# A straightforward synthesis of perbenzylated conduritols from alditols by ring closing olefin metathesis

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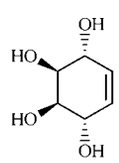
**The synthesis of perbenzylated conduritols A, E and F has been achieved in six steps by formal conversion of galactitol, D-mannitol and D-glucitol into the respective terminal dienes, followed by ring closing olefin metathesis.**

Conduritols (cyclohex-5-ene-1,2,3,4-tetrols) have recently become fashionable synthetic targets, not only because of the diverse biological activity of their simple derivatives such as epoxides and conduramines but also because of their widespread use as intermediates in chemical synthesis.[1–4]

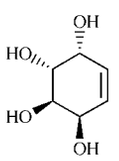
Several approaches[2–4] to the synthesis of conduritols have been made, the most popular being the microbial oxidation of benzene and halobenzenes and further manipulation of the resulting cyclohexa-3,5-diene-1,2-diols.[3] Carbohydrates and related polyoxygenated compounds have also been used as cheap commercially available starting materials.[4] Moreover, a number of unnatural analogs possessing the basic structure of conduritols with interesting biological activities have been prepared.[5]

Inspection of the general structure of conduritols such as **1**–**3**



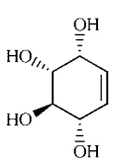
**1**

*meso*-Conduritol A



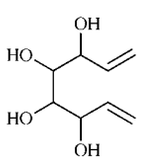
**2**

(1*R*,2*R*,3*R*,4*R*)-(−)-Conduritol E

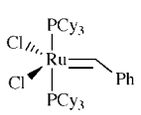


**3**

(1*S*,2*R*,3*R*,4*R*)-(−)-Conduritol F



**4**



**5**

led us to the conclusion that they could be prepared by ring closing olefin metathesis (RCM)[6] of the appropriate dienes of the general structure **4**, which in turn could be prepared from the respective alditols. While our study was in progress, a few reports appeared in the literature applying the RCM in the synthesis of carbocycles from carbohydrates,[7] one of them referred to the synthesis of conduritols B and F.[4h] However, our approach to the synthesis of the diene precursor is totally different.

Starting from D-mannitol, D-glucitol and galactitol, which have the stereochemistry of (−)-conduritol E (**2**), (−)-conduritol F (**3**) and conduritol A (**1**), respectively, their derivatives **6**, **9** and **12** were prepared in good overall yields by standard sugar manipulations:[5e] protection of the primary hydroxy groups by tritylation, then benzylation of the secondary hydroxy groups and finally selective removal of the trityl group by acidic hydrolysis. Subsequent Swern oxidation of diols **6**, **9** and **12** led to the respective dialdehydes, which without characterisation were subjected to Wittig olefination to give the desired dienes **7**, **10** and **13** in 50–53% overall yields (Scheme 1).† The presence of a catalytic amount of 12-crown-4 is crucial in the Wittig olefination, since its absence dramatically reduces the yields.

With the dienes **7**, **10** and **13** in our hands our attention was turned to establish the best conditions for RCM.[6] In initial experiments the easily handled ruthenium catalyst $(Cy_3P)_2$-Ru(=CH-CH=$CPh_2$)$Cl_2$ did not work at all and the dienes were quantitatively recovered. Schrock catalyst $PhMe_2CCH$=Mo=N(2,6-(*i*-Pr)$_2C_6H_3$)$(OCMe(CF_3)_2)_2$ was also disappointing and only traces of the cyclised products were formed. The results were much better, however, when we switched to the Grubbs catalyst **5**: after several attempts, the best results were obtained in a 0.01 M solution of dienes in refluxing $CH_2Cl_2$ for 72 h and with the catalyst used in 30% molar ratio relative to diene. The catalyst was added gradually in three equal portions.

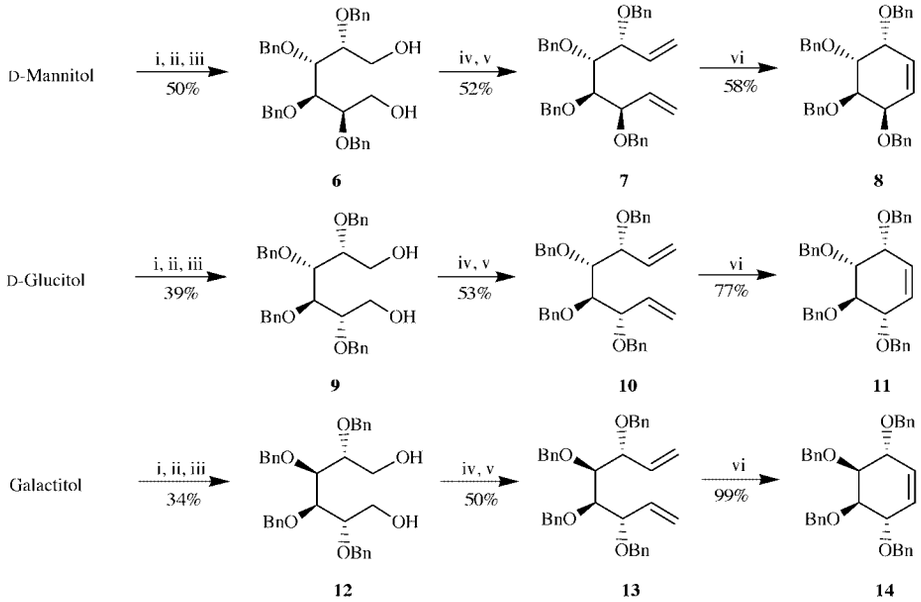
In the case of the D-mannitol derived diene **7**, the perbenzylated (−)-conduritol F **8** was obtained in 52% yield and 40% of the diene was recovered, while for diene **10** the protected (−)-conduritol E **11** was formed in 77% yield and 18% of unchanged **10** was recovered. Finally, the cyclisation of diene **13** was complete and the perbenzylated conduritol A **14** was obtained in quantitative yield.† It is apparent that the relative stereochemistry of the carbon backbone in dienes **7**, **10** and **13** is responsible for their difference in reactivity, although we are presently not able to point out the exact way the reaction is affected by the substituents. Regarding the deprotection of the perbenzylated conduritols prepared, a number of new and convenient methods for selective cleavage of benzyl ethers have been developed in the last few last years,[8] which do not affect an existing double bond, since it is apparent that hydrogenolysis ($H_2$/Pd) would lead to saturation of the double bond.

In conclusion, we have developed a simple and general method for converting the commercially available alditols to terminal dienes and then into the respective conduritols by ring closing metathesis. When asymmetric alditols are used (D-mannitol, D-glucitol) their chirality is transferred to the products and enantiomerically pure conduritols are thus prepared.

## Experimental

### (3*R**,4*S**,5*R**,6*S**)-3,4,5,6-Tetra-*O*-benzylocta-1,7-diene-3,4,5,6-tetrol, 13

A solution of dry DMSO (0.15 ml, 2.1 mmol) in dry $CH_2Cl_2$ (1 ml) was added to a solution of $(COCl)_2$ (0.1 ml, 1.11 mmol) in dry $CH_2Cl_2$ (2 ml) which had been cooled to −60 °C, under an argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min before a solution of **12** (0.243 g, 0.448 mmol) in dry $CH_2Cl_2$ (2 ml) was added carefully during a period of 5 min, while the temperature was kept between −60 and −55 °C. The stirring was continued for 15 min and then $Et_3N$ (0.63 ml, 4.48 mmol) was added at the same temperature. After another 10 min stirring at low temperature the mixture was allowed to warm to room temperature. Saturated aqueous NaCl (100 ml) was subsequently added and the solution was extracted with $CH_2Cl_2$ (3 × 100 ml). The organic layer was dried over $Na_2SO_4$, the solvent was removed on a




**Scheme 1** *Reagents and conditions*: i, $Ph_3CCl$, DMAP, $Et_3N$, DMF, 20 °C, 24 h; ii, DMF, NaH, 0 °C, then BnCl, 0 to 20 °C, 24 h; iii, $H_2SO_4$, MeOH, $CH_2Cl_2$, 20 °C, 1 h; iv, $(COCl)_2$, DMSO, $Et_3N$, −60 °C, 30 min; v, $Ph_3P^+CH_3Br^-$, n-BuLi, 12-crown-4, THF, −60 °C to 20 °C, 12 h; vi, **5** (30 mol%), $CH_2Cl_2$, 0.01 M, reflux, 72 h.

rotary evaporator and the resulting crude dialdehyde dried under vacuum and used without further purification. To a stirring solution of $Ph_3P^+CH_3Br^-$ (0.8 g, 2.24 mmol) and 12-crown-4 (0.079 g, 0.448 mmol) in THF (5 ml) n-BuLi (1.6 ml, 1.6 M in hexanes) was slowly added under argon at −78 °C. The mixture was allowed to reach 0 °C, then cooled again to −78 °C and a solution of the previous dialdehyde in THF (5 ml) was added. The reaction mixture was stirred overnight at room temperature, then water (100 ml) was added and extracted with $CH_2Cl_2$ (3 × 100 ml). Drying ($Na_2SO_4$) of the organic phase and removal of the solvent under vacuum, gave the crude product which was purified by column chromatography (ethyl acetate–hexane, 1 : 20), to give diene **13** (0.120 g, 50% overall yield).

Similarly, dienes **7** and **10** were prepared from **6** and **9**, in 52 and 53% overall yields respectively.

### (1*R**,2*S**,3*R**,4*S**)-1,2,3,4-Tetra-*O*-benzylcyclohex-5-ene-1,2,3,4-tetrol (tetra-*O*-benzylconduritol A), 14

To a stirring and degassed 0.01 M in $CH_2Cl_2$ solution of diene **13** (59 mg, 0.11 mmol), Grubbs catalyst **5** (9 mg, 0.011 mmol) was added and the mixture was refluxed for 72 h. The same amount of catalyst was then added twice again (every 24 h, total 27 mg, 30 mol%). The solvent was removed and the residue was purified by column chromatography (ethyl acetate–hexane, 1 : 20), to give compound **14** (0.055 g, 99%).

Perbenzylated conduritols **8** and **11** were also prepared from **7** and **10** by the same procedure, in 58 and 77% yields respectively. Chromatographic separation (silica gel, ethyl acetate–hexane, 1 : 20) of the mixture gave firstly the unchanged **7** or **10**, followed by the desired products **8** or **11**.

## Notes and references

† All new compounds gave satisfactory microanalyses (C ±0.25, H ±0.2) and spectral and analytical data consistent with their assigned structures. *Selected analytical data (J values are given in Hz)*: Compound **7**: Mp 67–68 °C ($Et_2O$–hexane); $[a]_D^{25}$ −37.5 (*c* 0.42, MeOH); $\delta_H$ (300 MHz, $CDCl_3$) 3.81 (2H, d, *J* 6.1), 4.03 (2H, dd, *J* 6.1, 7.3), 4.20 (2H, d, *J* 11.7), 4.51 (2H, d, *J* 11.1), 4.58 (2H, d, *J* 11.7), 4.68 (2H, d, *J* 11.1), 5.32 (2H, d, *J* 17.0), 5.34 (2H, d, *J* 11.0), 5.93 (2H, ddd, *J* 17.0, 11.0, 7.3), 7.42 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 69.88, 74.44, 80.36, 81.10, 119.54, 127.27, 127.40, 127.66, 127.85, 128.05, 128.24, 136.17, 138.43, 138.85. Compound **8**: oil [Found: (M + Na) (FAB) 529.2348. $C_{34}H_{34}O_4Na$ requires 529.2355]; $[a]_D^{25}$ −115.5 (*c* 0.42, MeOH); $\delta_H$ (300 MHz, $CDCl_3$) 3.98 (2H, s), 4.25 (2H, s), 4.64 (8H, m), 5.83 (2H, s), 7.27 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 71.55, 73.17, 73.32, 76.03, 127.40, 127.44, 127.56, 127.73, 127.88, 128.17, 138.58. Compound **10**: oil, $[a]_D^{25}$ +15.2 (*c* 2.62, $CHCl_3$); $\delta_H$ (300 MHz, $CDCl_3$) 3.71 (1H, dd as t, *J* 5.2), 3.81 (1H, dd as t, *J* 5.3), 3.96 (1H, dd as t, *J* 6.9), 4.05 (1H, dd as t, *J* 6.7), 4.12 (1H, d, *J* 11.5), 4.34 (1H, d, *J* 11.9), 4.50 (1H, d, *J* 11.5), 4.57 (1H, d, *J* 11.2), 4.60 (1H, d, *J* 11.9), 4.64 (1H, d, *J* 11.1), 4.78 (1H, d, *J* 11.2), 4.80 (1H, d, *J* 11.1), 5.26 (4H, m), 5.90 (2H, m), 7.28 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 69.94, 70.40, 73.96, 75.10, 80.50, 81.03, 81.28, 81.50, 118.90, 119.38, 127.26, 127.34, 127.47, 127.79, 128.00, 128.09, 128.24, 135.59, 135.95, 138.24, 138.57, 138.98. Compound **11**: oil [Found: (M + Na) (FAB) 529.2346. $C_{34}H_{34}O_4Na$ requires 529.2355]; $[a]_D^{25}$ −25 (*c* 0.5, MeOH); $\delta_H$ (300 MHz, $CDCl_3$) 3.53 (1H, dd, *J* 9.9, 3.4), 4.05 (1H, d, *J* 3.4), 4.07 (1H, d, *J* 7.5), 4.21 (1H, dd, *J* 9.9, 7.5), 4.75 (8H, m), 4.84 (1H, d, *J* 11.0), 5.01 (1H, d, *J* 11.0), 7.32 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 71.31, 71.73, 71.83, 72.69, 75.09, 79.72, 80.04, 80.21, 126.17, 127.43, 127.51, 127.70, 127.86, 128.02, 128.28, 131.06, 138.59, 138.73, 138.92. Compound **13**: Mp 85–86 °C ($Et_2O$–hexane); $\delta_H$ (300 MHz, $CDCl_3$) 3.83 (2H, s), 4.20 (2H, d, *J* 7.7), 4.30 (2H, d, *J* 12.0), 4.46 (2H, d, *J* 11.5), 4.61 (2H, d, *J* 11.5), 4.63 (2H, d, *J* 12.0), 5.26 (2H, d, *J* 10.9), 5.35 (2H, d, *J* 17.3), 5.94 (2H, ddd, *J* 17.3, 10.9, 7.7), 7.28 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 70.21, 74.35, 80.34, 81.50, 118.51, 127.31, 127.37, 127.62, 127.96, 128.12, 128.18, 136.59, 138.53, 138.69. Compound **14**: oil [Found: (M + Na) (FAB) 529.2348. $C_{34}H_{34}O_4Na$ requires 529.2355]; $\delta_H$ (300 MHz, $CDCl_3$) 3.90 (2H, d, *J* 5.0), 4.17 (2H, d, *J* 5.0), 4.57 (4H, s), 4.66 (4H, s), 5.84 (2H, s), 7.30 (20H, m); $\delta_C$ (75 MHz, $CDCl_3$) 71.65, 72.42, 75.34, 77.00 (overlapping with $CDCl_3$), 127.30, 127.36, 127.58, 128.07, 128.22, 138.42.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