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Synthesis of a Peracetylated Stereoisomer of De Rosa's Calditol: Some Questions about the Correctness of the Original Structure Assigned to this Natural Product

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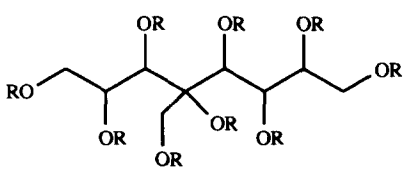
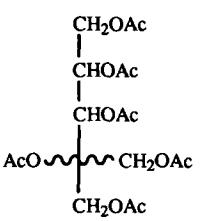
Abstract : Comparison of the ^{13}C nmr spectrum of the nonacetate of a synthetic stereoisomer of calditol with that of the nonacetate of the natural product, combined with a comparison of the ^{13}C nmr spectrum of the peracetate of a hexitol derived from calditol with all known peracetates of open chain hexitols, invalidates the originally proposed structure.

Calditol is a polyhydroxylated compound which was found to constitute a portion of complex macrocyclic tetraether lipids isolated from the membrane of thermoacidophilic archaebacteria of the *Caldariella* group.[1] The proposed structure was concluded[2] to be that of a unique branched chain nonitol **1**, of undefined stereochemistry. Part of the original basis for the proposal of this structure was an examination of the ^{13}C nmr spectra of both the nonacetate of calditol itself **2** and of the two peracetates, assigned as structures as **3** and **4**, which were derived from calditol by degradation involving sequential periodate oxidation, reduction and acetylation.



1 R=H
2 R=Ac



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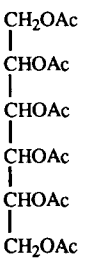


4

The degradation product **4** was assigned an open chain structure, though it was claimed that no stereochemical information could be obtained from this material. Being interested in this unique proposed structure of calditol, we promptly became intrigued by the structural assignment reported for **4** as that of a hexitol peracetate. In particular we noticed the large discrepancy between the two chemical shifts for the two

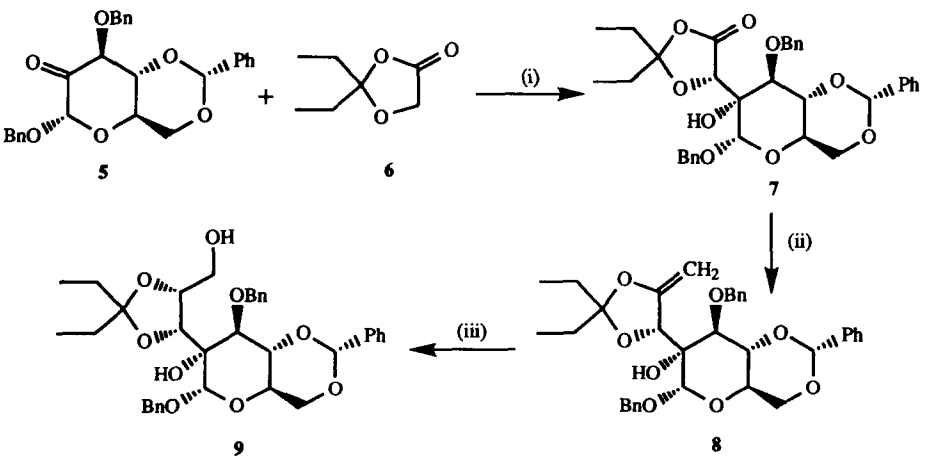
triplet carbons (8.6 ppm). For all possible open chain hexacetates (data by Angyal and Le Fur[3],Table 1), there is only an extremely small discrepancy between the signals of the triplet carbons which are always found around 62 ppm (plus or minus 0.5 ppm). Correspondingly the doublet carbons are always found between 67 and 70 ppm. Comparison of these values with those obtained for the degradation product **4** reveals the anomalies of a triplet at 70.86 ppm and a low field doublet at 77.11 ppm, indicating the inviability of the structural assignment of **4** as an open chain hexitol.

Table 1. ^{13}C Nmr Data for Hexitol Peracetates[3] and De Rosa's compound **4**

Carbon Atom	Allitol	Altritol	Galactitol	Glucitol	Iditol	Mannitol	**4**
1	61.8	62.1	62.3	62.0	61.8	62.0	70.86(t)
2	69.7	68.4	67.8	69.6	69.3	68.1	70.32(d)
3	69.4	69.1	67.7	68.7	68.9	67.7	77.11(d)
4	69.4	68.7	67.7	69.0	68.9	67.7	69.78(d)[a]
5	69.7	70.0	67.8	68.9	69.3	68.1	69.48(d)[a]
6	61.8	61.7	62.3	61.6	61.8	62.0	62.23(t)

(a) These signals are not unequivocally assigned.

We thus decided to synthesise a defined isomer of **2** in order to carefully compare the ^{13}C nmr data with that reported by De Rosa *et al.*. Condensation of the ketone **5**[4] with the lithium enolate[5] of the dioxolane **6**[6] yielded the lactone **7**[7] as the major reaction product[8] (Scheme 1) in 66% yield. Tebbe[9] methylenation of **7** was achieved without protection of the tertiary alcohol to yield the alkene **8** which was directly submitted to hydroboration to yield the alcohol **9**[10] as the sole reaction product (84% yield from **7**).



Scheme 1. Reagents: (i) LDA, THF, -78°C, 66% (also 20% recovered starting material); (ii) Tebbe[9], THF, pyridine, -40°C to room temp.; (iii) BH_3.DMS, THF, 0°C to room temp., 84% over two steps.

The absolute configuration of **9** was confirmed by crystallography[11] and the X-ray structure of this material is shown (Figure).

Conversion of the alcohol **9** to the calditol isomer **11** was achieved by a five step reaction sequence (Scheme 2). Acidic removal of both dioxalone and benzylidene protecting groups followed by acetylation of the crude reaction product with acetic anhydride and pyridine yielded the pentacetate **10**[12] in 97% yield. Removal of both benzyl groups was achieved by catalytic hydrogenation in the presence of palladium black. The crude reaction product was subsequently reduced with a large excess of sodium borohydride and then acetylated with acetic anhydride and pyridine, in the presence of a catalytic amount of DMAP, to finally yield the peracetylated calditol isomer **11** (46% yield over the last three steps).

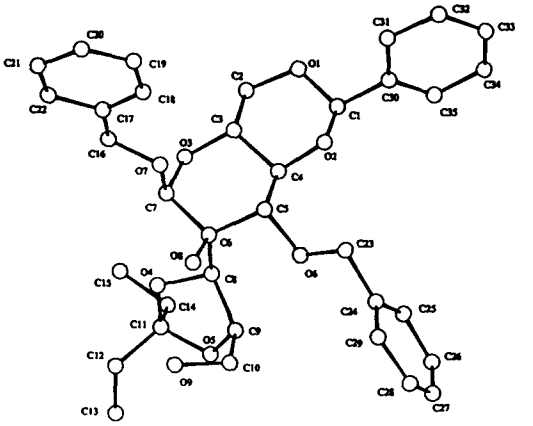
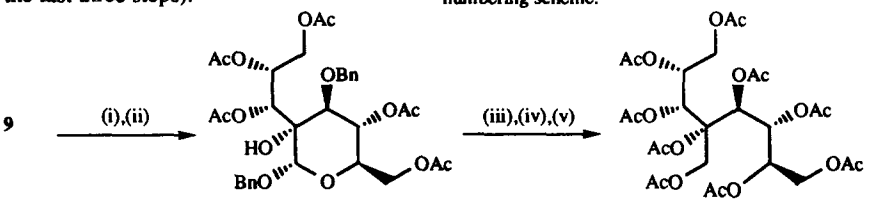


Figure X-Ray Structure of **9** showing crystallographic numbering scheme.



10 **11**

Scheme 2. Reagents: (i) TFA, H_2O, room temp.; (ii) Ac_2O, pyridine, room temp., 97% over two steps; (iii) H_2, Pd black, EtOH, room temp.; (iv) $NaBH_4$, EtOH, room temp.; (v) Ac_2O, pyridine, DMAP, room temp., 46% over two steps.

Comparison of the ^{13}C nmr skeletal chemical shifts of **11** with those given for the nonacetate of calditol **2** revealed several significant discrepancies (Table 2). For the synthetic isomer **11** all triplet carbons are found around 62 ppm (cf. all hexitol peracetates, Table 1), and all doublets between 68.7 and 71.5 ppm. Of particular note in the spectrum of **2** are the low field triplet at 70.0 ppm (assigned as C-1, which has the same chemical shift as C-2) and the two low field doublets (85.4 ppm assigned as C-3, and 80.3 ppm assigned as C-5). Also notable is the lack of multiplicity for the signal at 72.9 ppm (assigned to C-7).

Table 2. Comparison of ^{13}C nmr data (with multiplicities) of calditol peracetate **2** and synthetic nonacetate **11**

Carbon Atom / Compound	1	2	3	4	5	6	7	8	9
Calditol nonacetate **2**	70.0(t)	70.0(d)	85.4(d)	87.11(s)	80.3(d)[a]	73.1(d)[a]	72.9[a]	62.4(t)	58.8(t)
Synthetic isomer **11**[a]	61.88(t)	68.69(d)	69.00(d)	83.92(s)	69.23(d)	70.55(d)	71.50(d)	62.08(t)	62.58(t)

(a) These signals are not unequivocally assigned.

We feel that these discrepencies clearly invalidate the structural assignment of the peracetate of calditol as **2**. Comparison of ^1H nmr spectra of synthetic isomers[13] of structure **2** with those of the natural product is not particularly rewarding and does not reveal immediate structural discrepancies between the synthetic and natural materials.

Conclusion : This work firstly demonstrates that the structure of calditol originally proposed by De Rosa *et al.* is undoubtedly erroneous and that a reinvestigation is required to elucidate the correct structure of the natural product and secondly that the sequence of aldol condensation, Tebbe methylenation and hydroboration[14] can provide a facile and stereoselective route to higher carbon sugars. After this work was completed it came to our notice that two research groups have indeed recently proposed revised cyclopentane structures for calditol.[15]

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References and Notes.

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2. De Rosa, M.; De Rosa, S.; Gambacorta, A.; Bu'Lock, J.D. *Phytochemistry*, **1980**, *19*, 249-254.

3. Angyal, S.J.; Le Fur, R. *Carbohydr. Res.*, **1980**, *84*, 201-209; Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.*, **1983**, *41*, 27-66.

4. The starting ketone **5** was prepared via PCC oxidation (PCC, 4Å molecular sieves, CH_2Cl_2, room temp.) from the known benzyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (Lipták, A.; Imre, J.; Harangi, J.; Nánási, P. *Carbohydr. Res.*, **1983**, *116*, 217-225) in 96% yield. Selected data for **5**: white crystalline solid, m.p. 115-117°C (ethyl acetate/cyclohexane); $[\alpha]_D^{20}$ +42 (*c*, 1.15 in $CHCl_3$); δ_C ($CDCl_3$) 68.8, 70.6, 73.7 (3 x t, C-6, 2 x $\underline{C}H_2Ph$), 63.6, 81.0, 82.5 (3 x d, C-3, C-4, C-5), 100.3, 101.2 (2 x d, C-1, Ph$\underline{C}$H), 126.2, 127.9, 128.4, 128.5, 128.6, 128.8, 129.2 (7 x d, Ar), 136.1, 137.0, 137.6 (3 x s, Ar), 197.4 (s, C-2).

5. Untersteller, E. Thèse de Doctorat de l'Université Paris VI, December 1993; Untersteller, E.; Fairbanks, A.J.; Sinaÿ, P. *Carbohydr. Lett.*, in press.

6. Dioxolane **6** (Eb_{22Torr} 89°C) was easily prepared (76% yield) from glycolic acid and diethylketone, according to Greiner and Ortholand; Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.*, **1992**, *33*, 1897-1900.

7. Selected data for **7**: a white mousse; $[\alpha]_D^{20}$ +38 (*c*, 1.06 in $CHCl_3$); δ_C ($CDCl_3$) 7.3, 7.4 (2 x q, 2 x Me), 29.5, 30.2 (2 x t, 2 x Me$\underline{C}H_2$) 68.7, 70.0, 75.5 (3 x t, C-6, 2 x $\underline{C}H_2Ph$), 76.2 (s, C-2), 63.1, 74.3, 78.7, 81.4 (4 x d, C-3; C-4, C-5, C-7), 98.9, 101.1 (2 x d, C-1, Ph$\underline{C}$H), 114.7 (s, Et$_2\underline{C}$), 125.9, 127.3, 127.7, 128.0, 128.1, 128.4, 128.7 (7 x d, Ar), 136.1, 137.2, 138.4 (3 x s, Ar), 172.0 (s, C-8).

8. A small amount (5%) of isomeric material of as yet undefined stereochemistry and recovered starting material (20%) were also obtained.

9 Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.*, **1978**, *100*, 3611-3613.

10. Selected data for **9**: white crystalline solid, m.p. 87-89°C (CH_2Cl_2/cyclohexane); $[\alpha]_D^{20}$ +46 (*c*, 1.0 in $CHCl_3$); δ_C ($CDCl_3$) 8.6, 8.8 (2 x q, 2 x Me), 27.9, 29.7 (2 x t, 2 x Me$\underline{C}H_2$) 63.2, 69.0, 70.8, 76.0 (4 x t, C-6, C-9, 2 x $\underline{C}H_2Ph$), 76.8 (s, C-2), 63.2, 75.9, 79.0, 81.1, 81.4 (5 x d, C-3, C-4, C-5, C-7, C-8), 100.0, 101.4 (2 x d, C-1, Ph$\underline{C}$H), 110.5 (s, Et$_2\underline{C}$), 125.9, 127.8, 128.2, 128.2, 128.3, 128.6, 129.0 (7 x d, Ar), 136.4, 137.1, 137.8 (3 x s, Ar).

11. Selected X ray data for **9**: crystal system triclinic; Space Group P1; Z=1; two molecules ($C_{35}O_9H_{42}.C_6H_{12}$) in the asymmetric unit differing by phenyl group (C30 to C35) orientation; cell parameters: a=11.508(3), b=11.852(3), c=15.822(4), α=106.88(2), β=108.23(2), γ=91.48(2); radiation (Mo-Kα) λ=0.71069 Å; 403 variables for 1717 reflections; final R=0.069, R_W=0.072; Atomic coordinates have been deposited at the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK, and are available on request. Requests should be accompanied by a full citation for this paper.

12. Selected data for **10**: a white mousse; $[\alpha]_D^{20}$ +43 (*c*, 1.02 in $CHCl_3$); δ_C ($CDCl_3$) 20.5, 20.6, 20.7, 20.8, 21.0 (5 x q, 5 x Ac), 61.9, 62.7, 70.4, 76.0 (4 x t, C-6, C-9, 2 x $\underline{C}H_2Ph$), 76.7 (s, C-2), 68.0, 69.2, 71.3, 71.9, 81.0 (5 x d, C-3, C-4, C-5, C-7, C-8), 97.9 (d, C-1), 127.6, 127.7, 128.2, 128.4, 128.6 (5 x d, Ar), 136.3, 137.7 (2 x s, Ar), 169.2, 169.5, 170.3, 170.8, 171.0 (5 x s, 5 x Ac).

13. A total synthesis of two stereoisomers of calditol has been reported; Jeganathan, S.; Vogel, P. *Tetrahedron Lett.*, **1990**, *31*, 1717-20, but unfortunately the ^{13}nmr data of the peracetates of the synthetic isomers was not included.

14. Untersteller, E.; Xin, Y.C.; Sinaÿ, P. *Tetrahedron Lett.*, **1994**, *35*, 2537-2540.

15. The two differing cyclopentane structures have recently been proposed by D. Arigoni and O.W. Gräther (O.W. Gräther, Zur Struktur und Biosynthese der Tetraetherlipide der Archaea, Diss. ETH Nr. 10860, 1994, Zürich, Switzerland) and A. Sugai *et al.* (Sugai, A.; Sakuma, R.; Fukuda, I.; Kurosawa, N.; Itoh, Y.H.; Kori, K.; Ando, S.; Itoh, T. New Structure for nonitol of the ether lipid core of *Sulpholobus*, *International Workshop for Molecular Biology and Biotechnology of Extremophiles and Archaebacteria*, August 1-6, **1993**, 29-30, Wako, Japan; this later communication is quoted in Gambacorta, A.; Trincone, A.; Nicolaus, B.; Lama, L.; De Rosa, M. *System. Appl. Microbiol.*, **1994**, *16*, 518-527). These materials differ only in their stereochemistry at one centre.

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