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Synthesis of cryptoporic acid A methyl ester

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Abstract

An anti-tumor promoter, cryptoporic acid A methyl ester, has been synthesized by 1,4-addition of the enolate derived from the methoxycarbonylmethyl ether of albicanol to methyl maleate or fumarate as well as three other diastereoisomers. © 2000 Elsevier Science Ltd. All rights reserved.

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Cryptoporic acids A–F have been isolated from the fungi *Cryptoporus volvatus*, and their structures have been established by high resolution 2D NMR techniques, X-ray analysis, and chemical degradations to have very unusual structures: albicanol bonded to isocitric acid moiety by an ether linkage.[1–5] Moreover, their biological activities are very interesting; for example, superoxide anion release inhibition and anti-tumor promotion activities.[4,5] A simple Williamson ether synthesis could not be applied due to the instability of albicanyl bromide. Etherification using Olah's[6] and Nishizawa's[7] methods could not be applied according to the presence of ester functions.[8] Therefore, we have developed the 1,4-addition of the enolate of **7** derived from albicanol **6** to maleate and fumarate residues. We have succeeded in the first synthesis of cryptoporic acid A methyl ester **2**.

Albicanol **6** was treated with sodium hydride and then with bromoacetic acid in anhydrous THF (Scheme 1). The acidic fraction was isolated and treated with diazomethane to afford methyl ester **7** in 40% yield. The lithium enolate derived from ester **7** was subjected to reaction with dimethyl maleate and dimethyl fumarate. The 1,4-addition had occurred to give a trimethyl ester mixture of **2**, **3**, **4** and **5** in 22% (from maleate; 3:3:1:1) and 14% (from fumarate; 1:1:1:1), respectively. The ratio was determined by integration of the ^{1}H NMR spectrum of the crude mixture and by HPLC. The separation of each compound was accomplished by chiral HPLC (Chiralcel OD-H, 4.6ϕ×250 mm, hexane:*i*PrOH, 99:1) to afford **3**,[9] **4**,[10] and a mixture of **2** and **5**. The mixture of **2** and **5** was further separated by ordinal HPLC (Nucleosil 50-5, 4.6ϕ×250 mm, hexane:EtOAc, 9:1) to give **2**[11] and **5**,[12] respectively. Compound **2** was identical to the trimethyl ester derived from natural cryptoporic acid A **1** (Table 1). Compound **3** showed

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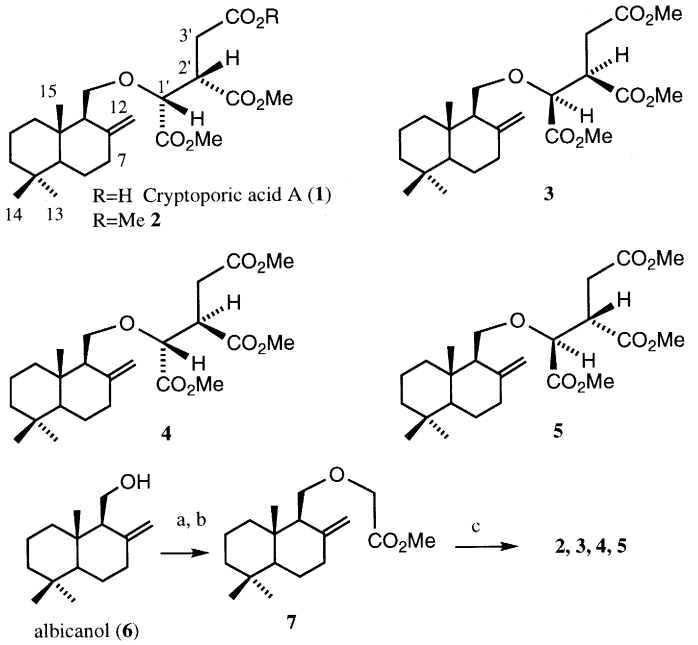

Scheme 1. *Reactions and conditions*: (a) NaH, THF; $BrCO_2COOH$, reflux; (b) CH_2N_2; (c) LDA, dimethyl maleate or dimethyl fumarate

Table 1
The ^1H NMR spectral data for compounds **2**–**5** (in $CDCl_3$)

C	2	3	4	5
7	2.05 m	2.02 m	2.05 m	2.05 m
	2.38 m	2.37 m	2.37 m	2.36 m
9	1.93 m	2.02 m	1.93 m	1.97 m
11	3.89 dd (9.5, 8.2)	3.92 dd (8.6, 4.0)	3.85 dd (9.6, 7.8)	3.84 dd (8.6, 3.6)
	3.52 dd (9.5, 3.4)	3.44 t (8.6)	3.47 dd (9.6, 4.0)	3.41 t (8.6)
12	4.75 br d (1.3)	4.46 br d (1.2)	4.67 br d (1.6)	4.47 br s
	4.85 br d (1.3)	4.80 br d (1.2)	4.82 br d (1.6)	4.79 br s
13	0.87 s	0.87 s	0.87 s	0.86 s
14	0.80 s	0.80 s	0.80 s	0.79 s
15	0.72 s	0.71 s	0.71 s	0.70 s
1'	4.11 d (5.1)	4.08 d (5.1)	4.29 d (4.8)	4.30 d (4.4)
2'	3.43 dt (8.8, 5.1)	3.43 dt (8.9, 5.1)	3.36 dt (9.1, 4.8)	3.36 dt (9.0, 4.4)
3'	2.57 dd (17.0, 5.1)	2.57 dd (17.2, 5.1)	2.51 dd (17.2, 4.8)	2.50 dd (17.4, 4.4)
	2.78 dd (17.0, 8.8)	2.80 dd (17.2, 8.9)	2.88 dd (17.2, 9.1)	2.88 dd (17.4, 9.0)
OMe	3.68 s	3.68 s	3.67 s	3.67 s
	3.68 s	3.69 s	3.70 s	3.70 s
	3.75 s	3.76 s	3.76 s	3.76 s

a doublet peak assignable to H-1′ at δ 4.08 (d, J=5.1 Hz), in the ^1H NMR spectrum, a similar position to that of **2**, showing the *cis* stereochemistry of protons at C-1′ and 2′.[13] But the exomethylene protons appeared at different positions (δ 4.46, 4.80), indicating that the configuration at C-1′ was different to

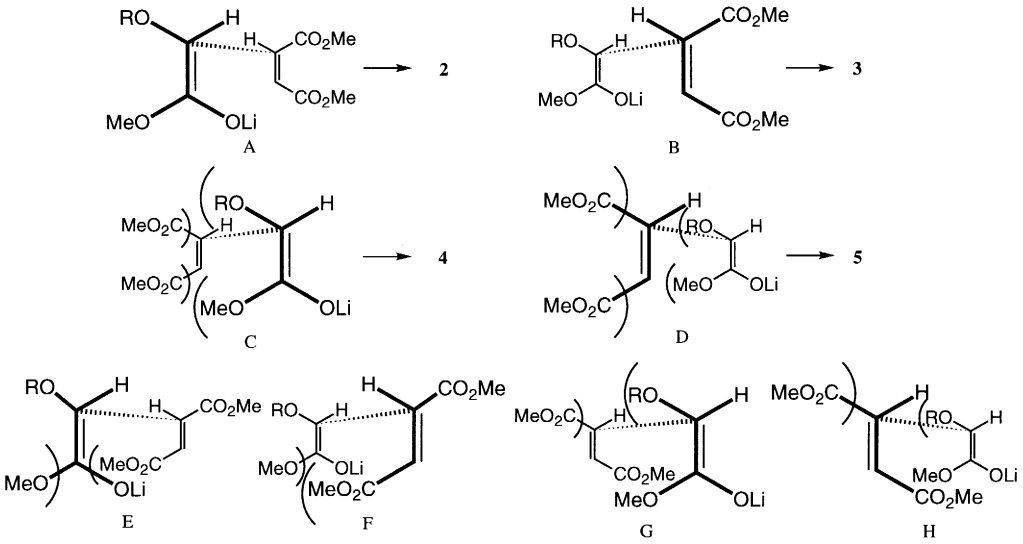

Fig. 1. Transition states of the reaction of the enolates with maleate and fumarate. Transition states A and B are favored, while C and D are disfavored due to steric interactions for maleate. There is no favored transition state for fumarate (E–H)

that of **2**. The proton at C-1′ for compounds **4** and **5** appeared at δ 4.29 (d, J=4.8 Hz) and δ 4.30 (d, J=4.4 Hz), respectively, shifted downfield compared to those of **2** and **3**, suggesting that protons at C-1′ and 2′ were *trans* to each other.[13] The exomethylene protons of **4** appeared at δ 4.67 and 4.82, similar to those of **2**. However, those of **5** appeared at δ 4.47 and 4.79, similar to those of **3**. Therefore, the structures of **4** and **5** were determined as depicted in the formula. The ratio of the formation of each product depends on the transition state (Fig. 1). Because maleate could approach the enolate derived from **7**, avoiding the steric interaction (Fig. 1A and B), **2** and **3** were the major products. However, fumarate always has an interaction with the enolate resulting in no selectivity and the yield is less than maleate.

Because cryptoporic acid A methyl ester **2** is highly active against certain cancer cells,[5] we will be evaluating the biological activities of diastereoisomers obtained in the present study.

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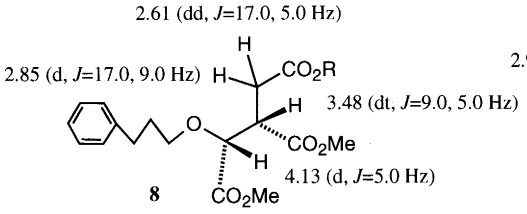
8. Isocitric acid with the same absolute configuration as the natural product was synthesized starting from (*R*)-(+)-malic acid; cf. the preceding paper.
9. Compound **3**: FTIR: 2930, 1750, 1740, 1720 cm^{-1}; MS (CI) *m/z* 437 $(M+H-2)^+$, 407, 389, 379, 235, 218, 204 (base), 186; HRMS (EI) calcd for $C_{24}H_{37}O_7$: 437.2539. Found: 437.2530 $(M+H-2)^+$; $[\alpha]_D$ −17.7 ($CHCl_3$, *c* 0.20).

10. Compound **4**: FTIR: 2930, 1750, 1740, 1720 cm^{-1}; MS (CI) *m/z* 439 $(M+H)^+$, 437, 407, 379, 235, 218, 205 (base), 186; HRMS (EI) calcd for $C_{24}H_{39}O_7$: 439.2696. Found: 439.2715 $(M+H)^+$; $[\alpha]_D$ +27.5 ($CHCl_3$, *c* 0.15).
11. Compound **2**: FTIR: 2940, 1760, 1740, 1730 cm^{-1}; MS (CI) *m/z* 439 $(M+H)^+$, 438, 422, 407, 389, 235, 218, 205 (base), 186; HRMS (EI) calcd for $C_{24}H_{39}O_7$: 439.2696. Found: 439.2691 $(M+H)^+$; $[\alpha]_D$ +39.8 ($CHCl_3$, *c* 0.25).
12. Compound **5**: FTIR: 2930, 1740 cm^{-1}; MS (CI) *m/z* 439 $(M+H)^+$, 437, 408, 235, 218, 205 (base), 186; HRMS (EI) calcd for $C_{24}H_{39}O_7$: 439.2696. Found: 439.2721 $(M+H)^+$; $[\alpha]_D$ −5.8 ($CHCl_3$, *c* 0.05).
13. We prepared model compounds **8** and **9** by similar procedures and protons were assigned as shown below.



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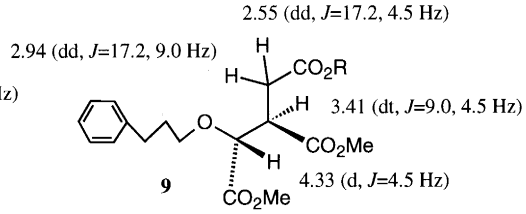

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