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Enantioselective Synthesis of the White Key Intermediate for the Synthesis of Trisporic Acids

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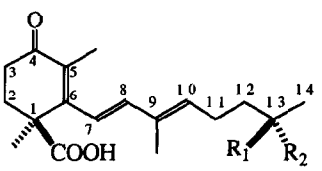
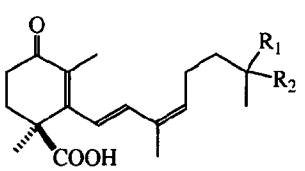
Abstract: The asymmetric construction of the alkylated cyclohexenone carboxylic acid moiety of trisporic acids A, B and C and the syntheses of related precursors are described. The syntheses feature a Michael addition in tandem with an aldol condensation as the central step.

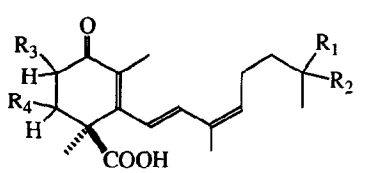
The trisporic acids constitute a family of naturally occurring fungal pheromones derived from β-carotene that included (9E)-trisporic acid A (**1a**), B (**1b**) and C (**1c**), their 9Z isomers **2a**, **2b** and **2c**, and the corresponding methyl esters. Recently, trisporic acid E (3*R*) (**3a**), E (3*S*) (**3b**) and D (2*S*) (**3c**), carrying a hydroxyl group on the cyclohexenone moiety, were also isolated and characterized.[1] Furthermore, the absolute stereochemistry at C-1 of trisporic acid C methyl ester was shown to be *S* on the basis of a CD study of the acetate of its tetrahydroderivative,[2] consequently, the same stereochemistry was assigned to all members of the family.



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



2a, R_1=R_2=H
2b, R_1, R_2=O
2c, R_1=OH, R_2=H



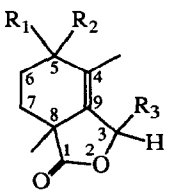
3a, R_1=H, R_2=OH, R_3=OH, R_4=H
3b, R_1=H, R_2=OH, R_3=OH, R_4=H
3c, R_1, R_2=O, R_3=H, R_4=OH

Although several synthetic routes have been described for the synthesis of trisporic acids, most of them are directed to a specific member of this group of natural products.[3-5] However, in 1985 White *et al.*[6] reported a general convergent approach to the synthesis of trisporic acids A, B and several related products, *via* a Wittig reaction of lactol **4a** with an appropriate phosphorane. To the best of our knowledge, there has been no report in

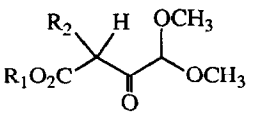
the literature on the synthesis of enantiomerically pure **4a**.

In view of the increasing interest in the development of synthetic methodologies for the construction of chiral quaternary carbon centres,[7] we decided to study the enantioselective synthesis of **4a** by employing a tandem Michael addition-aldol condensation sequence of a suitable Michael donor and ethyl vinyl ketone.

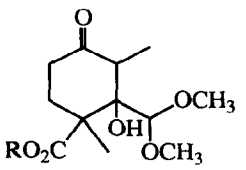
For the preparation of the Michael donor we started with the known β-keto ester **5a**,[5] which was first transformed into the corresponding 8-β-naphthylmenthyl ester **5b**[8] by a 4-(dimethylamino)pyridine-catalyzed ester exchange in the presence of molecular sieves[9] and then, exclusively, into the monoalkylated ester **5c** by treatment with methyl iodide and thallium (I) ethoxide.[10] We selected 8-β-naphthylmenthol[11] as chiral auxiliary hoping to achieve an acceptable degree of π-facial discrimination in the Michael addition step.[12] In fact, we have found that using potassium carbonate as base in methanol at -25°C, **5c** afforded a 7:2:0.5:0.5 mixture of aldol products (**6**).[8] Although the actual stereochemistry of these tertiary alcohols was not determined, the ratio was estimated by comparison of the areas under the signals at δ 4.14, 4.28, 4.31 and 4.35 assigned to the acetal proton of each diastereomer, in the ^{1}H NMR spectrum of the crude reaction product. Without separation, the diastereomeric adducts were treated with copper (II) sulfate adsorbed on silica gel in refluxing benzene.[13]



4a, R_1,R_2=O, R_3=OH
4b, R_1,R_2=O, R_3=OCH_3
4c, R_1=OH, R_2=H, R_3=H
4d, R_1,R_2=O, R_3=H



5a, R_1=CH_3, R_2=H
5b, R_1=8-β-naphthylmenthyl, R_2=H
5c, R_1=8-β-naphthylmenthyl, R_2=CH_3



6, R=8-β-naphthylmenthyl

Under these conditions the dehydration reaction occurred smoothly with elimination of the chiral auxiliary as a mixture of alkenes and, very interestingly, with the simultaneous formation of **4b**. Since **4b** is a nicely crystalline compound we decided to isolate it by direct crystallization from the reaction mixture. In summary, we have developed a simple approach to crystalline (-)-**4b**[8] through the sequence described above (**5b**→**5c**→**6**→**4b**), without purification of intermediates, in approximately 20% overall yield and in more than 95% enantiomeric excess.[14] Acidic hydrolysis of (-)-**4b** afforded quantitatively **4a**, showing a ^{1}H NMR spectrum coincident with that previously described for the racemic modification.[6]

For the determination of the absolute configuration at C-8† of (-)-**4b** and consequently of **4a**, we transformed this lactol into the enone lactone (-)-**4d** [mp 95.5-96.5°C, $[\alpha]_D^{20}$ -226 (c=0.35, $CHCl_3$), ee>95%[14]] by a sequence of reactions involving reduction with sodium borohydride in the presence of cerium (III) chloride followed by Jones oxidation of the resultant allylic alcohol (**4c**). The ^{1}H and ^{13}C NMR spectra of (-)-**4d** are coincident with the spectral data previously reported for (±)-**4d** (mp 58-60°C)[6] and also for (+)-**4d** [$[\alpha]_D^{20}$+181 (c=6.1, $CHCl_3$), ee 94%].[15] Since the absolute configuration at C-8 of (+)-**4d** has been established as *S*, we concluded that the absolute configuration at the same carbon of (-)-**4d** and consequently of (-)-**4b** and **4a** must be *R*.

† The numbering used in this paper is the one reported in ref 6.

Since the absolute configuration at C-8 of (+)-**4d** has been suggested on the basis of the preferred conformation of the chiral enamine used for its preparation,[15] we decided to confirm it through another methodology. Toward this end we developed a simple asymmetric approach to **4d**, an intermediate that had been used by White *et al.* for the preparation of (±)-**4a**,[6] by extending the procedure of Hajos and Parrish[16] to the diketolactone **7**, prepared in quantitative yield by condensation of α-methyltetronic acid and ethyl vinyl ketone. In practice, the aldol condensation of **7** catalyzed by (*S*)-(-)-proline afforded a mixture of hydroxy lactones from which, the *cis* fused hydroxy keto lactone **8** was isolated in 25% yield by fractional crystallization. Acidic dehydration of **8** afforded (+)-**4d** [mp 79-80°C, $[\alpha]_D^{20}$+150 (c=0.35, $CHCl_3$), ee 68%][14] in quantitative yield. The CD spectrum of (+)-**4d**[8] shows a positive n⟶π* band with the usual fine structure. Since the preferred conformation of the molecule is such that the C=C-C=O system is planar and therefore falls into the category of a transoid cyclohexenone with a flattened chromophore as defined by Snatzke,[17] the absolute configuration at C-8 must be *S*, as it is in the trisporic acids. This result also confirms the proposed stereochemistry for (-)-**4d**, (-)-**4b** and **4a**.

7 **8**

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8 - Relevant spectral and analytical data for selected compounds:
5b, IR 1718, 1748 cm^{-1}. ^1H NMR δ 7.80–7.39 (7H, m), 4.88 (1H, dt, J=10.7 and 4.4 Hz), 4.29 (1H, s), 3.27 (3H, s), 3.25 (3H, s), 2.67 (2H, dd, J=30.6 and 16.7 Hz), 1.43 (3H, s) 1.31 (3H, s), 0.88 (3H, d, J=6.4 Hz). The following signals of the enol form were also detected: δ 11.76 (br s), 4.92 (dt,

J=10.7 and 4.4 Hz), 4.49 (s), 4.44 (s) 3.21 (s), 3.18 (s), 1.33 (s). ^{13}C NMR δ 197.71 (s), 165.95 (s), 148.75 (s), 133.08 (s) 131.21 (s), 127.59 (d), 127.02 (d),126.94 (d), 125.54 (d), 124.87 (d), 124.72 (d), 122.49 (d), 102.63 (d), 74.95 (d), 54.07 (q x 2), 49.71 (d), 44.07 (t), 41.14 (t), 39.50 (s), 34.22 (t), 30.97 (d), 27.62 (q), 26.24 (t), 24.22 (q), 21.45 (q). The following signals of the enol form were also detected: δ 171.21 (s), 169.65 (s), 148.28 (s), 133.24 (s), 125.28 (d), 98.96 (d), 90.83 (d), 74.03 (d), 53.09 (q), 52.40 (q), 41.47 (t), 27.31 (q), 24.78 (q).

6, selected signals of the major isomer: IR 3418, 1708, 1684 cm^{-1}. ^1H NMR δ 7.85–7.30 (7H–m), 5.46 (1H, s, disappears upon addition of D_2O), 4.83 (1H, dt, J=10.7 and 4.2 Hz), 4.14 (1H, s), 3.36 (3H, s) 3.23 (3H, s), 2.45-2.25 (4H, m), 2.20-2.05 (2H, m), 1.85-1.60 (4H, m), 1.55-1.45 (1H, m), 1.43 (3H, s), 1.26 (3H, s), 1.01 (3H, d, J=6.6 Hz), 0.91 (3H, d, J=6.4 Hz). ^{13}C NMR δ 207.24 (s), 178.25 (s), 149.21 (s), 133.20 (s), 131.39 (s), 127.55 (d x 2), 127.06 (d), 125.72 (d), 125.10 (d), 124.65 (d), 122.58 (d), 111.80 (d), 80.33 (s), 75.87 (d), 58.92 (q), 57.50 (q), 48.77 (d), 48.07 (d), 44.67 (s), 40.34 (t), 39.50 (s), 35.02 (t), 34.30 (t), 30.94 (d), 28.75 (q), 26.62 (t), 24.50 (q), 24.02 (t), 21.67 (q), 19.29 (q), 7.01 (q).

(-)-**4b**, mp 140-142°C. $[\alpha]_D^{20}$ -17.14 (c=0.7, $CHCl_3$). IR. 1790, 1664 cm^{-1} ^1H NMR δ 5.82 (1H, s, H-3), 3.64 (3H, s, OMe), 2.78-2.42 (2H, m, H-6), 2.28-1.92 (2H, m, H-7), 1.81 (3H, s, C-4 Me), 1.57 (3H, s, C-8 Me). ^{13}C NMR δ 197.26 (C–5), 177.62 (C-1), 151.72 (C-9), 130.89 (C-4), 101.86 (C-3), 57.50 (OMe), 40.39 (C-8), 32.43 (C-6), 30.17 (C-7), 21.90 (C-8 Me), 10.26 (C-4 Me). The lack of NOE enhancement at δ 5.82 (H-3) when the signal of C-8 methyl group (δ 1.57) is irradiated strongly suggests that the configuration at C-3 is *S*.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.83; H, 6.72. Found: C, 62.49; H, 6.72.

4a, ^1H NMR (acetone-d_6) δ 7.23 (1H, br s, disappears upon addition of D_2O), 6.55 (1H, br s), 1.78 (3H, s), 1.53 (3H, s).

8, mp 147.5-148.5°C. ^1H NMR δ 4.04 (2H, dd, J=10.2 and 15 Hz), 2.59 (1H, q, J=8.5Hz), 2.40-1.70 (4H, m), 1.47 (3H, s), 1.13 (3H, d, J=8.5 Hz). ^{13}C NMR δ 206.90 (s), 178.95 (s), 81.40 (s), 72.17 (t), 48.60 (d), 46.33 (s), 35.05 (t), 29.99 (t), 13.09 (q), 5.92 (q).

(+)-**4d**, CD (acetonitrile, 2.848 mmol/l): λ_{max} (Δε)= 334.8 (2.04), 244.4 (-1.97), 222.8 (-6.58), 198.4 (8.88).

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