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First Enantiospecific Syntheses of Crotepoxide and *iso*-Crotepoxide from (–)-Quinic Acid

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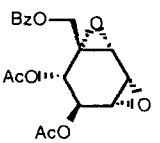
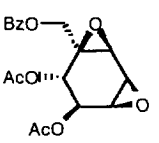
Abstract: The optically active crotepoxide **1** and *iso*-crotepoxide **2** have been constructed from quinic acid involving a singlet oxygen photooxygentation as the key step.

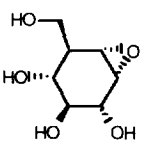
Recently, the chemotherapeutic potential of glycosidase inhibitors[1] as anti-HIV,[2] anti-metastasis,[3] and anti-hyperglycemic agents[4] has aroused considerable attention from the synthetic chemists. Crotepoxide **1**, a cyclohexane oxide[5] isolated from the fruits of *Croton macrostachys* [6] and of *Piper futokadzura*,[7] has been shown to display significant tumour-inhibitory activity against Lewis lung carcinoma in mice (LL) and Walker intramuscular carcinosarcoma in rats (WM).[6a] The structures of crotepoxide **1** and its diastereoisomer, *iso*-crotepoxide **2**, are related to those of (1*R*,6*S*)-cyclophellitol **3** and cyclophellitol **4**, respectively. (1*R*,6*S*)-cyclophellitol **3**[8,3b] and cyclophellitol **4**[9] have been shown to be potent β-D- and α-D-glucosidase inhibitors, respectively, presumably attributable to the structural resemblance with β-D- and α-D-glucose. Along the same vein of reasoning, tumour inhibitor crotepoxide **1** might reveal α-D-glucosidase inhibition and *iso*-crotepoxide **2** might inhibit β-D-mannosidase. The presence of ester groupings in **1** and in **2** may be advantageous because the anti-HIV activity of α-D-glucosidase inhibitors such as castanospermine and 1-deoxynojirimycin improved significantly by increasing the lipophilicity of the compounds *via* esterification of the hydroxy groups.[2b,10]



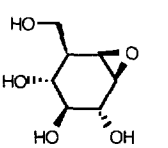
(+)-crotepoxide **1**



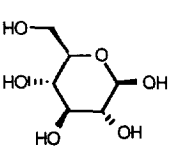
(–)-*iso*-crotepoxide **2**



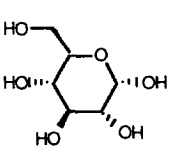
(1*R*,6*S*)-cyclophellitol **3**



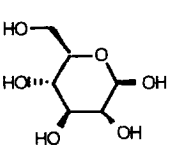
cyclophellitol **4**



β-D-glucose



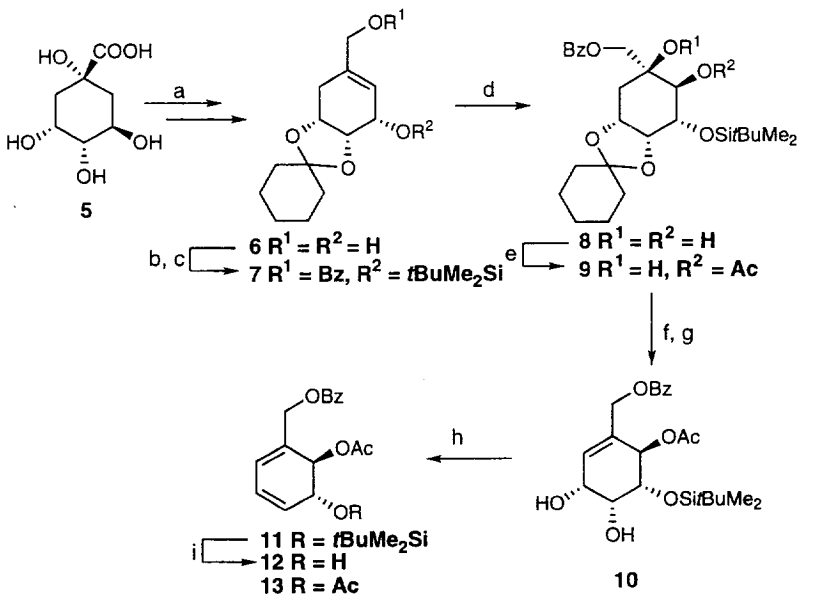
α-D-glucose



β-D-mannose

Since the glycosidase inhibitory activity of crotepoxide **1** has not been studied, a successful construction of enantiopure crotepoxide and related cyclohexane oxides would permit extensive biological evaluation. Hitherto there has been only one report on the synthesis of optically pure crotepoxide from a chemically resolved Diels-Alder adduct of furan and acrylic acid.[11] Our endeavours in natural and non-natural product synthesis from (–)-quinic acid **5** have already furnished anti-tumour agent 2-crotonyloxymethyl-(4*R*,5*R*,6*R*)-4,5,6-trihydroxycyclohex-2-enone (COTC),[12] pseudo-β-D-mannopyranose, pseudo-β-D-fructopyranose,[13] pseudo-α-D-glucopyranose, pseudo-α-D-mannopyranose,[14] glycosidase inhibitors cyclophellitol and its diastereoisomers,[15] and moreover valiolamine and its diastereoisomers.[16] In continuation with our investigation on the preparation of potential glycosidase inhibitors, we now disclose the first enantiospecific syntheses of **1** and **2**, and hence further demonstrate the versatility of quinic acid in the fabrication of heavily oxygenated cyclohexanoid natural products.

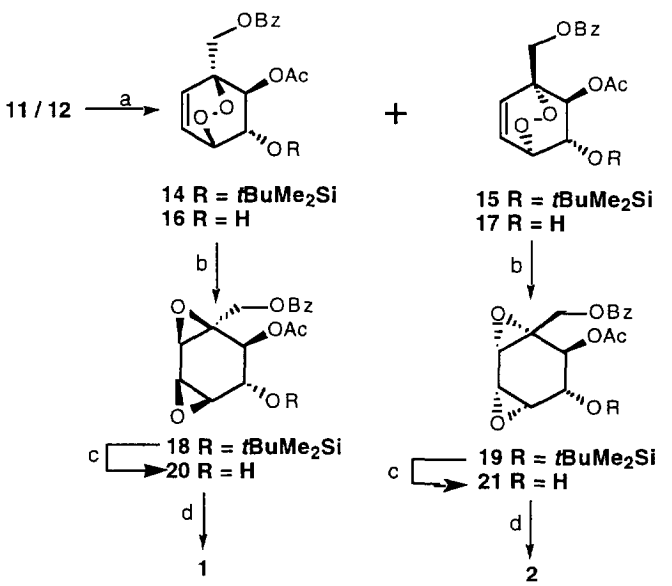
Our previous work[13,15] has shown that quinic acid **5** could be readily converted into the diol **6** in four steps with an overall yield of 64.5% (Scheme 1). Regioselective benzoylation[17] at the primary hydroxy group in **6** followed by silylation of the remaining alcohol afforded the silyl benzoate **7**.[18] The double bond in **7** was subjected to our recently developed ruthenium catalyzed flash dihydroxylation[19] protocol at the less hindered β-face to give, exclusively, the desired β-diol **8**.[18] Selective acetylation of the secondary hydroxy group in **8** gave the monoacetate **9**. Thionyl chloride[20] mediated elimination of the tertiary alcohol in **9** followed by selective hydrolysis of the cyclohexylidene ketal furnished the ene-diol **10**. Corey-Winter[21] deoxygenation of the vicinal diol moiety in **10** provided the diene **11** that now possessed the functionality required for the bisoxirane formation *via* a singlet oxygen oxidation reaction.[22]



Scheme 1. Syntheses of dienes **11**, **12**, and **13**: a) 4 steps, (64.5%), see ref. 13, 15; b) benzoyl chloride, collidine, CH_2Cl_2, room temp. (82%); c) *tert*-butylchlorodimethylsilane (*t*BuMe$_2$SiCl), imidazole, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp. (97%); d) RuO_4, $NaIO_4$, H_2O : CH_3CN : EtOAc (1:3:3), 0 °C (75%); e) Ac_2O, pyridine (pyr), DMAP, CH_2Cl_2, room temp. (97%); f) $SOCl_2$, pyr, CH_2Cl_2, 0 °C to room

temp. (81%); g) 50% aqueous CF_3CO_2H, CH_2Cl_2, room temp. (80%); h) 1,1'-thiocarbonyldiimidazole, toluene, reflux, then $P(OMe)_3$, reflux (68%); i) 48% aqueous HF, CH_3CN (80%).

Photo-oxygenation of the diene moiety in **11** proceeded at the sterically less hindered β-face, giving the β-endoperoxide **14** as the preponderant product (β-endoperoxide **14** : α-endoperoxide **15** = 54 : 1) as shown in Scheme 2. The use of *tert*-butyldimethyl silyl ether as the stereodirecting group in singlet oxygen oxidation reaction was therefore highly efficient. The isomeric endoperoxides were easily separable on silica chromatography. The photo-oxygenation reaction[22] of the desilylated **11**, i.e., the diene-alcohol **12**, was also examined and the ratio of β- **16** to α-endoperoxide **17** was 3 : 2. It is noteworthy that the diacetate **13** did not afford any observable reaction with singlet oxygen. Subjection of the silylated β-endoperoxide **14** to the cobalt-*meso*-tetraphenylporphyrin catalyzed rearrangement reaction[23] gave smoothly the diepoxide **18** in essentially quantitative yield.[18] Desilylation of **18** afforded alcohol **20** that was identical to the product from the same rearrangement reaction[23] of β-1,4-endoperoxide **16**. Acetylation of the free alcohol in **20** then yielded the target molecule crotepoxide **1**,[24] m.p. 146–148 °C (Et_2O/hexanes) (lit.[6a] m.p. 150–151 °C); $[\alpha]^{26}_D$ = + 71.9 (*c* = 0.6, $CHCl_3$) {lit.[6a] $[\alpha]^{25}_D$ = + 74 (*c* = 1.7, $CHCl_3$)}. Likewise reactions of α-endoperoxide **15** (→ **19**→ **21**→ **2**) or **17** (→ **21**→ **2**) furnished, for the first time, optically active *iso*-crotepoxide **2**, oil; $[\alpha]^{27}_D$ = - 35.8 (*c* = 0.67, $CHCl_3$).[18,24]



Scheme 2. Syntheses of **1** and **2**: a) O_2, hv, tetraphenylporphyrin (TPP), CCl_4, 0 °C (**14** : **15**, *ca.* 54 : 1, 80% from **11**), (**16** : **17**, *ca.* 3 : 2; 80% from **12**); b) cobalt-*meso*-tetraphenylporphyrin (CoTPP), $CHCl_3$, 0 °C (98%); c) HF-pyridine, THF, (85%); d) Ac_2O, pyr, DMAP, CH_2Cl_2, room temp. (98%).

In summary, we have described facile and efficient syntheses of enantiopure crotepoxide **1** and its diastereoisomer **2** from (–)-quinic acid and application of this flexible strategy to the fabrication of other cyclohexanoid natural products including boesenoxide, senepoxide, β-senepoxide, pipoxide, and tingtanoxide is underway.[5]

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24. Selected spectral data: for **1**, ^{1}H-NMR (250 Hz, $CDCl_3$) δ = 8.02 (d, 2H, J = 7.0 Hz), 7.57 (t, 1H, J = 7.6 Hz), 7.47 (t, 2H, J = 7.1 Hz), 5.71 (d, 1H, J = 9.0 Hz), 4.99 (dd, 1H, J = 1.6, 9.0 Hz), 4.58 (d, 1H, J = 12.1 Hz), 4.24 (d, 1H, J = 12.1 Hz), 3.67 (d, 1H, J = 2.7 Hz), 3.46 (dd, 1H, J = 2.7, 3.9 Hz), 3.11 (dd, 1H, J = 1.6, 3.9 Hz), 2.13 (3, 3H), 2.03 (s, 3H). For **2**, ^{1}H-NMR (250 Hz, $CDCl_3$) δ = 8.02 (d, 2H, J = 7.05 Hz), 7.60 (t, 1H, J = 7.1 Hz), 7.47 (t, 2H, J = 6.4 Hz), 5.36 (s, 2H), 4.39 (ABq, 2H, J = 12.3 Hz), 3.57 (dd, 1H, J = 2.7, 4.0 Hz), 3.50 (d, 1H, J = 2.7 Hz), 3.42 (d, 1H, J = 4.0 Hz), 2.11 (3, 3H), 2.00 (s, 3H).

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