agreement with the proposed structures for **21** and **22**.

The structure of **22** suggested that the condensation step had occurred mainly through the alternative enolate **23** [10]. The synthesis of a substrate in which only the enolate leading to the key intermediate **21** toward **2b** can be formed is in progress.



20 21 22

Reagents and conditions: a) EVK, EtOH, NaOH; b) 4% KOH (aq), MeOH, reflux, 7 h.



23

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