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

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The total synthesis of the naturally occurring triterpene α-onocerin was first accomplished by Stork and co-workers via the coupling of the hydroxy keto acid. We wish to report here an alternate independent synthesis of this key intermediate.

The keto benzoate was converted to the hydroxy keto acid in 96% yield following the method of Sondheimer. The ketone ketal, m.p. 126.5-128° (C, 71.29%; H, 9.46%) was obtained in 58% yield by first ketalization of the hydroxy ketone with ethylene glycol and then oxidation of the resulting hydroxy ketal with chromic acid in acetone. The conversion of the ketone ketal to the α-isopropoxymethylene derivative, m.p.
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85-86°C (C, 70.85%; H, 9.42%) was accomplished in 85% yield via the α-hydroxymethylene ketone ketal, m.p. 132-133°C (C, 68.59%; H, 8.56%) and isopropylation by the method of Johnson and Posvic⁶. Reduction with sodium borohydride and treatment of the resulting alcohol, m.p. 124-126°C (C, 70.38%; H, 9.94%) with aqueous mineral acid⁷ 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 (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 lithium aluminum hydride and then treatment with 3 N aqueous hydrochloric acid.

Further modification of the keto alcohol (7) proceeded by equilibration with ethyl vinyl ether to form the vinyl ether (8). Pyrolysis 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 the keto benzoate (1) was transformed to 5,5,9-trimethyl-trans-decalone-1. The α-n-butyliothiomethylene 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. On reduction with sodium borohydride and then

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 (C, 68.56%; H, 9.36%; N, 16.09%)]. Further reduction with sodium borohydride afforded the corresponding allylic alcohol, b.p. 115-116°C/0.8 mm. (C, 80.56%; H, 11.5%)

in 91% yield. When this alcohol was equilibrated with ethyl vinyl ether and the resulting vinyl ether pyrolyzed directly, there resulted a 72% yield of the 3-desoxyaldehyde, m.p. 37-38°C (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 (C, 71.29%; H, 9.65%) in 82% yield with ozone. Formation of the enol-lactone, m.p. 91-92°C (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 (C, 72.17%; H, 9.90%) in 73% yield. This latter ester was different (mixture m.p. 41-53°C) from the ester, m.p. 71-72°C (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°C-keto ester is assigned the β-oriented (equatorial) acetate side-chain, while the acids related to the 72°C-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
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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-workers³ and thus provides the link between the present work and the previously successful total synthesis of α-onocerin.

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