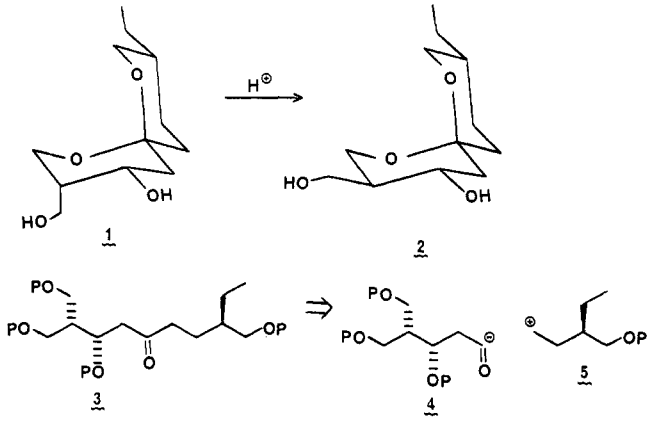
Communications

Synthesis of (–)-Talaromycin A

Summary: The spiroketal talaromycin A has been prepared in high optical and diastereomeric purity by using a [2,3]-sigmatropic (Wittig) rearrangement and a [3,3]-Claisen rearrangement as key steps in controlling absolute configuration.

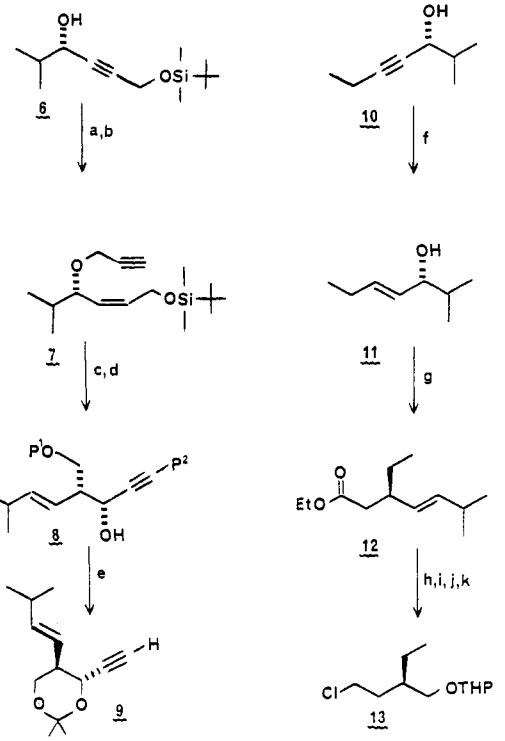
Sir: Talaromycins A (**1**) and B (**2**) are two toxic metabolites produced by *Talaromyces stipitatus*, a fungus which grows on chicken litter.[1] We herein report an enantioselective synthesis of talaromycin which provides good overall yield and high optical purity. This synthesis should provide ready access to all diastereomers as well as to structural analogues. A key process in this synthesis is the transfer of the chirality of readily available, enantiomerically enriched propargyl alcohols[2] to new carbon–carbon centers via [2,3]- and [3,3]-sigmatropic rearrangements.

Several syntheses of the thermodynamically more stable talaromycin B in racemic form have appeared.[3] These syntheses cannot directly provide the thermodynamically less stable talaromycin A (however, Schreiber has recently circumvented this problem).[3e] Recently, an enantioselective synthesis of (–)-talaromycins A and B (in 90–93% ee) was reported by Smith.[4] Our synthetic strategy was to prepare the open-chain precursor (**3**) of talaromycin by



coupling of subunits **4** and **5** of established absolute configuration. These subunits contain three of the chiral centers of talaromycin. Since it is known that spiroketals strongly prefer the configuration with the oxygens of one ring occupying the axial position with respect to the other ring (anomeric effect),[5] the final asymmetric center was expected to be formed correctly upon ketalization. Talaromycin A is essentially quantitatively transformed into the thermodynamically more stable talaromycin B upon treatment with acid. Therefore, a key consideration was to distinguish the prochiral CH_2OH units of **4** which would lead to talaromycin A or B in such a way that the alcohol would be liberated under nonacidic conditions.

Scheme I[a]



[a] (a) H_2/Pd-$CaCO_3$; (b) NaH, propargyl bromide, 64% from **6**; (c) 1.1 equiv of *n*-BuLi, 1.1 equiv of Me_3SiCl, 1.2 equiv of *n*-BuLi (P^1 = *t*-$BuMe_2Si$, P^2 = Me_3Si): (d) Bu_4NF (P^1 = P^2 = H), 85% from **7**; (e) $Me_2C(OMe)_2$, H^+, 52%; (f) $LiAlH_4$, 77%; (g) $MeC(OEt)_3$, 60%; (h) $LiAlH_4$, 70%; (i) Ph_3P, CCl_4, 70%; (j) O_3, $NaBH_4$; (k) DHP, H^+, 65%. Yields are of isolated product.

The synthesis of the left and right fragments is outlined in Scheme I. The acetylene compound **9** and chloride **13** were chosen as synthetic equivalents for subunits **4** and **5**. The starting propargyl alcohols **6** and **10** are obtained from asymmetric reduction of the corresponding propargyl ketones with (*S*)- and (*R*)-Alpine-Borane (from (–)- and (+)-α-pinene), respectively. The isopropyl group imparts essentially complete asymmetric induction, 92% ee for **6** and **10** from 92% ee α-pinene.[2] Fragment **8** was readily prepared in greater than 98% diasteromeric purity by [2,3]-sigmatropic rearrangement of the in situ generated trimethylsilyl propargyl ether of **7**.[6] Fragment **12** was prepared by using the Johnson ortho ester Claisen rearrangement[7] of *trans*-allylic alcohol **11** as the key step. Both

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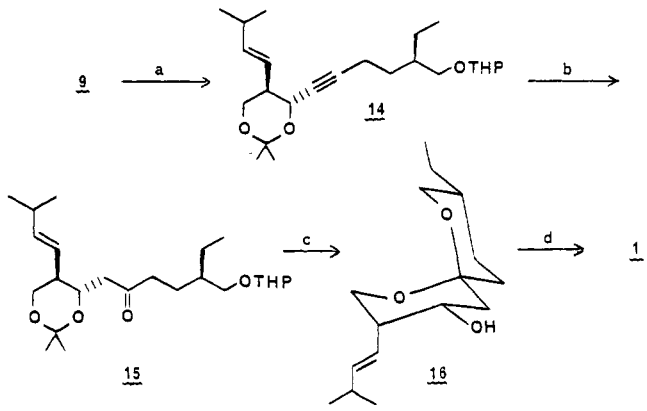
Scheme II[a]



[a] (a) *n*-BuLi, 13, 73%; (b) Sia_2BH, NaOH, H_2O_2, 40%; (c) MeOH, H^+, 94%; (d) O_3, $NaBH_4$, 73%. Yields are of isolated product.

of these rearrangements are known to proceed with essentially complete chirality transfer.[6,8]

The completion of the synthesis is depicted in Scheme II. The coupling of the two fragments to acetylene **14** was achieved in good yield in THF/HMPA (3:5). Assuming that this coupling takes place without diastereoselection, an increase in the enantiomeric purity of the coupled compound should result for statistical reasons.[9] The hydrolysis of acetylene **14** to ketone **15** was performed by a hydroboration–oxidation sequence using disiamylborane. Model studies revealed that this sequence could be highly regioselective. However, the acetonide **14** provided a 1:1 mixture of regioisomers. A 5:1 selectivity for the desired isomer was obtained from hydroboration of the unprotected triol but the overall yield was lower.

Treatment of ketone **15** with an acidic ion exchange resin provided the spiroketal **16** as a single isomer. Ozonolysis followed by reductive workup gave talaromycin A (**1**): $[\alpha]^{26}_D$ −124.9° (*c* 1.11, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ −110.2° (*c* 0.83, $CHCl_3$) for material of 90–93% ee]. The literature value provides a theoretical rotation of −118.5° to −122.4° for pure material. The high-field ^1H NMR spectrum was identical with the published data[1] and to that of the synthetic material.[4] Optically active talaromycin A has been previously converted to optically active talaromycin B under acid catalysis.[1,4]

This synthesis provides flexible control of the chiral centers of talaromycin. The absolute and relative chirality of the two fragments is controlled by the choice of (*R*)- or (*S*)-Alpine-Borane for the initial reduction. The prochiral CH_2OH units are distinguished as a protected alcohol and latent alcohol (i.e., an olefin). Interconversion of the two alcohols could thus be readily achieved through simple manipulations. These simple subunits are readily manipulated to provide structural analogues. Finally, the strategy of coupling two enantiomerically enriched subunits provides a product which is essentially enantiomerically pure.

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Use of Enzymatic Hydrolysis of Dimethyl Malates for a Short Synthesis of Tulipalin B and of Its Enantiomer

Summary: Pig liver esterase (PLE) hydrolyzes the ester function α to the hydroxyl group in dimethyl malate. This regiospecific reaction was used to synthesize (+)- and (−)-tulipalin B.

Sir: Malic acid has been proven to be an extremely valuable chiral synthon for the enantiospecific synthesis of several classes of compounds such as, for example, hydroxytetrahydrofurans,[1] dihydroxyuracil derivatives,[2] amphotericin B,[3] lactones,[4,5] and pheromones.[6,7]

Enzymatic methods for the preparation of bifunctional chiral synthons have recently been developed.[8] We describe here the hydrolysis of dimethyl malates by pig liver esterase (PLE). This commercially available hydrolase is known to cleave only one ester function of dicarboxylic esters.[9] We have taken advantage of this selectivity to devise a new synthesis of (+)- and (−)-tulipalin B.

Racemic dimethyl malate was incubated with PLE (400 units per 43 mmol of substrate) in a 200-mL phosphate pH 8 buffer solution. The reaction was monitored by a pH meter and the pH was maintained to 8.0 ± 0.1 with a 1 N NaOH solution. After 1 equiv of sodium hydroxide was consumed, the pH did not vary anymore, indicating completion of the reaction.

The ^1H NMR spectrum of the obtained compound showed only one methoxy (3.76 ppm) signal along with a COOH signal while the spectrum of dimethyl malate showed two methoxy signals for the two ester functions. That the reaction was regio- and not enantioselective was shown by a zero $[\alpha]_D$ value of the hemiester, a racemic mixture.

The regioselectivity of this reaction was established by reducing the acid function with $BH_3 \cdot Me_2S$, in THF. The ^1H NMR spectrum in the presence of D_2O showed an ABX

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(9) If one couples two *R* molecules of 90% ee (95% *R*, 5% *S*), the product will consist of 0.95 × 0.95 = 0.9025 parts *RR*, 2(0.95 × 0.05) = 0.095 parts *RS*, and 0.05 × 0.05 = 0.0025 parts *SS*. The final enantiomeric purity ((*RR* − *SS*)/(*RR* + *SS*) × 100) is 99.5%. The minor enantiomers of the fragments are removed as the diastereomers. A similar enhancement of enantiomeric purity has been achieved by Eliel in the synthesis of malyngolide (Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576).

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