Advances in the Chemical Synthesis of Medium-Sized Cyclitols

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Abstract: Densely hydroxylated, medium-sized carbocycles and their analogues have long been a somewhat neglected molecular progeny for two reasons: (a) the synthesis of such expanded and functionality rich rings is quite a challenging task that remains partially unsolved and (b) the biological significance of these constructs has not yet been thoroughly appreciated. This account mainly discusses recent approaches used to deal with this rare class of carbohydrate mimics with particular emphasis being placed on annulative strategies using ring-closing metathesis, aldol-based ring closure, intramolecular nitrile oxide and nitrone cycloaddition, and the Claisen rearrangement. Less documented annulative and non-annulative procedures including free-radical cyclisation, intramolecular coupling, and ring expansion and manipulation are also considered.

Keywords: Cyclitols, carbasugars, medium-sized rings, chemical synthesis, glycosidase inhibitors.

1. INTRODUCTION

Cyclitols, structural entities where a stereodefined sequence of hydroxyl groups adorns variable carbocyclic core units, usually five- or six-membered rings, represent an important class of natural and synthetic compounds that exhibit far-reaching biological functions [1]. For example, inositols and, in particular, phosphorylated *myo*-inositol [(**1**), Fig. (**1**)] derivatives play a central role in cellular signal transduction, calcium mobilisation, insulin stimulation, and cytoskeletal regulation [2], whereas carbasugar compounds, encompassing skeletal motifs such as validamine (**2**), valienamine (**3**), mannostatin A (**4**), gabosine C (**5**), conduritol A (**6**), cyclophellitol (**7**), oseltamivir (**8**) and 5a-carba-α-D-galactose (**9**) are reported to be effective inhibitors of various glycosidase enzymes, and may have therapeutic application for the treatment of, among others, viral infections, HIV, cancer, and hyperglycemias and disorders related to these conditions, such as obesity and diabetes mellitus [3].

Compared to the rich progeny of these five- and six-membered ring compounds, densely hydroxylated medium-sized homologues, be they strictly related to the carbasugars or merely ring expanded cyclitol entities, constitute a scattered, understated subclass of compounds. Nonetheless, a recent body of work does exist which focuses on the rational construction of these compounds, mainly seven- and eight-membered rings, in a chiral non-racemic format.

This review will cover recent representative syntheses of this rare class of richly functionalised carbocycles and particular emphasis will be paid to the strategies of chemical construction employed. The article is organised into four main sections, where the most appealing and effective

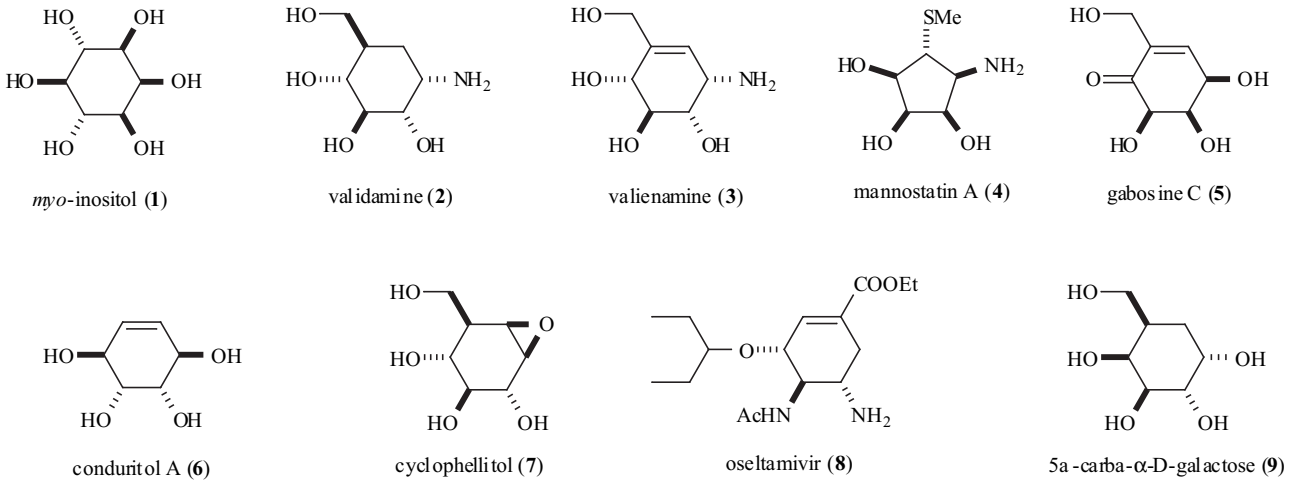

Fig. (1). Notable cyclitol representatives.

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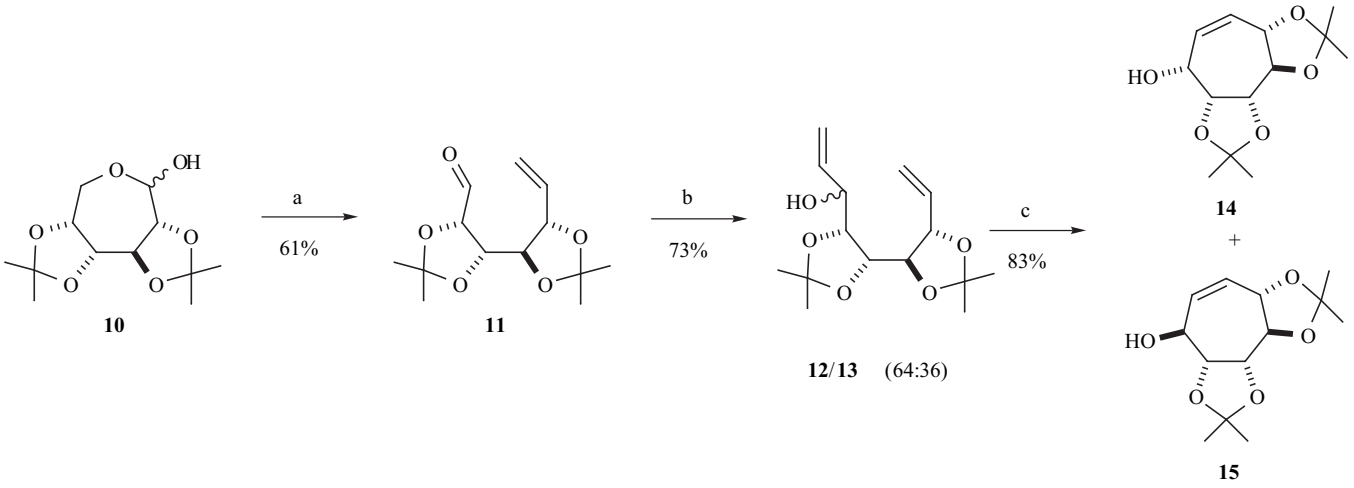
methods of implementing the carbocycle frameworks are discussed in-depth. Methods based on ring-closing metathesis protocols (RCM) are given in section 2 and those based on aldol-based ring closure (ARC) are grouped in section 3; whilst sections 4 and 5 summarise methods based on [2+3] cycloaddition techniques (INOC/INC) and the Claisen rearrangement (CR), respectively. Finally, several lesser investigated annulative and non-annulative protocols for medium-sized carbocycles are included in section 6 (miscellaneous), which precedes the ultimate chapter of concluding remarks and future directions (section 7).

2. USING RING-CLOSING METATHESIS (RCM)

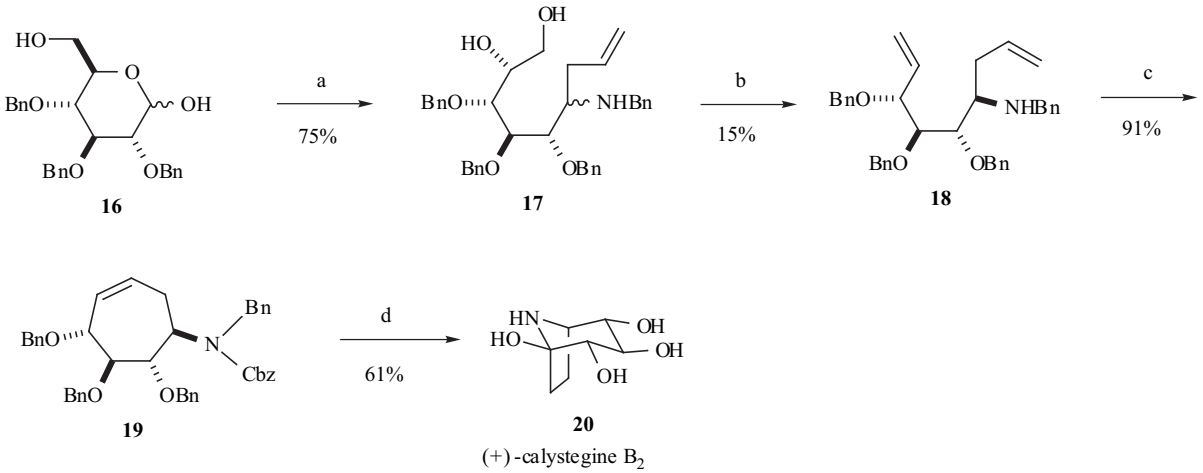
Transition metal-catalysed ring-closing metathesis (RCM) of 1,ω-diene compounds is undoubtedly the most direct and economical method for the synthesis of unsaturated carbocycles, and recent improvement of catalyst performance has tremendously expanded the scope of this reaction by increasing functional group and chirality tolerance [4]. The unique synthetic potential of this carbon-carbon bond-forming manoeuvre was recently exploited by Marco-Contelles [5] to assemble a varied repertoire of unsaturated cycloheptitols and cyclooctitols by starting with enantiopure, carbohydrate-derived 1,ω-dienes. As shown in Scheme **1**, suitable diene precursors, namely a 64:36 epimeric mixture of **12** and **13**, were first synthesised by simple transformation of bis-isopropylidene-locked septanose **10** *via* a three-step sequence consisting of a Wittig-based one-carbon homologation, followed by oxidation to **11** and vinylation.

With this mixture in hand, the RCM reaction was carried out using a typical experimental protocol involving Grubbs' catalyst, $(PCy_3)_2Cl_2Ru{=}CHPh$. The cycloheptene derivatives **14** and **15** were obtained, as expected, and proved readily separable (83% total yield). By paralleling exactly this chemistry a variety of 7-membered and 8-membered unsaturated cyclitols were assembled, thus demonstrating the



Scheme 1.

Conditions: (a) i: $Ph_3P{=}CH_2$, THF, –20°C; ii: DMSO, DCC, TFA, toluene; (b) $CH_2{=}CHMgBr$, THF, 0°C; (c) Grubbs' catalyst (10%), CH_2Cl_2.



Scheme 2.

Conditions: (a) i: $BnNH_2$, toluene, 80°C; ii: $CH_2{=}CHCH_2MgBr$, Et_2O; (b) I_2, Ph_3P, imidazole; (c) i: CbzCl, $NaHCO_3$, AcOEt; ii: Grubbs' catalyst (7.7%), CH_2Cl_2; (d) i: $BH_3{\cdot}THF$, THF, –50 to 0°C; ii: NaOH, H_2O_2, 0°C; iii: Dess-Martin periodinane, CH_2Cl_2; iv: H_2, Pd/C.

synthetic power and viability of the RCM transformation in this field.

Application of the above-discussed chemical sequence was exploited by the same author to enter the calystegine compound **20** (Scheme **2**). The synthesis commenced with the transformation of the D-glucopyranose derivative **16** to aminated alkene **17**, which was transformed into diene **18** *via* the Garegg protocol. Exposure of **18** to RCM conditions efficiently gave rise to carbocycle **19**, a known precursor of calystegine B_2 (**20**).

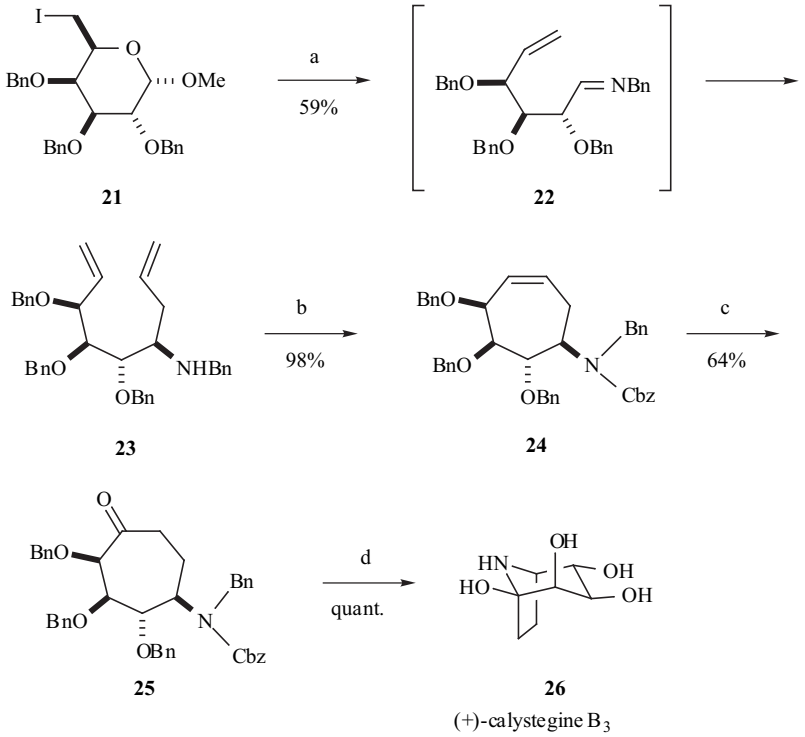
Calystegines B_2, B_3, and B_4 were synthesised from 6-iodogluco-, galacto-, and mannopyranosides respectively, by using a clever zinc-mediated domino reaction followed by a RCM reaction [6, 7]. As an example, galactose derivative **21** nicely served as the progenitor of calystegine B_3 (**26**), as displayed in Scheme **3**. Sonication of a mixture of galactose **21** and excess of zinc dust in dry THF caused a reductive fragmentation and generated an unsaturated aldehyde intermediate (not shown), which was trapped in situ as the corresponding benzyl imine **22**. Allylation of **22** using allyl bromide then led to major diene **23** in a good yield with a high level of diastereoselection. After protection as Cbz-derivative, diene **23** was exposed to modified Grubbs' catalyst $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru$=CHPh, leading to cycloheptene **24**. One-pot hydroboration and oxidation of **24** gave ketone **25**, from which calystegine B_3 (**26**) was easily obtained by hydrogenolytic global deprotection.

In 2001 Boyer and Hanna also reported a short synthesis of enantiopure (+)-calystegine B_2 by adopting almost exactly the same sort of reaction sequence outlined in Scheme **3** [8].

The RCM construction protocol was further validated by Hanna and co-workers by subjecting stereochemically varied carbohydrate-derived diene and dienyne precursors, utilising both the original Grubbs' catalyst $(PCy_3)_2Cl_2Ru$=CHPh and the more sterically demanding unsaturated *N*-heterocyclic carbene catalysts $(PCy_3)(C_3H_2N_2mes_2)Cl_2Ru$=CHPh and $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru$=CHPh [9-11]. The results are collected in Scheme **4**, which highlights the wide variety tolerated in the substrate substitution patterns of the precursors. Noteworthy is the fact that highly interesting fused carbabicyclic systems (e.g. compounds **44** and **46**) became available *via* a tandem RCM of suitably protected, densely functionalised dienyne derivatives.

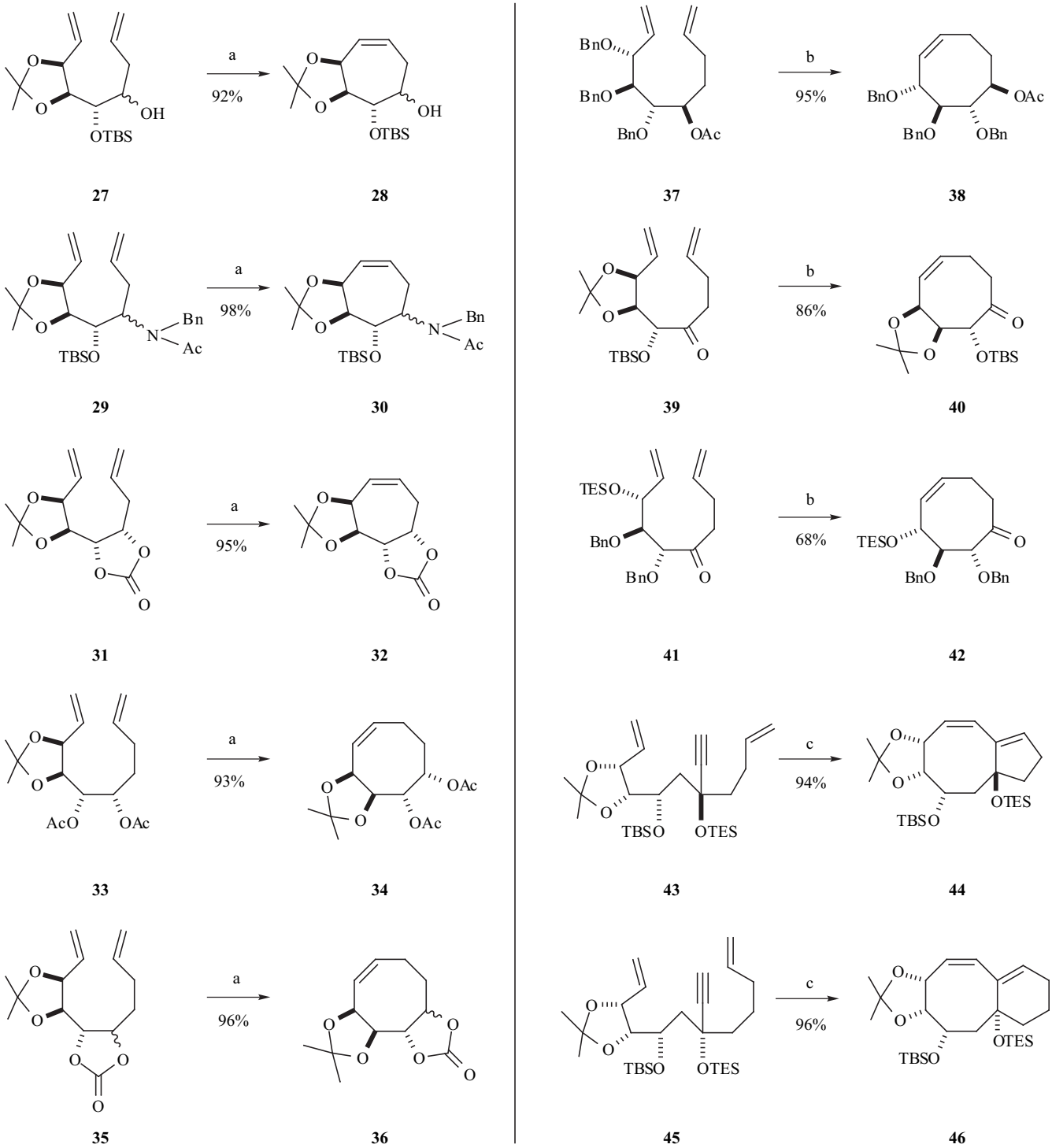
C_2-symmetric L-*ido* bis-epoxide **47**, readily available from D-mannitol, was the precursor with which Le Merrer completed the synthesis of 8-membered hexaol **51** [12]. In the event (Scheme **5**), exposure of **47** to lithium divinyl cyanocuprate cleanly afforded diene **48** *via* bilateral homologation at both electrophilic termini.

During the decisive cyclisation step, use of 13 mol% $(PCy_3)_2Cl_2Ru$=CHPh in CH_2Cl_2 efficiently gave the expected cyclooctene **49** in 87% yield, with retention of the original C_2 symmetry. The presence of an unsaturated moiety in the tetraol **49** offered a suggestive opportunity for subsequent functionalisation, allowing it to be transformed into both hexahydroxylated octitol **51** and epoxide **52**, a homologue structural unit reminiscent of naturally occurring cyclophellitols.



Scheme 3.

Conditions: (a) Zn, $BnNH_2$, CH_2=$CHCH_2Br$, THF, sonication, 40°C; (b) i: CbzCl, $KHCO_3$, EtOAc, H_2O; ii: $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru$=CHPh (2%), CH_2Cl_2, rt; (c) i: BH_3·THF, THF, –50 to 0°C; ii: NaOH, H_2O_2, 0°C; iii: Dess-Martin periodinane, CH_2Cl_2; (d) H_2, Pd/C.

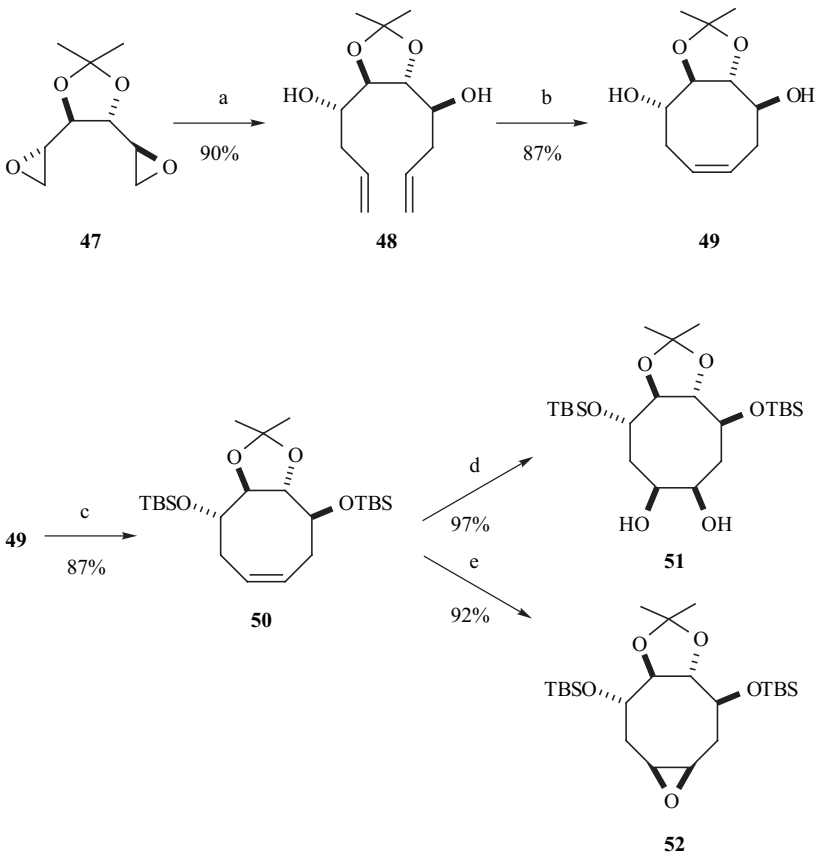


Scheme 4.

Conditions: (a) $(PCy_3)_2Cl_2Ru$=CHPh (5%), CH_2Cl_2; (b) $(PCy_3)(C_3H_2N_2mes_2)Cl_2Ru$=CHPh (10%), CH_2Cl_2, reflux; (c) $(PCy_3)(C_3H_4N_2mes_2)Cl_2Ru$=CHPh (10%), CH_2Cl_2, reflux.

Quite recently, Sinaÿ and co-workers [13] reported a nice, stereodivergent synthesis of new polyhydroxylated seven- and eight- membered carbocycles using suitably protected D-arabinose **53** as the common precursor, and exploiting the RCM strategy to implement the ring frameworks.

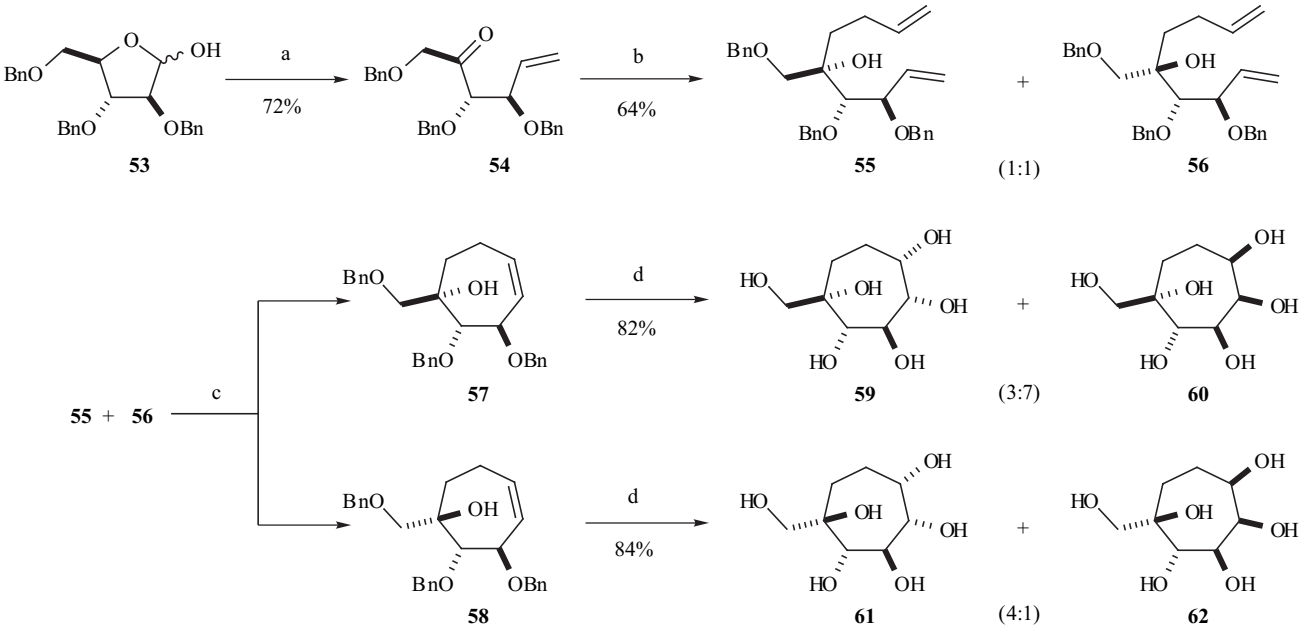
As a highlighting example, conversion of arabinose **53** into carbaseptanoses **59**, **60** and **61**, **62** is displayed in Scheme **6**. Thus, **53** was subjected to Wittig olefination and subsequent oxidation with PCC to furnish ketone **54** which, by exposure to butenylmagnesium bromide, gave rise to 1,8-diene-ols **55** and **56** as an inseparable 1:1 mixture of diastereoisomers. Compounds **55** and **56** were then subjected to a RCM reaction assisted by the modified Grubbs' catalyst $(PCy_3)(C_3H_2N_2mes_2)Cl_2Ru$=CHPh leading to cycloheptenes **57** and **58** in almost quantitative yield. Finally, individual



Scheme 5.

Conditions: (a) $(H_2C{=}CH)_2CuCNLi_2$, THF, –78 to 20°C; (b) $(PCy_3)_2Cl_2Ru{=}CHPh$ (13%), CH_2Cl_2; (c) TBSCl, imidazole, DMF; (d) OsO_4 (5%), NMO; (e) MCPBA, $NaHCO_3$.

alkenes **57** and **58** were subjected to *syn*-dihydroxylation to furnish, after hydrogenolytic removal of the benzyl protecting groups, polyhydroxylated cyclitols **59**, **60** and **61**, **62**, respectively, in high isolated yields.



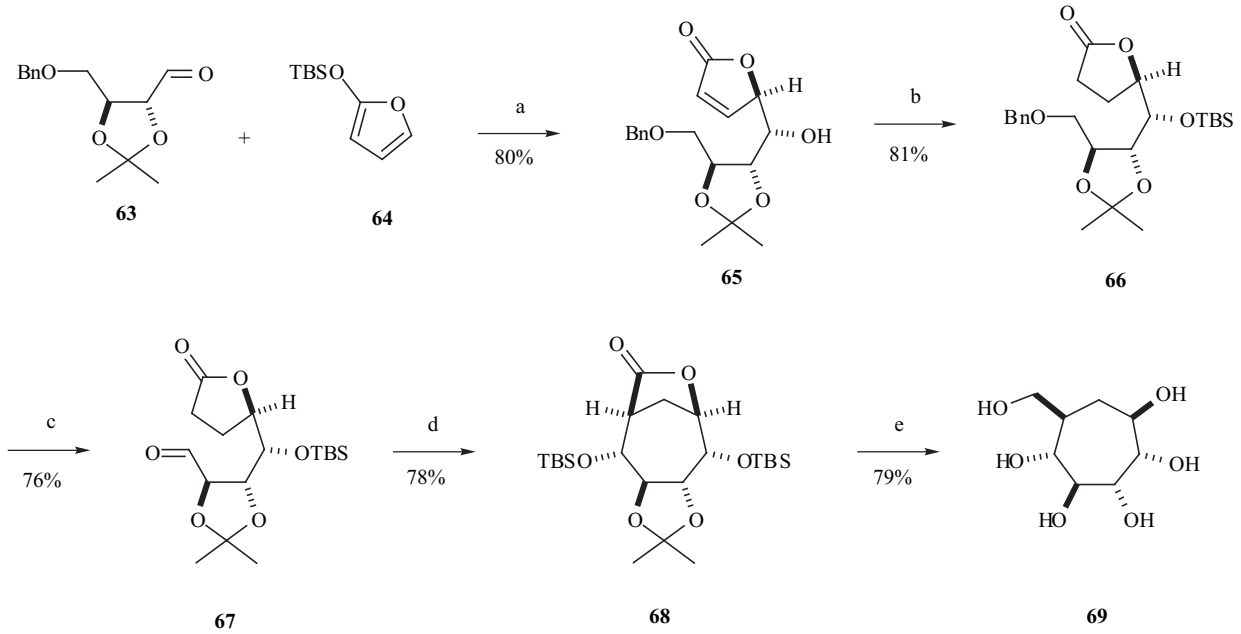
Scheme 6.

Conditions: (a) i: Ph_3PCH_3Br, ^{n}BuLi, THF, –78°C to rt; ii: PCC, MS, CH_2Cl_2, Et_2O; (b) $CH_2{=}CH(CH_2)_2Br$, Mg, Et_2O, THF; (c) $(PCy_3)(C_3H_2N_2mes_2)Cl_2Ru{=}CHPh$ (10%), CH_2Cl_2; (d) OsO_4 (2.5%), NMO, ^{t}BuOH, acetone, H_2O; ii: H_2, Pd/C, MeOH, EtOAc.

The entire collection of synthesised cyclitols was also assayed for the inhibitory activity towards 25 commercially available glycosidases, showing that seven-membered representatives were more active than the corresponding cyclooctanose congeners.

3. USING ALDOL-BASED RING CLOSURE (ARC)

The aldol reaction represents one of the most reliable carbon-carbon bond-forming tools in synthetic organic chemistry, and this manoeuvre has been successfully applied in both intermolecular and intramolecular environments [14]. Within the realm of the medium-sized rings, a full-aldol approach was devised and exploited by Rassu and co-workers to forge the carbon skeleton of a variety of cycloheptane and cyclooctane carbasugar representatives [15].



Scheme 7.

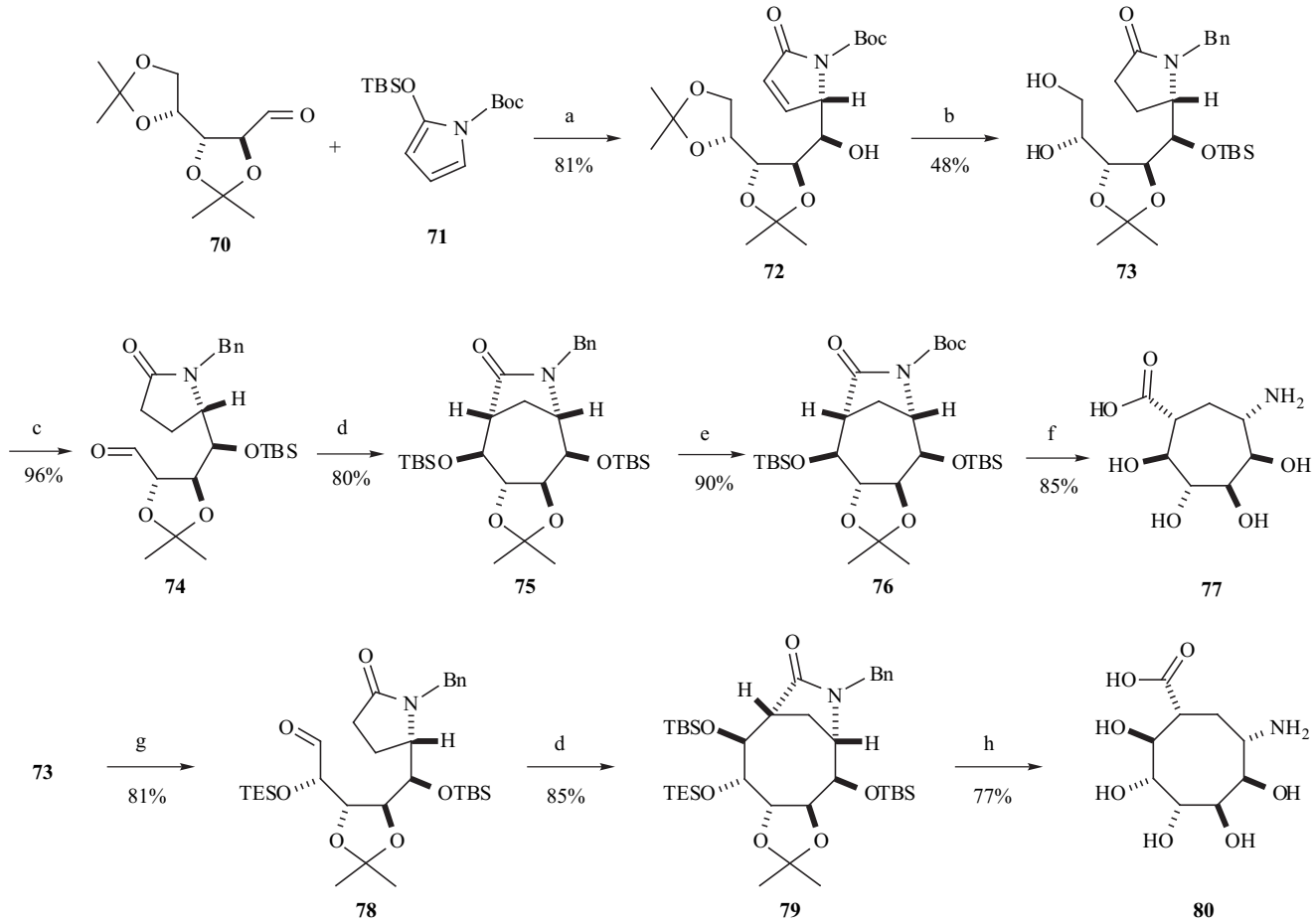
Conditions: (a) $BF_3 \cdot OEt_2$, CH_2Cl_2, –80°C; (b) i: $NaBH_4$, $NiCl_2$ (cat), MeOH; ii: TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) i: H_2, $Pd(OH)_2$, MeOH; ii: $(COCl)_2$, DMSO, CH_2Cl_2, –78°C, then Et_3N; (d) TBSOTf, DIPEA, CH_2Cl_2; (e) i: $LiBH_4$, THF; ii: 6N HCl, THF, MeOH.

An emblematic example, i.e. the total synthesis of chiral non-racemic 6a-carba-β-D-glycero-D-guloseptanose **69**, is outlined in Scheme **7**. The point of departure was the known L-threose **63**, prepared, in turn, from *R*,*R*-tartaric acid dimethyl ester. Boron trifluoride-assisted vinylogous aldol reaction between aldehyde **63** and dienoxyfuran **64** proceeded smoothly to provide the lactone adduct **65** in high yields and excellent diastereoselectivity. Chemoselective saturation of the double bond within **65** and silylation delivered protected lactone **66**, which was manipulated into aldehyde **67** *via* selective debenzylation and Swern oxidation. With **67** in hand, the crucial ARC reaction was performed according to a highly efficient silylative protocol triggered by the Lewis acid/Lewis base system TBSOTf/DIPEA. Silylated tricyclic compound **68** was eventually formed in a 78% yield with little, if any, diastereomeric contamination. To complete the construction of **69**, tricycle **68** was exposed to $LiBH_4$ to liberate the C_1 pseudoanomeric hydroxyl and the terminal hydroxymethyl unit. This delivered a partially protected intermediate, which was fully liberated by acidic treatment to furnish the targeted carbasugar **69**.

As a further, productive example of this ARC tactic, the same research group also succeeded in preparing the rare 7-membered and 8-membered ring amino carbauronic acids **77** and **80**, according to the flexible, divergent route shown in Scheme **8**. Readily available diisopropylidene-D-arabinose **70**, a common precursor, was thus coupled to dienoxy-pyrrole **71** under the guidance of $SnCl_4$ to deliver the vinylogous aldol adduct **72**. A series of five simple transformations then allowed manipulation of **72** into diol **73**, which represents the divergent intermediary compound of the synthesis.

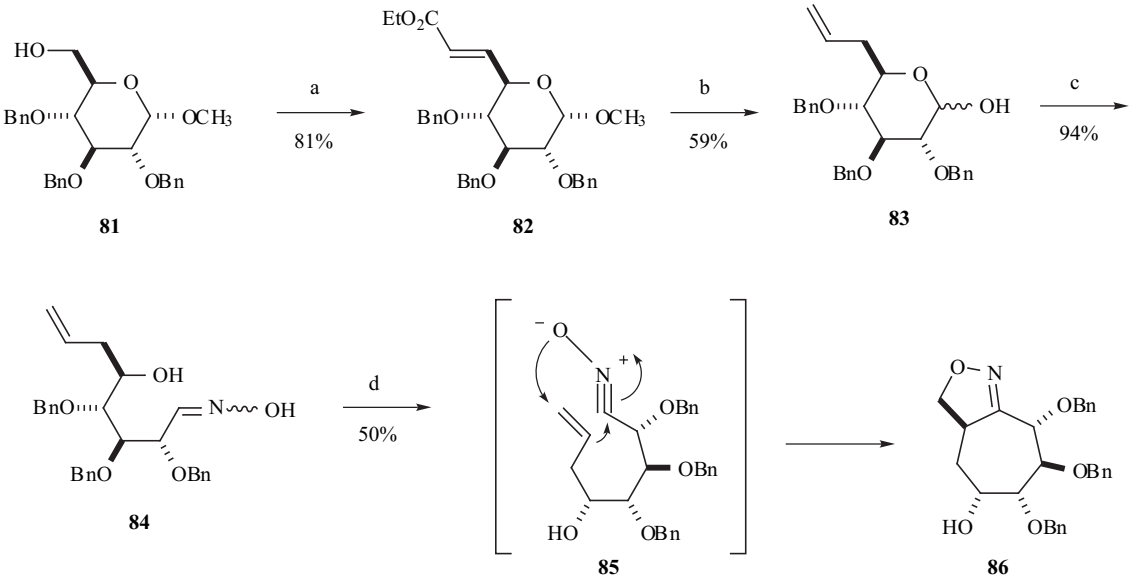
At first, the one-carbon oxidative shortening of **73** furnished aldehyde **74**, which was then converted to tricyclic compound **75** by following the previously disclosed ARC protocol. Rather conventional chemistry was then used to hydrolytically open **75** and transform it into the desired γ-amino acid **77**, in both a high yield and selectivity. On the other hand **73**, in maintaining all of its carbon length, lent itself to form amino acid **80**, which embodies a cyclooctane framework adorned with seven consecutive stereocentres.

Thus, **73** was converted to aldehyde **78** which was subjected to silylative ARC conditions. In the event, tricyclic compound **79** was formed selectively, and this material was finally cleaved and deprotected to cyclooctane amino acid **80**. During the same research programme, this methodology was also exploited to assemble additional medium-sized cyclitols, testifying that the ARC protocol is



Scheme 8.

Conditions: (a) $SnCl_4$, Et_2O, –80°C; (b) i: $NaBH_4$, $NiCl_2$ (cat), MeOH; ii: TBSOTf, 2,6-lutidine, CH_2Cl_2; iii: CAN (cat), MeCN, reflux; iv: BnCl, KH, THF, 60°C; v: aq. AcOH, 50°C; (c) aq. $NaIO_4$, SiO_2, CH_2Cl_2; (d) TBSOTf, DIPEA, CH_2Cl_2; (e) i: Na/NH_3, THF, –78°C; ii: Boc_2O, DMAP, MeCN; (f) 6N HCl, reflux, then DOWEX 50W x 8; (g) i: TESOTf, pyridine, DMAP; ii: $(COCl)_2$, DMSO, CH_2Cl_2, –78°C, then Et_3N; (h) i: Na/NH_3, THF, –78°C; ii: Boc_2O, DMAP, MeCN; iii: 6N HCl, reflux, then DOWEX 50W x 8.



Scheme 9.

Conditions: (a) i: $(COCl)_2$, DMSO, CH_2Cl_2, –78°C, then Et_3N, –78 to 40°C; ii: $Ph_3P{=}CHCO_2Et$, – 40°C to rt; (b) i: H_2, Ra/Ni, MeOH; ii: $LiAlH_4$, Et_2O, 0°C to rt; iii: I_2, PPh_3, CH_2Cl_2, pyridine, 0°C; iv: ^{t}BuOK, THF; v: Ac_2O, H_2SO_4 (cat), $CHCl_3$; vi: MeONa, MeOH; (c) NH_2OH, HCl, MeONa, MeOH, reflux; (d) 1.75M NaOCl, CH_2Cl_2.

a viable solution to the challenging task of assembling densely hydroxylated medium-sized carbocyclic motifs.

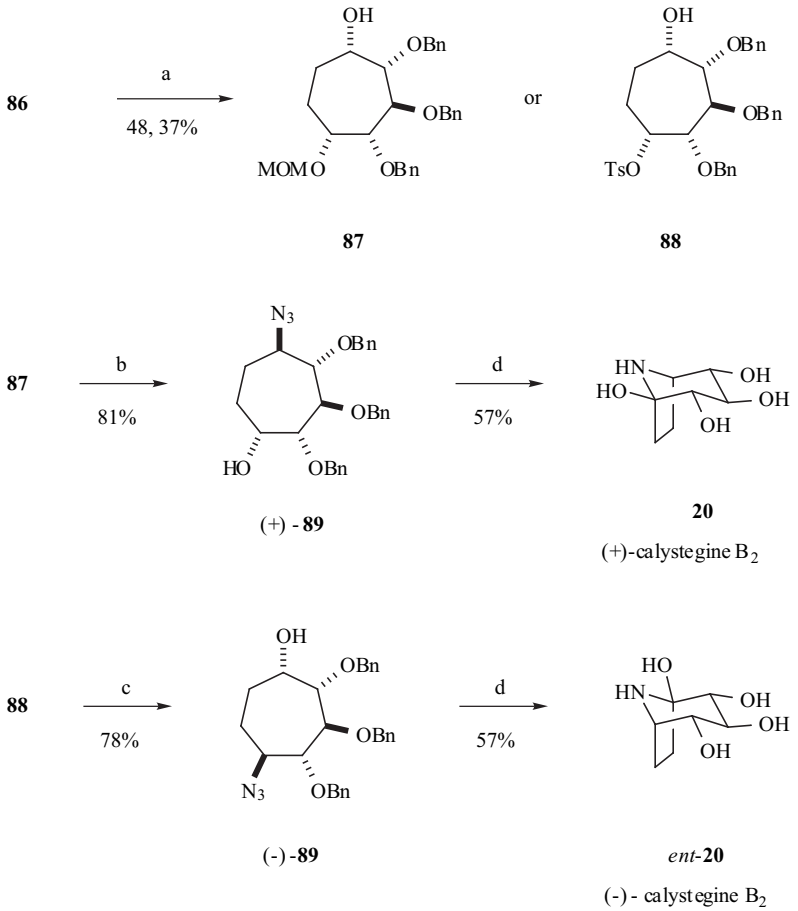
4. USING INTRAMOLECULAR NITRILE OXIDE AND NITRONE CYCLOADDITION (INOC/INC)

In 1992, Depezay and co-workers [16, 17] described a brilliant, divergent synthesis of both enantiomers of calystegine B_2 by adopting, as a key ring-forming manoeuvre, the nitrile-oxide cycloaddition (INOC) protocol. As shown in Scheme **9**, the synthesis began with the preparation of olefinic aldehydo sugar **83** that was readily prepared from partially protected D-methylglucoside **81**.

Pyranose **83** was next converted to oxime **84**, which was cyclised to isoxazoline **86** *via* the intermediacy of nitrile oxide **85**. In a divergent manner, alcohol **86** was elaborated either into **87** or **88** by simple chemistry consisting of isoxazoline ring opening and removal of the hydroxymethyl moiety (Scheme **10**). In order to synthesise each of the two calystegine B_2 enantiomers **20** and *ent*-**20**, cycloheptitols **87** and **88** were independently converted to azido alcohols (+)-**89** and (–)-**89**, the immediate precursors of (+)- and (–)-calystegine B_2.

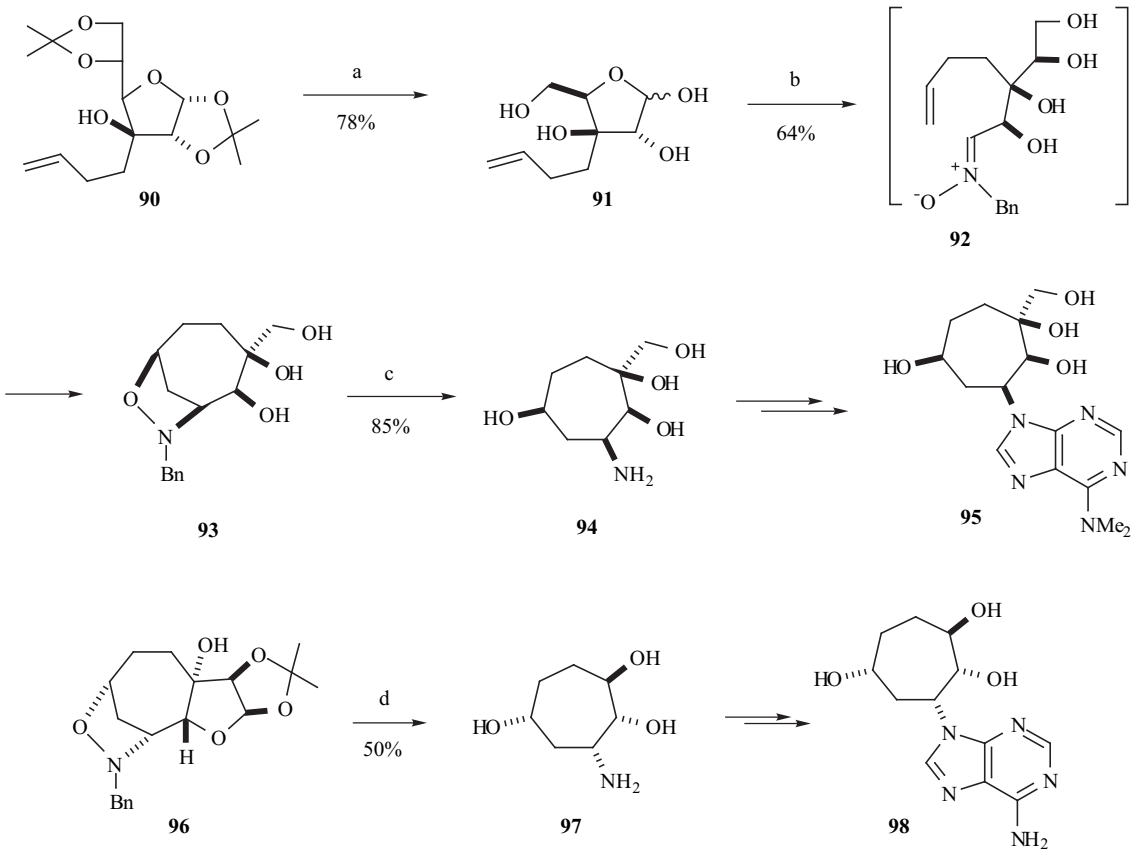
The nitrone cycloaddition route (INC) was independently exploited by Mandal [18-20] and Marco-Contelles [21] to prepare densely functionalised cycloheptane frameworks by utilising carbohydrates as chiral non-racemic progenitors. The Mandal's synthesis began with the conversion of D-glucose-derived compound **90** to aldehydo-furanose **91** (Scheme **11**), which was transformed to nitrone **92** in a high yield. Compound **92** spontaneously underwent 1,3-dipolar cycloaddition furnishing, after sequential $NaIO_4$ and $NaBH_4$ treatment, isoxazolidino-carbocycle **93** that was quickly transformed into the fully deprotected seven-ring carbaketose **94**. Interestingly, carbocycle **94** and other cycloheptanoid analogues (e.g. compound **97**) were used to assemble quite rare ring-expanded purine nucleosides of type **95** and **98** by simple adaptation of techniques documented in the literature.

A rather similar chemistry was also adapted by Marco-Contelles [21] to annulate acyclic, chiral *N*-benzyl nitrone derivatives (Scheme **12**). Indeed, exposure of nitrone **99** (ex α-D-mannofuranose) to thermal INC conditions did produce tricyclic *N*-benzyl isoxazolidine **100**, which was isolated as a 60:40 diastereomeric mixture. Remarkably, the presence of a dioxolane ring constraint was decisive for the successful outcome of annulation.



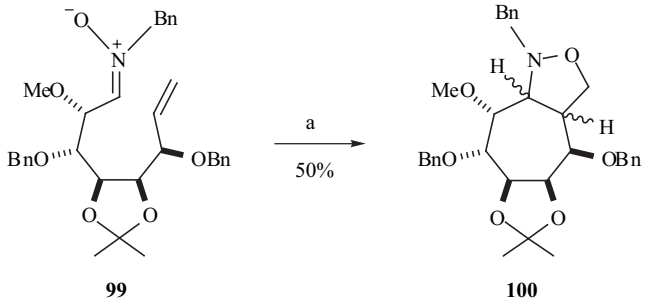
Scheme 10.

Conditions: (a) i: MOMCl, DIPEA, CH_2Cl_2 or TsCl, pyridine; ii: H_2, Ra/Ni, MeOH:H_2O, $B(OH)_3$; iii: excess $(COCl)_2$/DMSO, CH_2Cl_2, – 60°C, then Et_3N; iv: Zn, TMEDA, AcOH, EtOH; v: DIBAL-H, Et_2O, –50°C; (b) i: $Zn(N_3)_2 \cdot 2Py$, PPh_3, DIAD; ii: MeOH, H^+; (c) NaN_3, DMF, 80°C; (d) i: $(COCl)_2$, DMSO, CH_2Cl_2, – 60°C, then Et_3N; ii: H_2, Pd black, aq. AcOH.



Scheme 11.

Conditions: (a) i: AcOH/H_2O (1:1), 60°C; ii: $NaIO_4$, EtOH, H_2O; iii: $NaBH_4$, MeOH; iv: 4% H_2SO_4, dioxane, H_2O; (b) i: BnNHOH, 2-fluoroethanol; ii: $NaIO_4$, EtOH, H_2O; iii: $NaBH_4$, MeOH; (c) Pd/C, cyclohexene, reflux; (d) i: 4% H_2SO_4, MeCN, H_2O; ii: $NaIO_4$, EtOH, H_2O, 10°C; iii: $NaBH_4$, MeOH, 10°C; iv: Pd/C, cyclohexene, EtOH, reflux.



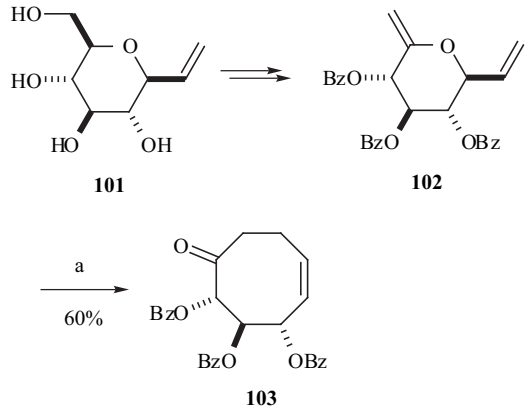
Scheme 12.

Conditions: (a) chlorobenzene, 130°C.

5. USING CLAISEN REARRANGEMENT (CR)

The Claisen rearrangement of 2-methylene-6-vinyl-tetrahydropyrane derivatives to afford cyclooctane-based carbocycles was first adopted by Paquette [22] for the synthesis of a variety of naturally occurring compounds. A skill adaptation of this simple chemical manoeuvre was introduced by Werschkun and Thiem in 1997 [23] where a skeletal rearrangement with loss of the sugar structure was exploited to convert the readily available β-*C*-vinylglycoside **102** into eight-membered carbocycle **103** (Scheme **13**).

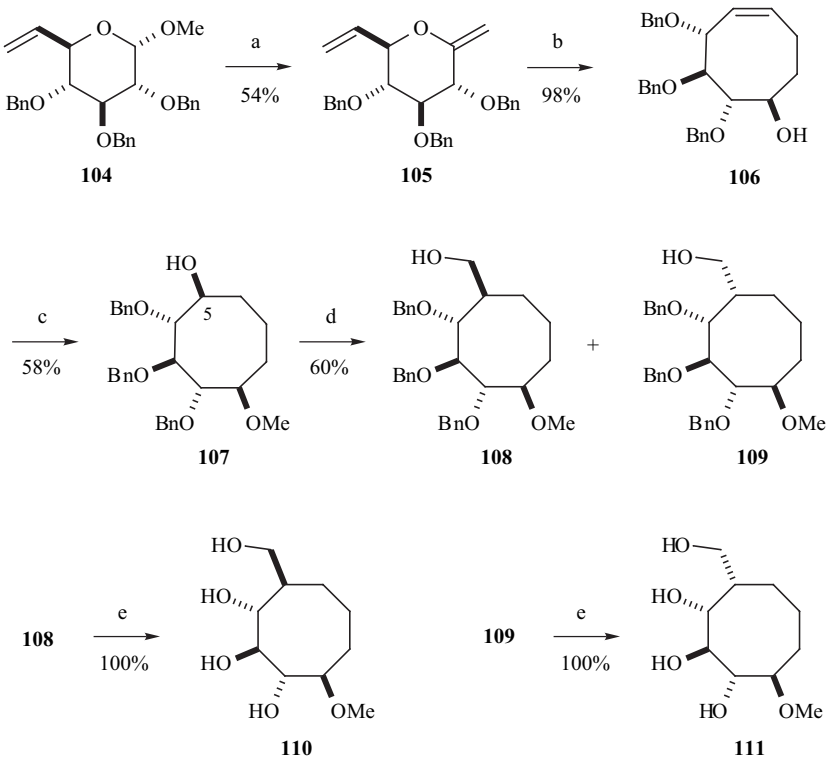
Thus, moving from glucose-derived pyranose **101**, the Claisen precursor **102** was synthesised as a pure anomer, which was then subjected to thermal rearrangement in boiling xylene. As expected, unsaturated cyclooctanone **103** was obtained in a good 60% yield as the result of a clean sigmatropic rearrangement.



Scheme 13.

Conditions: (a) xylene, reflux.

A reductive variant of this reaction, using triisobutylaluminium (TIBAL) as a promoter-reductant, was recently adopted by Sinaÿ and co-workers [24-26] and applied to a number of carbohydrate derivatives with the intent of obtaining a new family of carbaoctanose

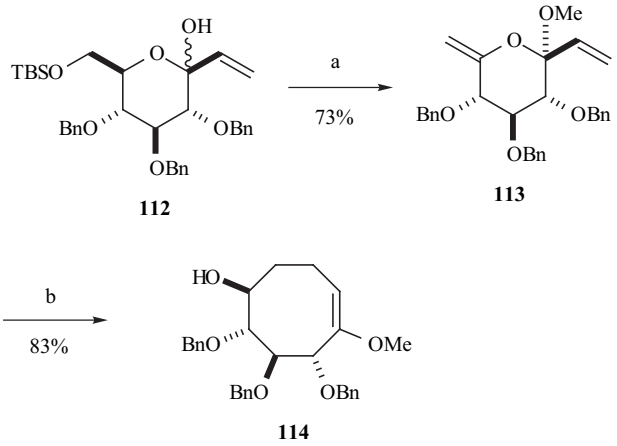


Scheme 14.

Conditions: (a) i: TfOH, AcOH, H_2O, 80°C; ii: PCC, 4Å MS, CH_2Cl_2, 0°C to rt; iii: Tebbe reagent, pyridine/THF (1:1), –78°C to rt; (b) TIBAL, toluene, 50°C; (c) i: NaH, MeI, DMF; ii: BH_3·THF, then 11% NaOH, 35% H_2O_2, 0°C to rt; (d) i: PCC, MS, CH_2Cl_2, 0°C; ii: Tebbe reagent, pyridine, THF, –78°C to rt; iii: BH_3·THF, then 11% NaOH, 35% H_2O_2, 0°C to rt; (e) H_2, Pd/C, EtOAc, MeOH.

compounds. To highlight this procedure, the preparation of D-*gluco*- and L-*ido*-configured mimetics **110** and **111** is displayed in Scheme **14**.

The opening move was the transformation of the known glucopyranoside **104** into exo-methylene vinylpyranose **105**. TIBAL-promoted Claisen rearrangement of **105** provided the cyclooctene derivative **106** almost quantitatively, which was then transformed to protected carbaoctanose **107** by methylation followed by hydroboration-oxidation.



Scheme 15.

Conditions: (a) i: MeOH, K-10 clay, 3Å MS, CH_2Cl_2; ii: TBAF, THF; iii: I_2, imidazole, PPh_3, toluene; iv: NaH, DMF; (b) TIBAL, toluene.

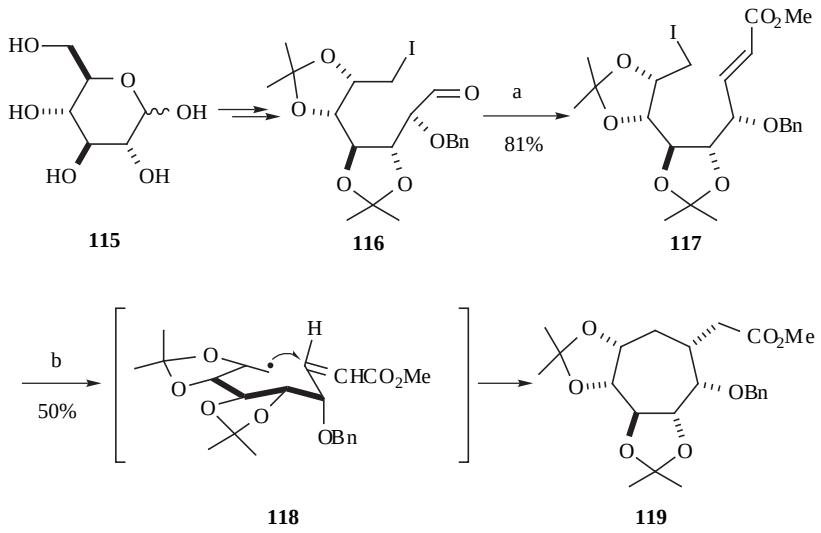
Installation of the hydroxymethyl function at C_5 required three further operations; oxidation of the C_5-hydroxyl, Tebbe methylenation, and hydroboration-oxidation. In the event, a mixture of epimeric cyclooctanoids **108** and **109** was formed, which were efficiently elaborated into the targeted carbasugars **110** and **111**.

By adopting the same noteworthy TIBAL-mediated carbocyclisation technique, preparation of unsaturated octanoid **114** (Scheme **15**) was successfully accomplished by the van Boom group [27, 28], during a study aimed at the synthesis of conformationally locked L-idose analogues.

Thus, ketose **112** was first methylated and then subjected to a three step transformation including desilylation followed by iodination and hydride-promoted HI elimination. This furnished vinyl ketoside **113** whose treatment with excess TIBAL ensured smooth Claisen rearrangement to afford carbocycle **114** in an excellent yield.

6. MISCELLANEOUS

This section groups a few asymmetric syntheses of densely functionalised medium-sized carbocycles employing rarely adopted strategies such as free-radical cyclisation, intramolecular pinacol coupling, and ring expansion and manipulation. Quite recently, Marco-Contelles [5, 29] has made use of free radical cyclisation and ring-closing metathesis in order to develop useful synthetic protocols to access a number of chiral non-racemic, densely oxygenated medium-sized carbocycles from carbohydrate precursors. As



Scheme 16.

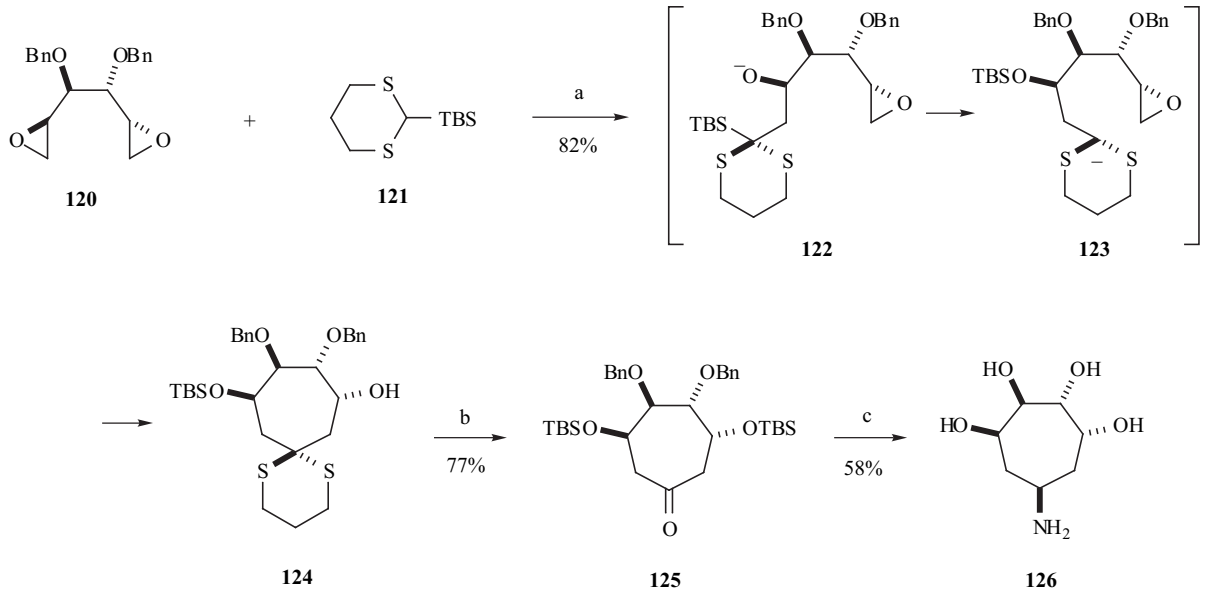
Conditions: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2; (b) AIBN, Bu_3SnH, toluene, 80°C, slow addition.

a highlighting example, conversion of D-glucose **115** into methyl 6a-carbaoctoseptanuronate **119** is displayed in Scheme **16**. Wittig elongation of aldehyde **116**, easily obtained from D-glucose with carboxymethylmethylene triphenyl phosphorane, gave rise to *E*-configured unsaturated ester **117**, which proved ready for the free radical cyclisation. Exposure of **117** to AIBN-Bu_3SnH under slow addition conditions remarkably resulted in ring annulation and produced carbaseptanuronic ester **119** in a reasonable yield.

Mechanistically, in the transition state leading to **119**, conformer **118** should be the operative species as it bears most of the substituents in a pseudoequatorial orientation and would result in formation of a carbocycle having the substituent at the newly formed stereocentre located in the α-orientation. During the same study, the Spanish researchers also succeeded in the construction of a variety of cycloheptitols and cyclooctitols bearing different substitutions and chirality.

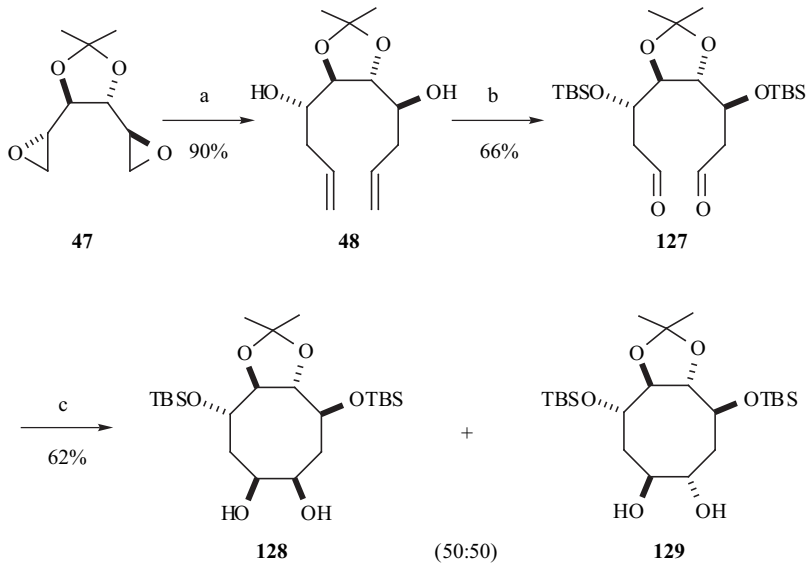
Pseudo-C_2-symmetric aminocyclitols of type **126** (Scheme **17**) were obtained by Le Merrer and co-workers [30] by adopting a concise and efficient methodology involving a tandem alkylation-cyclisation of C_2-symmetric bis-epoxides (L-*ido*- or D-*manno*-configured) with 2-lithio-1,3-dithiane derivatives.

As an example, the reaction of D-*manno*-configured bis-epoxide **120** with the lithiated derivative of **121** afforded, *via* 1,4-Brook rearrangement (**122** → **123**), the cycloheptane **124**, which, in turn, was transformed into C_2-symmetric



Scheme 17.

Conditions: (a) ^nBuLi, $^nBu_2Mg$, THF, HMPA, rt; (b) i: TBSCl, imidazole, DMF, 70°C; ii: NBS, aq. acetone, –30°C; (c) i: $BnNH_2$, $Ti(O^iPr)_4$, then $NaBH_3CN$, EtOH, rt; ii: TBAF, THF, rt; iii: H_2, Pd, AcOH.



Scheme 18.

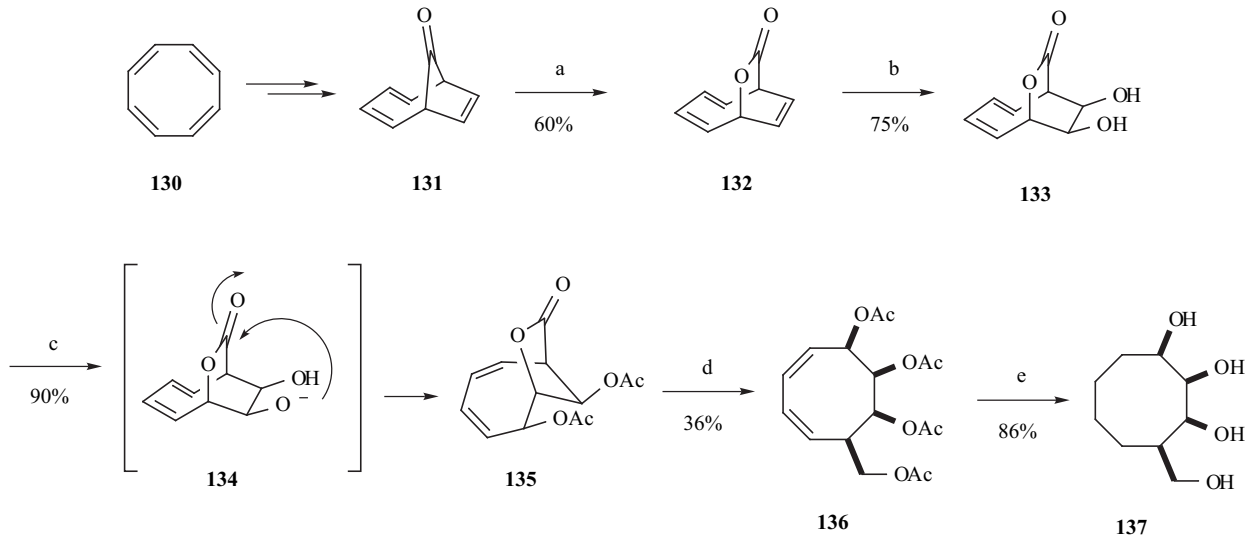
Conditions: (a) $(H_2C{=}CH)_2CuCNLi_2$, THF, –78 to 20°C; (b) i: TBSCl, imidazole, DMF; ii: O_3, CH_2Cl_2, MeOH; iii: $P(OMe)_3$; (c) SmI_2, THF, –20 to 0°C, ^{t}BuOH, HMPA.

cycloheptanone **125** by silylation of the free secondary hydroxyl and dithioketal hydrolysis. Reductive amination of **125** followed by removal of the protecting groups finally produced enantiomerically pure aminocycloheptitol **126** in good yield.

The reductive pinacol coupling of acyclic 1,ω-dialdehyde compounds was exploited by the same research group [12] to prepare optically pure polyhydroxylated cyclooctanes starting from L-*ido* bis-epoxide **47**. Thus, for example (Scheme **18**), reductive coupling of dialdehyde **127** (ex diene **48**) using samarium diiodide in the presence of *tert*-butanol and HMPA furnished a 1:1 diastereomeric mixture of *cis*- and *trans*-configured cyclitols **128** and **129** in an acceptable yield.

Related chemistry was also exploited by König [31] to assemble unprecedented ten-membered cyclic enediynes embodying four adjacent hydroxyl functions with a D,L-*ido* configuration.

A clever approach to cyclooctitols from inexpensive cyclooctatetraene was proposed by Metha and Pallavi [32] for the construction of a series of highly hydroxylated octanoid structures in a racemic format. As shown in Scheme **19**, for all-*cis* tetraol **137**, the synthesis commenced with bicyclo[4.2.1]nonanone **131** (ex cyclooctatetraene **130**) which was subjected to Baeyer-Villiger oxidation to form δ-lactone **132**. OsO_4-catalysed dihydroxylation of **132** proceeded with complete regio- and stereocontrol to furnish the exo-1,2-diol **133**. Acetylation of **133** under conventional



Scheme 19.

Conditions: (a) MCPBA, CH_2Cl_2; (b) OsO_4, NMO; (c) Ac_2O, pyridine; (d) i: $LiAlH_4$, THF; ii: Ac_2O, pyridine; (e) i: H_2, Pd/C (10%), EtOAc; ii: K_2CO_3, MeOH.

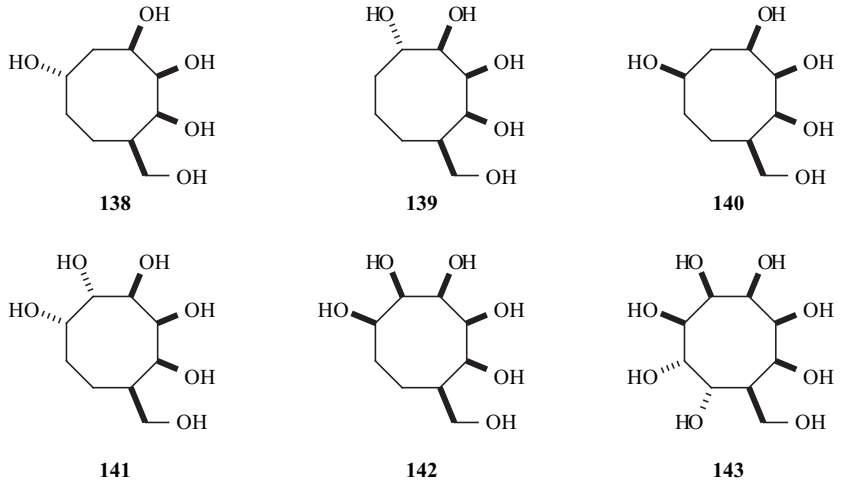
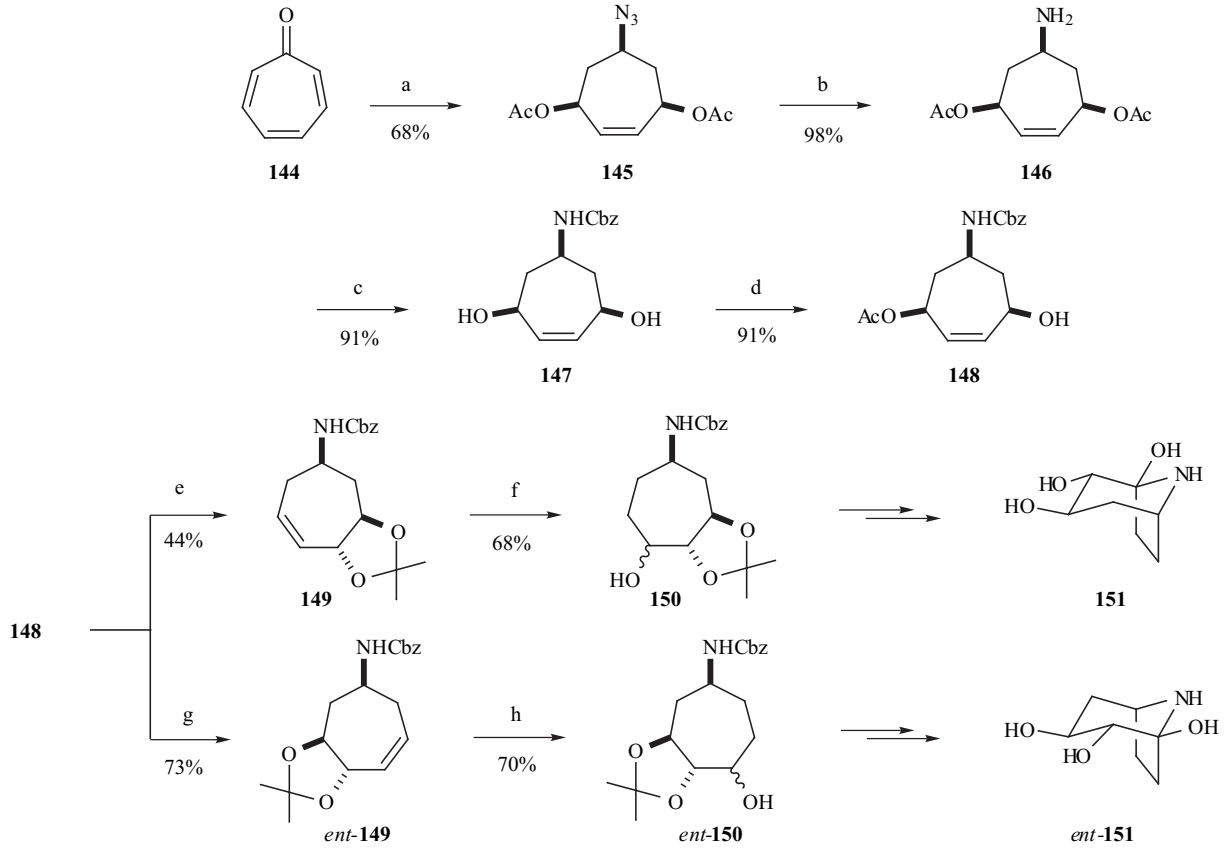


Fig. (2).

Ac_2O/pyridine conditions unexpectedly resulted in a rearrangement leading to γ-lactone **135** *via* the intermediate **134**. Lactone **135** was further elaborated to furnish unsaturated tetraol **136** from which the targeted cyclitol **137** was obtained by double bond reduction and deprotection.

Interestingly, by amplifying the network of hydroxyl functionalities within lactone **135**, a rich repertoire of variously shaped cyclooctane polyols, encompassing the six stereodefined structures **138**-**143** as shown in Fig. (**2**), were assembled.



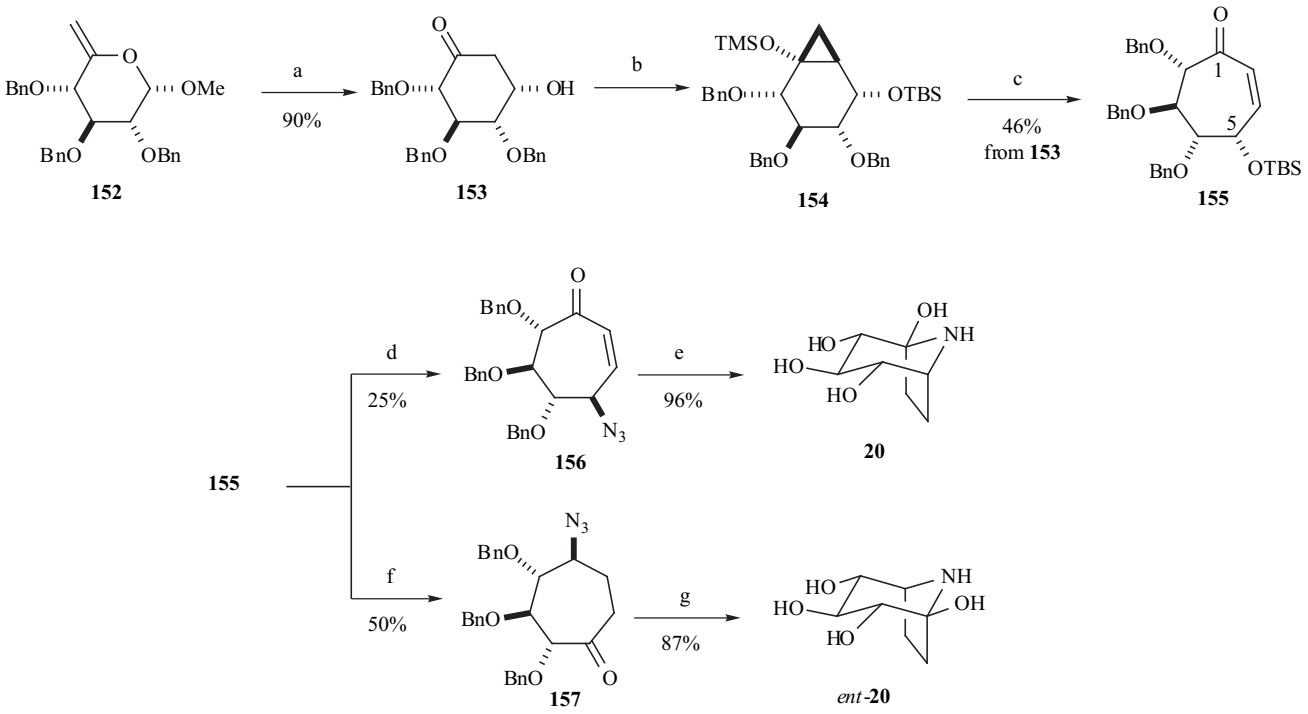
Scheme 20.

Conditions: (a) i: $NaBH_4$, MeOH, –15°C; ii: $LiOAc{\cdot}2H_2O$, $Pd(OAc)_2$, MnO_2, AcOH, benzoquinone; iii: MsCl, Et_3N, 0°C; iv: NaN_3, DMF, 75°C; (b) H_2, Lindlar catalyst, EtOH; (c) i: $ClCO_2Bn$, Na_2CO_3, $EtOAc/H_2O$; ii: K_2CO_3, MeOH; (d) Amano P-30 lipase, isopropenyl acetate, 50°C; (e) i: TBSCl, imidazole, DMF; ii: NaCN, MeOH; iii: MsCl, Et_3N; iv: $NaBH_4$, Ph_2Se_2; v: H_2O_2, THF, CH_2Cl_2; vi: HF, CH_3CN; vii: acetone, Amberlyst 15; (f) $BH_3{\cdot}DMS$, Et_2O, –20°C to 0°C, then 30% H_2O_2, 2N NaOH; (g) i: MsCl, Et_3N, 0°C; ii: $NaBH_4$, Ph_2Se_2, 0°C; iii: H_2O_2, THF, CH_2Cl_2, –78°C to rt; iv: K_2CO_3, MeOH; v: 2,2-dimethoxypropane, *p*-TsOH, acetone; (h) $Thexyl{\cdot}BH_2$, Et_2O, –30°C to –15°C, then 30% H_2O_2, 2N NaOH.

A nice total synthesis of both enantiomers of aminated 6a-carbahexoseptanoses **150** and *ent*-**150**, the immediate precursors of the tropane alkaloids calystegines A_3 (**151** and *ent*-**151**), was accomplished by Johnson and Bis [33, 34], which was centred upon the enzymatic desymmetrisation of *meso* aminotropanediol **147** (Scheme **20**).

Starting with tropone **144**, the azido compound **145** was first synthesised, which was chemoselectively reduced to unsaturated amine **146** by the Lindlar catalyst; next, this material was elaborated to the *meso* carbamate **147**, ready for enzymatic asymmetrisation. Treatment of **147** with Amano P-30 lipase in the presence of isopropenyl acetate resulted in formation of the enantiomerically pure (>98% ee) monoacetate **148**, the common intermediate to both calystegines **151** and *ent*-**151**. Using conventional chemistry, elaboration of the functional groups within tropane **148** resulted in the formation of protected diol **149**, which was subjected to hydroboration-oxidation to deliver triol **150** as a mixture of isomers. Alternatively, **148** was employed to produce *ent*-**150** *via* the intermediacy of carbamate *ent*-**149**. Carbasugars **150** and *ent*-**150** were not far from the targeted alkaloids and these transformations were effected without trouble.

The idea of exploiting the latent symmetry of an intermediate to arrive at the target enantiomers in a divergent manner lay at the base of the strategy developed by Boyer and Lallemand [35] for the total synthesis of **20** and *ent*-**20**. As shown in Scheme **21**, the starting point was the exo-methylene sugar **152** (ex D-glucose), which was subjected to the Ferrier rearrangement to afford cyclohexanone **153**. A sequence of conventional transformations allowed cyclopropane bicycle **154** to be prepared which was quickly enlarged to cycloheptenone **155** by the treatment with iron trichloride in DMF and subsequent dehydrochlorination. Ketone **155** represented the branching point of the synthesis due to its masked symmetric nature. In fact, when the azido group was installed on C_1 and a carbonyl group was introduced onto C_5, compound **157**, the precursor of (–)-calystegine B_2 (*ent*-**20**) was obtained. Whereas, when the azido group was implemented at C_5 leaving the C_1 carbonyl unscathed, compound **156** was obtained which proved to be none other than the precursor of (+)-calystegine B_2 (**20**).



Scheme 21.

Conditions: (a) $Hg(OAc)_2$, acetone, 90% aq. AcOH (1%); (b) i: TBSOTf, 2,6-lutidine, CH_2Cl_2; ii: LDA, TMSCl, THF, –70°C; iii: Et_2Zn, CH_2I_2, toluene, 0°C; (c) i: $FeCl_3$, DMF, 70°C; ii: NaOAc, MeOH, reflux; (d) i: TBAF, THF; ii: MsCl, pyridine; iii: DIBAL-H, Et_2O, – 60°C; iv: NaN_3, DMF; v: Dess-Martin reagent, pyridine, CH_2Cl_2; (e) i: H_2, Pd/C, AcOH, H_2O; ii: Permutite 50, aq. NH_3; (f) i: H_2, Pd/C, EtOH; ii: DIBAL-H, Et_2O, – 60°C; iii: MsCl, DMAP, pyridine; iv: NaN_3, DMF, 80°C; v: TBAF, THF; vi: PCC, CH_2Cl_2; (g) i: H_2, Pd/C, AcOH, H_2O; ii: Permutite 50, aq. NH_3.

These manoeuvres were carried out as indicated and enabled the synthesis to be completed in style.

7. CLOSING REMARKS AND FUTURE DIRECTIONS

Nature has taken simple five- and six-membered carbocycles rings and endowed those scaffolds with a rich array of functionalities and stereochemistry, generating a huge number of bioactive molecular entities. The medium-sized cyclitol family is a different matter however; this is a small, almost neglected subclass of carbohydrate mimics. Although a diverse range of biochemical and biological activities are expected for these compounds, to date

relatively little is known about the biology of this molecular repertoire. Nonetheless, a vast array of structural and stereochemical issues have emerged and have been dealt within this article. These findings enrich the interesting field of future design and synthesis of potentially significant biological agents. The interesting topology exhibited in this family of compounds has provided the synthetic organic chemists with a variable and challenging set of targets, and it is expected that synthetic work in this subject will continue to provide chemists with novel and viable approaches. It seems likely that additional members of this subclass of ring-expanded carbohydrate mimics will soon be available to chemical synthesis and will set the stage for extensive investigations in the biological domain.

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