Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 19, pp. 2307-2312, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00326-2

TOTAL SYNTHESIS OF NOVEL CONDURITOL RELATED COMPOUNDS CAPABLE OF MODULATING INSULIN RELEASE.

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Abstract : The syntheses of the six isomeric conduritols A - F, and of a series of bicyclic and tricyclic polyols related to the conduritols are described. Conduritols A and B, and representative analogues are able to modulate the release of insulin from isolated pancreatic islets in the presence of varying concentrations of glucose, in both a stimulatory and an inhibitory sense.

Conduritols A **(9)** and F **(3)** are naturally occuring 5-cyclohexene-1,2,3,4-tetrols.[1] Whilst optically active **(3)** is found in small quantities in almost all green plants (as the L isomer) the occurance of *meso* **(9)** is restricted to specific subfamilies of tropical plants.[2] The 4 other possible isomeric conduritols designated B,C,D, and E exist as one *meso* compound (conduritol D **(13)**) and three **D/L** pairs (conduritols B,C and E, **(8)** ,**(2)** and **(15)**) and are not found in nature.[1] Conduritol A is present, along with numerous other complex natural products, in the leaves of *Gymnena Sylvestre*, a shrub which has formed the basis of a folk remedy for diabetes used in India and Asia for over 2000 years.[3,4] Recent reports of the hypoglycaemic activity of conduritol A ,[5] and speculation that this activity is the basis of *Gymnena Sylvestre* based therapy, prompted us to examine the chemistry and pharmacology of the conduritols.

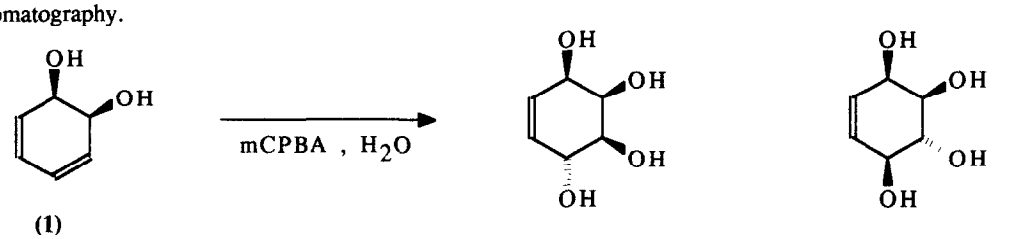
We report here the ability of conduritols A and B to modify insulin release from isolated pancreatic islets. Based on this activity, and the reported hypoglycaemic activity of conduritol A , we have synthesised a range of polycyclic analogues of conduritol A, and examined their ability to modify insulin release *in-vitro*. The synthesis and *in-vitro* biological activity of several of these new compounds **(18)** & **(20)** - **(25)** is reported. These compounds may provide new leads for the development of modulators of insulin secretion.[6]

The synthesis of conduritols and related compounds was comprehensively reviewed in 1990,[1] and other synthetic approaches to these molecules have appeared more recently, concentrating mainly on enantiospecific routes.[7,8,9] In addition, numerous chemoenzymatic syntheses of conduritols, and cyclitols in general have been reported.[10] We chose to synthesise the six conduritols for preliminary testing as *meso* compounds or as racemic **D/L** pairs by modification of published routes as shown in Schemes 1- 4.

Treatment of the commercially available [11] *cis*-diol **(1)** with one equivalent of mCPBA in water at room temperature over 16h gave a mixture of racemic conduritols C and F (**Scheme 1**) .[8] The two conduritols were easily obtained in pure form by direct crystallisation followed by washing with ethanol (conduritol C crystallises first, followed by conduritol F) .

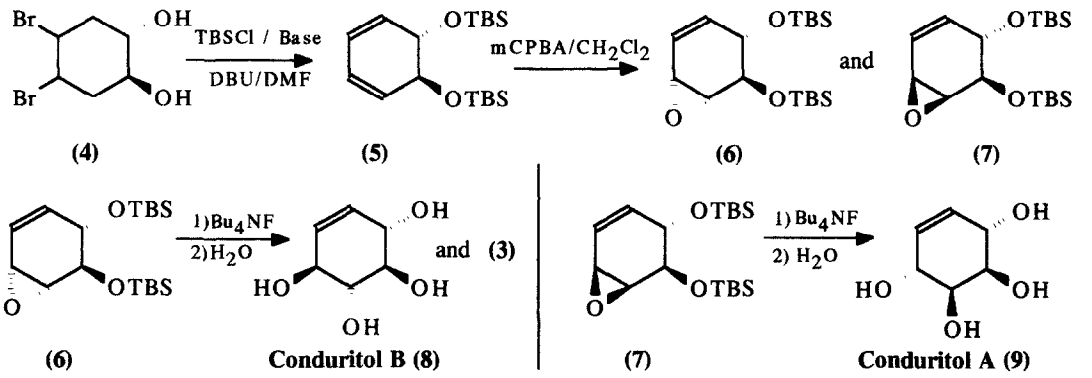
Protection of the known [12] dibromo diol **(4)** as its bis-TBS ether, followed by base catalysed elimination of HBr (DBU/DMF 80°C) gave the protected diene **(5)** (**Scheme 2**) . Epoxidation of **(5)** using

mCPBA in CH_2Cl_2 gave a 1:1 mixture of two epoxides **(6)** and **(7)** , which were easily separable by chromatography.



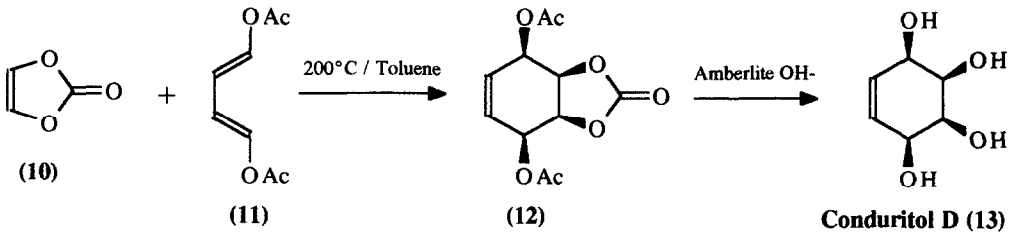
Scheme 1

Removal of the TBS protecting groups from **(6)**, followed by epoxide opening in water gave a 1:1 mixture of conduritols B and F which were separated by chromatography, whilst similar ring opening of epoxide **(7)** gave pure conduritol A .[13]



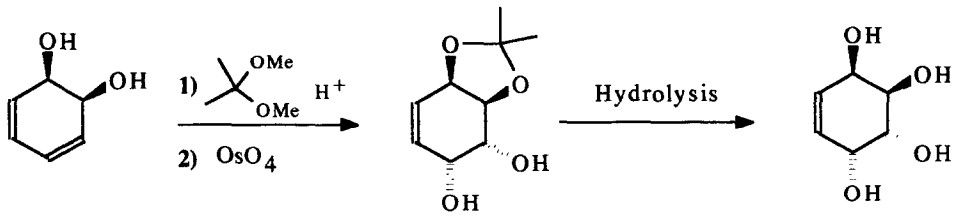
Scheme 2

Fully protected conduritol D **(12)** was obtained from the high pressure Diels-Alder reaction between vinylene carbonate **(10)** and the diene **(11)** (**Scheme 3**) . Subsequent treatment of **(12)** with a basic ion exchange resin then gave pure conduritol D **(13)** .[14]



Scheme 3

The final isomer, conduritol E (**15**) was also prepared from the *cis*-diol (**1**), by protection as the isopropylidene acetal, followed by oxidation to the protected tetrol (**14**) using catalytic OsO_4 at room temperature. Removal of the acetal protecting group then gave pure conduritol E (**15**) (**Scheme 4**) .[9]



(**1**) (**14**) **Conduritol E (15)**

Scheme 4

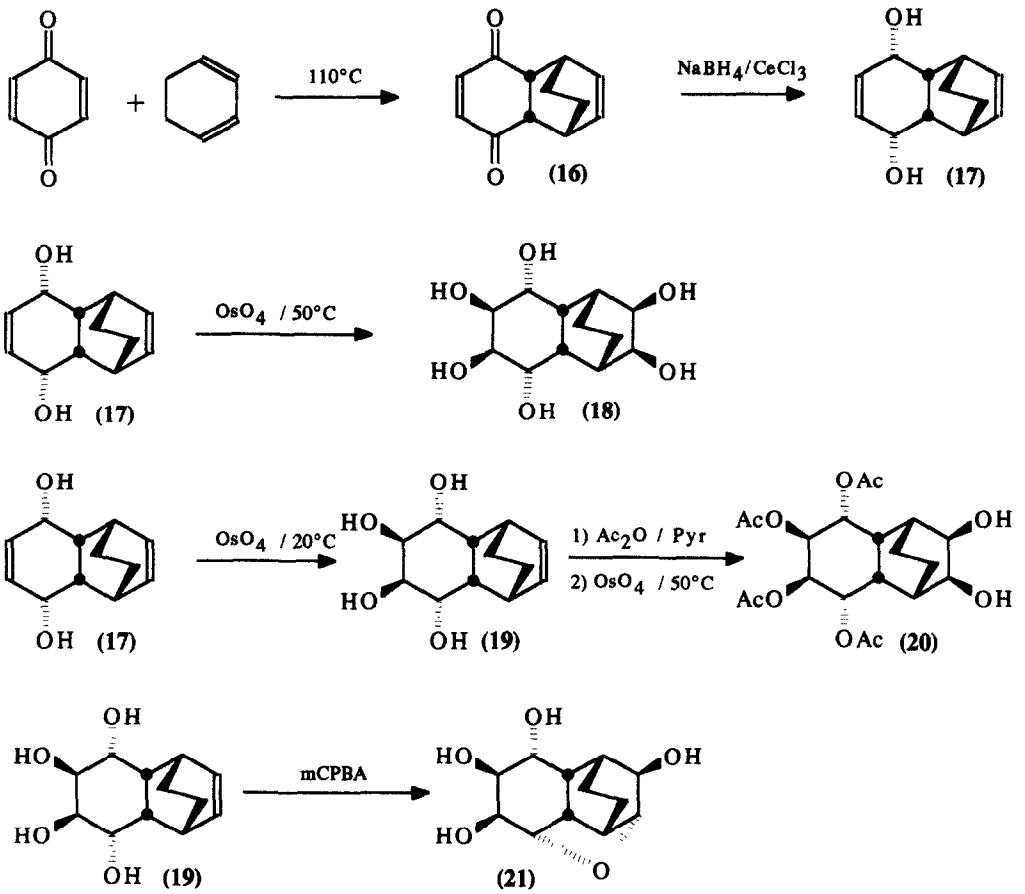
The conduritols thus obtained were tested for their ability to modulate the release of insulin from pancreatic islets, at two glucose concentrations, and the results are shown in **Table 1**. Briefly, islets of Langerhans were obtained from male Sprague-Dawley rats by the method of Lacy.[15] Islets were incubated at 37°C in the presence of either 2.8 or 16.7mM glucose for 4h in the presence or absence of drug, and insulin secretion measured.[16] Data are presented as the percentage increase or decrease in insulin secretion compared to the mean secretion obtained at each glucose concentration, in the absence of drug. All compounds were tested at 10^{-4}M with 8 replicates per incubation.

Given the interesting effects of conduritol A and B on insulin secretion shown in **Table 1**, a series of analogues of conduritol A were prepared, with fused rings in place of the conduritol double bond. These analogues were based on the hypothesis that the four hydroxyl groups of conduritol A in the $\alpha,\beta,\beta,\alpha$ stereo chemistry were responsible for biological activity, with the double bond probably acting as a conformational restraint , as the saturated analogue of conduritol A is significantly less active (**Table 1**).

Conduritol Isomer	% change at 2.8mM glucose	% change at 16.7mM glucose
Conduritol **A** (**9**)	+45	- 30
Conduritol **B** (**8**)	+41	+50
Conduritol **C** (**2**)	+27	- 20
Conduritol **D** (**13**)	0	0
Conduritol **E** (**15**)	+12	+15
Conduritol **F** (**3**)	+ 9	- 3
Saturated **A**	- 16	- 13

Table 1

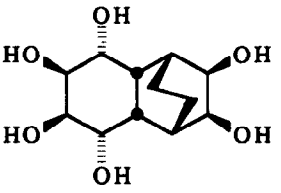
The analogues were all prepared by a Diels-Alder strategy ,[17] followed by sequential stereoselective reductions ($NaBH_4$ + $CeCl_3$) and / or oxidations (OsO_4 ; or mCPBA ; or tBuOOH + Vanadyl AcAc) to give the required hydroxyl substituents. The syntheses of several representative examples are given below in **Scheme 5** .[18] Cycloaddition between 1,3-cyclohexadiene and benzoquinone at 110°C in toluene gave the adduct (**16**). Stereoselective reduction of (**16**) using cerium(III) chloride / $NaBH_4$ in 50:50 CH_2Cl_2 / MeOH then gave the *cis* diol (**17**) . Oxidation of (**17**) with catalytic OsO_4 at elevated temperature resulted in the



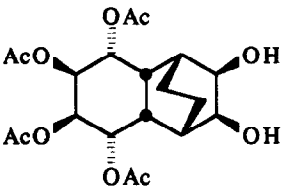
Scheme 5

cis hydroxylation of both double bonds, giving hexol **(18)**. Alternatively, treatment of **(17)** with catalytic OsO_4 at 20°C and careful control of the reaction time gave selectively the tetrol **(19)**. Acetylation of **(19)** with acetic anhydride in pyridine, followed by a second treatment with catalytic OsO_4 , this time at 50°C gave the tetraacetylated hexol **(20)**. Attempted formation of a *trans* diol system *via* mCPBA treatment of **(19)** led to *in-situ* intramolecular opening of the epoxide by the proximal OH group, and isolation of compound **(21)**. Compounds (**24)** and **(25)** were synthesised by routes identical to those used for compounds (**18)** and **(21)** using the Diels-Alder adduct obtained from benzoquinone and γ−terpinene as a starting material. The biological activity of these compounds is presented together with their chemical structures in **Table 2.**

Several interesting points arise from the data presented in **Tables 1& 2.** In contrast to the conduritols, which show a range of both stimulatory (Conduritols A, B and C at low glucose and B at high glucose) and inhibitory effects (Conduritols A and C at high glucose) , the bicyclic analogues are almost all inhibitors of



(18)



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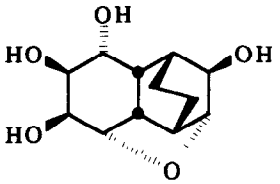

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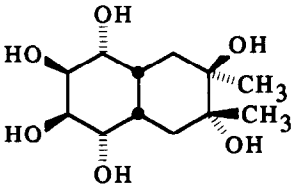

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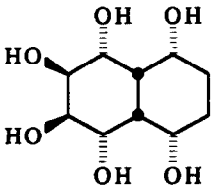

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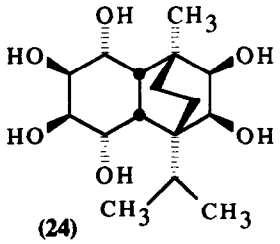

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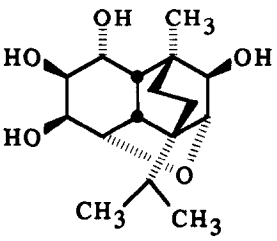

(25)

Compound number	% change at 2.8mM glucose	% change at 16.7mM glucose
(18)	- 18	+44
(20)	- 60	- 23
(21)	0	- 70
(22)	- 60	0
(23)	- 45	- 35
(24)	- 30	- 30
(25)	- 60	- 45

Table 2

insulin secretion at all glucose concentrations. Compounds (**24**) and (**25**) for example show marked inhibition of insulin secretion at both glucose concentrations. In contrast compound (**22**) shows marked inhibition at low glucose, but has no effect at high glucose concentration, and compound (**21**) has no effect at low glucose but shows marked inhibition at high glucose concentration .

These molecules therefore provide useful pharmacological tools for studies of the modulation of insulin secretion *in-vitro.*

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6) In the general context of cyclitols and insulin action, derivatives of *chiro*-inositol derived from the GPI anchor molecule have been shown to exert weak insulin like activity, and these compounds may represent mediators of insulin action . See for example : Ley, S.V., Yeung, L.L., *Synlett.* **1992**, 997. Reddy, K.K.; Falck, J.R.; Capdevila, J., *Tetrahedron Lett.* **1993**, *34*, 7869.

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16) **Method :** Islets of Langerhans were obtained from male Sprague-Dawley rats by collagenase digestion, according to the method of Lacy.[15] Routinely 150 islets were obtained from each rat. Following isolation, islets were incubated at 37°C in Kreb's Ringer bicarbonate buffer at pH7.4, containing 0.5% bovine serum albumin and either 2.8 or 16.7mM glucose. These concentrations were chosen to achieve basal (2.8mM) or maximal (16.7mM) stimulation of insulin secretion from the islets. After incubation for 4h two 50μl aliquots from each incubate were sampled and used for measurement of insulin (Pasedeph kit, pharmacia, France). Data are presented as the percentage increase or decrease in insulin secretion compared to the mean secretion obtained at each glucose concentration, in the absence of drug. Under these conditions, the mean basal and maximally stimulated rates of insulin secretion were 14.5 +/- 2.6 (n=8) and 27.5 +/- 3.2 (n=8) . All synthetic compounds were tested at 10^{-4}M with 8 replicates per incubation.

17) For a related Diels-Alder strategy which appeared after this work was completed, see : Hudlicky, T.; McKibben, B.P., *J. Chem. Soc. Perkin Trans. I* **1994**, 485.

18) All compounds gave satisfactory TLC, HPLC, ^{1}H NMR, ^{13}C NMR, mass spectral, and elemental analysis data, in agreement with their assigned structures.

(*Received in Belgium* 30 *June* 1994; *accepted* 29 *August* 1994)