106. Synthesis of Reactive Intermediates for Natural Cyclopentane Derivatives from (−)-Quinic Acid: Preparation of 11α-Hydroxy-13-oxa-prostanoic Acid

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Dedicated to the memory of Prof. *Frantisek Sorm*

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Summary

We describe a flexible, stereocontrolled synthesis of enantiomerically pure substituted cyclopentenes and cyclopentanes - including 11α-hydroxy-13-oxa-prostanoic acid **20** - from (−)-quinic acid *via* an acyclic precursor **6** by an intramolecular aldolisation-dehydration reaction.

Synthetic approaches to enantiomerically pure, substituted cyclopentanes are of high interest, because they are decisive intermediates in the total synthesis of natural cyclopentane derivatives [1] such as prostaglandines [2] [3], methylenomycins [4], bredfeldines [5] and pentenomycines [6]. Since our manifold interest in the natural cyclopentane derivatives lies especially in their pharmacological activity, we needed cyclopentanes which are substituted in one proper natural configuration.

We report in this communication, a short and flexible, stereocontrolled synthesis of cyclopentenes of types **7** (3-benzyloxy-5,5-(ethylenedithio)-1-cyclopentene-1-carbaldehyde), **9** (4-benzyloxy-2-(1,3-dioxa-2-cyclohexyl)-2-cyclopenten-1-one) and **20** (11α-hydroxy-13-oxaprostanoic acid) from (−)-quinic acid.

Intermediates recorded in this paper are also amenable to the preparation of all the prostanoids and biologically active five-membered and fused five-membered ring natural products [1].

One retrosynthetic analysis of the target molecules suggests that they can be constructed from an acyclic precursor **6** (3-benzyloxy-5,5-(ethylenedithio)hexanedial by an intramolecular aldolisation-dehydration sequence. The requisite intermediate for the synthesis was the hydroxy ketone **1** (3,4-(1,1-cyclohexylenedioxy)-5-hydroxy-1-cyclohexanone) which was readily available in three steps and 75% overall yield from (−)-quinic acid [7].

Thus, treatment of **1** with ethanedithiol in the presence of boron trifluoride etherate in anhydrous chloroform furnished [8] **2** (5,5-(ethylenedithio)-1,2,3-cyclo-

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hexanetriol) in 95% yield, m.p. 129–130°, $[\alpha]_D = -41°$ ($c = 1.4$, CH_3OH). The cyclohexylidene protecting group was needed for the preparation of the benzyl ether **4** (1-benzyloxy-2,3-(1,1-cyclohexylenedioxy)-5,5-(ethylenedithio)cyclohexane). Therefore the triol **2** was reconverted into its cyclohexylidene derivative **3** (2,3-(1,1-cyclohexylenedioxy)-5,5-(ethylenedithio)cyclohexanol (95%, m.p. 138–140°, $[\alpha]_D = -44°$ ($c = 1$, $CHCl_3$)) by reaction with 1,1-dimethoxycyclohexane in the presence of a catalytic amount of sulfuric acid in *N, N*-dimethylformamide.

Benzylation of the free hydroxyl group in **3** using sodium hydride and benzyl bromide in *N, N*-dimethylformamide provided the crystalline **4** in 95% yield, m.p. 68–69°, $[\alpha]_D = -50°$ ($c = 1.6$, $CHCl_3$).

Acid hydrolysis of **4** using aq. acetic acid yielded the solid **5** (3-benzyloxy-5,5-(ethylenedithio)-1,2-cyclohexanediol in virtually quantitative yield, m.p. 135–136°, $[\alpha]_D = -72°$ ($c = 1{,}05$, $CHCl_3$).

Lead tetraacetate oxidation of the diol **5** in anhydrous toluene at room temperature afforded **6** in quantitative yield as a colourless oil, $[\alpha]_D = -11°$ ($c = 2{,}4$, $CHCl_3$). As the dialdehyde is particularly unstable, it was directly cyclized under N_2 with a catalytic amount of 1N pyrrolidine acetate in anhydrous toluene at 0° overnight to give **7** in 95% yield. Acetalisation of **7** using 1,3 propanediol at room temperature in anhydrous toluene containing a catalytic amount of *p*-toluenesulfonic acid produced **8** (4-benzyloxy-2-(1,3-dioxa-2-cyclohexyl)-1,1-(ethylenedithio)-2-cyclopentene) in 80% yield, m.p. 70–71°, $[\alpha]_D = +86$ ($c = 1.1$, $CHCl_3$). The absolute configuration of the asymmetric C-atom of **8** was secured by X-ray crystallographic analysis [9] *(Figure)*.

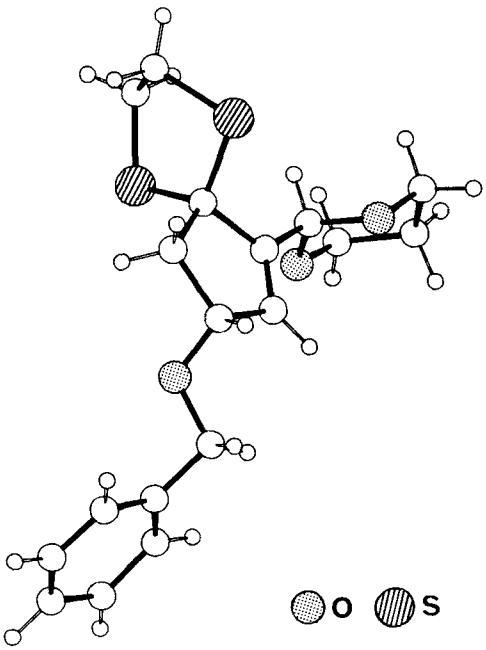
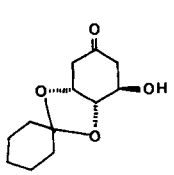
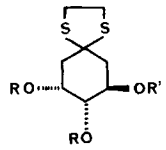


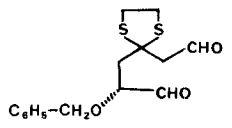
Figure. *Three-dimensional view of* **8** *as determined by X-ray analysis*



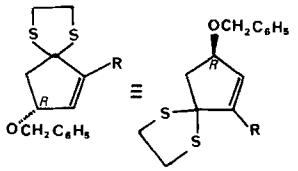
1

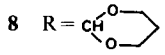


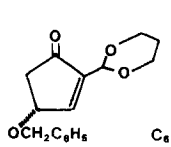
2 R = R' = H
3 R + R = ⬡ ; R' = H
4 R + R = ⬡ ; R' = $CH_2C_6H_5$
5 R = H; R' = $CH_2C_6H_5$



6



7 R = CHO
8 R = 



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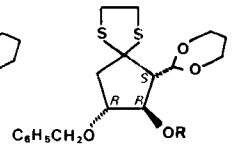
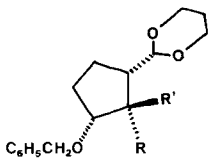


10 R = H
11 R = n-C_7H_{15}

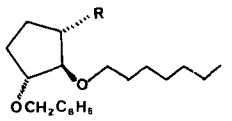
To demonstrate the versatility of **8**, the latter was used as a relay compound for the synthesis of **9** (4-benzyloxy-2-(1,3-dioxa-2-cyclohexyl)-2-cyclopenten-1-one) and **10** (2-benzyloxy-5-(1,3-dioxa-2-cyclohexyl)-4,4-(ethylenedithio)cyclopentanol).

The preparation of **9** was accomplished in straightforward fashion by treating **8** with phenylselenic anhydride [10] and propylene oxide to give **9** (68%), m.p. 42–43°, $[\alpha]_D = +42°$ ($c = 1$, $CHCl_3$).

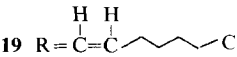
The synthesis of **10** involved the hydroboration of **8** with diborane followed by alkaline hydrogen peroxide oxidation to yield the desired compound **10** (35%, $[\alpha]_D = -40°$ ($c = 1.3$, $CHCl_3$)). Alkylation of the latter using heptyl iodide, sodium

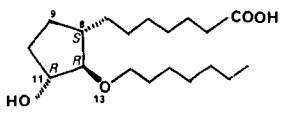


12 R = H; R' = OH
13 R = H; R' = O-C_7H_{15}
14 R = OH; R' = H
15 R = H; R' = OAc
16 R = OAc; R' = H
17 (R + R') = O



18 R = CHO

19 R = 



20

hydride in *N,N*-dimethylformamide furnished in 80% yield, the syrupy product **11** (1-benzyloxy-3-(1,3-dioxa-2-cyclohexyl)-4,4-(ethylenedithio)-2-heptyloxycyclopentane). It was expected that the hydroboration of **8** would proceed in an anti-*Markovnikov* fashion and the procedure would provide **10** with correct absolute configuration at the three asymmetric centres for the synthesis of 11α-hydroxy 13-oxaprostanoic acid **20**. *Raney*-nickel desulfurisation of **10** and **11** gave **12** (2α-benzyloxy-5α-(1,3-dioxa-2-cyclohexyl)cyclopentanol), $[\alpha]_D = +5°$ ($c = 0.75$, $CHCl_3$), and **13** (1α-benzyloxy-3α-(1,3-dioxa-2-cyclohexyl)-2β-heptyloxycyclopentane), $[\alpha]_D = +5°$ ($c = 1$, $CHCl_3$) in yields of 70% and 75%, respectively. In order to corroborate further the stereochemical assignment of **12** and hence **20**, the β alcohol **12** was oxidized with dipyridine-chromium(VI) oxide [11] to the corresponding keto derivative **17** (2-benzyloxy-5-(1,3-dioxa-2-cyclohexyl)-1-cyclopentanone). Sodium borohydride reduction of the latter produced a mixture of the epimeric alcohols **12** and **14** (2-benzyloxy-5-(1,3-dioxa-2-cyclohexyl)-1α-cyclopentanol) in a ratio of 13:87, which were separated and readily converted into their acetates **15** (1β-acetoxy-2-benzyloxy-5-(1,3-dioxa-2-cyclohexyl)cyclopentane) and **16** (1α-acetoxy-2-benzyloxy-5-(1,3-dioxa-2-cyclohexyl)cyclopentane).

Differentiation between the two structures **15** and **16** was possible on the basis of their ^{1}H-NMR. parameters by comparison with appropriate literature values [12] [13]. [^{1}H-NMR. (80 MHz, benzene-d_6): (of *trans*-acetate **15**): 2.4 (*m*, $J_{1,5} = 4.5$, 1 H, H–C(5)); 5.75 (*qa*, $J_{1,2} = 4.5$, 1 H, H–C(1)); 3.9 (*m*, 1 H, H–C(2))]; (of *cis*-acetate **16**): 2.25 (*m*, $J_{1,5} = 3.5$ Hz, 1 H, H–C(5)); 5.9 (*t*, $J_{1,2} = 3.5$, 1 H, H–C(1)); 3.6 (*m*, 1 H, H–C(2)).

Moreover, the ^{13}C-NMR. data of the parent alcohols *'trans'*-**12** and *'cis'*-**14** were in excellent agreement with the assigned structures. The chemical shifts of the C-atoms C(1), C(2), C(5) of the *'cis'*-isomer **14** appeared at higher field [13] [14] than those of the *'trans'*-isomer **12**. [^{13}C-NMR. ($CDCl_3$); (of *'trans'*-**12**): 49.1 (C(5)); 79.7 (C(1)); 85 (C(2)); (of *'cis'*-**14**): 46.3 (C(5)); 71.5 (C(1)); 81.4 (C(2))].

The attachement of the carboxylic acid side chain to the aldehyde **18** (readily obtained by acid hydrolysis of the acetal function in **13** (92%)) relied on the *Wittig* condensation and proceeded smoothly. Thus, treatment of **18** (3-benzyloxy-2-heptyloxy-cyclopentanecarbaldehyde) with the ylide derived from 5-carboxypentyl-triphenylphosphonium bromide gave the oily unsaturated product **19** (11α-hydroxy-6,7-dehydro-13-oxaprostanoic acid) (55%), $[\alpha]_D = -45°$ ($c = 0.35$, $CHCl_3$). Subsequent catalytic hydrogenation of the double bond with concomitant hydrogenolysis of the benzyl group in **19** was achieved in 90% yield affording the target 11α-hydroxy-13-oxaprostanoic acid **20**, $[\alpha]_D = +19°$ ($c = 0.75$, $CHCl_3$).

While the focus of this work has been the preparation of the synthons **7**, **8**, **9** and **20** 11α-hydroxy 13-oxaprostanoic acid), it is clear that all prostanoids and their congeners and other cyclopentanoid natural products are accessible through applications of the present strategy[1]).

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[1]) Satisfactory IR. spectra, ^{1}H- and ^{13}C-NMR. spectra, mass spectra, and analytical data were obtained on purified, chromatographically homogeneous samples of all intermediates here.

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