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# Determination by Enantioselective Synthesis of the Absolute Configuration of CPE, a Potential Intermediate in Coronatine Biosynthesis

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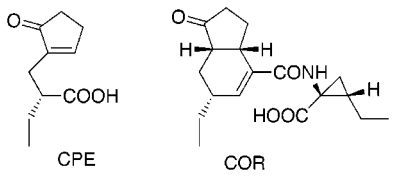
## ABSTRACT




**The first enantioselective synthesis of the methyl ester of CPE, a potential intermediate in coronatine (COR) biosynthesis, is described. Comparison of the specific rotation of the synthetic ester with that of the methyl ester of natural CPE established that the latter possesses the (*R*) configuration. This configuration is the same as that found at the corresponding asymmetric center of coronatine.**

Coronatine (COR) (Figure 1) is a novel phytotoxin produced by five distinct pathovars of *Pseudomonas syringae*.[1] Infection of the host plants by these bacteria induces chlorosis on the leaves due to COR production.[1] In addition to chlorosis, COR also induces hypertrophy, inhibits root elongation, and stimulates ethylene biosynthesis.[1] Recently, several reports have noted the structural and functional similarities between COR, jasmonic acid, and 12-oxophytodienoic acid, suggesting that COR may function as a molecular mimic of the octadecanoid signaling molecules of higher plants.[1]

The COR molecule is composed of two building blocks of distinct biosynthetic origin.[2] One of these is the cyclopropyl amino acid coronamic acid, which is derived from L-isoleucine via the intermediacy of L-alloisoleucine.[2] The other component is coronafacic acid (CFA) (Figure 1), which is a polyketide derived from acetate, butyrate, and a four-carbon unit derived from α-ketoglutarate.[2,3] Mitchell[4] has shown that the fermentation broth of several strains of *P. syringae* contains small amounts of a cyclopentenone carboxylic acid (CPE) (Figure 1) in addition to significant quantities of COR and CFA. The structure of CPE and the organization of the genes in the CFA polyketide synthase suggest that CPE may be an intermediate in CFA biosynthesis.[5] Since the release of intermediates in polyketide biosynthesis is a relatively rare occurrence,[6] a more detailed investigation of the potential role of CPE in CFA biosynthesis is clearly warranted. We have begun this investigation with

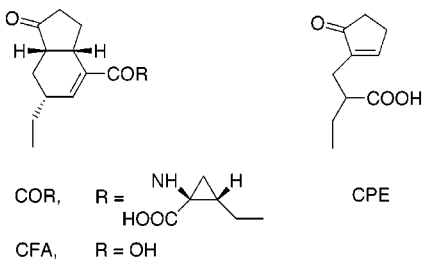



**Figure 1.** Structures of COR, CFA, and CPE.

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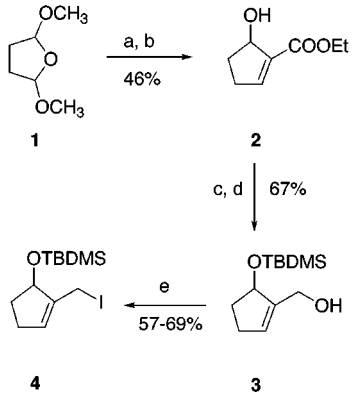
a determination by enantioselective synthesis of the absolute configuration of naturally occurring CPE.

The structure of CPE suggested that an enantioselective synthesis of the compound could be accomplished by means of an alkylation reaction. It was anticipated that the (*R*) enantiomer of CPE could be obtained by alkylation of (*S*)-4-benzyl-3-butyryl-2-oxazolidinone with a protected halomethylcyclopentenol.[7] The synthesis of a suitable halomethylcyclopentenol derivative is shown in Scheme 1. The

**Scheme 1**[a]

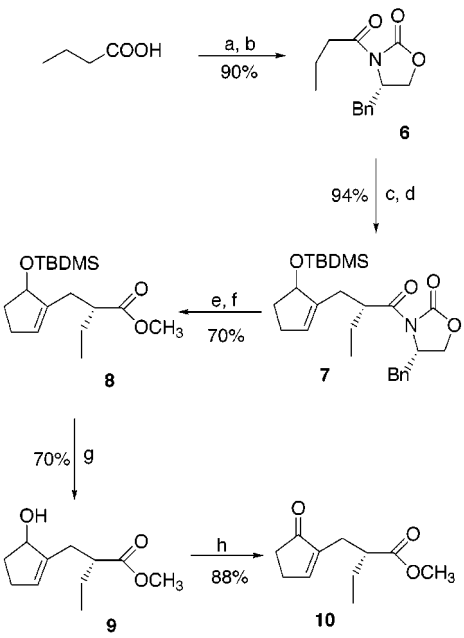



[a] (a) 1 N HCl, 70 °C, 1 h; (b) $(EtO)_2P(O)CH_2COOEt$, $K_2CO_3$; (c) TBDMSCl, imidazole, DMF; (d) DIBAL-H, toluene, $CH_2Cl_2$, −70 °C; (e) EtOOCN=NCOOEt, $Ph_3P$, $ZnI_2$, THF, 0 °C.

synthesis began with the conversion of 2,5-dimethoxytetrahydrofuran **1** into 2-carbethoxycyclopenten-1-ol **2**.[8] Attempts to prepare **2** by reduction of 2-carbethoxycyclopenten-1-one [9] with sodium borohydride and ceric chloride[10] produced mostly the saturated alcohol ester. Protection of the hydroxyl group of **2** with TBDMS chloride followed by reduction with DIBAL generated the protected hydroxymethylcyclopentenol **3**. Cyclopentenol **3** was converted into the iodo derivative **4** by reaction with diethylazodicarboxylate, triphenylphosphine, and zinc iodide.[11]

The remaining stages of the synthesis are shown in Scheme 2. (*S*)-4-Benzyl-3-butyryl-2-oxazolidinone **6** was synthesized by reaction of the lithium salt of (*S*)-4-benzyl-2-oxazolidinone **5** with the mixed anhydride formed between butanoic acid and pivaloyl chloride.[12] Treatment of **6** with sodium hexamethyldisilazide in THF followed by 2.5 equiv of the

**Scheme 2**[a]




[a] (a) $(CH_3)_3CCOCl$, $Et_3N$, THF, −78 to 0 °C; (b) Li salt of **5**, THF, −78 to 0 °C; (c) $NaN[Si(CH_3)_3]_2$, THF, −78 °C; (d) **4**, THF, −78 °C; (e) $H_2O_2$, LiOH, THF−$H_2O$, 0 °C; (f) $CH_2N_2$; (g) HF−$C_5H_5N$, 0 °C; (h) DDQ, benzene, 25 °C.

iodide **4** gave the desired alkylation product **7** in greater than 90% yield based upon **6**. NMR analysis indicated that only a single diastereomer was produced in the alkylation reaction. Initial experiments using the TBDPS[13] analogue of **4** gave poorer yields of the desired alkylation product. Furthermore, removal of the oxazolidinone chiral auxiliary from the alkylation product was accompanied by some loss of the TBDPS group. In contrast, the chiral auxiliary could be cleanly removed from **7** by standard methods[14] without loss of the TBDMS group to produce the free carboxylic acid, which was then converted to the methyl ester **8** with diazomethane. Attempts to remove the silyl group from **8** with TBAF produced a mixture of the desired alcohol **9** and the $\delta$-lactone formed between the carboxylic acid and the freed OH group, with the latter predominating. However, when ester **8** was treated with HF-pyridine,[15] the free alcohol **9** was produced as the major product, accompanied by less than 10% of the $\delta$-lactone. (*R*)-CPE methyl ester **10** was obtained in high yield from **9** by oxidation of the allylic alcohol group with DDQ in benzene.[16] The synthetic compound exhibited $[\alpha]^{23}_D = -32.9°$ (*c* 0.17, $CHCl_3$).

To determine the absolute configuration of naturally occurring CPE, the compound was isolated as its methyl ester from the fermentation broth of *P. syringae* pv. *glycinea*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PG4180. The fermentation was carried out in modified Hoitink−Sinden medium[17] at 18 °C.

HPLC analysis[18] indicated that maximum CPE production occurred after 3 days. CPE methyl ester (3 mg) was isolated and purified from 24 L of 3-day-old fermentation broth. The first step in the purification utilized preparative TLC ($SiO_2$, 8% $^i$PrOH in hexane, two developments). This was followed by normal-phase preparative HPLC purification (8% $^i$PrOH in hexane, 10 mm × 250 mm $SiO_2$ column). The final stage of the purification was accomplished by reverse-phase preparative HPLC (MeOH/$H_2O$, 7:3, 10 mm × 250 mm $C_{18}$ column). The natural sample of CPE methyl ester purified in this way displayed chromatographic and spectral properties identical to those of the synthetic compound, and it exhibited $[\alpha]^{23}_D = -33.0°$ (*c* 0.12, $CHCl_3$). Natural CPE methyl ester therefore possesses the (*R*) configuration. This configuration is the same as that found at the corresponding asymmetric center of CFA, an observation that is consistent with the intermediacy of CPE in CFA biosynthesis. The availability of synthetic CPE should facilitate additional investigations of the details of CFA biosynthesis.

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**Supporting Information Available:** Detailed experimental procedures and spectroscopic data for all new compounds, as well as details for the isolation and purification of CPE methyl ester from the fermentation broth of *P. syringae* PG4180. This material is available free of charge via the Internet at http://pubs.acs.org.

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