Tetrahedron Letters No. 35, pp 3233 - 3236.

0040-4039/78/0822-3233$02.00/0

AN ASYMMETRIC SYNTHESIS OF NATURALLY OCCURRING CANADENSOLIDE

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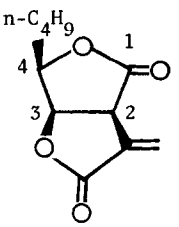
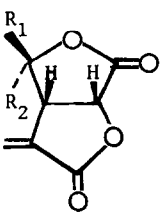
Canadensolide, a mold metabolite elaborated by Penicillium canadense displaying anti-germinative activity against fungi, was isolated by McCorkindale and co-workers[1] who deduced the gross structure represented in 1. The relative stereochemistry shown was subsequently clarified by Kato and co-workers[2] as a result of synthetic studies during which compound 1 as well as its C-4 epimer were both prepared in racemic forms. The absolute stereochemistry has so far not been promulgated, and our interest was aroused by the resemblance of 1 to the epimeric pair avenaciolide 2 and isoavenaciolide 3. The absolute stereochemistries of the natural metabolites as expressed in 2 and 3 resulted from asymmetric syntheses[3,4], which effectively revoked assignments made earlier on the basis of degradative studies. In this communication we report that the absolute stereochemistry of naturally-occurring (-) canadensolide is 2S, 3R, 4R as shown in 1

The earlier syntheses of avenaciolide[3] and isoavenaciolide[4] had demonstrated the ideality of "diacetone glucose"[5], 4, as a chiral synthon for di-γ-lactones. For the synthesis of 1, the C-3 hydroxyl group was protected prior to the usual two-step degradation to the aldehyde 5.[4] Wittig reaction of 5 ($C_3H_7P^+Ph_3Br^-$,THF, BuLi, room temperature), and hydrogenation with Raney nickel afforded 6 in 64 percent overall yield. Methanolysis proceeded smoothly giving a nearly quantitative yield of 7, the α and β anomers of which are separable chromatographically.

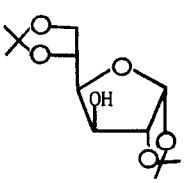


1



2 R_1 = n-C_8H_{17}; R_2 = H

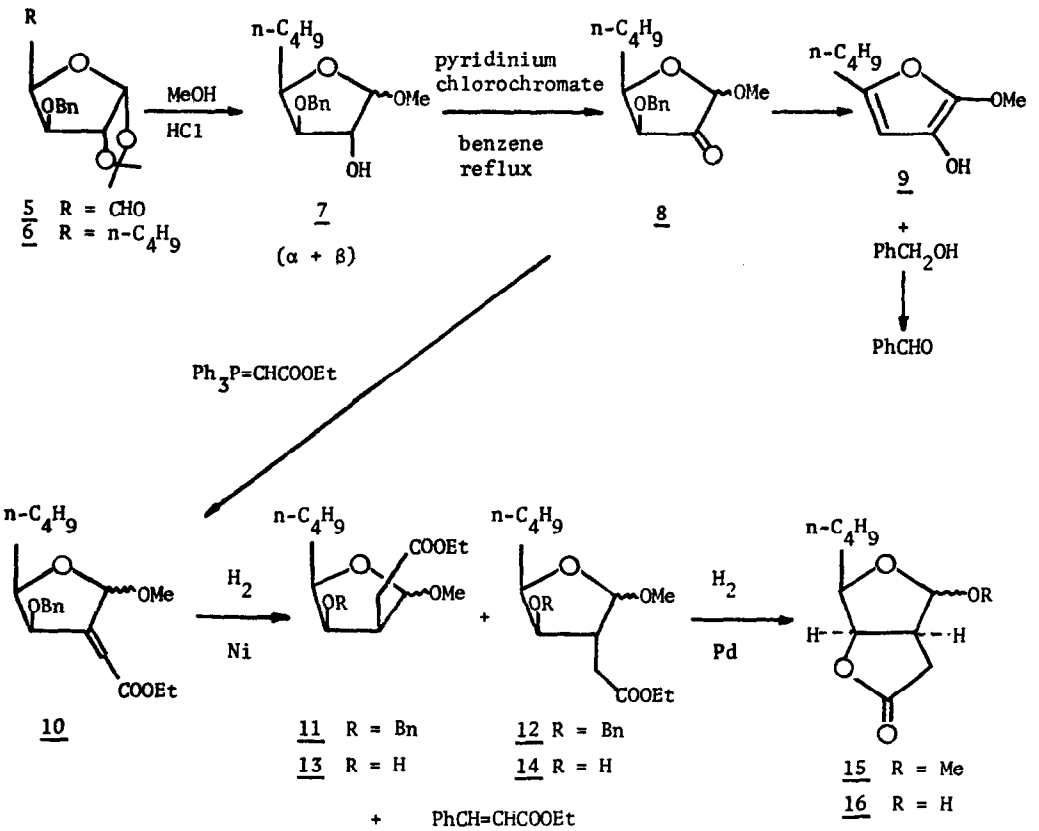
3 R_1 = H ; R_2 = n-C_8H_{17}



4

Oxidation of 7 (α+β) proved to be a most troublesome undertaking for two reasons. Firstly the material was unaffected by a wide variety of oxidation media and, secondly, if and when oxidation did occur, the ketone 8 underwent substantial decomposition. The presence of benzaldehyde among the oxidation products indicated that β-elimination of benzyl alcohol was occurring although a careful search failed to identify 9 in the detritus of the reaction. Pyridinium chlorochromate[6] in refluxing benzene proved to be the most acceptable procedure and the crude product was used directly, since it was also found that ketone 8 would not tolerate column chromatography.

SCHEME 1 (Bn = $PhCH_2$)



5 R = CHO
6 R = n-C_4H_9

7 (α + β)

8

9

10

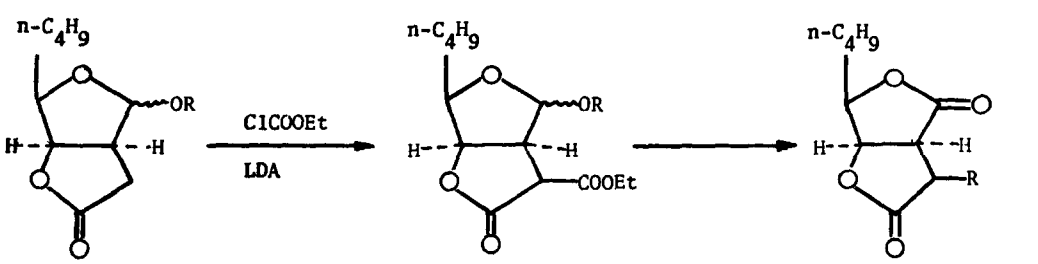
11 R = Bn
13 R = H

12 R = Bn
14 R = H

+ PhCH=CHCOOEt

15 R = Me
16 R = H

SCHEME 2



15 R = Me
19 R = α-ethoxyethyl

18 R = Me
20 R = α-ethoxyethyl
21 R = H

17 R = H
22 R = COOEt
23 R = COOH
1 R = CH_2

Thus the oil containing 8 and benzaldehyde was treated as indicated in Scheme 2. The products from the Wittig reaction in acetonitrile (room temperature) were hydrogenated over Raney nickel. Stereochemical control in this reaction was of crucial importance, and our earlier choice of the benzyl group for protection was based on the expectation that its bulk would induce addition from the α face giving a preponderance of 11 over 12. Not surprisingly, it proved impossible to measure the success of this stereocontrol in view of the presence of four diastereomers 11 (α+β) + 12 (α+β).

Hydrogenolysis of the mixture (11 + 12) and chromatography of the resulting product enabled removal of the ethyl β-phenylpropionate, and fractions were obtained which, judging from spectroscopic data, contained the alcohol 14 and lactone 15, the latter having been formed *in situ* from 13. (Direct hydrogenation of 10 into 15 was in fact possible, but unacceptably large quantities of catalyst were required.) Hydrolysis of 15 with sulfuric acid in dioxan converted 15 into the hemiacetal 16 which was isolated chromatographically.

The transformations shown in Scheme 2 which afforded a 7.3 percent yield of 16 from 7 involved working with complex mixtures there being no opportunity to make complete structural assignments. It was therefore necessary to ensure the correctness of 16, an objective which was rendered all the more imperative since the material appeared, chromatographically, to contain two components. Fortunately these proved to be the α and β anomers of 16, since Jones' oxidation of the mixture gave the crystalline bis-lactone 17[7] in 87 percent yield. The NMR and IR data for 17 were identical to those reported for its racemic modifications prepared by Kosugi and co-workers in connection with their attempts to synthesize canadensolide[8].

As with Kosugi and co-workers[8] we found that compound 17 could not be alkylated, acylated or carboxylated selectively at the α-methylene position. Deprotonation has been reported to occur preferentially at carbon-2[8] and we were unable to develop conditions that prevented this. We therefore focussed our attention on the lactone-acetal 15.

A variety of α-methylenation techniques including the selenation route of Grieco[9] and and the use of Eschenmoser's salt developed by Danishefsky[10] failed when applied to 15. Ethoxycarbonylation gave 18, but we were unable to hydrolyze the acetal. Acidic media either left the molecule unaffected or they hydrolyzed both the acetal and the ester, with the result that decarboxylation to 16 ensued.

The presence of a compatible protecting group for the acetal of 18 was therefore pivotal. Accordingly attempts were made to benzylate 16 but the result was decomposition.

A timely report by Grieco[11] on the use of pyridinium p-toluenesulfonate (PPTS) as a gentle acid catalyst provided the solution to our dilemma. Our attempts to protect 16 with dihydropyran or ethyl vinyl ether with p-toluenesulfonic acid as catalyst had resulted in decomposition. However room temperature reaction of 16 with ethyl vinyl ether in methylene chloride containing a catalytic amount of PPTS was complete in 2 hours giving an 88 percent yield of 19, and ethoxycarbonylation gave 20 (87%). The latter was now smoothly deacetalated following Grieco's prescription[11], by treating with hot (55°) ethanol containing PPTS for 8 hours. The yield of 21 was quantitative. Jones' oxidation now gave the crystalline

bis-lactone 22[12] in 76 percent yield.

The final steps to canadensolide were patterned after the procedure of Kato and co-workers[2]. Thus compound 22 was deesterified by heating in dioxan containing 6N hydrochloric acid, and the resulting acid (23) was subjected to a Mannich condensation (Et_2NH,CH_2O,HOAc) whereupon canadensolide 1 was obtained in 41 percent yield (from 22) after purification by preparative layer chromatography.

Although our material has so far failed to crystallize, its NMR and IR spectra are identical with those of the natural[1] and synthetic[2] substances kindly supplied by Drs. McCorkindale and Yoshikoshi respectively. Furthermore the specific rotation of our sample ($[\alpha]_D^{23}$=-162.5°) is in excellent agreement with a revised value (-168.9°) obtained from Dr. McCorkindale[13].

It is interesting to note that the naturally-occurring forms of all three bis-lactones, (-) 1, (-) 2 and (-) 3 are all prepared from diacetone glucose[5].

ACKNOWLEDGEMENTS

We are grateful to the National Research Council for financial support of this work. We also express our thanks to Drs. McCorkindale and Yoshikoshi for sending us samples and spectra of their preparations of canadensolide.

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12. For the bis-lactone 22: m.p. 107.5-108.5°. $[\alpha]_D^{23}$ =-28.1° (c,3.39 in chloroform) Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C,57.90; H,6.78.
13. Private communication from N.J. McCorkindale. The specific rotation quoted previously[1] was -141°.

(Received in USA 22 May 1978; received in UK for publication 4 July 1978)