Tetrahedron Letters No. 1, pp. 34-38, 1961. Pergamon Press Ltd. Printed in United States of America

A NOVEL APPROACH TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF α-ONOCERIN

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(Received 20 December 1960)

The total synthesis of the naturally occurring triterpene α-onocerin was first accomplished by Stork and co-workers[3] via the coupling of the hydroxyketo acid(11). We wish to report here an alternate independent synthesis of this key intermediate.

The keto benzoate(1)[4] was converted to the hydroxyketone(2) in 96% yield following the method of Sondheimer[4]. The ketone ketal(3), m.p. 126.5-128°(C,71.29%; H,9.46%) was obtained in 58% yield by first ketalization of the hydroxy ketone(2) with ethylene glycol and then oxidation of the resulting hydroxy ketal with chromic acid in acetone[5]. The conversion of the ketone ketal(3) to the α-isopropoxymethylene derivative(4), m.p.

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[1] Sun Oil Company Fellow, 1959-60.

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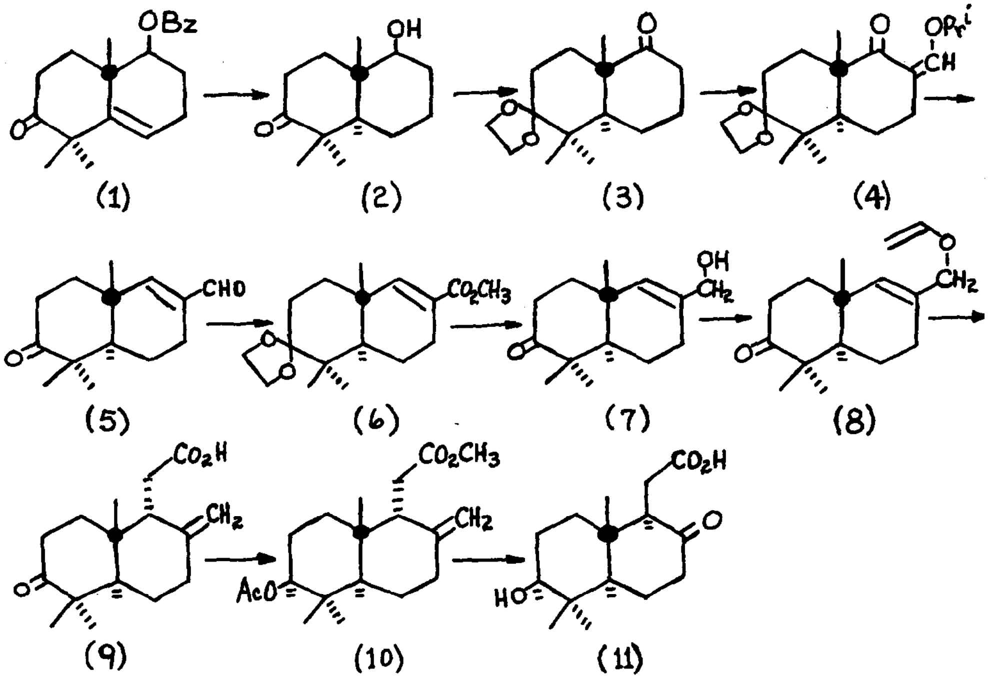
85-86°(C,70.85%; H,9.42%) was accomplished in 85% yield <u>via</u> the α-hydroxymethylene ketone ketal, m.p. 132-133°(C,68.59%; H,8.56%) and <u>iso</u>propylation by the method of Johnson and Posvic[6]. Reduction with sodium borohydride and treatment of the resulting alcohol, m.p. 124-126°(C,70.38%; H,9.94%) with aqueous mineral acid[7] resulted in the formation of the keto aldehyde(5), which without further purification was oxidized with silver oxide to the corresponding acid, m.p. 202-204°(C,71.38%; H,8.60%) in 62% overall yield. Esterification with diazomethane and ketalization with



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ethylene glycol afforded a 93% yield of the ketal ester(6) m.p. 71-73°(C,69.30%; H,8.97%). The keto alcohol(7), m.p. 65-66°(C, 75.78%; H,9.93%) was then readily available in 84% yield [41% overall yield from the ketone ketal(3)] by reduction with lithiu aluminum hydride and then treatment with 3 *N* aqueous hydrochlori acid.

Further modification of the keto alcohol(7) proceeded by equilibration[8] with ethyl vinyl ether to form the vinyl ether(8) Pyrolysis[9] of this oily vinyl ether afforded a 53% overall yield of the corresponding aldehyde, m.p. 76-79°(C,77.32%; H,9.72%) which was oxidized with silver oxide in 85% yield to the acid(9) m.p. 143-145°(C,72.75%; H,9.03%).

In order to ascertain the configuration of the newly-introduced acetic acid residue, the keto acid(9) was reduced by the Wolff-Kishner method in 91% yield to the 3-desoxyacid(9) m.p. 147-148°(C,76.67%; H,10.37%). This same acid was also prepared independently from the keto benzoate(1). Thus following the method of Sondheimer[4] the keto benzoate(1) was transformed to 5,5,9-trimethyl-*trans*-decalone-1. The α-*n*-butylthiomethylene derivative, m.p. 68-69°(C,73.38%; H,10.17%; S,10.62%) of this ketone was then prepared in 92% yield by the method of Ireland and Marshall[10]. On reduction with sodium borohydride and then

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steam distillation from 2% aqueous sulfuric acid, the thiomethylene derivative afforded a 77% yield of the 3-desoxyaldehyde(5) [semicarbazone, m.p. 224-226°(C,68.56%; H,9.36%; N,16.09%)]. Further reduction with sodium borohydride afforded the corresponding allylic alcohol, b.p. 115-116°/0.8 mm.(C,80.56%; H,11.50%) in 91% yield. When this alcohol was equilibrated with ethyl vinyl ether[8] and the resulting vinyl ether pyrolyzed[9] directly, there resulted a 72% yield of the 3-desoxyaldehyde, m.p. 37-38° (C,81.89%; H,11.21%). Oxidation of this aldehyde with silver oxide then afforded a 91% yield of the 3-desoxyacid(9)[42% overall yield from the starting decalone].

In order to determine the configuration of the acetic acid side-chain, the 3-desoxyacid(9) was converted to the corresponding keto acid, m.p. 136-138°(C,71.29%; H,9.65%) in 82% yield with ozone. Formation of the enol-lactone, m.p. 91-92°(C,77.00%; H, 9.54%) in 55% yield with acetic anhydride-sodium acetate followed by methanolysis with sodium methoxide afforded a keto ester, m.p. 63-64)(C,72.17%; H,9.90%) in 73% yield. This latter ester was different (mixture m.p. 41-53°) from the ester, m.p. 71-72°(C, 72.23%; H,9.91%) obtained from the original keto acid directly with diazomethane. By virtue of its formation under basic conditions the 64°-keto ester is assigned the β-oriented (equatorial) acetate side-chain, while the acids related to the 72°-keto ester possess an α-oriented (axial) acetic acid residue.

In order to obtain the desired β-configuration of the side-chain in the 3-oxygenated series, the acid(9) was converted in

69% yield to the acetoxy ester(10), m.p. 121-122°(C,70.67%; H, 9.33%) by successive treatment with diazomethane, sodium borohydride and then acetic anhydride-pyridine. Ozonization and alkaline hydrolysis of the resulting keto ester, afforded the acid (11) m.p. 185-187° in 51% yield. This acid was identical [mixture m.p., infra-red] to that previously prepared by Stork and co-workers[3] and thus provides the link between the present work and the previously successful total synthesis of α-onocerin.

Acknowledgement: The authors' acknowledge the support of the Research Corporation and are grateful to Prof. Stork and Dr. Meisels for providing a sample of the acid(11).