Cyclohexane Epoxides − Chemistry and Biochemistry of (+)-Cyclophellitol

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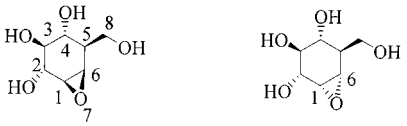
This account reviews the biochemistry and chemistry of cyclophellitol (**1**). Particular emphasis is given to the different synthetic approaches described for cyclophellitol and related analogues. Each reported synthesis has been critically evaluated and analyzed.

1. Introduction

In the course of our continuing and current program directed towards the development of new synthetic approaches for the preparation of carbocycles from sugars[1,2] we were particularly attracted to the cyclohexane epoxide type of molecules. These compounds belong to a growing family of molecules, the interesting biological and pharmacological properties of which have been the subject of some reviews[3,4] and an ongoing synthetic effort in different laboratories. Results obtained recently in this area have prompted us to update and review this subject. In this Microreview we will focus on the chemistry and biochemistry of (+)-cyclophellitol and analogues.

(+)-Cyclophellitol (**1**) {1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-(hydroxymethyl)-7-oxabicyclo[4.1.0]heptane-2,3,4-triol} (Figure 1) is a carbasugar analogue of D-glucopyranose, with an epoxide ring on the β-face of the molecule. This compound was isolated in 1990 by Umezawa and co-workers from the culture filtration of a mushroom, *Phellinus sp.*,[5] and was shown, as a sub-microgram inhibitor of β-glucosidase, to be a potential inhibitor of the human immunodeficiency virus (HIV) with possible metastatic therapeutic activity.[6] On the other hand, its unnatural diastereomer (1*R*,6*S*)-cyclophellitol (**2**) (Figure 1) is an inhibitor of α-glucosidase.[7]



1 **2**

Figure 1. Structure of (+)-cyclophellitol (**1**) and (+)-1,6-*epi*-cyclophellitol (**2**)

The unique structure and attractive biological properties of **1** have prompted steady interest in it and related molecules. As a result, several syntheses of **1**, **2**, and analogues, both in their enantiomerically pure forms and as racemic mixtures, have been described. For the synthesis of enantiomerically pure compounds, two strategies have been employed: (a) the use of the "chiral pool" of commercially available molecules, in the form of sugars or chiral inositols, and (b) conventional asymmetric synthesis.

The first synthesis of (+)-cyclophellitol (**1**) was achieved by Tatsuta and co-workers[8,9] in 1990, using the intramolecular 1,3-dipolar cycloaddition (1,3-DC) of an unsaturated nitrile oxide derived from L-glucose as the methodology for carbocycle formation. Three years later, Fraser-Reid and McDevitt described a formal total synthesis of both compounds from D-glucal, a more readily available starting material.[10] In this case, a rather elaborate strategy was necessary, involving an intramolecular *6-exo-dig* free radical cyclization as the method of choice for carbocycle formation; this approach demonstrated the potential of free radical chemistry for the synthesis of complex carbocycles. In the same year, Sato and co-workers[11] reported an elegant approach for the formation of the carbocycle; it was based on

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José Marco-Contelles studied chemistry at the Universidad Complutense de Madrid (UCM), where he obtained his PhD under Professor Benjamin Rodriguez (Institute of Organic Chemistry, Consejo Superior de Investigaciones Cientificas, CSIC) in 1984. After two years working as a post-doctoral fellow under Dr. H.-P. Husson (Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France) (CNRS methods) (1984−1985), he worked as an associate researcher under Professor Wolfgang Oppolzer (Département de Chimie Organique, Université de Geneve, Suisse) (aldol reaction) (1986) and was a visiting Professor at the Department of Chemistry, Duke University, North Carolina, working with Professor B. Fraser-Reid (free-radical chemistry; annulated sugars; formal total synthesis of phyllanthocin) (1988−1989). In 1986 he was appointed as Associate Researcher, and in 1992 he was promoted to Research Scientist in the CSIC. His present interests include the development of new synthetic methodologies in free-radical chemistry, carbohydrate chemistry, and Pauson−Khand reactions in sugar templates. He is also very active in asymmetric synthesis (Michael reaction) and biological evaluation of heterocyclic systems (CSIC reaction, tacrine analogues, and 2-amino-4H-pyrans). He was visiting Professor at the Université Pierre et Marie Curie, Paris VI (June 2000).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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a Ferrier-II reaction on D-glucose derivatives. The Ferrier-II reaction was also subsequently used as the methodology for carbocycle synthesis by other authors, such as Jung et al.[12] (on D-mannose derivatives in 1995), and, as regards D-glucose derivatives, Uzan and co-workers[13] in 1997 [in retrospect and in view of some results reported later by Ziegler et al. (see ref.[15,16]), the synthesis of some of the derivatives described by this group constitutes a formal total synthesis of compound **1**], and Ikegami et al.[14] in 1998. Also in 1998, Ziegler and Wang[15,16] reported the synthesis of cyclophellitol (**1**) by ring-closing metathesis (RCM) on D-xylose derivatives.

In addition to carbohydrates, inositols have also been a convenient source of chirality and structural/functional groups for the synthesis of cyclophellitol (**1**). In fact, one of the earliest syntheses of this molecule was reported by Ozaki and co-workers[17,18] from L-quebrachitol. In 1993, in a series of dense papers, Shing and Tai[19−21] successfully investigated the viability of (−)-quinic acid as starting material for these ventures. Finally, Trost and Hembre[22] very recently reported the synthesis of cyclophellitol (**1**) by asymmetric kinetic resolution of racemic conduritol B.

Synthetic efforts towards the same goal, but using classical asymmetric synthesis, have been rather sporadic. In 1995, Schlessinger and Bergstrom described a sophisticated approach[23] using the asymmetric Diels−Alder reaction between furans derivatized with chiral auxiliaries and allenes.

Lastly, Vogel and Moritz in 1992[24a] and Plumet−Arjona et al. in 1996[25,26] reported the synthesis of the cyclophellitols in racemic form, from 7-oxanorbornanone derivatives. However, it should be emphasized that these methods can easily be adapted for the synthesis of the enantiomerically pure products.[24]

This review focuses on the synthesis of cyclophellitol (**1**) in a critical and chronological order, beginning with analyses of the syntheses of the enantiomerically pure molecules by the "chiral pool" methodology, starting from sugars and inositols, and then by asymmetric synthesis with chiral auxiliaries. Finally, this analysis ends with the reported racemic synthesis.

Since most of the synthetic approaches thus far reported gave not only the natural isomer, but also, with the aid of slight strategic modifications, the unnatural 1,6-*epi* isomer, and because interesting cyclophellitol analogues have also been prepared in some cases, the reader is directed to the original papers for complementary and additional details.

2. Biochemistry of Cyclophellitols

The structure of (+)-cyclophellitol (**1**) was ascertained by means of full spectroscopic and X-ray crystallographic analysis. These data show that this molecule is a unique cyclitol incorporating an epoxide moiety, while the configuration of the hydroxy groups is closely related to that in nojirimycin.[27]

Subsequent biological studies showed that **1** inhibits almond β-glucosidase activity by 50% at 0.8 μg/mL and is a competitive inhibitor of almond β-glucosidase as determined by Lineweaver−Burck plot. This value is lower than the IC_{50} of 1-deoxynojirimycin (30 μg/mL) and of castanospermine (12 μg/mL). Cyclophellitol (**1**) is inactive against yeast α-glucosidase, β-glucosidase, β-glucuronidase, α-L-fucosidase, and β-*N*-acetylglucosamidase, α-mannosidase, and cellulase. Almond β-glucosidase treated with cyclophellitol (**1**) was equally suppressed after dialysis; thus it is likely that **1** binds almond β-glucosidase irreversibly. The inhibitor was found by fluorimetric assay to be active against β-glucosidase but inactive toward α-glucosidase in the Molt-4 microsomal fraction. It also inhibited Molt-4 β-glucocerebrosidase completely at 2 μg/mL when the enzyme was assayed with a synthetic labelled substrate, and the inhibitory activity was more than one hundred times greater than that of nojirimycin, castanospermine, or of deoxynorimycin. Mice administered 1 mg of cyclophellitol (**1**) daily for 5 d began to exhibit severe nervous system abnormalities similar to those found in Gaucher's mouse.[6] Cyclophellitol (**1**) shows no antimicrobial activity, and no cytotoxicity on NIH3T3 cells, Molt-4 cells, and P288 cells at 100 μg/mL.[5] Cyclophellitol (**1**) is a specific inhibitor of β-glucosidase but, unlike castanospermine, does not inhibit experimental metastasis. However, its structural analogue, 1,6-*epi*-cyclophellitol (**2**), inhibited both α-glucosidase and β-glucosidase, and also inhibited experimental metastasis. Compound **2** depressed α-glucosidase activity in cultured B16/F10 cells after 48 h of incubation. Preincubation of B16/F10 cells with **2** for 48 h inhibited invasion of the cells in a Boyden chamber assay at the doses effective in inhibiting α-glucosidase in situ. Pulmonary metastasis of B16/f10 cells in mice was inhibited by pretreatment of the cells with **2** in culture. The inhibitor reduced the collagen type I and IV mediated attachment of the cells, whereas it had no effect on laminin-mediated attachment. These results suggest that α-glucosidase in tumor cells is essential for the metastatic process, through cellular interaction with collagen types I and IV.[28]

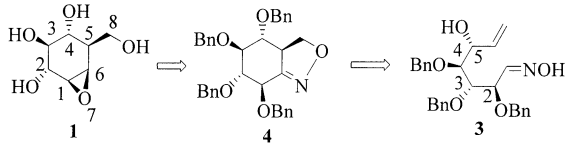
3. Chemistry of (+)-Cyclophellitol

(A) Synthesis of Enantiomerically Pure Compounds

(A1) From Sugars

(A1−1) Tatsuta's Approach

In a preliminary communication published in 1990[8] and a full paper in 1991,[9] Tatsuta et al. described the first total asymmetric synthesis of (+)-cyclophellitol (**1**). Tatsuta's strategy is shown in Scheme 1.



1 **4** **3**

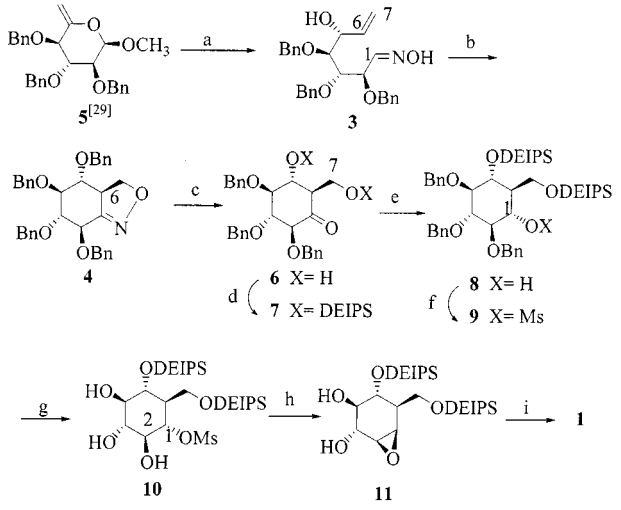
Scheme 1. Tatsuta's approach to the synthesis of **1**

Retrosynthetic analysis of compound **1** suggests:

1. The stereochemistry at carbon atoms C-1/C-4 in the natural product correlates with the stereochemistry at carbon atoms C-2/C-5 in the selected precursor, L-glucose. This is an expensive (Aldrich: 60 $ per 1 g; compare with D-glucose: 13 $ per 500 g) and not readily commercially available starting material.

2. An intramolecular 1,3-DC reaction between an olefin situated at carbon atoms C-6 and C-7 (sugar numbering) and a nitrile oxide at C-1, obtained in situ by oxidation of the corresponding oxime **3**. This process should afford the carbocycle **4**, ideally functionalized for further transformations leading to the final product **1** (Scheme 1).

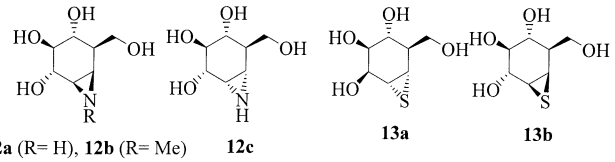
Some of the important intermediates of this successful synthesis are shown in Scheme 2.



Scheme 2. Tatsuta's approach to the synthesis of compound **1**; transformation of intermediate **3**;[8,9] reagents: (a) i. dicyclohexylborane, THF, then H_2O_2, NaOH (85%); ii. Swern + Wittig (75%); iii. HCl, aq. dioxane, then hydroxylamine hydrochloride, py (80%); (b) NaOCl, CH_2Cl_2, 25 °C (70%); (c) H_2, Raney Ni-W_4, AcOH, aq. dioxane (80%); (d) diethylisopropylsilyl triflate (DEIPSOTf), 2,6-lutidine, (90%); (e) $Me_2S{\cdot}BH_3$/THF (60%); (f) MsCl, py (75%); (g) H_2, $Pd(OH)_2$, MeOH; (h) MeONa, CH_2Cl_2, 0 °C; (i) nBu$_4$NF, THF (40% from **10**)

Fortunately, the carbocyclization step proceeds stereoselectively, giving only one single compound **4**, in which the configuration at the newly formed stereocenter C-6 was correct for the synthesis of compound **1**. This could be demonstrated by NMR analysis of the intermediates **4**−**11** leading to cyclophellitol (**1**) and by the synthesis itself of this molecule. The authors claim that this high diastereoselectivity can be explained by a "*syn periplanar steric interaction between the nitrile oxide and α-benzyloxy group in this transition state.*"[8] On reduction of the oxo group in compound **7**, the major isomer **8**, with the correct configuration at C-1, was obtained together with the undesired β-alcohol (20% yield; this compound was recycled by reoxidation and fresh reduction). No justification was provided for this stereochemical result. After some standard manipulations, the epoxide was formed by base-mediated treatment of mesylate **10**, at the desired position and with the required absolute configuration. Compound **10** was obtained after mesylation and hydrogenolysis of alcohol **8**.

In summary, the synthesis of **1** from intermediate **3** took place over 8 steps and with an 8% overall yield. Compound **3** was obtained from *xylo*-hex-5-enopyranoside **5** (Scheme 2) in 4 steps (54% yield). Thus, the described procedure for the synthesis of (+)-cyclophellitol (**1**) took place over 12 steps and in 4% overall yield from intermediate **5**. This compound was prepared from L-glucose as described.[29] In subsequent papers, the enantiospecific synthesis of (+)-1,6-*epi*-cyclophellitol (**2**)[7] and analogues **12** and **13**[30,31] (Figure 2) were also described by this group.



12a (R= H), **12b** (R= Me) **12c** **13a** **13b**

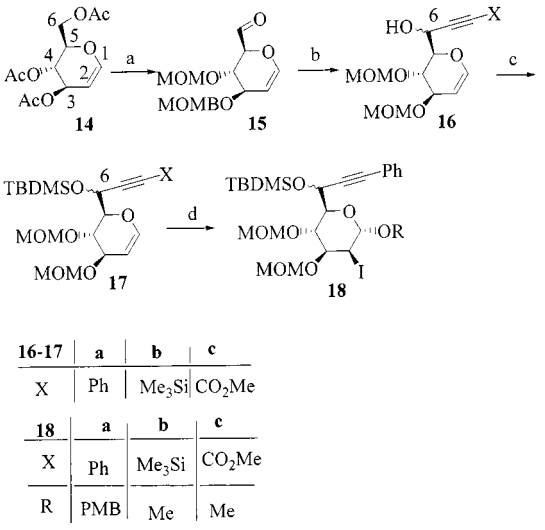
Figure 2. Structure of cyclophellitol analogues **12** and **13**

In conclusion, Tatsuta's approach to (+)-cyclophellitol (**1**) can be summarized as follows. Full experimental data were provided, an efficient and stereocontrolled intramolecular 1,3-DC cycloaddition reaction of an unsaturated nitrile oxide was the method for the assembly of the carbocycle ring, high stereochemical retention was observed on going from the starting material to the target molecule, and a poor overall yield was obtained, with a relatively long synthetic scheme. However, these authors were pioneers in these synthetic ventures and paved the way for other alternative approaches.

(A1−2) Fraser-Reid's Approach

In 1989, in the context of an ambitious project directed towards the development of free radical based methods for the synthesis of carbocycle-containing natural products such as cyclophellitol (**1**), one of the first examples of a 6-*exo-dig* free radical cyclization in sugar derivatives was carried out.[32,33] Scheme 3 shows the transformations that were performed. Some trivial manipulations on 3,4,6-tri-*O*-acetyl-D-glucal (**14**) starting material produced aldehyde **15** in good yield and multigram quantities. This unstable material was immediately transformed into compound **16a** by treatment with lithium phenylacetylide; silylation and stereospecific glycosylation under Thiem conditions[34] then afforded compound **18a** as a mixture of isomers (in 1.2:1 ratio) at C-6. These were impossible to separate and were converted together (see below). Similar treatment of **14** with lithium trimethylsilylacetylide (to give **16b**) or lithium methyl propiolate (to give **16c**) and identical further treatment afforded compounds **18b** and **18c**, respectively (Scheme 3).

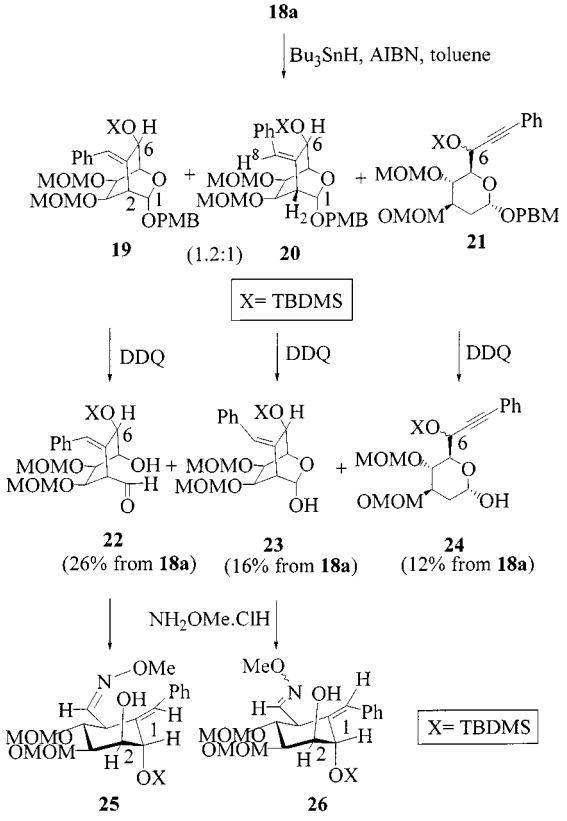
With these radical precursors in hand, the free radical cyclization was performed. Unfortunately, products **18b** and **18c** only gave complex reaction mixtures which could not be elaborated further. Conversely, the mixture of isomers **18a** (see above) gave a mixture of compounds **19** and **20** (the ratio **19**/**20** was found to be 1.2:1) and **21** (Scheme 4). Products **19** and **20** were the expected 6-*exo-dig* cyclization derivatives, and compound **21** was the reduced, non-cy-



16-17	a	b	c
X	Ph	Me_3Si	CO_2Me

18	a	b	c
X	Ph	Me_3Si	CO_2Me
R	PMB	Me	Me

Scheme 3. Synthesis of radical precursor **18** from 3,4,6-tri-*O*-acetyl-D-glucal (**14**);[32] reagents: (a) i. MeONa, MeOH, room temp. (99%); ii. ClSi*t*BuMe$_2$, imidazole, THF, room temp. (80%); iii. ClCH$_2$OCH$_3$, *i*Pr$_2$EtN, CH$_2$Cl$_2$, room temp. (72%); iv. *n*Bu$_4$NF, THF, room temp. (90%); v. PCC, CH$_2$Cl$_2$, NaOAc, room temp. (56%); (b) i. phenylacetylene, *n*BuLi, 0 °C (X = Ph; **16a**: 70%); ii. trimethylsilylacetylene, *n*BuLi, 0 °C (X = SiMe$_3$; **16b**: 80%); iii. methyl propiolate, LDA, 0 °C (X = CO$_2$Me; **16c**: 36%); (c) ClSi*t*-BuMe$_2$, imidazole, THF, room temp. (X = Ph, **17a**: 96%; X = SiMe$_3$, **17b**: 87%; X = CO$_2$Me, **17c**: 45%); (d) i. NIS, *p*-methoxybenzyl alcohol, acetonitrile (X = Ph, R = PBM; **18a**: 96%); ii. NIS, methyl alcohol, acetonitrile (X = SiMe$_3$, R = Me; **18b**: 80%, X = CO$_2$Me, R = Me; **18c**: 85%)



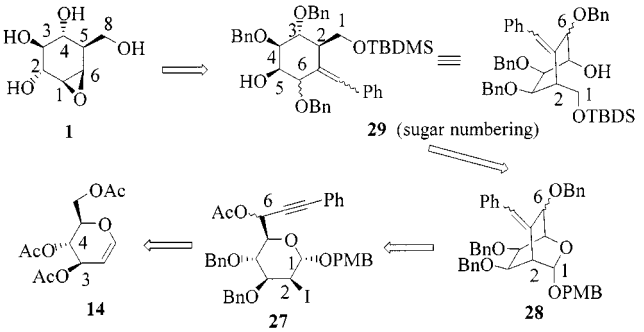
Scheme 4. Free-radical cyclization of compound **18a** and transformation of intermediates **19**−**21** obtained from 3,4,6-tri-*O*-acetyl-D-glucal **14**

clized material. In the ^{1}H NMR spectrum of carbocycle **20**, an NOE was detected between 8-H and 2-H, allowing the geometry of the double bond to be assigned as (*Z*), and thus that in isomer **19** as (*E*). In order to have pure samples and to isolate strictly "open" carbocycles, the hydrolysis of the glycoside was examined, using DDQ as reagent. In this way, pure compounds **22**, **23**, and **24** (as a mixture of isomers at C-6 in a *de* of 90%) were isolated and characterized. Further treatment of adducts **22** and **23** with *O*-methyl hydroxylamine hydrochloride produced derivatives **25** [only the (*Z*)-oxime ether isomer was detected and isolated] and **26** [isolated as a mixture of (*E*) and (*Z*) isomers in 1:1 ratio], each in 50% yield. ^{1}H NMR analysis of both substrates showed a small coupling constant for 1-H/2-H (4.1 Hz and 3.1 Hz, respectively), values typical of H_{eq}/H_{eq}, confirming that the stereochemistry at C-6 is (*S*) in both compounds. In summary, from these results it was concluded that during the cyclization step (Scheme 4) the C-6 (*S*) isomer in precursor **18a** preferentially gave products **19** and **20**, while the C-6 (*R*) isomer in precursor **18a** preferentially gave the reduced non-cyclized material **21**.

The above results[32] effectively facilitated a new synthetic approach to the cyclophellitols some years later.[10] In this report a formal total asymmetric synthesis of **1** and **2** starting from D-glucal was communicated.

The retrosynthetic analysis is shown in Scheme 5. The configurations at C-3 and C-4 in cyclophellitol (**1**) correlate well with the absolute configurations at C-4 and C-3, respectively, in 3,4,6-tri-*O*-acetyl-D-glucal (**14**), the starting material. The key step is also a similar 6-*exo*-*dig* free radical cyclization[33] of a radical at C-2 over a triple bond introduced at C-6 in compound **27** (compare with intermediate **18a** in Scheme 3).[32] Note that the protecting groups at C-3/C-4 and at C-6 have been changed, from MOM (= methoxymethyl ether) and TBDMS (= *tert*-butyldimethylsilyl ether), respectively, to benzyl and acetyl groups at similar positions. Conversely, the only useful free radical acceptor, the phenylacetylene moiety, and the PMB (= *p*-methoxybenzyl) group as the *O*-glycoside at C-1, as previously described (see above), were investigated directly. Cyclization, presumably yielding product **28**, followed by standard manipulation, should afford compound **29**. Note that a mixture of isomers at C-6 (sugar numbering) should be possible; after separation, one group could be applied towards the synthesis of cyclophellitol (**1**) and the other to 1,6-*epi*-cyclophellitol (**2**). In both cases the stereochemistry at C-5 in intermediate **29** is not the correct one, and a technique for inversion of the stereochemistry would have to be devised.

The more relevant steps of this synthetic sequence are outlined in Scheme 6. After oxidation of compound **30**,[35] addition of lithium phenylacetylide and acetylation afforded a mixture of C-6 isomers **31** in 82% overall yield. Glycosylation (92% yield) and free radical cyclization (100% yield), deacetylation, and benzylation afforded compounds **28** and **32** (ratio 4:1). This mixture was treated with DDQ (95% yield), then reduced and silylated to afford compound **29**. This material was separated into fraction **29a** (C-



Scheme 5. Fraser-Reid's approach to the synthesis of **1** from 3,4,6-tri-*O*-acetyl-D-glucal (**14**)

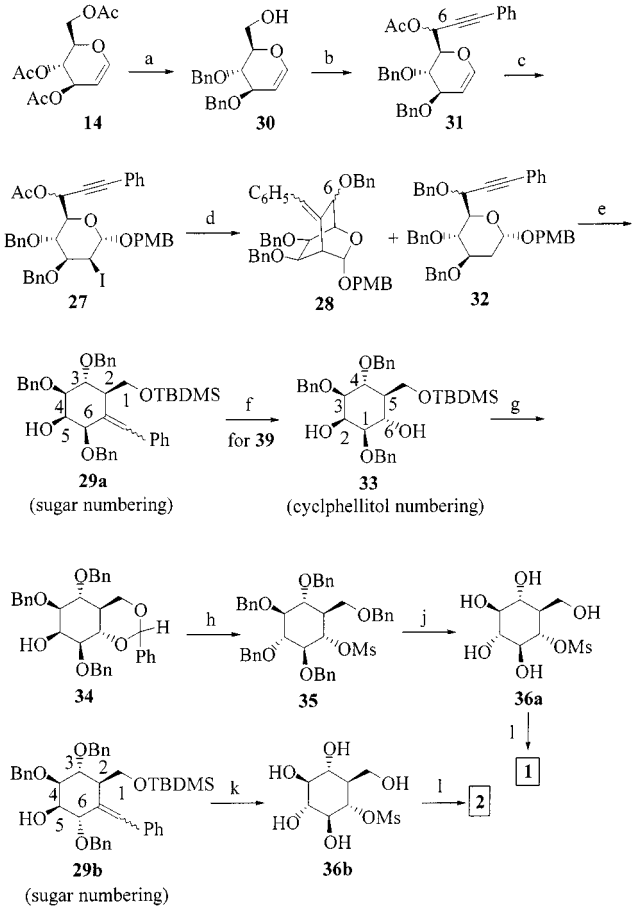
6*R*) and fraction **29b** (C-6*S*). Fraction **29a** (C-6*R*) (isolated as a mixture of double-bond isomers) was transformed into Tatsuta's intermediate **36a**,[9] thus establishing a formal total synthesis of cyclophellitol (**1**), in 21 steps from glucal **30**. Following a similar protocol, fraction **29b** (C-6*S*) (isolated as a mixture of double bond isomers) was converted into Tatsuta's intermediate **36b**,[9] establishing a formal total synthesis of 1,6-*epi*-cyclophellitol (**2**).

(A1−3) Sato's Approach

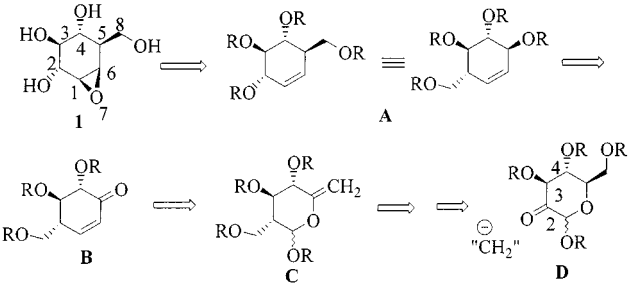
In a 1994 preliminary communication, Sato and coworkers reported a new synthesis of **1** from D-glucose.[11] Scheme 7 outlines the retrosynthesis. As shown, the configurations at C-3 and C-4 in D-glucose are retained and incorporated into (+)-cyclophellitol (**1**) as the configurations at C-4 and C-3, respectively. In contrast, the stereochemistry at C-2 and C-5 is sacrificed in order to build up other functional groups later. The CH_2OH branch (C-8) is introduced at C-2 by means of an anionic "CH_2" synthon-mediated nucleophilic attack on a ketone at C-2 (sugar numbering) in a derivative of type **A**, followed by deoxygenation, and the carbocycle is obtained using the Ferrier II reaction[36] with a convenient D-glucose derivative **B**.

The more relevant intermediates are summarized in Scheme 8. Compound **37** (obtained in five steps from D-glucose), when treated with lithium dichloromethylenide, gave a tertiary alcohol with a dichloromethylene branched chain at C-2. This, after treatment with sodium borohydride in DMSO and acetylation, afforded the deoxygenated compound **38**. The usual Hanessian−Hullar[37] and Ferrier[36] synthetic sequence for carbocyclization afforded compound **39**, which after regio- and stereoselective reduction from the α-face, gave an alcohol. This in turn, after silylation and ester hydrolysis, produced intermediate **40**. The primary hydroxy-directed epoxidation from the α-face again yielded one product, which, after acid hydrolysis, provided **1**. Note the high stereochemical control in the deoxygenation leading to compound **38**, and in the reduction of ketone **39**; the efficient epoxidation of triol **41** is also of interest.

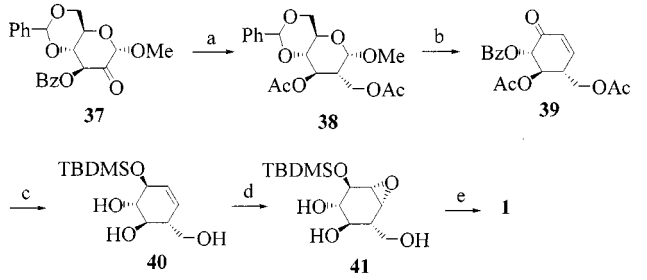
In summary, (+)-cyclophellitol (**1**) was obtained in 14 steps and 13% overall yield from intermediate **37**. No full experimental details have been further reported. It is important to note that this was the *first published* report in which the branch at C-8 (cyclophellitol numbering) was introduced at C-2 of a readily available sugar derivative. In addition, this report represents the first approach to the epoxidation step based on oxidation of a conveniently functionalized cyclohexene derivative. This is in contrast with other alternative strategies (as shown previously), in which an intramolecular substitution reaction has been used as the method for the epoxide ring formation. As shown later,



Scheme 6. Formal total synthesis of **1** and **2** according to Fraser-Reid; reagents: (a) ref.[35]; (b) i. Swern oxidation; ii. phenylacetylene, *n*BuLi; Ac_2O (82%); (c) NIS, *p*-methoxybenzyl alcohol (92%); (d) i. Bu_3SnH, AIBN, benzene (100%), ii. deacetylation; iii. benzylation; (e) i. DDQ (95%); ii. reduction; iii. silylation; (f) i. O_3; ii. $NaB(OAc)_3H$; (g) i. HCl; ii. $PhCH(OMe)_2$; (h) i. Dess−Martin, ii. $BH_3{\cdot}Me_2S$; iii. BnBr, iv. $NaCNBH_3$; v. HCl; vi. MsCl; (j) Pd/C, H_2 (63%); (k) i. Dess−Martin; ii. $NaBH_4$; iii. BnBr; iv. O_3; v. $Me_2S{\cdot}BH_3$; vi. H_2, Pd/C; (l) ref.[9]



Scheme 7. Sato's approach to the synthesis of **1** from D-glucose intermediates

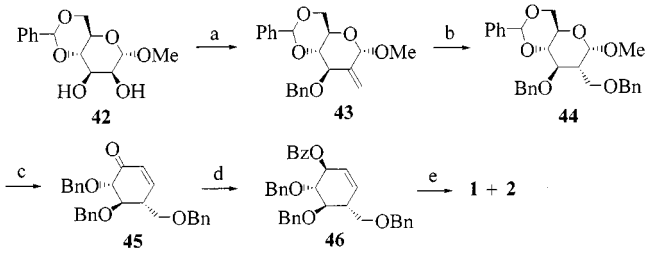


Scheme 8. Synthesis of **1** according to Sato and co-workers;[11] reagents: (a) i. LDA, CH_2Cl_2 (82%); ii. $NaBH_4$, DMSO (82%); iii. Ac_2O, py (100%); (b) i. NBS, $BaCO_3$; ii. NaI, acetone, then DBU (56% from 39); iii. $HgCl_2$, then MsCl, Et_3N (86%); (c) i. $NaBH_4$, $CeCl_3$ (67%); ii. TBDMCl, imidazole (94%); iii. KOH/EtOH (80%); (d) MCPBA (84%); (e) 70% AcOH/H_2O (100%)

other approaches have also used these strategies as analyzed by Sato (with some modifications).

(A1−4) Jung's Approach

In a 1995 preliminary communication, Jung et al. reported an asymmetric synthesis of **1** from D-mannose.[12] In this case the retrosynthetic analysis was conceptually similar to the Sato approach (see Scheme 7), but made use of D-mannose as the starting material. Consequently, the configurations at C-3 and C-4 in D-mannose are retained and incorporated into (+)-cyclophellitol (**1**) as the configurations at C-4 and C-3, respectively. Similarly, the carbocycle was obtained by using the Ferrier II reaction[36] and a convenient D-mannose derivative. The major difference was based on how the CH_2OH branch (C-8) (cyclophellitol numbering) could be introduced with the correct stereochemistry at C-2 (sugar numbering): A tedious, five-step procedure (Wittig reaction − hydroboration − oxidation − epimerization − reduction) was developed accordingly. Scheme 9 shows how these ideas have been implemented in practice. In this manner, compound **42** (obtained in two steps from D-mannose) was transformed, via **43**, into **44**. Here, the Hanessian−Hullar protocol[37] was replaced by a lithium aluminium hydride reduction of the benzylidene moiety,[38] followed by iodination of the primary alcohol; after elimination, the resulting enol ether was transformed in the usual manner to give the unsaturated ketone **45**.[36] Sodium borohydride reduction of this compound in the presence of cerium trichloride,[39] followed by protection, afforded compound **46**, which was submitted to epoxidation and deprotection to produce a mixture (no ratios reported) of **1** and **2**. In a footnote, Jung et al. refer to Shing's report[19] for this final transformation. Note, however, that Singh's full paper[20] reports that this transformation of product **46**, as shown in Scheme 9, has not been accomplished in this manner. As discussed later (see below), a series of transformations was carried out on product **46** in order to produce an independent and stereoselective synthesis of **1** and **2**. In addition, it is possible that inversion of the order of steps − epoxidation first, and then deprotection − would have been beneficial for the **1/2** ratio. After hydrogenolysis of compound **46**, a product similar to **40** (Sato's approach, Scheme 8) would have been obtained, epoxidation of which would probably have afforded compound **1** exclusively, cleanly, and stereoselectively.

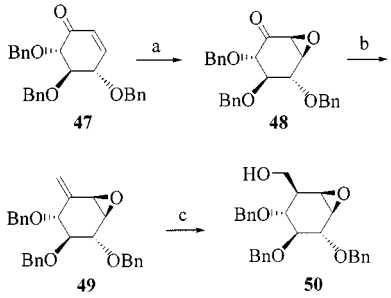


Scheme 9. Synthesis of **1** according to Jung et al.;[12] reagents: (a) i. Bu_2SnO, then BnBr (70%); ii. DMSO/TFAA, then $Ph_3P{=}CH_2$ (70%); (b) i. $Me_2S.BH_3$ (75%); ii. Swern (81%); iii. Et_3N (100%); iv. $NaBH_4$ (92%); v. NaH/BnBr (96%); (c) i. LAH (80%); ii. Ph_3P, I_2 (96%); iii. DBU (74%); iv. $HgCl_2$ (90%); v. MsCl, py (78%); (d) i. $NaBH_4$, $CeCl_3$ (93%); ii. BzCl, py 80%); (e) MCPBA, then K_2CO_3, then Pd/C, H_2 (63%)

In summary, the "cyclophellitols" were obtained in 19 steps and 5% overall yield from intermediate **42**. The final balance is favorable to Sato's approach[11] in view of the number of steps, overall chemical yield, and selectivity in the epoxidation step.

(A1−5) Uzan's Proposal

Uzan and co-workers have described the preparation of an advanced intermediate **50**, of potential utility for the synthesis of compound **1**[13] (Scheme 10).



Scheme 10. Synthesis of intermediate **50** according to Uzan et al.;[13] reagents: (a) *t*BuO_2H (72%); (b) Wittig (62%); (c) $NaBH_4$, $Et_2O{\cdot}BF_3$, H_2O_2, NaOH (55%)

The starting material was the readily available intermediate **47**,[40] obtained from methyl α-D-glucopyranoside in four steps and 32% yield after standard Ferrier II treatment of the appropriate derivative. Epoxidation of this material gave only the epoxide **48** in good yield. Note the convenient establishment of the cyclophellitol (**1**) C-1/C-4 and C-6 stereocenters and functionality in a short and simple synthetic scheme. The hydroboration of compound **49** afforded compound **50** in moderate yield. The configurations at the new stereocenters were assigned by a detailed ^1H NMR analysis. Hydrogenolysis of this product should yield **1**, but this transformation was not described and, very surprisingly, Uzan and co-workers refrained from performing one of the more simple and attractive possible approaches to this natural product. However, in view of Ziegler's results (see be-

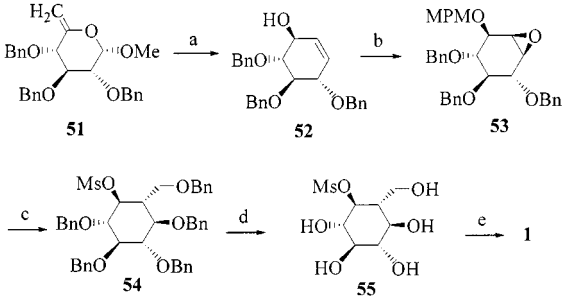
low, Scheme 13), the synthesis[15] of product **50** constitutes a formal total synthesis of compound **1**.

(A1−6) Ikegami's Approach

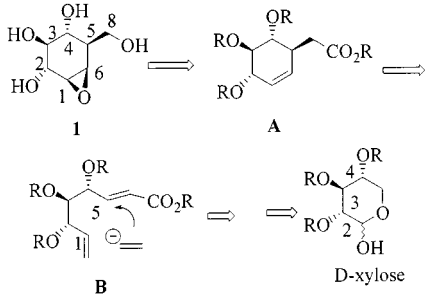
Ikegami and co-workers[14] have described (in preliminary form) a synthesis of cyclophellitol (**1**) from D-glucose. Their strategy also incorporates the concept advanced by Sato et al.[11] The hydroxymethyl group at C-8 was introduced by nucleophilic attack on a conduritol epoxide obtained after carbocycle formation by means of a Ferrier II reaction on a D-glucose derivative, reduction, and epoxidation. Some aspects of this approach are detailed in Scheme 11. The synthesis of epoxide **53** from sugar **51** via **52** was effected by means of some standard manipulations. The opening of the epoxide, at the correct carbon atom and with the desired stereoselectivity, to give **54** was the challenging task, and this was efficiently accomplished by using (lithiomethyl)dimesitylborane as the nucleophile, with the PMB group at the vicinal hydroxy group. As the authors suggest, these conditions proved optimal for a conformational change in the precursor that directed the nucleophilic attack to the desired position. The final steps of the synthesis to **55** and **1** are trivial. In summary, cyclophellitol (**1**) was obtained from intermediate **51** in 11 steps and 18% overall yield.

(A1−7) Ziegler's Approach

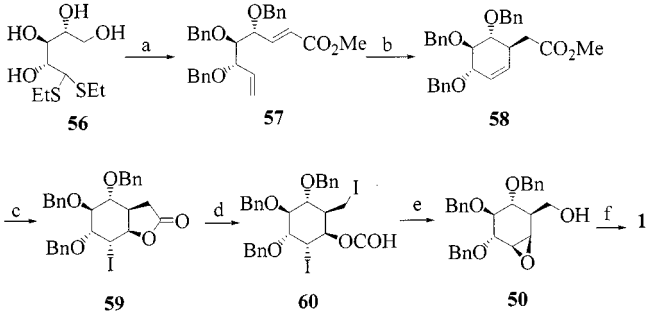
The last synthesis of cyclophellitol (**1**) from a sugar derivative is that reported by Ziegler and Wang.[15,16] Scheme 12 shows the key elements of this approach. The strategy for carbocycle formation was a metathesis[41] reaction, performed on D-xylose derivatives. Effectively, in this substrate the stereocenters at C-2/C-4 have the same absolute configuration as at the same carbon stereocenters in **1**. Compounds of type **A** could be prepared by metathesis reaction of intermediate **B**, which in turn could be obtained by simple one-carbon homologation at C-1, or by two-carbon elongation at C-5, in D-xylose intermediates.



Scheme 11. Synthesis of **1** according to Ikegami et al.;[14] reagents: (a) i. $PdCl_2$ (81%); ii. MsCl, Et_3N (74%); iii. $NaBH_4$, $CeCl_3$ (87%); (b) MCPBA (100%); ii. NaH/MPMCl (93%); (c) i. Mes_2BCH_2Li (78%); ii. NaH, BnBr (93%); iii. DDQ (96%); iv. MsCl, Et_3N (91%); (d) Pd/C, H_2 (63%); (e) NaOH (82%)



Scheme 12. Ziegler's approach to the synthesis of **1** from D-xylose



Scheme 13. Ziegler's approach to the synthesis of **1**;[15,16] reagents: (a) i. TBDMSCl, imidazole (90%); ii. NaH/BnBr (80%); iii. $HgCl_2$ (80%); iv. Tebbe's reagent (80%); v. TBAF (88%); vi. Swern, then Ph_3PCHCO_2Me (89%); (b) i. $(CH_2{=}CH)_2CuMgBr$ (90%); ii. Grubbs' catalyst (92%); (c) i. LiOH, then I_2 (92%); (d) i. DIBALH (85%); ii. $PhI(OAc)_2$ (78%); (e) i. KOH (76%); ii. Bu_3SnH, O_2 (70%); (f) $Pd(OH)_2/C$, H_2 (85%)

The synthesis started with the readily available D-xylose diethyl dithioacetal **56** (Scheme 13). After standard steps for protection (benzyl ethers), deprotection, and activation at C-1 and C-5, according to the planned strategy, product **57** was obtained in good yield. Michael addition to this substrate proved highly efficient, as only one diastereoisomer was detected and isolated; the configuration at the new stereocenter was not determined at this point, but follows from the known reactivity of similar substrates[42] under the same experimental conditions and from the final synthesis of compound **1**. The key metathesis reaction was observed to give carbocycle **58** in 92% yield. After formation of lactone **59**, setting up the leaving group for the final epoxide formation, the decarboxylation step was tested using Suárez's conditions.[43] Compound **60** resulted and was efficiently transformed, via intermediate **50** (Scheme 10), into compound **1**. In summary, this is a very elegant synthetic scheme (16 steps and 7% overall yield from compound **56**), which proves the power of metathesis reactions for ring formation and its application to natural product synthesis.

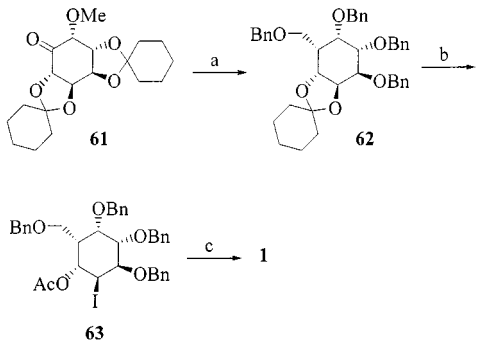
(A2) From Chiral Inositols

(A2−1) Ozaki's Approach

In 1991, this group published the first report of a cyclophellitol **1** synthesis using readily available inositols as start-

ing materials. In Ozaki's approach, L-quebrachitol was the selected product.[17,18] Note that in these approaches, and in contrast with the strictly "open sugar" strategies described above, the carbocycle is already present in the starting material, with some of the correct absolute configurations at the different carbon atoms. In L-quebrachitol, this is the case for carbon atoms C-2, C-3, C-4, and C-6 (cyclophellitol numbering) (Figure 3). The only synthetic operations to perform consist of: (a) introduction of the branch at C-5 with the correct stereochemistry, (b) adjustment of the functionality at C-1 for epoxide ring formation, and (c) deprotection of the methyl ether.

Scheme 14 presents the essential features of this synthetic venture. Compound **61** (readily available from L-quebrachitol in two steps) was submitted to Peterson olefination and hydroboration. A mixture of the desired branched-chain inositol and the undesired one resulted in a 1:1 ratio. This is the essential limitation in this scheme. After benzoylation, selective deprotection of the cyclohexylidene group with simultaneous unblocking of the methyl ether, followed by perbenzylation, afforded compound **62**. The final steps, through **63**, were devoted to the formation of the epoxide with the correct stereochemistry, and to deprotection.



Scheme 14. Ozaki's approach to the synthesis of **1**;[17,18] reagents: (a) i. Me_3SiCH_2MgCl, then KH (58%); ii. BH_3, then H_2O_2/NaOH, then BzCl (34%); iii. $AlCl_3$, nBu$_4$NI (63%); iv. NaH/BnBr (85%); (b) i. CF_3CO_2H/MeOH (90%); ii. Tf_2O, py (98%); iii. Ac_2O, py (95%); iv. nBu$_4$NI (96%); (c) i. NaOMe/MeOH (93%); ii. H_2, Pd/C (100%)

In summary, this constitutes an early synthesis of (+)-**1** from L-quebrachitol (Aldrich: 57 $ per 100 mg!), over 11 steps and with 9% overall yield, from compound **61**. Note that the introduction of the branched hydroxymethylene group by means of hydroboration of an *exo*-methylene group was used some years later by Jung et al.[12] in their approach to cyclophellitol (**1**), but in this case the authors

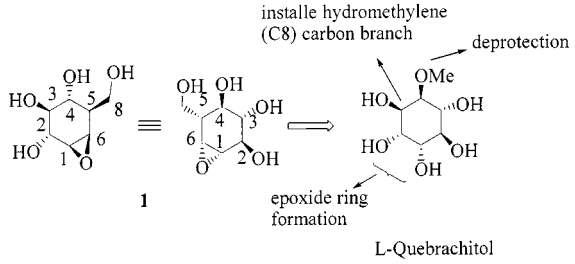
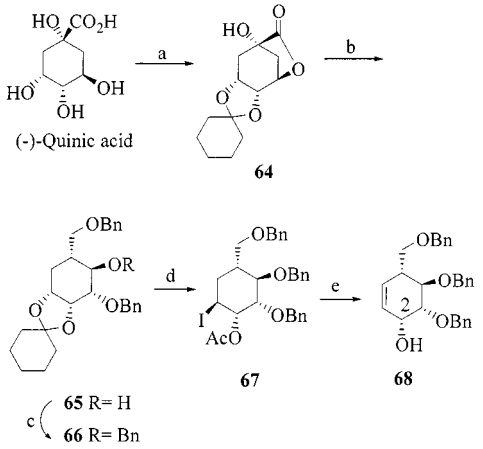


Figure 3. Stereochemical correlation of L-quebrachitol with **1**

did not use the oxidation and epimerization methodology to improve the ratio of diastereomers.

(A2−2) Shing's Approach

In the framework of a systematic analysis of the possibilities of (−)-quinic acid in the synthesis of carbocyclic, poly-



Scheme 15. Synthesis of precursor **68** from (−)-quinic acid (Shing et al.);[18−21] reagents: (a) i. cyclohexanone, H_2SO_4 (83%); (b) ref.[44]; (c) NaH, BnBr (82%); (d) i. CF_3CO_2H (90%); ii. $SOCl_2$, then $NaIO_4$, $RuCl_3$ (89%); iii. nBu$_4$NI (83%); iv. Ac_2O, py (95%); (e) i. DBU (83%); ii. MeONa/MeOH (95%)

functionalized natural products, Shing and co-workers exploited this commercially available product (Aldrich: 81 $ per 100 g) for the synthesis of **1**, **2**, and some cyclophellitol analogues.[19−21] The key intermediates of this approach are shown in Scheme 15.

The synthesis of compound **65** from lactone **64** had been described by Shing et al. in a previous work.[44] The subsequent steps (**64** to **68**) are trivial. Note that the configuration at C-2 (cyclophellitol numbering) in compound **68** has to be inverted. The Mitsunobu inversion afforded compound **46** (Scheme 9), a compound that Jung et al. prepared from D-mannose one year later,[12] and transformed according to Shing's analysis. In fact, the epoxidation of compound **46** afforded a mixture of epoxides **69** and **70** (Figure 4) in 66% yield and 3:7 ratio. Obviously, the benzoate-directed epoxidation was unsatisfactory, and a method for a more stereoselective synthesis of **1** was necessary. Basic hydrolysis of intermediate **46** and subsequent silylation gave compound **71**, epoxidation of which provided epoxides **72** and **73**, in 61:39 ratio and 72% yield (Scheme 16). After separation, intermediate **72** was submitted to desilylation and hydrogenolysis to afford product **1**.

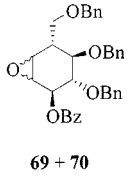
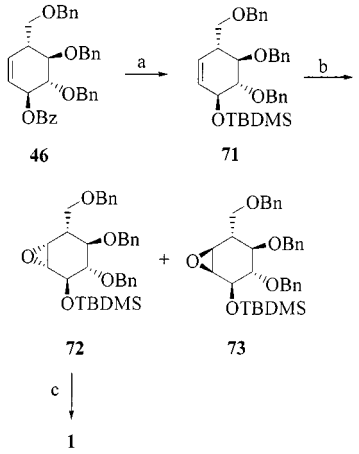


Figure 4. Epoxidation products from intermediate **46**

In summary, this amounts to 11 steps and 11% overall yield from intermediate **65**, readily available from (−)-



Scheme 16. Final steps of the synthesis of **1** according to Shing et al.; reagents: (a) i. MeONa/MeOH (94%); ii. TBDMSCl, imidazole (91%); (b) MCPBA (72%); (c) i. nBu$_4$NF (94%); ii. H_2, Pd/C (93%)

quinic acid in six steps. The limitation was the necessary, time-consuming methodology for inversion − protection − deprotection − epoxidation at C-2 (OH) in product **68** (Scheme 15).

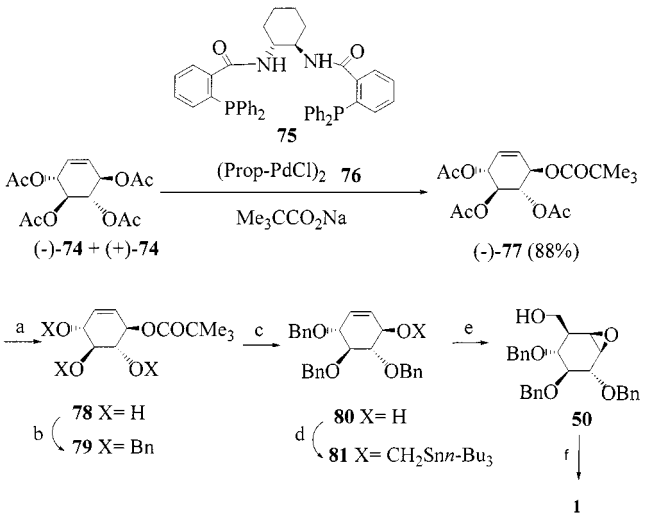
(A2−3) Trost's Approach

The last reported synthesis of cyclophellitol (**1**) has been described in preliminary form by Trost et al.,[22] who used the asymmetric kinetic resolution of racemic conduritol B as their key element. As shown in Scheme 17, treatment of racemic conduritol B tetracetate (**74**) with sodium pivalate in the presence of catalytic amounts of phosphane **75** and Pd reagent **76** gave (−)-conduritol (−)-**77** in 88% yield. A series of trivial steps through **78**−**80** afforded intermediate **81**. The lithium-mediated carbanionic 2,3-sigmatropic rearrangement of this material put the hydroxymethyl group in place; after sequential epoxidation and deprotection, product **50** was obtained. This compound had been described before by Uzan et al.[13] (Scheme 10) and by Ziegler et al. (Scheme 13).[15] The hydrogenolysis of product **50** by Ziegler's method gave **1** in a very straightforward way. In total, starting from racemic **74**, this amounts to 8 steps and 23% overall chemical yield.

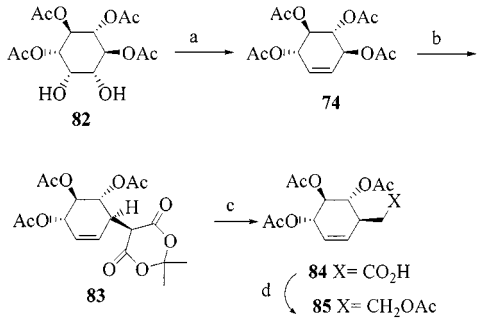
In this context, it is appropriate to comment on the results reported by Barton et al. (see Scheme 18).[45] The palladium-catalyzed alkylation of racemic conduritol B (**74**), prepared from **82**, with Meldum's acid afforded the branched-chain cyclitol **83**. After acidic hydrolysis to **84**, decarboxylation, and free-radical decarboxylation, followed by acetylation, this gave compound **85**, a potential useful precursor for total racemic synthesis of compound **1**. Unfortunately, neither full experimental details for these transformations, nor the synthesis of *rac*-**1** according to this interesting strategy have been published.

(A3) By Asymmetric Synthesis

The Schlessinger approach,[23] using an asymmetric Diels−Alder reaction between chiral furans and allenes, has until now been the only reported preparation of enantio-

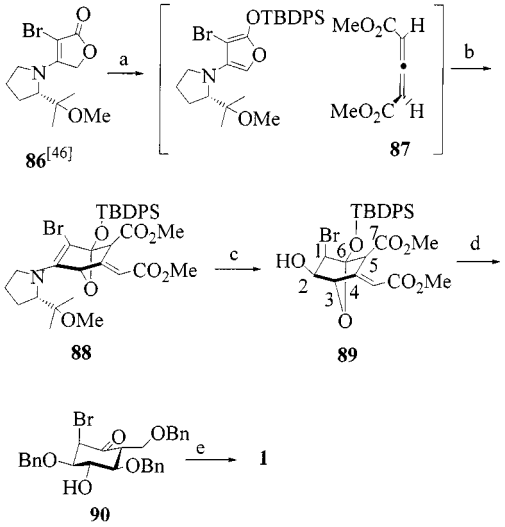


Scheme 17. Synthesis of **1** according to Trost et al.;[22] reagents: (a) NH_4OH/MeOH (95%); (b) BnBr, KH (79%); (c) DIBALH (90%); (d) $ICH_2Sn$$n$$Bu_3$ (88%); (e) i. nBuLi (72%); ii. MCPBA (78%); (f) $Pd(OH)_2$/C, H_2 (85%)



Scheme 18. Synthesis of a possible precursor **85** for the preparation of cyclophellitol **1**;[45] reagents: (a) i. thiophosgene (87%), ii. $P(OMe)_3$ (89%); (b) Meldrum's acid, $Pd(PPh_3)_4$ (73%); (c) AcOH/H_2O (82%); (d) i. Na salt of N-hydroxypyridine-2-thione, $(CO)_2Cl_2$; ii. $(PhS)_3Sb$; iii. Ac_2O (71%)

merically pure cyclophellitol (**1**) based on typical asymmetric "chiral auxiliary for diastereomeric differentiation" methods. As shown in Scheme 19, the synthetic sequence started with the reaction between the easily available chiral lactone **86**[46] and the racemic allene 2,3-pentadienedioate **87**, via the corresponding *tert*-butyldiphenylsilyl dienol ether, to give adduct **88** (99% *ee*) as the only isolated material. Note that in this Diels−Alder reaction the result was a doubly diastereofacially selective reaction with kinetic resolution of the allene. Compound **88** was transformed into product **89**. As can be seen in compound **89** (cyclophellitol numbering), (a) the bromine substituent at C-1 is the leaving group for the formation of the epoxide, (b) the oxo group at C-2 needs to be stereoselectively reduced, (c) the configuration at C-5 has to be epimerized and the ester reduced, and finally, (d) the *exo*-olefin at C-4 has to be oxidized and the resulting ketone conveniently reduced. All these steps have been accomplished with high stereochemical control, giving intermediate **90**, ideally functionalized for the final synthesis of compound **1**.



Scheme 19. Asymmetric synthesis of **1** according to Schlessinger et al.;[23] reagents: (a) i. KHMDS, TBDPSCl, 89 (91%); (b) −100 °C; (c) i. HCl (93%); ii. $NaBH_4$ (94%); (d) i. DMAP (79%); ii. O_3 (86%); iii. DIBALH (81%); iv. $BnOC(NH)CCl_3$ (84%); v. $Et_2O{\cdot}BF_3$ (85%); (e) i. DDMPO (74%); ii. KHDMS (92%); iii. H_2, Pd/C (97%)

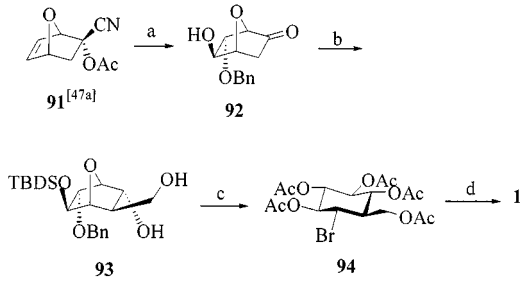
In summary, the synthesis of cyclophellitol (**1**) was achieved in 11 steps and 18% overall yield from chiral lactone **86**. Overall, the synthesis is extremely efficient and elegant. Note also that in adduct **88** only one carbon atom (C-3) has the desired stereochemistry; the others are created with the aid of highly stereoselective reactions.

(B) Synthesis of Racemic Cyclophellitols

The second strategy (B) comprises two approaches to the synthesis of racemic mixtures from 7-oxanorbornanone derivatives: (B1) Vogel's approach[24a] and (B2) Plumet−Arjona's approach.[25,26] Methodology has been set up[24b−24d] in order that both enantiomeric forms of cyclophellitol can be reached with the same ease.

(B1) Vogel's Approach

As shown in Scheme 20, the synthesis began with cyanohydrin **91**[47a] [obtained by Diels−Alder reaction between furan and 2-(acetoxy)acrylonitrile]. Intermediate **91** was transformed, after a four-step sequence (65% overall yield), into ketone **92**.[47b] This compound was submitted

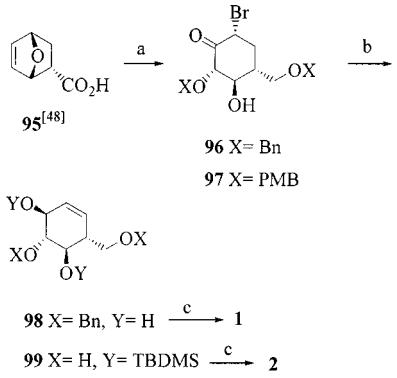


Scheme 20. Synthesis of racemic **1** according to Vogel et al.;[24a] reagents: (a) ref.[47b]; (b) i. TBDMSCl (82%); ii. KHDMS, TBDMSCl (87%); iii. CH_2O (89%); iv. $NaBH_4$ (95%); (c) i. HBr, AcOH (69%); (d) MeONa/MeOH, then Ac_2O, py (90%)

to a series of standard reaction techniques to establish the hydroxymethyl branched chain and the reduction of the ketone; the resulting compound **93** possessed all the required functional groups, correctly positioned and with the necessary relative configurations, for the synthesis of **1** (characterized as its peracetate). This was finally performed after ring opening to **94** and base-promoted epoxide formation. In total, this constitutes 12 steps and 19% overall yield from product **91**.

(B2) Plumet−Arjona's Approach

Plumet−Arjona et al. reported a synthesis of racemic **1** and **2** using 7-oxanorbornanone derivatives.[25,26] As shown in Scheme 21, the synthetic sequence started with compound **95**,[48] the Diels−Alder adduct of furan and acrylic acid. After seven steps, following methods previously developed by this group,[49,50] cyclohexanone **96** was obtained in 43% overall yield. This key intermediate not only had three stereocenters, at C-3, C-4, and C-5, with the correct configuration for compounds **1** or **2**, but additionally possessed functionality for the incorporation of the *endo* double bond and, after reduction of the ketone and/or deprotection of the primary hydroxy group, direction of the epoxidation of this double bond from the desired face to obtain **1** or **2**. The approach thus proved highly flexible, simple, and attractive.

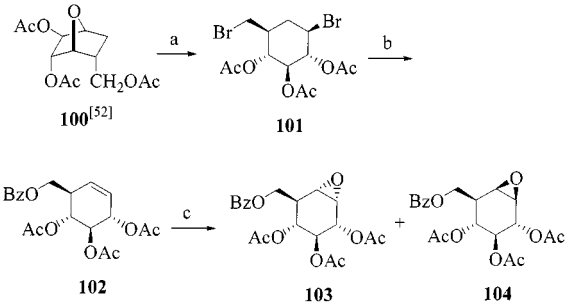


Scheme 21. Synthesis of racemic **1/2** according to Plumet−Arjona et al.;[25,26] reagents: (a) ref.[49,50]; (b) (from **96**) i. $CaCO_3$ (70%); ii. $NaBH_4$, $CeCl_3$ (83%); (c) (from **98**) i. MCPBA (71%); ii. H_2, Pd/C, then Ac_2O (80%); (b) (from **97**) i. $CaCO_3$ (58%); ii. $NaBH_4$, $CeCl_3$ (80%); iii. TBSOTf (100%); iv. DDQ (75%); (c) (from **99**) i. MCPBA (81%); ii. nBu$_4$NF, then Ac_2O (75%)

As stated, elimination of bromine and subsequent reduction of the ketone **96** afforded compound **98** with the correct configuration at C-2 (cyclophellitol numbering) as the only isomer. Hydroxy-directed epoxidation of compound **98** yielded, after hydrogenolysis, compound **1**, characterized as its peracetate. For the synthesis of 1,6-*epi*-cyclophellitol (**2**), the authors were forced to repeat the scheme, but using the di-PMB ether derivative **97**[49,50] (Scheme 21). After a similar sequence of reactions, followed by silylation, treatment with DDQ unblocked the benzylic ethers to afford a primary/secondary diol **99**. After hydroxy-directed epoxidation from the α-face, this afforded the precursor of compound **2**, characterized as its peracetate. In summary, for com-

pound **1**, this scheme required 12 steps and gave a 14% overall yield.

Finally, and as a nice proof of the potential value of some pioneering work in the synthesis of pseudosugars performed by Ogawa and co-workers, it is interesting to point out that in 1980 this group, in the context of a total synthesis of DL-hydroxyvalidamine and DL-validamine,[51] described the preparation of compounds **102** and **103** (Scheme 22). These products were obtained from compound **100**[52] after a series of simple but low-yielding reactions that afforded the carbocyclic derivative **101** and **102**. After treatment of compound **102** with *m*-chloroperbenzoic acid, two epoxides (**103** and **104**) were isolated in 67% yield as a mixture of stereoisomeric compounds in 1:2 ratio. The authors were unable to determine which of them was the major component in the mixture. Note that compounds **103** and **104** could potentially be transformed into 1,6-*epi*-cyclophellitol (**2**) and cyclophellitol (**1**), respectively, by simple manipulations.[53]



100[52] **101** **102** **103** **104**

Scheme 22. Synthesis of compounds **103** and **104** according to Ogawa et al.;[51] reagents: (a) HBr, AcOH (70%); (b) BzONa, LiBr, DMF (25%); (c) MCPBA (67%)

4. Conclusions

The natural product (+)-cyclophellitol (**1**) was isolated and characterized in 1990. To summarize the synthetic approaches towards it since then: 13 syntheses have been reported, 9 of which are total asymmetric syntheses, 2 are racemic, and 2 are formal total asymmetric syntheses. As is to be expected, the preferred chiral starting materials have been readily available sugars and, less frequently, inositols. In the synthetic approaches from sugars (D-glucose, D-mannose, or D-xylose), by far the method of choice for carbocycle synthesis has been the Ferrier II reaction (4 times); other reported methodologies being the 1,3-dipolar cycloaddition, a free-radical carbocyclization process, and the metathesis ring annulation. In the racemic series, Diels−Alder cycloaddition has been the method of choice. Of the inositols, L-quebrachitol, (−)-quinic acid, and conduritol B have been the selected materials. Note also that, for the important epoxidation step, the oxidation of conveniently functionalized cyclohexenes has been the method used most of the time. It is hoped that the results summarized here will serve as an additional resource for the pursuit of new synthetic ventures towards this and related molecules.

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Note added in proof (February 7, 2001): In a recent communication Jung et al. (S. W. T. Choe, H. E. Jung, *Carbohydr. Res.* **2000**, *329*, 731−744) have described an efficient synthesis of C-2 branched carbohydrates using intramolecular radical reactions.

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