Polycyclitols — Novel conduritol and carbasugar hybrids as new glycosidase inhibitors[1]

Goverdhan Mehta and Senaiar S. Ramesh

Abstract: A family of novel carbasugar analogues (bicyclitols) based on *cis*-hydrindane and *cis*-decalin frameworks has been conceptualized. These novel entities can be regarded as conduritol and carbasugar hybrids. Syntheses of these polyhydroxylated entities have been achieved in stereo- and regioselective manners, starting from the readily available Diels–Alder adducts of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and appropriate dienophiles like cyclopentadiene or *p*-benzoquinone, that embody a masked 7-ketonorbornenone moiety. Thermally induced chelotropic elimination of CO from the appropriately functionalized 7-ketonorbornenone derivatives to deliver annulated bicyclic 1,3-cyclohexadiene derivatives was the key step in this synthetic endeavor. Further oxy-functionalization of the 1,3-cyclohexadiene moiety delivered the targeted polycyclitols. A preliminary investigation of the glycosidase inhibitory potency of these bicyclitols, identified compounds **18** and **54** as potent and selective inhibitors of α-glucosidase (yeast).

Key words: carbasugar, conduritol, glycomimics, glycosidase inhibitors.

Résumé : On a conceptualisé une nouvelle famille d'analogues de carbasucres (bicyclitols) reposant sur des squelettes de *cis*-hydrindane et de *cis*-décaline. Ces nouvelles entités peuvent être considérées comme des hybrides du conduritol et des carbasucres. Des synthèses de ces entités polyhydroxylées ont été réalisées de façons stéréo- et régiosélectives à partir d'adduits de Diels–Alder facilement accessibles du 5,5-diméthoxy-1,2,3,4-tétrachlorocyclopentadiène et de diénophiles appropriés, tels le cyclopentadiène ou la *p*-benzoquinone, qui comportent une portion 7-cétonorbornénone marquée. L'étape clé de ces synthèses implique une élimination chélotropique thermiquement induite de CO à partir des dérivés fonctionnalisés d'une façon appropriée de la 7-cétonorbornénone qui permet d'obtenir les dérivés cyclohexa-1,3-diènes bicycliques annelés. Une oxy-fonctionnalisation subséquente de la portion cyclohexa-1,3-diène conduit aux polycyclitols recherchés. Une étude préliminaire du pouvoir inhibiteur de la glycosidase de ces bicyclitols a permis d'identifier les composés **18** et **54** comme actifs et comme inhibiteurs sélectifs de l'α-glucosidase (levure).

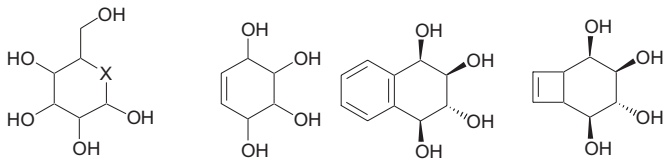
Mots clés : carbasucre, conduritol, glycomimique, inhibiteurs de la glycosidas.

[Traduit par la Rédaction]

Introduction

Glycosidases and related enzymes are crucial in many biological processes that are vital for the normal functioning of cells. Hence, inhibitors of these carbohydrate-processing enzymes have received increased attention in the past few decades from a synthetic as well as a biological activity perspective. These pursuits have been largely fuelled by the realization of their potential as therapeutic agents for the treatment of a variety of carbohydrate-mediated diseases like diabetes, cancer, AIDS, and viral infections (1, 2). The basic premise for the design of glycosidase inhibitors has been to generate transition state mimics by replacing the endocyclic oxygen atom of a monosaccahride by a carbon (carbasugar, **1**) or nitrogen atom (azasugar, **2**). The lack of a glycosidic linkage in these entities, which otherwise resemble the monosaccharides in shape, size, and functionalization, renders them hydrolytically stable. In this context, a range of carbasugars, azasugars, and their analogues, with diverse functionalization and stereochemical features have been devised, and their glycosidase inhibitory activities evaluated (1, 2). Additionally, conduritols **3** (1,2,3,4-tetrahydroxy-5-cyclohexenes) and their various derivatives have also attracted attention because of their glycosidase inhibitory properties (3). Several bicyclic and tricyclic conduritol variants like **4** and **5** have also been synthesized and evaluated for their efficacy against various glycosidases (4).

Naturally occurring alkaloids like 1-deoxynojirimycin (**6**) can be regarded as simple azasugar analogues of D-glucose and have been found to be potent inhibitors of α- and β-



1 X = CH_2
2 X = NH

3 **4** **5**

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Dedicated in appreciation of the many notable contributions of Professor Howard Alper to chemistry.

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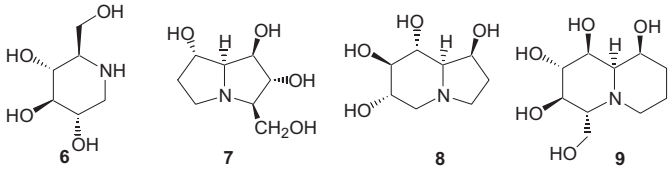
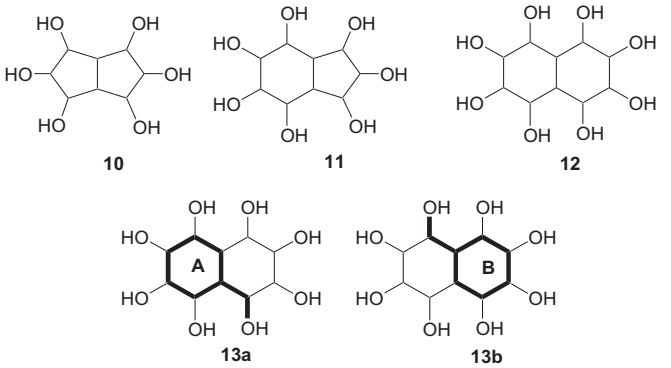
glucosidases. Besides nojirimycins, several other mono- and bicyclic alkaloids based on polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, indolizidine, and quinolizidine frameworks have also been identified as carbohydrate mimics. Typical examples include bicyclic pyrrolizidine alkaloid alexine **7**, indolizidine alkaloid castanospermine **8**, and quinolizidine alkaloid **9** (5).

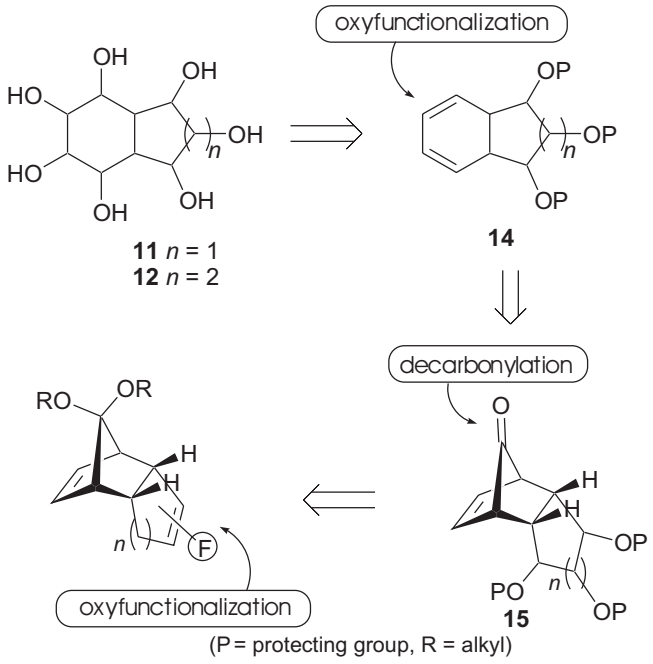


Spurred by the heightened interest in the design of potent inhibitors of glycosidases and inspired by the structures of bicyclic alkaloids **7**–**9**, we have conceived of a new family of polyhydroxylated diquinanes **10**, hydrindanes **11**, and decalins **12**, collectively termed as "polycyclitols", as potential glycomimics (6, 7). Among these bicyclitols, **11** and **12** can be considered as ring-annulated carbasugar entities and more interestingly, the decalin polyol **12** can be regarded as a hydrid of two carbasugars A and B (see bold portions in **13a** and **13b**). The presence of the additional hydroxyl groups on the annulus, it is presumed, may provide additional binding points for these analogues at the receptor site. The effect of annulation on the biological profile of biomolecules can be profound, as seen in the case of the natural glycosidase inhibitors, deoxynojirimycin **6** and castanospermine **8**. The former, a nitrogen analogue of glucose, inhibits yeast α-glucosidase, but is inactive against almond β-glucosidase. On the other hand **8**, a ring-annulated analogue of **6**, is a potent inhibitor of β-glucosidase, but exhibited no inhibition against yeast α-glucosidase (5). The bicyclitols **11** and **12** conceptualized here have a similar structural relationship to carbasugars as castanospermine **8** has to deoxynojirimycin **6**. Indeed, these bicyclitols can be visualized as the carbon analogues of castanospermine **8** and other bicyclic alkaloids exhibiting glycosidase activity. Alternatively, these novel bicyclic entities can be regarded as annulated conduritol, with **12** being a hydrid of two conduritols with shared, common ring junction carbon atoms.



Herein, we report the stereo- and regioselective synthesis of the newly conceptualized polyhydroxylated carbocyclic entities, with as many as nine (in **11**) and 10 (in **12**) stereogenic centers, starting from readily available Diels–Alder adducts, following fairly general and flexible synthetic sequences. We also report on the glycosidase inhibitory activity of the newly synthesized polycyclitols, two of which have exhibited an impressive and selective inhibition of yeast α-glucosidase.

Scheme 1. Retrosynthetic analysis of **11** and **12**.



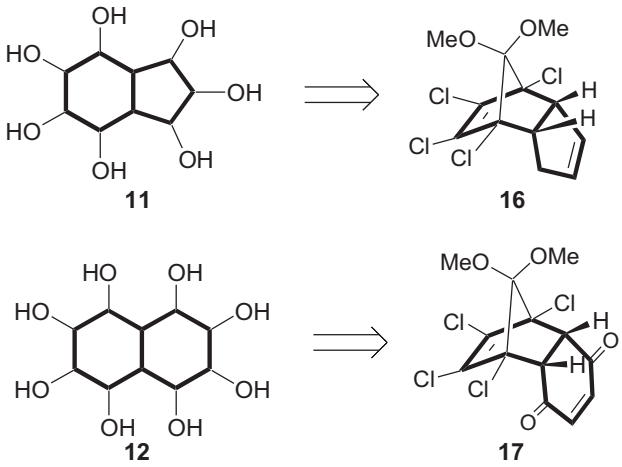
Results and discussions

Retrosynthetic analysis

A general retrosynthetic analysis for accessing hydrindane **11** and decalin **12** based bicyclitols is depicted in Scheme 1. It was visualized that the hydroxyl group pattern on the six-membered ring could be generated through oxyfunctionalization of diene **14** (n = 1, 2), which in turn could be obtained by the thermal or photochemical decarbonylation of the 7-ketonorbornyl moiety in **15**. The precursor tricyclic ketones **15** (n = 1, 2) are readily obtainable via Diels–Alder cycloaddition between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and an appropriate cyclic dienophile (Scheme 1).

Thus, tricyclic precursors **16** and **17** were obtained via a Diels–Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and cyclopentadiene or *p*-benzoquinone, respectively. While the tricyclic endo-adduct **16** was to serve as the starting point for the hydrindane based polyols **11** (see bold portion), the benzoquinone derived Diels–Alder endo-adduct **17** was chosen as the starting material for the decalin based polyols **12** (bold portion) (Scheme 2). The main advantage in the choice of endo-adducts **16** and **17** as our basic launching pad was that their tricyclic framework built on a norbornyl matrix confers on them a topological bias towards exo-selectivity. This built-in facial bias in **16** and **17** was, therefore, expected to ensure stereoselective operations, particularly oxyfunctionalization maneuvers. The foregoing retrosynthetic analysis provided

Scheme 2.



the road map for the synthesis of the targeted new family of bicyclitols.

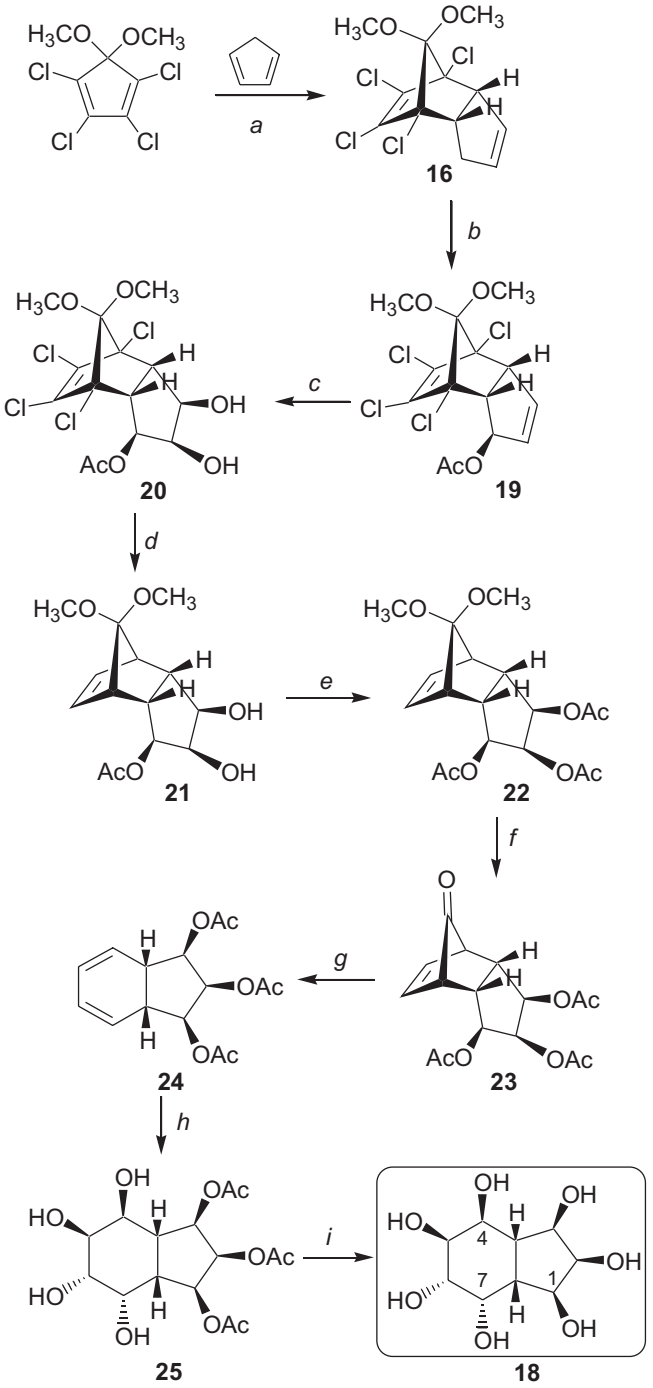
Synthesis of hydrindane based bicyclitols

The synthesis of the first galacto-configured *cis*-hydrindane-based polyol **18**, emanated from the tricyclic Diels–Alder adduct **16**, obtained by the [4 + 2] cycloaddition of 5,5,-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and cyclopentadiene (Scheme 3) (8). Adduct **16** was subjected to allylic oxidation, using in-situ-generated $Mn(OAc)_3$, to deliver the exo-acetate derivative **19** (Scheme 3) (9). The exo-acetate **19** was subjected to dihydroxylation following the Upjohn catalytic OsO_4–NMMO protocol (10) to generate diol **20**, which on reductive dehalogenation (**21**) followed by acetylation furnished the C_s-symmetric triacetate **22** (Scheme 3) (8*a*). All three acetate functionalities in **22** were cis disposed, owing to the exo-propensity of the topology of the endo-fused system **19**.

The tricyclic 7-ketal derivative **22** upon exposure to Amberlyst-15 in moist acetone, resulted in ketal deprotection and furnished the 7-ketonorbornenone derivative **23** (Scheme 3). As contemplated earlier, decarbonylation in **23** through thermal activation by heating in nitrobenzene (~160 °C) furnished the C_s-symmetric cyclohexa-1,3-diene derivative **24** in moderate yield (Scheme 3) (11). The cyclic 1,3-diene moiety in **24** was subjected to exhaustive dihydroxylation employing the catalytic OsO_4–NMMO protocol (10) to furnish a single tetrahydroxy-triacetate **25**, which was devoid of any symmetry. Loss of symmetry during the double dihydroxylation reaction on the diene secured the stereochemistry of **25**, which required the two hydroxylations on diene **24** to occur from the exo- and endo-faces, respectively, of the *cis*-hydrindane (Scheme 3). Mild base hydrolysis of triacetate **25** gave the targeted heptahydroxy bicyclitol **18**, an annulated 5a-carbagalactose derivative.

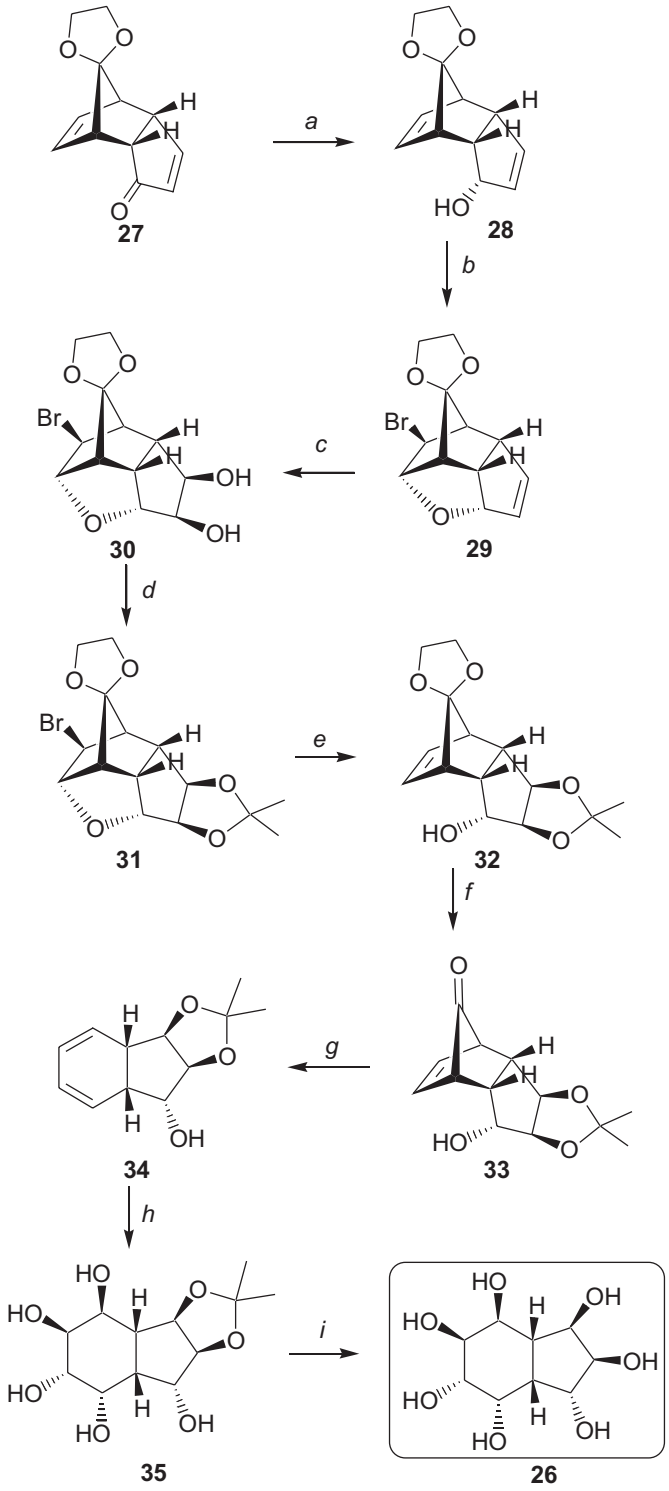
The synthesis of diastereomeric *cis*-hydrindane-based carbasugar analogue **26** started from the readily available endo-tricyclic enone **27**. Enone **27** was obtained following the protocol reported by Schuda et al. (12) involving [4 + 2] dimerization of the ethylene ketal of 2,4-cyclopentadienone and chemoselective deketalization. Enone **27** was converted to endo-allylic alcohol **28** via DIBAL-H reduction from the exo-face and the norbornene double bond was protected

Scheme 3. Reagents and conditions: (*a*) toluene, reflux, 24 h, 70%; (*b*) $Mn(OAc)_3$, AcOH, 70 °C, 1 h, 64%; (*c*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 12 h, 80%; (*d*) Na, liq. NH_3, THF, EtOH, –33 °C, 30 min, 72%; (*e*) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 2 h, 88%; (*f*) Amberlyst-15, acetone, rt, 1 h, 89%; (*g*) $C_6H_5NO_2$, heat, 160 °C, 2 h, 50%; (*h*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 48 h, 88%; (*i*) aq. NaOH, rt, 1 h, 60%.



through intramolecular bromoetherification to give **29** (Scheme 4). The cyclopentene double bond in **29** was stereoselectively dihydroxylated and the resulting *cis*-diol **30** was protected as acetonide **31**. The norbornene double bond

Scheme 4. Reagents and conditions: (*a*) DIBAL-H (1 mol/L in hexane), CH_2Cl_2, –78 °C, 15 min, 90%; (*b*) NBS, CH_2Cl_2, rt, 3 h, 80%; (*c*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH, (5:5:2), rt, 12 h, 82%; (*d*) Amberlyst-15, acetone, 4 Å molecular sieves, rt, 3 h, 95%; (*e*) Zn dust, AcOH, MeOH, rt, 4 h, 85%; (*f*) Amberlyst-15, acetone, reflux, 3 h, 81%; (*g*) $C_6H_5NO_2$, 160 °C, 4 h, 67%; (*h*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 48 h, 83%; (*i*) 30% CF_3COOH, rt, 30 min, 89%.

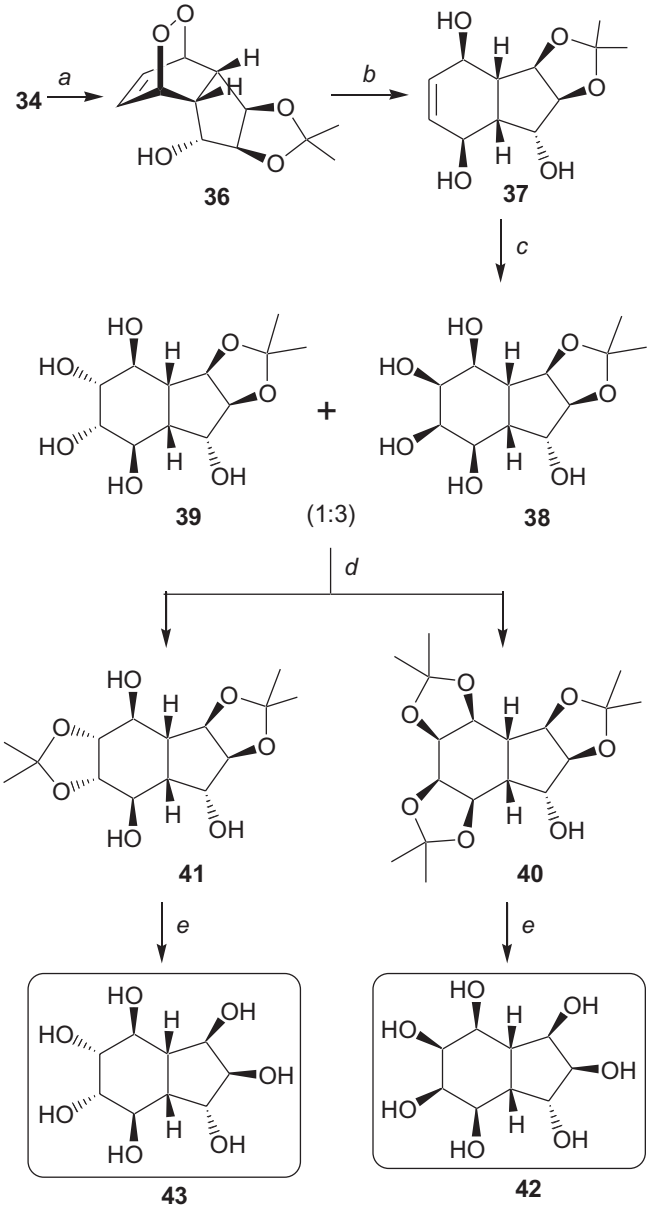


was now unmasked with Zn metal to render **32** (Scheme 4) (8*a*). The ketal moiety in **32** was carefully deprotected in the presence of Amberlyst-15 to furnish the crystalline 7-norbornenone derivative **33** (Scheme 4). Tricyclic ketone **33**, on heating in nitrobenzene (160 °C), quite readily converted to the 1,3-cyclohexadiene derivative **34** through extrusion of CO (11). At this point, it was recognized that diene **34** was well suited for generating stereochemically diverse oxygenation patterns through appropriate sequencing of the oxyfunctionalization protocol.

Towards this end, the *cis*-hydrindane diene **34** was subjected to exhaustive dihydroxylation under catalytic OsO_4 conditions to furnish the pentahydroxy compound **35** (Scheme 4). The stereochemical assignment for **35** followed from an incisive analysis of the spectral data in analogy with that of compound **25**. In addition, it is expected that the directing influence of the free α-hydroxyl group at the peri position in diene **34** would lead to the preferred stereostructure of **35**. Mild acid hydrolysis of the acetonide protecting group in **35** furnished the targeted heptahydroxylated hydrindane **26**, which was an epimer of **18** at C1. Polyol **26**, like **18**, embodies a 5a-carbagalactose moiety, with the hydroxylated carbocyclic annulation spanning the C_{5a}-C_6 atoms of the carbasugar (Scheme 4).

In another stereochemical variation in the hydroxylation pattern on the hydrindane framework, [4 + 2] cycloaddition of singlet oxygen ($^1O_2$) was effected on **34** to deliver endoperoxide **36** as the sole product in good yield with the addition of $^1O_2$ to **34** from the preferred convex face of the molecule (Scheme 5) (13). The peroxide linkage in **36** was cleanly cleaved with lithium aluminum hydride to yield the 1,4-diol derivative **37** and further dihydroxylated under the standard catalytic OsO_4 conditions to give a 3:1 mixture of tetrols **38** and **39**, respectively. All attempts to separate the mixture of tetrols at this stage were unsuccessful. At this point, we reasoned that one of the stereoisomers from the dihydroxylation should have the hydroxyl groups in an all cis orientation while the other diastereomer would have a trans–syn–trans arrangement of the hydroxyl groups on the six-membered ring. Hence, it was reasoned that the protection of the hydroxyl groups in the mixture of **38** and **39** as the corresponding acetonides, would result in the formation of a tris-acetonide derivative in the case of **38** and a bis-acetonide in the case of **39** and would thus be rendered amenable to separation. Consequently, the mixture of **38** and **39** was treated with Amberlyst-15 in acetone medium to furnish, as anticipated, tris-acetonide **40** and bis-acetonide **41**, respectively, which were then readily separable by column chromatography (Scheme 5). The major isomer **40** originates from dihydroxylation of **37** from the syn-face of allylic alcohols, an outcome that is in conflict with Kishi's rule (14) for dihydroxylation of allylic alcohols. The stereochemical outcome in this case can be attributed to the overwhelming topological preference of the *cis*-hydrindane moiety in **37** to react from the less-hindered, convex face to yield syn-dihydroxylated **38** as the major product. The acetonide deprotection in **40** and **41** in the presence of 30% trifluoroacetic acid cleanly furnished the diastereomeric heptahydroxylated hydrindanes **42** and **43**, respectively (Scheme 5). The bicyclic carbasugar analogues **42** and **43** correspond to the

Scheme 5. Reagents and conditions: (*a*) O_2, hν, methylene blue, $CHCl_3$, 20 °C, 8 h, 90%; (*b*) $LiAlH_4$, THF, rt, 1 h, 54%; (*c*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 1 h; (*d*) Amberlyst-15, acetone, 4 Å molecular sieves, followed by silica gel separation (62% for **40** and 21% for **41**); (*e*) 30% CF_3COOH, 92% for **42**, and 88% for **43**.

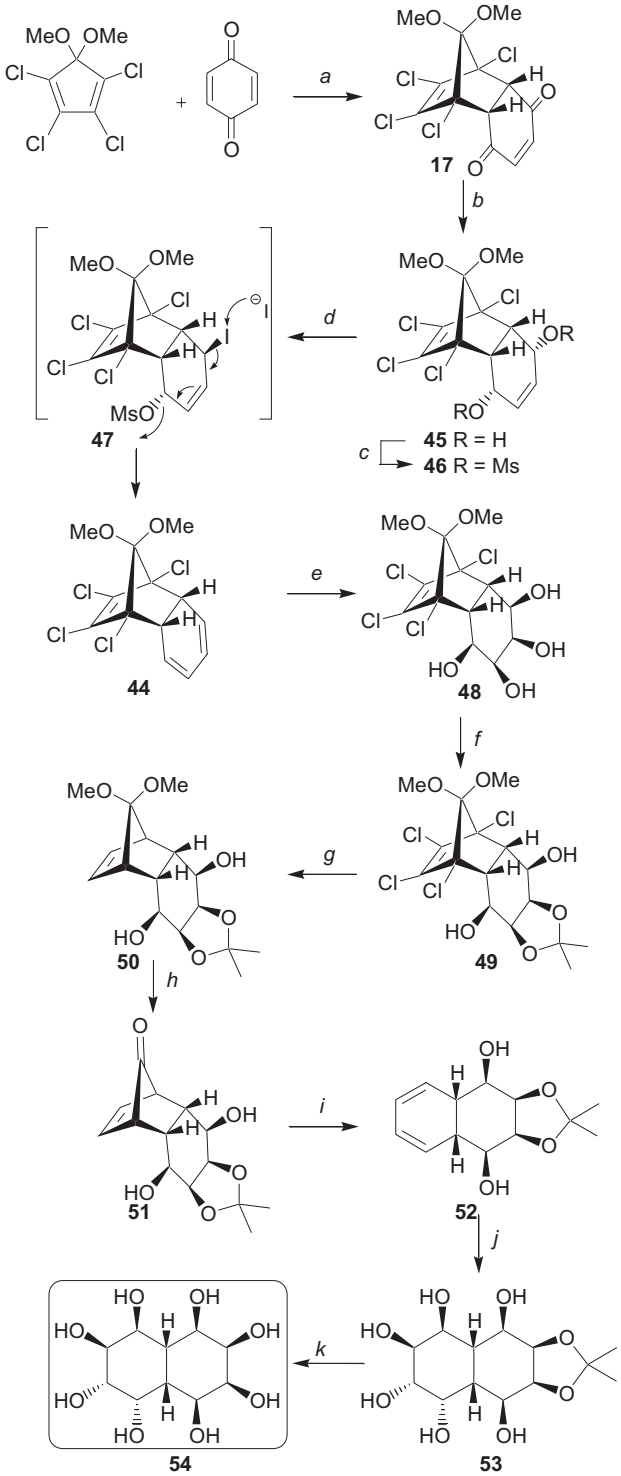


α-allopyranose and α-mannopyranose configurations, respectively.

Synthesis of *cis*-decalin-based bicyclitols

The synthetic venture towards *cis*-decalin-based carbasugar analogues of type **12** emanated from the readily available Diels–Alder adduct **17** of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and *p*-benzoquinone (Scheme 6) (15). Tricyclic quinone **17** was elaborated to the symmetrical tricyclic diene **44** essentially following a literature procedure (16). Adduct **17** was subjected to Luche reduction ($NaBH_4$-$CeCl_3{\cdot}7H_2O$) (17) to give endo,endo-diol **45** and was further

Scheme 6. Reagents and conditions: (*a*) toluene, reflux, 24 h, 83%; (*b*) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 10 min, 69%; (*c*) MsCl, pyridine, DMAP, CH_2Cl_2, rt, 24 h, 72%; (*d*) NaI, $C_2H_5COCH_3$, reflux, 8 h, 80%; (*e*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 48 h, 66%; (*f*) Amberlyst-15, acetone, 4 Å molecular sieves, rt, 3 h, 75%; (*g*) Na, liq. NH_3, THF, EtOH, –33 °C, 30 min, 49%; (*h*) Amberlyst-15, acetone, rt, 2 h, 98%; (*i*) $C_6H_5NO_2$, 160 °C, 4 h, 63%; (*j*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 48 h, 85%; (*k*) 30% CF_3COOH, rt, 30 min, 95%.



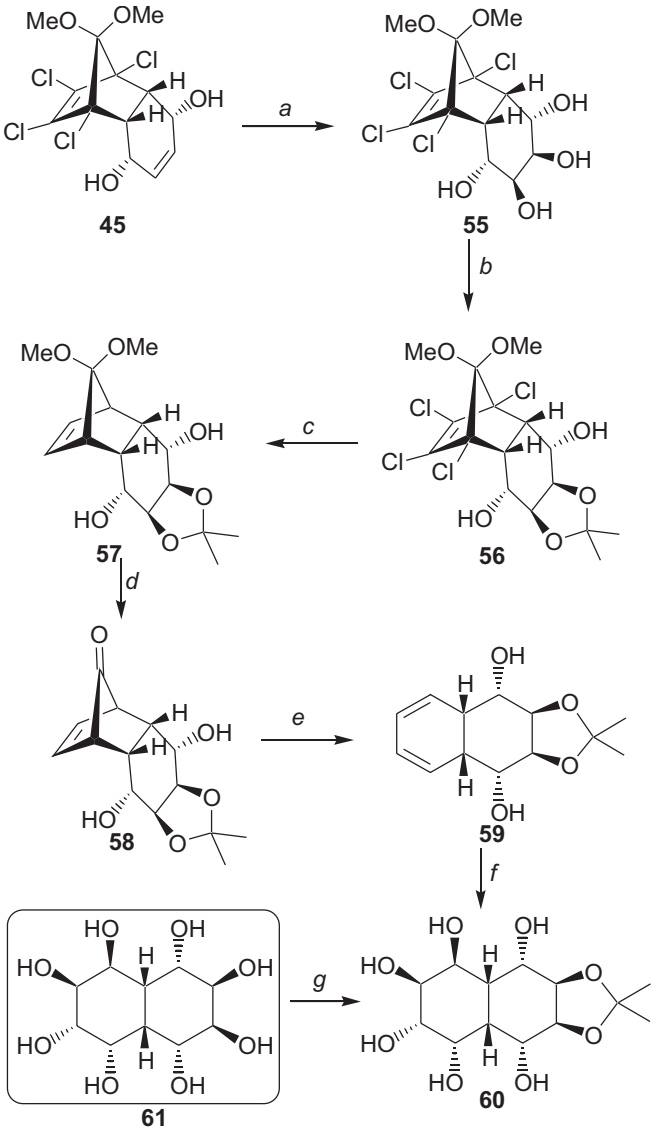
converted to dimesylate **46**, and NaI-mediated 1,4-elimination (via **47**) in **46** led to the desired C_s-symmetric tricyclic diene **44** (Scheme 6). Exhaustive catalytic-OsO_4-mediated dihydroxylation on tricyclic diene **44** furnished tetrol **48** (Scheme 6). The symmetrical nature of the ^1H and ^{13}C NMR spectra of **48** indicated an all cis relationship of the hydroxyl groups, which implied that the double dihydroxylation occurred from the exo-face of the tricyclic diene. Acetonide protection of the vicinal hydroxyl groups in tetrol **48** resulted in selective formation of the symmetrical monoacetonide **49** (Scheme 6). Acetonide **49** was subjected to reductive dechlorination in Na – liquid ammonia milieu to give the symmetrical olefin **50** in a modest yield (Scheme 6). The ketal deprotection in **50** proceeded quite uneventfully to furnish the crystalline 7-norbornenone derivative **51** in quantitative yield (Scheme 6). As contemplated earlier, thermally induced decarbonylation in tricyclic ketone **51** led to the C_s-symmetric bicyclic cyclohexadiene derivative **52** (11).

Bicyclic diene **52** was subjected to exhaustive dihydroxylation employing catalytic OsO_4 to stereoselectively furnish the hexahydroxylated decalin **53** as a single diastereomer (Scheme 6). The stereochemical assignments for **53** were done on the basis of loss of symmetry (NMR) during dihydroxylation and in analogy with earlier observations for compound **25** (see Scheme 3). The acetonide protection in **53** was relieved by exposure to 30% trifluoroacetic acid to deliver the targeted octahydroxylated decalin based carbasugar analogue **54**. Bicyclitol **54** can be regarded as embodying an α-carbagalactopyranose configuration on a *cis*-decalin framework (Scheme 6).

To generate stereochemical variations of hydroxyl groups on the decalin framework, tricyclic endo,endo-diol **45** was dihydroxylated stereoselectively to furnish tetrol **55** (Scheme 7). Dihydroxylation in **55** occurred exclusively from the convex face because of the exo-propensity of the tricyclic system built on a norbornyl scaffold, and the structure of **55** was secured on the basis of symmetry (C_s) revealed by its ^1H and ^{13}C NMR spectra. The cis-diol moiety in **55** was protected using Amberlyst-15 in acetone medium to furnish acetonide **56**. Reductive dechlorination in **56** under Birch reduction conditions delivered the C_s-symmetric olefin **57** (Scheme 7). The ketal moiety in **57** was next deprotected to unmask the carbonyl group and furnish norbornenone derivative **58** (Scheme 7). On thermal activation, tricyclic ketone **58** underwent smooth decarbonylation to furnish the C_s-symmetric bicyclic cyclohexadiene derivative **59** (Scheme 7) (11). Bicyclic diene **59** was diastereomeric with **52** (Scheme 6), and hence the protocol adopted earlier for the elaboration of **52** could be extended to diene **59** for the realization of the targeted octahydroxy polyol.

The 1,3-cyclohexadiene moiety in **59** was double dihydroxylated (OsO_4–NMMO) to furnish the hexahydroxylated *cis*-decalin derivative **60**, which was devoid of any symmetry as indicated by its NMR (^1H and ^{13}C) spectral analysis. Hence, as observed in the case of **25** and **53** (vide supra), the two sequential dihydroxylations on the diene moiety had occurred from opposite faces, thereby generating a cis–trans–cis arrangement of the hydroxyl groups in **60** (Scheme 7). The acetonide deprotection in **60** delivered octahydroxylated decalin **61**, a diastereomeric sibling of **54**.

Scheme 7. Reagents and conditions: (*a*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 1.5 h, 75%; (*b*) Amberlyst-15, acetone, 4 Å molecular sieves, rt, 1 h, 82%; (*c*) Na, liq. NH_3, THF, EtOH, –33 °C, 40 min, 88%; (*d*) Amberlyst-15, acetone, rt, 2 h, 95%; (*e*) $C_6H_5NO_2$, 160 °C, 3 h, 43%; (*f*) OsO_4 (1 mol%), NMMO, Me_2CO–H_2O–*t*-BuOH (5:5:2), rt, 48 h, 73%; (*g*) 30% CF_3COOH, rt, 30 min, 90%.



With the availability of the designer polycyclitols **18**, **26**, **42**, **43**, **54**, and **61**, our attention was turned towards the evaluation of their efficacy as glycosidase inhibitors.

Glycosidase inhibitory potencies of bicyclitols

Evaluation of the glycosidase inhibitory activity of the newly synthesized bicyclitols **18**, **26**, **42**, **43**, **54**, and **61** was carried out against various commercially available glycosidases, α-glucosidase (yeast), β-glucosidase (sweet almond), α-galactosidase (green coffee beans), β-galactosidase (*Escherichia coli*), α-mannnosidase (jack bean) and β-mannnosidase (snail acetone powder), using their corresponding *ortho*- or *para*-nitrophenylglycosides at the optimum pH and temperature for each enzyme (see Experimental) (18). All assays

were done up to 1 mmol/L concentration of the polyols. Gratifyingly, the decalin-based carbasugar analogue **54** exhibited an impressive inhibition of yeast α-glucosidase, with an inhibition constant K_i = 12 μmol/L (cf. K_i = 25 μmol/L for deoxynojirimycin). However, the same compound **54** did not show any significant inhibitory activity against almond β-glucosidase up to 1 mmol/L concentration, thus highlighting the selectivity of **54** towards α-glucosidase. To our further delight, the hydrindane-based polyol **18** exhibited a moderate and selective inhibition of yeast α-glucosidase (K_i = 84 μmol/L) but, like **54**, was totally inert to the almond β-glucosidase. Both these compounds failed to elicit any inhibition of the galactosidases and mannosidases. The other polyols **26**, **42**, **43**, and **61** failed to exhibit any significant (<1 mmol/L) inhibitory activity against the glycosidases examined. The lack of inhibitory activity of polyols **26**, **42**, **43**, and **61** when compared with their diastereomeric siblings **18** and **54**, which inhibited α-glucosidase, brings forth the effect of subtle variations in the stereochemical dispositions of the hydroxyl groups on their inhibitory potency against the carbohydrate processing enzymes. At present, the precise reasons for the selective affinity of **18** and **54** against α-glucosidase and the effect of subtle stereochemical variations on their inhibitory activity is not clear and remains a matter that still tickles our curiosity. Further investigations will hopefully illuminate this puzzling observation.

Conclusion

We have delineated a relatively short and fairly general synthetic access to novel bicyclic carbasugar analogues based on *cis*-decalin and *cis*-hydridane frameworks with as many as eight to seven hydroxyl groups, respectively. The synthetic approaches leading to secured stereochemistry at all the stereogenic centers (nine in **11** and 10 in **12**) in the bicyclitols are notable for their simplicity and stereoselectivity. The decalin-based polyol **54** and hydrindane bicyclitol **18** exhibited significant and selective inhibition of yeast α-glucosidase.

Experimental section

General

Melting points were recorded on a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR 410 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-LA 300 or a Bruker AMX 400 or a Bruker DRX 500 instrument in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are reported with respect to tetramethylsilane (Me_4Si) as the internal standard (for ^{1}H NMR) and the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C NMR). The chemical shifts are expressed in parts per million (δ) downfield from Me_4Si. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (*J*), whenever discernible, have been reported in Hz. Low resolution mass spectra (LR-MS) were recorded either on a Shimadzu GC–MS-QP 5050A spectrometer (EI or CI mode) or on a Q-TOF Micromass mass spectrometer. High resolution mass spectra (HR-MS) were recorded on a Q-TOF Micromass mass spectrometer. Elemental analyses were obtained on a Carlo Erba 1106 CHN analyzer. Silica gel from Acme (100–200 mesh particle size) was used for column chromatography. All moisture- and air-sensitive reactions were performed under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions using standard syringe–septum techniques. Yields reported are of isolated materials judged homogeneous by thin layer chromatography (TLC) and NMR. All solvent extracts were washed with water/brine as appropriate and dried over anhydr. Na_2SO_4 before removal of the solvent on a rotary evaporator under reduced pressure. The glycosidase enzymes and their corresponding substrates (*ortho*- or *para*-nitrophenolates) were purchased from the Sigma Chemical Company, USA.

1,7,8,9-Tetrachloro-10,10-dimethoxytricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ylacetate (19)

Cyclopentadiene (12 g, 0.18 mol) was added to a solution of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (50 g, 0.18 mol) in dry toluene (80 mL) and the resulting solution was refluxed for 24 h. Excess solvent was distilled off from the reaction mixture and the residue obtained was distilled under reduced pressure (130–140 °C/5 torr, 1 torr = 133.3224 Pa) to yield adduct **16** (41.6 g, 70%). To a solution of the $Mn(OAc)_2 \cdot H_2O$ (10.8 g, 44 mmol) in AcOH (40 mL) was added Ac_2O (14 mL) and the mixture was refluxed for 20 min. Solid $KMnO_4$ (1.74 g, 10.1 mmol) was carefully added and the resulting mixture was refluxed for an additional 30 min. After cooling to 70 °C, adduct **16** (12 g, 36.4 mmol) and KBr (720 mg, 6 mmol) were added and the reaction mixture was stirred at the same temperature until complete consumption of the starting material. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The filtrate was extracted with hexane (3 × 100 mL) and the residue obtained after the usual work-up, was chromatographically purified on a silica gel column (5% ethyl acetate – hexane) to afford the exo-acetate **19** (9 g, 64%), mp 111 to 112 °C (lit. value (8*a*) mp 110 °C). IR (Nujol, cm^{-1}): 1740.

10,10-Dimethoxy-3,5-di(acetyloxy)tricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl acetate (22)

To the solution of exo-acetate **19** (4 g, 10.3 mmol) in acetone–water–*t*-BuOH (5:5:1, 25 mL), OsO_4 (26 mg, 1 mol%), and 50% aq. NMMO solution (2.65 mL, 11.3 mmol) were added sequentially. The pale yellow reaction mixture was stirred at room temperature for 12 h prior to quenching of the reaction by addition of solid $NaHSO_3$ (1 g). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a residue, which on chromatographic purification on a silica gel column furnished diol **20** (3.5 g, 80%). The solution of diol **20** (2.2 g, 5.2 mmol) in dry THF (25 mL) and absolute EtOH (10 mL) was added to freshly distilled liquid ammonia (250 mL) and to this solution, freshly cut pieces of sodium (1 g) were carefully added, until the blue color of the solution persisted. The reaction mixture was stirred for 15 min, prior to quenching the reaction with solid NH_4Cl (1 g). Ammonia was allowed to evaporate overnight, the residue obtained was diluted with ice-cooled water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The usual work-up and evaporation of volatiles under reduced pressure fur-

nished a residue (**21**) that was dissolved in dry pyridine (10 mL), then Ac_2O (1 mL) and catalytic DMAP (100 mg) were added. The reaction mixture was stirred at room temperature for 2 h before diluting with water. The reaction mixture was extracted with CH_2Cl_2 (3 × 60 mL) and after the usual work-up was purified by silica gel column chromatography (20% ethyl acetate – hexane) to furnish triacetate **22** (1.2 g, 64%), mp 140–142 °C. IR (Nujol, cm^{-1}): 1725.

3,4,5-Tri(acetyloxy)tricyclo[5.2.1.0^{2,6}]dec-8-en-10-one (23)

A solution of ketal **22** (200 mg, 0.543 mmol) in moist acetone (8 mL) was stirred with Amberlyst-15 (~30 mg) at room temperature for 1 h. The resin was filtered through a cotton plug and the filtrate was concentrated to give a residue, which was subjected to chromatography on a silica gel column (15% ethyl acetate – hexane) to furnish ketone **23** (155 mg, 89%). IR (Nujol, cm^{-1}): 3036, 1778, 1743. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.69 (t, J = 2.4 Hz, 2H), 5.37 (t, J = 3.4 Hz, 1H), 4.55–4.49 (m, 2H), 3.16–3.13 (m, 2H), 2.98–2.96 (m, 2H), 2.14 (s, 3H), 2.05 (s, 6H). LR-MS (CI) m/z: 323 [M^+ + 1]. Anal. calcd. for $C_{16}H_{18}O_7$: C 59.62, H 5.63; found: C 59.66, H 5.69.

1,3-Di(acetyloxy)-2,3,3a,4,5,7a-hexahydro-1*H*-2-indenyl acetate (24)

Ketone **23** (85 mg, 0.264 mmol) was heated to 160 °C in nitrobenzene solvent (2 mL) for 2 h. The reaction mixture was cooled to 80 °C and the nitrobenzene was distilled under reduced pressure. The residue obtained was chromatographed on a silica gel column (10% ethyl acetate – hexane) to deliver the crystalline cyclohexadiene triacetate **24** (39 mg, 50%), mp 198.6–199.9 °C. IR (Nujol, cm^{-1}): 1740. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.88–5.84 (m, 2H, C=C*H*), 5.70–5.66 (m, 2H, C=C*H*), 5.25 (t, J = 4.5 Hz, 1H, C*H*OAc), 5.09–5.05 (m, 2H, C*H*OAc), 3.10 (br s, 2H), 2.09 (s, 3H, COCH_3), 2.07 (s, 6H, COCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.1 (2C, *C*OCH$_3$), 170.0 (*C*OCH$_3$), 124.7 (2C, C=CH), 122.4 (2C, C=CH), 78.0 (2C, *C*HOAc), 69.5 (*C*HOAc), 38.9 (2C, *C*H$_{bridgehead}$), 20.7 (2C, CO*C*H$_3$), 20.6 (CO*C*H$_3$). LR-MS (EI, 70 eV) m/z: 252 [M^+ – Ac + 1]. Anal. calcd. for $C_{15}H_{18}O_6$: C 61.22, H 6.16; found: C 61.70, H 6.42.

1,3-Di(acetyloxy)-4,5,6,7-tetrahydroxyperhydro-2-indenyl acetate (25)

To a solution of diene **24** (35 mg, 0.119 mmol) in acetone–water–*t*-BuOH (5:5:2, 2 mL), catalytic OsO_4 (0.3 mg, 1 mol%) and 50% aq. NMMO (83 μL, 0.357 mmol) were sequentially added at 0 °C. The resulting pale yellow reaction mixture was stirred at room temperature for 48 h. The reaction was cooled to 0 °C, prior to quenching by addition of solid $NaHSO_3$ (10 mg). The resulting mixture was diluted with ethyl acetate (15 mL), filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue obtained was subjected to silica gel column chromatography (5% methanol – ethyl acetate) to afford tetrol **25** (38 mg, 88%). IR (Nujol, cm^{-1}): 3290, 1743. ^{1}H NMR (300 MHz, D_2O) δ: 5.38 (t, J = 6.3 Hz, 1H), 5.27 (dd, J = 6.3, 1.8 Hz, 1H), 5.08 (t, J = 6.9 Hz, 1H), 3.97 (br s, 1H), 3.90 (t, J = 3.9 Hz, 1H), 3.78 (dd, J = 7.8, 3.6 Hz, 1H), 3.66 (dd, J = 8.1, 3 Hz, 1H), 2.52 (m, 1H), 2.40 (br s, 1H), 1.99 (s, 6H, COCH_3), 1.95 (s, 3H, COCH_3). ^{13}C NMR (75 MHz, D_2O) δ: 174.2 (*C*OCH$_3$), 174.1 (*C*OCH$_3$), 173.2 (*C*OCH$_3$), 75.0, 74.7, 71.7, 71.1, 70.0, 69.0, 68.6, 45.6 (CH$_{bridgehead}$), 43.5 (CH$_{bridgehead}$), 20.9 (*C*OCH$_3$), 20.8 (CO*C*H$_3$), 20.5 (CO*C*H$_3$). Anal. calcd. for $C_{15}H_{22}O_{10}$: C 49.72, H 6.12; found: C 49.53, H 6.52.

Bicyclitol 18

Tetrol **25** (22 mg, 0.061 mmol) was stirred with aq. NaOH (0.5 mol/L, 200 μL) at room temperature for 1 h and the volatiles were removed under reduced pressure. The residue obtained was dissolved in double distilled water and the solution was filtered with Dowex cation-exchange resin (50 W × 8, H^+ form). The filtrate was concentrated to furnish **18** (8 mg, 60%). ^{1}H NMR (300 MHz, D_2O) δ: 4.13 (t, J = 4.3 Hz, 1H), 3.98–3.85 (m, 4H), 3.73 (dd, J = 7.3, 4.0 Hz, 1H), 3.61 (dd, J = 7.6, 2.8 Hz, 1H), 2.21–2.08 (m, 2H). ^{13}C NMR (100 MHz, D_2O) δ: 76.4 (*C*HOH), 75.0 (*C*HOH), 74.6 (*C*HOH), 74.4 (*C*HOH), 73.1 (*C*HOH), 71.9 (*C*HOH), 71.8 (*C*HOH), 48.3 (CH$_{bridgehead}$), 47.2 (CH$_{bridgehead}$). LR-MS (CI) m/z: 237 [M^+ + 1]. Anal. calcd. for $C_9H_{16}O_7$: C 45.76, H 6.83; found: C 45.84, H 6.79.

(2*R,3*R**,7*S**,8*R**,9*S**)-5,5-Dimethylspiro[dihydro[1,3]dioxolane]-2,13-4,6-dioxatetracyclo[8.2.1.0^{2,9}.0^{3,7}]tridecen-8-ol (32)**

To a magnetically stirred solution of alcohol **28** (8) (2 g, 9.7 mmol) in CH_2Cl_2 (20 mL), NBS (2.1 g, 11.6 mmol) was added in one portion at room temperature and the resulting suspension was stirred for 3 h. Upon complete consumption of the starting material (TLC), the reaction mixture was diluted with CH_2Cl_2 (80 mL) and water (50 mL). Following the usual work-up, subsequent evaporation of the solvent gave a residue, which on chromatographic purification on a silica gel column furnished **29** (2.2 g, 80%). Osmium tetroxide (16 mg, 1 mol%) and 50% aq. NMMO (2.28 mL, 9.75 mmol) was added to a solution of bromoether **29** (1.85 g, 6.5 mmol) in an acetone–water–*t*-BuOH (5:5:2, 25 mL) solvent system, and the resulting pale yellow reaction mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to ice-bath temperature, diluted with ethyl acetate (70 mL), and the osmate ester was hydrolyzed by addition of solid $NaHSO_3$ (500 mg). The solution was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to furnish the crude diol **30** (1.76 g). The crude diol **30** was dissolved in dry acetone (20 mL) and Amberlyst-15 (300 mg) and powdered molecular sieves (1 g) were added. The reaction mixture was stirred for 3 h at room temperature and then was filtered through a Celite pad. The filtrate obtained on complete removal of the solvent was chromatographed on a silica gel column to furnish acetonide **31** (1.76 g, 75%). To a solution of bromoether **31** (1 g, 2.78 mmol) in MeOH (15 mL), acetic acid (0.1 mL) and Zn dust (550 mg, 8.34 m atom) were added sequentially at room temperature and the resulting suspension was stirred for 4 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue obtained was diluted with CH_2Cl_2 (60 mL) and evaporation of the solvent furnished a residue, which on purification on a silica gel column gave alcohol **32** (660 mg, 85%), mp 96 to 97 °C (lit. value (8*a*) mp 98 °C). IR (Nujol, cm^{-1}): 3400.

(2*R,3*R**,7*S**,8*R**,9*S**)-8-Hydroxy-5,5-dimethyl-4,6-dioxatetracyclo[8.2.1.0^{2,9}.0^{3,7}]tridec-11-en-13-one (33)**

Ketal **32** (350 mg, 1.24 mmol) was stirred with Amberlyst-15 (~50 mg) in moist acetone (10 mL), under reflux for 3 h. Upon complete consumption of the starting material, the reaction mixture was cooled, diluted with acetone (25 mL), and the resin was filtered through a cotton plug. The filtrate was concentrated under reduced pressure and the residue obtained was chromatographed on a silica gel column (30% ethyl acetate – hexane) to give ketone **33** (237 mg, 81%), mp 179 to 180 °C. IR (Nujol, cm^{-1}): 1771. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.64 (m, 1H), 6.48 (m, 1H), 4.36 (dd, *J* = 9.3, 5.4 Hz, 1H), 4.10 (d, *J* = 5.4 Hz, 1H), 4.03 (t, *J* = 5.4 Hz, 1H), 3.20 (dt, *J* = 8.7, 3.9 Hz, 1H), 3.14–2.95 (m, 3H), 1.44 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.1 (C=O), 135.2 (C=*C*H), 130.3 (C=*C*H), 110.8 (C_q), 89.4 (*C*H$_{acetonide}$), 82.0 (*C*H$_{acetonide}$), 81.3 (*C*HOH), 49.2, 49.0 (CH), 47.1 (CH), 44.4 (CH), 27.9 (CH$_{3acetonide}$), 25.3 (CH$_{3acetonide}$). LR-MS (EI, 70 eV) *m*/*z*: 237 [M$^+$ + 1]. Anal. calcd. for $C_{13}H_{16}O_4$: C 66.09, H 6.83; found: C 66.46, H 7.22.

(3a*R,3b*S**,7a*R**,8*R**,8a*S**)-2,2-Dimethyl-3b,7a,8,8a-tetrahydro-3a*H*-indeno[1,2-*d*][1,3]dioxol-8-ol (34)**

A solution of ketone **33** (220 mg, 0.932 mmol) in nitrobenzene (6 mL) solvent was heated, with vigorous stirring, to 160 °C and reacted for 4 h. Upon complete consumption of the starting material (TLC), the reaction mixture was cooled to 80 °C and the solvent was distilled off under reduced pressure. The resulting dark brown residue was charged on the silica gel column and chromatographed (25% ethyl acetate – hexane) to give diene **34** (130 mg, 67%) as a white solid, mp 190.6–191.2 °C. IR (Nujol, cm^{-1}): 3470. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.17 (dd, *J* = 9.9, 5.1 Hz, 1H, C= C*H*), 5.80 (dd, *J* = 9.9, 4.8 Hz, 2H, C= C*H*), 5.72–5.70 (m, 1H), 4.74 (d, *J* = 6.0 Hz, 1H, H$_{acetonide}$), 4.45 (d, *J* = 6 Hz, 1H, H$_{acetonide}$), 4.03 (br s, 1H, C*H*OH), 3.08–3.05 (m, 2H, H$_{bridgehead}$), 2.26 (d, *J* = 2.4 Hz, 1H, H$_{bridgehead}$), 1.42 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 129.2 (C=*C*H), 127.6 (C=*C*H), 123.3 (C=*C*H), 122.9 (C=*C*H), 110.4 (C_q), 87.3 (*C*H$_{acetonide}$), 83.9 (*C*H$_{acetonide}$), 79.6 (*C*HOH), 45.3 (CH), 39.6 (CH), 26.8 (CH$_{3bridgehead}$), 24.3 (CH$_{3bridgehead}$). LR-MS (EI, 70 eV) *m*/*z*: 208 [M$^+$]. Anal. calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 68.88, H 7.52.

(3a*R,3b*R**,4*S**,5*S**,6*S**,7*S**,7a*S**,8*R**,8a*S**)-2,2-Dimethylperhydroindeno[1,2-*d*][1,3]dioxole-4,5,6,7,8-pentaol (35)**

To a solution of diene **34** (45 mg, 0.216 mmol) in an acetone–water–*t*-BuOH (5:5:2, 4 mL) solvent system, catalytic OsO_4 (1 mol%, 0.5 mg) and 50% aq. NMMO (151 μL, 0.648 mmol) were added at 0 °C. The resulting pale yellow reaction mixture was stirred at room temperature for 48 h, before diluting with ethyl acetate (10 mL) and quenching with solid $NaHSO_3$ (10 mg). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (5% methanol – ethyl acetate) to afford pentaol **35** (49 mg, 83%). ^{1}H NMR (300 MHz, D_2O) δ: 4.70–4.65 (m, 1H), 4.35 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.06 (m, 1H), 3.98–3.93 (m, 2H), 3.69–3.58 (m, 2H), 2.59–2.51 (m, 1H, H$_{bridgehead}$), 2.41–2.37 (m, 1H, H$_{bridgehead}$), 1.32 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ: 111.0 (C_q), 87.9 (*C*H$_{acetonide}$), 83.0 (*C*H$_{acetonide}$), 77.1 (*C*HOH), 70.5, 70.4, 70.3, 69.2, 45.8, 45.6, 25.8 (C$_{bridgehead}$), 23.4 (C$_{bridgehead}$). LR-MS (EI, 70 eV) *m*/*z*: 258 [M$^+$ – H_2O].

Bicyclitol 26

Acetonide **35** (25 mg, 0.09 mmol) was stirred in 30% trifluoroacetic acid (1 mL) at room temperature for 30 min until all the starting material had been consumed. The volatiles were removed under reduced pressure to furnish polyol **26** (19 mg, 89%). ^{1}H NMR (300 MHz, D_2O) δ: 4.19–4.15 (m, 1H), 4.01–3.81 (m, 4H), 3.68–3.64 (m, 1H), 3.61–3.56 (m, 1H), 2.40–2.33 (m, 1H), 2.13–2.07 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 77.9, 77.2, 73.6, 72.9, 72.3, 68.4, 67.4, 45.9, 41.8. LR-MS (CI) *m*/*z*: 237 [M$^+$ + 1]. Anal. calcd. for $C_9H_{16}O_7$: C 45.76, H 6.83; found: C 45.88, H 7.32.

(2*S,3*R**,7*S**,8*R**,9*R**)-5,5-Dimethyl-4,6,11,12-tetraoxatetracyclo[8.2.2.0^{2,9}.0^{3,7}]tetradec-13-en-8-ol (36)**

A slow stream of oxygen gas was bubbled through a solution of diene **34** (60 mg, 0.288 mmol) in chloroform (6 mL), contained in a specially designed reaction flask with an outer water jacket, in the presene of methylene blue (~5 mg) as the sensitizer and under irradiation from a 500 W tungsten lamp. The temperature of the reaction mixture was maintained at 20 °C by circulating cold water through the outer jacket of the reaction flask. Upon complete consumption of the starting material (TLC, 8 h), the solvent was evaporated under reduced pressure. The residue obtained was chromatographed over a silica gel column (20% ethyl acetate – hexane) to furnish the endo-peroxide **36** (62 mg, 90%). IR (KBr, cm^{-1}): 3445. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78 (m, 1H, C=C*H*), 6.59 (m, 1H, C=C*H*), 4.85–4.80 (m, 2H, H$_{peroxy}$), 4.36 (dd, *J* = 9.0, 5.2 Hz, 1H, H$_{acetonide}$), 4.17 (t, *J* = 5.2 Hz, 1H, H$_{acetonide}$), 4.11 (d, *J* = 6.0 Hz, 1H), 3.33 (dt, *J* = 8.7, 4.0 Hz, 1H, H$_{bridgehead}$), 3.08 (dd, *J* = 8.7, 5.2 Hz, 1H), 1.47 (s, 3H, C*H*$_3$), 1.26 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.3 (C=*C*H), 130.2 (C=*C*H), 111.7 (C_q), 88.0, 80.9, 79.9, 70.9 (*C*H$_{peroxy}$), 70.8 (*C*H$_{peroxy}$), 44.5, 44.0, 27.8, 25.2. LR-MS (CI) *m*/*z*: 241 [M$^+$ + 1]. Anal. calcd. for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 60.21, H 6.83.

(3a*R,3b*R**,4*R**,7*S**,7a*S**,8*R**,8a*S**)-2,2-Dimethyl-3b,4,7,7a,8,8a-hexahydro-3a*H*-indeno[1,2-*d*][1,3]dioxole-4,7,8-triol (37)**

$LiAlH_4$ (12 mg, 0.312 mmol) was added to a solution of the endo-peroxide **36** (50 mg, 0.208 mmol) in dry THF (6 mL) at 0 °C under an atmosphere of N_2. The resulting suspension was stirred at room temperature for 1 h, before quenching the reaction by careful addition of ethyl acetate (15 mL) followed by addition of a cold, satd. Na_2SO_4 solution (2 mL). After dilution with ethyl acetate, the aluminium salts were filtered through a Celite pad. Evaporation of the solvent under reduced pressure, after the usual work-up, gave a residue that was chromatographed over a silica gel column (60% ethyl acetate – hexane) to furnish the 1,4-diol **37** (27 mg, 54%), mp 210 to 211 °C. IR (Nujol, cm^{-1}): 3444. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.69 (br s, 2H, C=CH), 4.71

(d, *J* = 5.7 Hz, 1H), 4.42 (d, *J* = 5.7 Hz, 1H), 4.13 (br s, 1H), 4.07 (d, *J* = 4.8 Hz, 1H), 3.81 (d, *J* = 7.8 Hz, 1H), 2.36 (m, 1H), 1.90 (t, *J* = 8.4 Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.6 (C=*C*H), 129.9 (C=*C*H), 111.5 (C_q), 86.0, 83.2, 77.7, 66.5, 62.5, 46.3, 46.1, 25.7, 23.5. LR-MS (CI) *m*/*z*: 243 [M^+ + 1]. Anal. calcd. for $C_{12}H_{18}O_5$: C 59.49, H 7.49; found: C 59.63, H 7.52.

(3a*R,3b*R**,4*S**,5*S**,6*R**,7*R**,7a*S**,8*R**,8a*S**)-2,2-Dimethylperhydroindeno[1,2-d][1,3]dioxole-4,5,6,7,8-pentaol (38) and (3a*R**,3b*R**,4*S**,5*R**,6*S**,7*R**,7a*S**,8*R**,8a*S**)-2,2-dimethylperhydroindeno[1,2-d][1,3]dioxole-4,5,6,7,8-pentaol (39)**

To a solution of diol **37** (55 mg, 0.227 mmol) in an acetone–water–*t*-BuOH (5:5:2, 5mL) solvent system, catalytic OsO_4 (0.6 mg, 1 mol%), and 50% aq. NMMO (64 μL, 0.272 mmol) were added sequentially at 0 °C and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of solid $NaHSO_3$ (10 mg), diluted with ethyl acetate (15 mL), and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to yield a residue, whose ^{1}H NMR spectrum was found to be a mixture of diastereomers **38** and **39** (60 mg) in a 3:1 ratio. However, their chromatographic separation was unsuccessful and the mixture was used as such for the next step.

(3a*R,3b*S**,6a*S**,6b*S**,6*R**,9a*S**,10*R**,10a*R**,10b*R**)-2,2,5,5,8,8-Hexamethylperhydrodi[1,3]dioxolo-[4′,5′:1,2:4′,5′:6,7]indeno[4,5-*d*][1,3]dioxole-10-ol (40) and (3a*R**,3b*R**,4*S**,4a*R**,7a*S**,8*R**,8a*R**,9*R**,9a*S**)-2,2,6,6-tetramethylperhydro[1,3]dioxolo[4′,5′:1,2]indeno[5,6-*d*][1,3]dioxole-4,8,9-triol (41)**

The solution of mixture of **38** and **39** (60 mg) in dry acetone (10 mL) was treated sequentially with Amberlyst-15 resin (~5 mg) and 4 Å molecular sieves (~30 mg) and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue obtained was charged on a silica gel column and chromatographed with a 10% ethyl acetate – hexane solvent system to furnish trisacetonide **40** (48 mg, 62%). Further elution of the column with 30% ethyl acetate –hexane gave bisacetonide **41** (14 mg, 21%). Compound **40:** mp 210 to 211 °C. IR (Nujol, cm^{-1}): 3361. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.75 (d, *J* = 6.0 Hz, 1H), 4.42 (dd, *J* = 9.6, 5.1 Hz, 2H), 4.36 (dd, *J* = 13.5, 5.1 Hz, 1H), 4.28 (dd, *J* = 6.9, 4.5 Hz, 1H), 4.08 (d, *J* = 5.1 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 1H), 2.64–2.55 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H). LR-MS (EI, 70 eV) *m*/*z*: 356 [M^+]. Compound **41**: mp 190 to 191 °C. IR (Nujol, cm^{-1}): 3372. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.74 (br d, *J* = 5.1 Hz, 1H), 4.49 (d, *J* = 5.1 Hz, 1H), 4.41 (br d, *J* = 5.4 Hz, 1H), 4.15–4.10 (m, 2H), 4.02–3.96 (m, 1H), 3.73 (dd, *J* = 12.3, 6.9 Hz, 1H), 2.53–2.50 (m, 2H), 1.51 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), and 1.30 (s, 3H). LR-MS (EI, 70 eV) *m*/*z*: 317 [M^+ + 1].

Bicyclitol 42

Trisacetonide **40** (35 mg, 0.098 mmol) was stirred with 30% trifluoroacetic acid (500 μL) at room temperature for 30 min. Upon complete consumption of the starting material, the volatiles were removed under reduced pressure to afford **42** (21 mg, 92%). ^{1}H NMR (300 MHz, D_2O) δ: 4.03 (dd, *J* = 6.9, 4.5 Hz, 1H), 3.89–3.85 (m, 2H), 3.74–3.70 (m, 3H), 3.62 (dd, *J* = 6.6, 3 Hz, 1H), 2.46 (dd, *J*= 14.4, 6.9 Hz, 1H), 2.11 (dd, *J* = 12.3, 6.9 Hz, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 78.9, 77.6, 72.7, 72.2, 71.5, 70.8, 70.1, 47.5, 41.0. LR-MS (CI) *m*/*z*: 237 [M^+ + 1]. Anal. calcd. for $C_9H_{16}O_7$: C 45.76, H 6.83; found: C 45.53, H 6.79.

Bicyclitol 43

Bisacetonide **41** (10 mg, 0.032 mmol) was treated with 30% trifluoroacetic acid (150 μL) and the resulting biphasic mixture was stirred vigorously at room temperature for 30 min. The volatiles were removed under reduced pressure to furnish **43** (7 mg, 88%). ^{1}H NMR (300 MHz, D_2O) δ: 4.10 (t, 1H, *J* = 5.7 Hz), 4.00 (t, 1H, *J* = 5.4 Hz), 3.86 (t, *J* = 5.4 Hz, 1H), 3.83 (dd, *J* = 14, 7.2 Hz, 1H), 3.75–3.70 (m, 1H), 3.66–3.61 (m, 2H), 2.36 (dd, *J* = 15, 6.9 Hz, 1H), 1.93 (dd, *J* = 14.4, 6.9 Hz, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 77.8, 77.1, 74.0, 73.2, 72.3, 72.0, 68.8, 48.6, 44.2. LR-MS (CI) *m*/*z*: 237 [M^+ + 1]. Anal. calcd. for $C_9H_{16}O_7$: C 45.76, H 6.83; found: C 45.77, H 6.98.

(2*R,3*S**,6*R**,7*S**)-1,8,9,10-Tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-diol (45)**

To a solution of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (63 mL, 0.36 mol) in dry toluene (300 mL), *p*-benzoquinone (40 g, 0.37 mol) was added and the resulting solution was refluxed for 24 h. Excess solvent was distilled off under reduced pressure and the residue obtained was recrystallized from hexane to furnish adduct **17** (110 g, 83%). Adduct **17** (10 g, 26.8 mmol) was dissolved in dry MeOH (150 mL) and to this solution at 0 °C under an inert atmosphere, $CeCl_3 \cdot 7H_2O$ (1 g, 10 mol%) and $NaBH_4$ (2 g, 53.6 mmol) were added in sequential portions. The resulting solution was stirred at the same temperature for 10 min until the starting material was completely consumed. The reaction mixture was diluted with ethyl acetate (150 mL) and quenched by the addition of water (80 mL). The organic layer was separated and after the usual work-up furnished residue **45** (6.9 g, 69%), mp 162 to 163 °C (lit. value (16) mp 167 to 168 °C). IR (Nujol, cm^{-1}): 3450.

(2*R,7*S**)-1,8,9,10-Tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undeca-3,5,9-triene (44)**

To a magnetically stirred solution of diol 45 (5 g, 13.3 mmol) in dry CH_2Cl_2 (25 mL), triethylamine (5.6 mL, 39.9 mmol), DMAP (162 mg, 10 mol%), and methanesulphonyl chloride (2.5 mL, 29.2 mmol) were added sequentially at 0 °C under an inert atmosphere and the resulting solution was stirred at room temperature for a further 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) prior to quenching the reaction by adding water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The residue obtained by the usual work-up was subjected to chromatographic purification on a silica gel column (35% ethyl acetate – hexane) to furnish dimesylate **46** (5.1 g, 72%). Dimesylate **46** (8.4 g, 15.7 mmol) was dissolved in 2-butanone (60 mL) and so-

dium iodide (8.2 g, 54.9 mmol) was added to this solution. The dark brown solution was then refluxed for 8 h. The reaction mixture was cooled to ice bath temperature and diluted with diethylether (100 mL) and water (80 mL). The usual work-up and evaporation of the solvent under reduced pressure gave a residue, which on purification on a silica gel column (hexane) furnished the tricyclic diene **44** (4.3 g, 80%), mp 162 to 163 °C (lit. value (16) mp 167 to 168 °C).

(2*R,3*S**,4*S**,5*R**,6*R**,7*S**)-1,8,9,10-Tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undec-9-ene-3,4,5,6-tetraol (48)**

A solution of diene **44** (1.2 g, 3.51 mmol) in an acetone–water–*t*-BuOH solvent system (5:5:2, 50 mL) was treated sequentially with catalytic OsO_4 (8 mg, 1 mol%) and 50% aq. NMMO (2.5 mL, 10.53 mmol). The resulting pale yellow solution was stirred vigorously at room temperature for 48 h, during which all the starting material was consumed (TLC). The reaction was quenched by addition of solid $NaHSO_3$ (500 mg), diluted with ethyl acetate (100 mL), and filtered through a Celite pad. The filtrate was concentrated under reduced pressure to give a residue, which was chromatographed on a silica gel column (70% ethyl acetate – hexane) to furnish tetrol **48** (950 mg, 66%). IR (Nujol, cm^{-1}): 3430. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.76 (br s, 2H), 3.66 (br s, 2H), 3.63 (s, 3H), 3.56 (s, 3H), 3.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 129.7 (2C, C=*C*Cl), 111.7 (C_q), 70.7 (2C, *C*HOH), 68.0 (2C, *C*HOH), 52.8 (2C, *C*-Cl), 52.5 (2C, OMe), 51.8 (2C, CH). LR-MS (EI, 70 eV) *m*/*z*: 410 [M$^+$ + 1].

(2*R,3*S**,4*S**,8*R**,9*R**,10*S**)-1,11,12,13-Tetrachloro-14,14-dimethoxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-ene-3,9-diol (49)**

Tetrol **48** (950 mg, 2.32 mmol) was stirred with Amberlyst-15 (~100 mg) and 4 Å molecular sieves (500 mg) in dry acetone (30 mL) at room temperature for 3 h. Upon complete consumption of the starting material, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to give a residue, which was chromatographed over a short silica gel column (25% ethyl acetate – hexane) to afford acetonide **49** (783 mg, 75%), mp 180.1–181.4 °C. IR (Nujol, cm^{-1}): 3346. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.44 (s, 2H), 3.63 (s, 3H), 3.59 (s, 3H), 3.11–3.01 (m, 2H), 2.29 (d, *J* = 6.6 Hz, 2H), 1.57 (s, 3H), 1.37 (s, 3H). LR-MS (EI, 70 eV) *m*/*z*: 451 [M$^+$ + 1]. Anal. calcd. for $C_{16}H_{20}O_6Cl_4$: C 42.69, H 4.48; found: C 42.84, H 4.80.

(2*R,3*R**,4*R**,8*S**,9*S**,10*S**)-14,14-Dimethoxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-ene-3,9-diol (50)**

Liquid ammonia (300 mL) was distilled into a 250 mL three-necked round-bottomed flask equipped with a condenser, KOH guard tube, and septum. Acetonide **49** (10 g, 22.22 mmol) in dry THF (40 mL) and absolute EtOH (40 mL) were added to the flask. Small pieces of freshly cut sodium were introduced into the reaction mixture with stirring at –33 °C until the blue color persisted. The mixture was stirred for 30 min and solid NH_4Cl (1 g) was added. The excess ammonia was allowed to evaporate, and a cold aq. satd. NH_4Cl solution (50 mL) and water (100 mL) were added to the resulting residue, which was subsequently extracted with ethyl acetate (3 × 200 mL). Removal of the volatiles, followed by purification of the residue by silica gel column chromatography (50% ethyl acetate – hexane) gave the dechlorinated product **50** (3.4 g, 49%), mp 173–175 °C. IR (Nujol, cm^{-1}): 3460, 3380. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.93 (s, 2H, C=C*H*), 4.38 (s, 2H), 3.24 (s, 3H), 3.17 (s, 5H), 3.05 (s, 2H), 2.60–2.50 (m, 2H), 1.91 (s, 1H), 1.88 (s, 1H), 1.53 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.8 (2C, C=*C*H), 118.9 (C_q), 110.0 (C_q), 76.6 (2C, $C_{acetonide}$), 68.8 (2C, *C*HOH), 52.0 (O*C*H$_3$), 50.0 (O*C*H$_3$), 46.8 (2C, CH), 40.4 (2C, CH), 25.9 (CH), 24.0 (CH). LR-MS (EI, 70 eV) *m*/*z*: 312 [M$^+$]. Anal. calcd. for $C_{16}H_{24}O_6$: C 61.52, H 7.74; found: C 61.83, H 7.90.

(2*R,3*R**,4*R**,8*S**,9*S**,10*S**)-3,9-Dihydroxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-en-14-one (51)**

A solution of ketal **50** (1 g, 3.20 mmol) in moist acetone (40 mL) was stirred with Amberlyst-15 (~150 mg) at room temperature for 2 h. Upon complete consumption of the starting material, the reaction mixture was filtered through a cotton plug. The filtrate on concentration gave a solid residue, which on purification by chromatography over a short silica gel column (50% ethyl acetate – hexane) afforded ketone **51** (834 mg, 98%), mp 213–215 °C. IR (Nujol, cm^{-1}): 3270, 1777.

(3a*R,4*R**,4a*S**,8a*R**,9*S**,9a*S**)-2,2-Dimethyl-3a,4,4a,8a,9,9a-hexahydronaphtho[2,3-*d*][1,3]dioxole-4,9-diol (52)**

A solution of ketone **51** (300 mg, 1.13 mmol) in nitrobenzene (15 mL) was heated, with vigorous stirring, at 160 °C for 4 h. Upon complete consumption of the starting material (TLC), the reaction mixture was cooled to 80 °C and the solvent was distilled off under reduced pressure. The residue left behind was chromatographed over a silica gel column (30% ethyl acetate – hexane) to furnish diene **52** (169 mg, 63%) as a colorless solid, mp 189 to 190 °C. IR (KBr, cm^{-1}): 3356. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.87–5.83 (m, 2H, C=C*H*), 5.65–5.61 (m, 2H, C=C*H*), 4.42–4.40 (m, 2H, $H_{acetonide}$), 3.74 (br s, 2H, C*H*OH), 3.00–2.98 (m, 2H, O*H*), 2.70–2.67 (m, 2H), 1.55 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.8 (2C, C=*C*H), 122.6 (2C, C=*C*H), 109.3 (C_q), 74.8 (2C, $C_{acetonide}$), 69.0 (2C, *C*HOH), 35.4 (2C, CH), 26.0 (CH), 24.4 (CH). LR-MS (EI, 70 eV) *m*/*z*: 239 [M$^+$ + 1]. Anal. calcd. for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.90, H 7.72.

(3a*R,4*R**,4a*R**,5*S**,6*S**,7*S**,8*S**,8a*S**,9*S**,9a*S**)-2,2-Dimethylperhydronaphtho[2,3-*d*][1,3]dioxole-4,5,6,7,8,9-hexol (53)**

Diene **52** (25 mg, 0.105 mmol) was treated sequentially with catalytic amounts of OsO_4 (0.2 mg, 1 mol%) and 50% aq. NMMO (54 μL, 0.231 mmol) in an acetone–water–*t*-BuOH solvent system (5:5:2, 5 mL) at 0 °C and the resulting pale yellow reaction mixture was stirred at room temperature for 48 h. The reaction mixture was cooled to 0 °C and diluted with ethyl acetate (20 mL) prior to quenching with

solid $NaHSO_3$ (10 mg). The mixture was filtered through a Celite pad and the filtrate was concentrated. The residue thus obtained was chromatographed over a silica gel column (8% methanol – ethyl acetate) to furnish hexol **53** (27 mg, 85%). IR (Nujol, cm^{-1}): 3350. ^1H NMR (300 MHz, D_2O) δ: 4.46–4.43 (m, 1H), 4.35–4.31 (m, 1H), 4.13–4.11 (br t, *J* = 3.3 Hz, 1H), 3.97 (br dd, *J* = 6.6, 2.7 Hz, 1H), 3.92 (br s, 1H), 3.85 (br dd, *J* = 12.0, 3.0 Hz, 1H), 3.71 (br dd, *J* = 8.7, 2.1 Hz, 1H), 3.64–3.61 (m, 1H), 2.21 (m, 1H), 2.06 (m, 1H), 1.39 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ: 111.1 (C_q), 77.9, 76.6, 72.8, 71.3, 70.9, 70.7, 68.4, 66.2, 40.0 (CH), 38.9 (CH), 26.2, 24.9. LR-MS (EI, 70 eV) *m*/*z*: 289 [$M^+ - H_2O + 1$]. Anal. calcd. for $C_{13}H_{22}O_8$: C 50.97, H 7.24; found: C 50.63, H 7.52.

Bicyclitol 54

Acetonide **53** (20 mg, 0.065 mmol) was stirred vigorously with 30% trifluoroacetic acid (800 μL) at room temperature for 30 min. The volatiles were removed under reduced pressure to furnish **54** (16 mg, 95%). ^1H NMR (300 MHz, D_2O) δ: 4.19 (br s, 1H), 4.00 (br s, 1H), 3.96–3.81 (series of m, 4H), 3.75–3.60 (m, 2H), 2.22–2.18 (m, 2H). ^{13}C NMR (75 MHz, D_2O) δ: 77.0, 76.7, 76.0, 74.2, 73.2, 71.2 (3C), 43.1 (CH), 40.5 (CH). LR-MS (EI, 70 eV) *m*/*z*: 264 [$M^+ - 2$]. Anal. calcd. for $C_{10}H_{18}O_8$: C 45.11, H 6.81; found: C 45.32, H 7.01.

(2*R,3*S**,4*S**,5*R**,6*S**,7*S**)-1,8,9,10-Tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undec-9-ene-3,4,5,6-tetrol (55)**

A solution of diol **45** (1 g, 2.66 mmol) in acetone–water–*t*-BuOH (5:5:2, 15 mL) was treated sequentially with OsO_4 (7 mg, 1 mol%) and 50% aq. NMMO (747 μL, 3.19 mmol) at 0 °C. The resulting pale yellow reaction mixture was stirred at room temperature for 1.5 h, at which point all the starting material had been consumed (TLC). The reaction mixture was cooled to 0 °C and quenched by the addition of solid $NaHSO_3$ (500 mg). The mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue obtained was chromatographed over a silica gel column (30% ethyl acetate – hexane) to furnish **55** (817 mg, 75%). IR (Nujol, cm^{-1}): 3420, 3315, 3245. ^1H NMR (300 MHz, DMSO) δ: 3.83 (br s, 4H), 3.50 (s, 3H), 3.43 (s, 3H), 3.00 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ: 128.7 (2C, C=*C*Cl), 114.6 (C_q), 77.1 (2C, *C*-Cl), 68.4 (2C, *C*HOH), 67.3 (2C, *C*HOH), 52.4 (O*C*H_3), 51.5 (O*C*H_3), 46.2 (2C, CH). LR-MS (EI, 70 eV) *m*/*z*: 374 [$M^+ - Cl + 1$]. Anal. calcd. for $C_{13}H_{16}Cl_4O_4$: C 38.08, H 3.93; found: C 37.88, H 3.88.

(2*R,3*R**,4*S**,8*R**,9*R**,10*S**)-1,11,12,13-Tetrachloro-14,14-dimethoxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-ene-3,9-diol (56)**

To a solution of tetrol **55** (750 mg, 1.829 mmol) in dry acetone (25 mL), Amberlyst-15 (~100 mg) and 4 Å molecular sieve powder (250 mg) were added sequentially and the resulting mixture was stirred at room temperature for 1 h. Upon complete consumption of the starting material (TLC), the reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a solid residue. The residue was chromatographed over a silica gel column (6% ethyl acetate – hexane) to afford acetonide **56** (675 mg, 82%), mp 210–212 °C. IR (KBr, cm^{-1}): 3260. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.43 (s, 2H, $H_{acetonide}$), 4.29 (br s, 2H, *C*HOH), 3.79 (s, 3H, O*C*H_3), 3.57 (s, 3H, O*C*H_3), 3.04 (s, 2H, $H_{bridgehead}$), 1.45 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 129.4 (2C, C=*C*Cl), 114.7 (C_q), 108.4 (C_q), 76.7 (2C, $C_{acetonide}$), 75.6 (2C, *C*-Cl), 65.1 (2C, *C*HOH), 53.1 (OCH_3), 51.7 (OCH_3), 46.3 (2C, *C*H), 26.1 ($CH_{3acetonide}$), 23.3 ($CH_{3acetonide}$). LR-MS (EI, 70 eV) *m*/*z*: 451 [$M^+ + 1$]. Anal. calcd. for $C_{16}H_{20}O_4Cl_6$: C 42.69, H 4.48; found: C 43.04, H 4.62.

(2*R,3*R**,4*R**,8*S**,9*R**,10*S**)-14,14-Dimethoxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-ene-3,9-diol (57)**

Liquid ammonia (100 mL) was distilled into a three-necked round-bottomed flask equipped with a Dewar condenser, KOH guard tube, and septum. The solution of acetonide **56** (1 g, 2.22 mmol) in dry THF (10 mL) and absolute EtOH (5 mL) was added to the reaction flask. Small pieces of freshly cut sodium were introduced, with stirring, into the resulting mixture until the blue color of the solution persisted. The mixture was stirred for 40 min and quenched by addition of solid NH_4Cl (~1 g). The excess ammonia was allowed to evaporate and the residue obtained was diluted with cold aq. satd. NH_4Cl solution (20 mL) and water (50 mL). The residue, resulting from the usual work-up, was purified by silica gel column chromatography (70% ethyl acetate – hexane) to furnish the olefin diol **57** (610 mg, 88%), mp 200–202 °C. IR (Nujol, cm^{-1}): 3420, 1260. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.17 (t, 2H, *J* = 3.0 Hz, C=C*H*), 3.94 (br s, 2H, $H_{acetonide}$), 3.32 (s, 3H, OCH_3), 3.13 (br s, 3H, OCH_3), 3.04 (br s, 2H, C*H*OH), 2.92 (s, 2H), 1.65 (s, 2H), 1.44 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 132.0 (2C, C=*C*H), 119.4 (C_q), 108.4 (C_q), 78.5 (2C, $C_{acetonide}$), 71.4 (2C, *C*HOH), 52.0 (2C, OCH_3), 49.8 (2C), 46.7 (2C), 26.7 ($CH_{3acetonide}$), 23.0. LR-MS (EI, 70 eV) *m*/*z*: 312 [M^+]. Anal. calcd. for $C_{16}H_{24}O_6$: C 61.52, H 7.74; found: C 61.90, H 7.52.

(2*R,3*R**,4*R**,8*S**,9*R**,10*S**)-3,9-Dihydroxy-6,6-dimethyl-5,7-dioxatetracyclo[9.2.1.0^{2,10}.0^{4,8}]tetradec-12-en-14-one (58)**

Ketal **57** (220 mg, 0.705 mmol) was dissolved in moist acetone (20 mL) and stirred with Amberlyst-15 resin (~50 mg) for 2 h, when all the starting material had been consumed (TLC). The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a solid residue, which was chromatographed over a silica gel column (50% ethyl acetate – hexane) to furnish the 7-ketonorbornene **58** (178 mg, 95%), mp 220–221.5 °C. IR (KBr, cm^{-1}): 3443, 1778.

(3a*R,4*S**,4a*S**,8a*R**,9*R**,9a*S**)-2,2-Dimethyl-3a,4,4a,8a,9,9a-hexahydronaphtho[2,3-*d*][1,3]dioxole-4,9-diol (59)**

A solution of ketone **58** (90 mg, 0.338 mmol) in nitrobenzene (10 mL) was heated to 160 °C, with vigorous stirring, for 3 h. Upon complete consumption of the starting material (TLC), the reaction mixture was cooled to 80 °C and the solvent was distilled off under reduced pressure. The

resulting residue was subjected to silica gel column chromatography (30% ethyl acetate – hexane) to afford diene **59** (35 mg, 43%), mp 188.5–190 °C. IR (KBr, cm^{-1}): 3321, 3034. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.97–5.94 (m, 2H, C=C*H*), 5.54–5.50 (m, 2H, C=C*H*), 4.50–4.49 (m, 2H, $H_{acetonide}$), 3.86 (br s, 2H), 3.53 (d, *J* = 6.9 Hz, 2H), 3.20 (br s, 2H, $H_{bridgehead}$), 1.46 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 125.8 (2C, C=*C*H), 123.8 (2C, C=*C*H), 108.6 (C_q), 74.9 (2C, $C_{acetonide}$), 69.7 (2C, *C*HOH), 32.4 (2C), 26.6 ($CH_{3acetonide}$), 24.0 ($CH_{3acetonide}$). LR-MS (EI, 70 eV) *m*/*z*: 239 [M^+ + 1]. Anal. calcd. for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.90, H 7.52.

(3a*R,4*S**,4a*R**,5*S**,6*S**,7*S**,8*S**,8a*S**,9*R**,9a*S**)-2,2-Dimethylperhydronaphtho[2,3-*d*][1,3]dioxole-4,5,6,7,8,9-hexol (60)**

To a solution of diene **59** (25 mg, 0.105 mmol) in acetone–water–*t*-BuOH (5:5:2, 6 mL), catalytic amounts of OsO_4 (0.5 mg, 1 mol%) and 50% aq. NMMO (75 μL, 0.315 mmol) were sequentially added at 0 °C. The resulting pale yellow reaction mixture was stirred at room temperature for 48 h. The reaction mixture was cooled to 0 °C prior to quenching with solid $NaHSO_3$ (15 mg). The resulting mixture was diluted with ethyl acetate (20 mL), filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (10% methanol – ethyl acetate) to afford hexol **60** (23 mg, 73%). IR (Nujol, cm^{-1}): 3460. ^1H NMR (300 MHz, D_2O) δ: 4.27 (d, *J* = 3 Hz, 1H), 4.20 (dd, *J* = 8.4, 5.4 Hz, 1H), 4.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 4.03 (t, *J* = 3 Hz, 1H), 3.97–3.92 (m, 1H), 3.86 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.79 (dd, *J* = 8.4, 5.4 Hz, 1H), 3.52 (dd, *J* = 10.2, 3.3 Hz, 1H), 2.54–2.20 (m, 2H), 1.39 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (75 MHz, D_2O) δ: 110.5 (C_q), 80.1 ($CH_{acetonide}$), 78.3 ($CH_{acetonide}$), 72.7, 72.3, 72.0, 71.5, 67.4, 66.4, 41.9 ($CH_{bridgehead}$), 39.3 ($CH_{bridgehead}$), 28.6, 26.6. LR-MS (EI, 70 eV) *m*/*z*: 306 [M^+]. Anal. calcd. for $C_{13}H_{22}O_8$: C 50.97, H 7.24; found: C 50.90, H 7.51.

Bicyclitol 61

Acetonide hexol **60** (14 mg, 0.046 mmol) was stirred vigorously with 30% TFA (500 μL) at room temperature for 30 min. The volatiles were removed under reduced pressure to furnish **61** (11 mg, 90%). ^1H NMR (300 MHz, D_2O) δ: 4.06 (m, 1H), 3.93 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.87 (br s, 1H), 3.81 (m, 1H), 3.75 (t, *J* = 3.9 Hz, 1H), 3.73 (t, *J* = 3.0 Hz, 1H), 3.68 (t, *J* = 3.3 Hz, 1H), 3.52 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.35 (dt, *J* = 6.6, 2.7 Hz, 1H), 2.28 (m, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 73.6, 72.8, 71.3, 70.7, 70.4, 69.3, 69.1, 67.4, 40.2, 38.4. LR-MS (CI) *m*/*z*: 266 [M^+]. Anal. calcd. for $C_{10}H_{18}O_8$: C 45.11, H 6.81; found: C 45.45, H 7.12.

General procedure for enzymatic assays

The enzymes assayed were α-glucosidase (EC 3.2.1.20) from yeast, β-glucosidase (EC 3.2.1.21) from sweet almonds, α-galactosidase (EC 3.2.1.22) from green coffee beans, β-galactosidase (EC 3.2.1.23) from *E. coli*, α-mannnosidase (EC 3.2.1.24) from jack bean, and β-mannosidase (EC 3.2.1.25) from snail acetone powder. The substrates for the glycosidase were the corresponding *ortho*- or *para*-nitrophenylglycosides. The α-glucosidase (0.135 units/mL)[3] was assayed using *p*-nitophenyl-α-D-glucopyranoside (2.53 mmol/L) as the substrate at pH 6.8 (100 mmol/L phosphate buffer) at 37 °C, while β-glucosidase (0.133 units/mL) was assayed using *p*-nitrophenyl-β-D-glucopyranoside (2.57 mmol/L) as the substrate at pH 5.0 (10 mmol/L acetate buffer) at 37 °C. The potency of α-galactosidase (0.1 units/mL) and β-galactosidase (0.91 units/mL) was studied using *p*-nitrophenyl-α-D-galactopyranoside (2.12 mmol/L) and *o*-nitrophenyl-β-D-galactopyranoside (2.34 mmol/L) as substrate at pH 6.5 (100 mmol/L phosphate buffer) and pH 7.3 (100 mmol/L phosphate buffer) at 25 and 37 °C, respectively. The assay involving α-mannosidase (0.116 units/mL) was carried out using *p*-nitrophenyl-α-D-mannopyranoside (2.01 μmol/L) as substrate at pH 4.5 (10 mmol/L acetate buffer) at 25 °C, while β-mannosidase (0.125 units/mL) was assayed using *p*-nitrophenyl-α-D-mannopyranoside (2.15 mmol/L) as substrate at pH 4 (10 mmol/L acetate buffer) at 25 °C.

Typical assays were carried out in 1.5 mL disposable Eppendorf tubes, with the reaction volume being maintained at 200 μL. The mixture of enzyme and potential inhibitor in the optimum buffer medium was preincubated for 5 min and the reaction was initiated by adding the corresponding substrate solution (prepared in double-distilled water) to the reaction mixture. After incubation for 30 min at the optimum temperature for the enzyme, the reaction was quenched by addition of 800 μL of Na_2CO_3 buffer (400 mmol/L) solution. The enzyme activity was determined by measuring the absorption of the nitrophenolate ion released at 400 nm (in the case of *p*-nitrophenol) or 410 nm (in the case of *o*-nitrophenol). In the control experiments, the inhibitor was replaced by a corresponding buffer solution. The K_i was calculated using the Lineweaver–Burk plot.

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[3] One unit of enzyme is defined as the amount that liberated 1 μmol of corresponding nitrophenol per min.

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