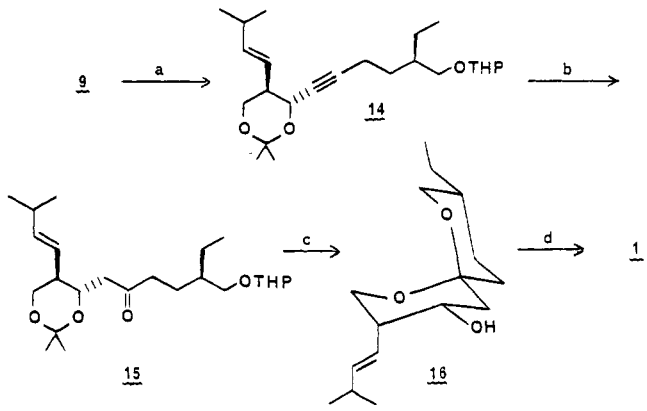
Scheme II[a]



[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.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM 24517) and the Committee on Research, University of California, Riverside. We thank Professor Amos Smith for the ^1H NMR spectrum of talaromycin A.

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Received November 26, 1984

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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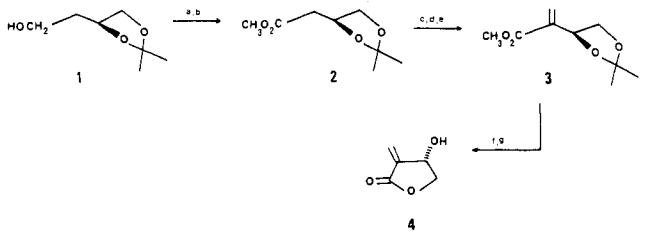
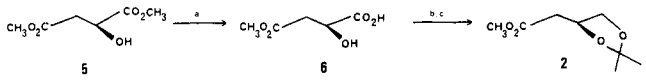
Scheme I[a]



[a] (a) $KMnO_4$, 18-crown-6, benzene; (b) ICH_3; (c) LDA, $CH_2{=}N^+(CH_3)_2I^-$; (d) ICH_3; (e) DBU; (f) $Ba(OH)_2$; (g) 1 N HCl.

Scheme II[a]



[a] (a) PLE; (b) $BH_3{\cdot}Me_2S$; (c) acetone, *p*-TsOH.

signal (H_A 2.52, H_B 2.72, J_{AX} = 6.4, J_{BX} = 7.0, J_{AB} = 15.9) for the group $CH_X(OD)CH_AH_BCO_2CH_3$ and an AMX signal (H_A 3.66, H_M 4.16, J_{AM} = 6.40; J_{MX} = 4.00; two dd) for the group $CH_X(OD)CH_AH_M(OD)$. If instead the other ester function had been hydrolyzed and then reduced, leading to compound $HOCH_2CH_2CH(OH)CO_2CH_3$, the NMR spectrum would have been different (in particular dt or even more complicated multiplets would have been present). The regioselectivity of the hydrolysis of the ester function with an α-OH group is therefore demonstrated.[10]

This half-ester was used toward the synthesis of tulipalin B (**4**), a natural product with cutaneous allergenic activity.[11] A lengthy synthesis of this compound has already been reported, starting from isopropylidene-D-glyceraldehyde.[12] We have developed two syntheses of tulipalin B on the basis of the malic acid derivatives.

The key compound **1**[13] in the first synthesis outlined in Scheme I is obtained from malic acid.

Oxidation of (−)-(**S**)-**1** with $KMnO_4$ in benzene containing 10% of 18-crown-6 and trapping the carboxylate with methyl iodide led to the ester **2** (43% yield; 40% of the starting compound **1** are recovered, $[\alpha]_D$ +17.0° (c 2.00, $CHCl_3$). Treatment[14] of the anion of **2** with Eschenmoser salt followed by permethylation and elimination of the resulting trimethylammonium salt (acetone, DBU) gave **3** in an 11% yield ($[\alpha]_D$ +15.7° (c 1.80, $CHCl_3$); 80% of **2** are recovered) which, after saponification and acid treatment, gave pure (−)-tulipalin B (**4**) ($[\alpha]_D$ −81° (c 1.32, $CHCl_3$), lit.[11] $[\alpha]_D$ −82° ($CHCl_3$)).

In Scheme II, the second synthesis involves dimethyl malate half-ester. Starting from optically pure dimethyl (*S*)-(−)-malate, we have obtained by the above described method the optically pure ester **6** ($[\alpha]_D$ +1.5° (*c* 1.80, $CHCl_3$) which, upon reduction with 2 equiv of $BH_3{\cdot}Me_2S$,[15] and treatment with acetone in the presence of *p*-TsOH gave compound **2** in 73% yield.

A sequence identical with that used in Scheme I led to tulipalin B. This short route was followed for the synthesis of (+)-tulipalin B.

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Received December 28, 1984

An Extremely Facile Ring Opening of Substituted 1-(Alkylthio)cyclopropenes via Vinylcarbene Intermediates

Summary: Thermal ring opening of 1-(methylthio)cyclopropenes **2** takes place readily to give indene and/or butadiene derivatives in good yields, and product analysis of the reaction in methanol as well as kinetic studies of **2b** gave strong evidence for the intermediacy of vinylcarbene in the ring opening of **2**.

Sir: In these 2 decades the chemistry of cyclopropene has attracted considerable interest because of its high strain energy.[1] Theoretical calculations suggest that the ring opening of cyclopropene proceeds directly to a diradical planar intermediate.[2] To explain the products of photochemical ring opening of cyclopropene, a diradical and/or a vinylcarbene intermediate has been postulated.[3] In contrast, a mechanistic studies on the thermal ring opening of cyclopropene have been scarce,[4] and to the best of our knowledge none of the effects of heteroatom substitution on the reactivity of cyclopropene has been reported. In this communication we report an easy route for the preparation and facile ring-opening reaction of 1-(alkylthio)cyclopropenes **2**.

To a suspension of 1,2-diphenyl-3-(methylthio)cyclopropenium bromide (**1a**)[5] in dry benzene was added methylmagnesium bromide (3 times excess) in one portion, and the mixture was stirred to give a clean solution. After 5 min the resulting solution was quenched with ice water and the organic layer was separated. ^1H NMR spectroscopic analyses revealed that the crude product was a mixture of two isomeric cyclopropenes (**2a** and **3a**). The major component was separated by column chromatography and confirmed to be 1,3-diphenyl-3-methyl-2-(methylthio)cyclopropene (**2a**).[6] Similar treatment of **1a** and **1b** with other Grignard reagents, R′MgX, yielded the corresponding cyclopropenes **2** in good yields together with isomeric cyclopropenes **3** (Table I).

It has been reported that tetraphenylcyclopropene rearranges at temperatures as high as 235–240 °C to give

(10) This result allowed the assignment of the signals of the esters in dimethyl malate ($CH(OH)CO_2CH_3$ δ 3.68; $CH_3CO_2CH_2$ δ 3.78).

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(14) Alkylation of the α position of dimethyl malates has been reported to proceed with moderate yields. See: Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. Papageorgiou, C.; Benezra, C. *Tetrahedron Lett.* **1984**, *25*, 1303.

(15) The first equivalent forms the borate between adjacent hydroxy groups.

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(6) **2a**: oil; IR (neat) 1980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (3 H, s, Me), 2.39 (3 H, s, MeS), 6.9–7.6 (10 H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 16.5 (q, MeS), 22.1 (q, Me), 31.9 (s, C-3), 116.0 (s), 117.6 (s), 125.3 (d), 125.9 (d), 126.1 (d), 127.2 (d), 127.8 (d), 128.0 (d), 128.6 (d), 146.8 (s); MS, *m/z* 252 (M^+).

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