Synthesis of Tricyclic Precursors of Cyclitols

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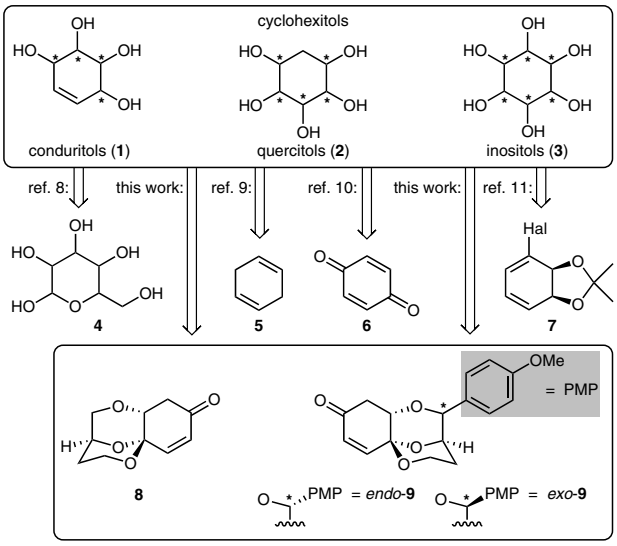
Abstract: Stereoselective syntheses of three tricyclic cyclohexenones are described. These compounds were conceived as novel precursors of synthetic conduritols, quercitols, and inositols because they allow diastereoselective C=O reductions, C=C osmylations, and C=C epoxidations to be performed. These functionalizations created up to three uniformly configured oxygen-bearing stereocenters. One of the follow-up products was a tricycle that was amenable to successive cleavages of its 1,4-dioxane and 1,3-dioxane rings. This rendered the pentaesters of *neo*-quercitol, which contain five stereogenic C–O bonds, with *ds* = 85:15.

Key words: α-hydroxy ketone, cyclohexadienones, diastereoselectivity, 1,2-diol, hypervalent iodine reagent, oxidative cyclization

Polyhydroxycyclohexenes and polyhydroxycyclohexanes are important representatives of a family of compounds, both natural and unnatural, which are collectively known as cyclitols.[2] As specified in Scheme 1 they encompass tetrahydroxycyclohexenes [conduritols (**1**)], pentahydroxycyclohexanes [quercitols (**2**)], and hexahydroxycyclohexanes [inositols (**3**)].[3] Their structures appear simple but are markedly diverse because of an abundance of stereostructures: Counting enantiomers as distinct, there are ten stereoisomeric conduritols (**1**), 16 quercitols (**2**), and nine inositols (**3**). These stereoisomers differ from their carba-analogues, anhydrodeoxypentopyranoses, deoxypentopyranoses, and pentopyranoses, by the inclusion of *meso*-isomers; there are two *meso*-configured conduritols, four *meso*-configured quercitols, and seven *meso*-configured inositols.

The strong interest in cyclitol chemistry is due to the importance of the derived monophosphates and oligophosphates, plus notably diacylglycerol esters thereof, for biological signaling.[4] For accessing such compounds[5] the sole affordable source is synthesis, with or without the aid of enzymes. Regioselectivity is a major issue when introducing the phosphate substituent(s)[6] while a prime concern in preparing the underlying cyclitol cores is achieving stereocontrol.[3b,7] As Scheme 1 indicates this has been possible, inter alia, starting from pyranoses (**4**),[8] cyclohexa-1,4-diene (**5**),[9] *p*-benzoquinone (**6**)[10] or enantiomerically pure acetonides **7**[11] of *cis*-configured 3-halocyclohexa-3,5-diene-1,2-diols. The present publication describes the development of novel starting materials for synthesizing cyclitols, namely the tricyclic cyclohexenones **8**, *endo*-**9**, and *exo*-**9**. Their cyclohexenone moieties stem from hydroquinone monoethers.



Scheme 1 Stereoselective syntheses of cyclitols such as conduritols (**1**), quercitols (**2**) or inositols (**3**) from a pyranose (**4**),[8] from cyclohexa-1,4-diene (**5**),[9] from *p*-benzoquinone (**6**),[10] and from the acetonide of enantiopure *cis*-3-halocyclohexa-3,5-diene-1,2-diols (**7**)[11] (all established) or from the tricyclic cyclohexenones **8**, *endo*-**9**, and *exo*-**9** (suggested in the present study).

The tricyclic cyclohexenone **8** was obtained as shown in Scheme 2. The enantiomerically pure ketal **10**[12] was etherified under Mitsunobu conditions[13] with hydroquinone monoacetate (**11**[14]) giving ketal **12** (91% yield). Hydrolysis rendered 92% of the diol-containing hydroquinone monoether **13**. The latter cyclized when exposed to $PhI(O_2CCF_3)_2$.[15] An inseparable 78:22 mixture of the benzoquinone monoketal isomers **14** (97% ee)[16] and **15** was formed (85% yield). Their ketal moieties were six- and seven-membered rings, respectively. When this mixture was deprotonated with NaH, the major isomer (**14**) only underwent an intramolecular oxa-Michael addition. This led to 81% of the tricyclic cyclohexenone **8** (relative to the fraction of ketal **14** in the **14**/**15** mixture).

The sp^2-carbon atoms in the C=O and the C=C bond of the tricyclic cyclohexenone **8** were transformed to oxygenated stereocenters with very high diastereocontrol (Scheme 3). $LiAlH_4$ attacked exclusively the β-face of the C=O bond, generating the cyclohexenol **16** with *ds* = 98:2. Without prior purification, it was acetylated under the reaction conditions. This allowed the isolation of the corresponding acetate **17** as a pure diastereomer (88%). The

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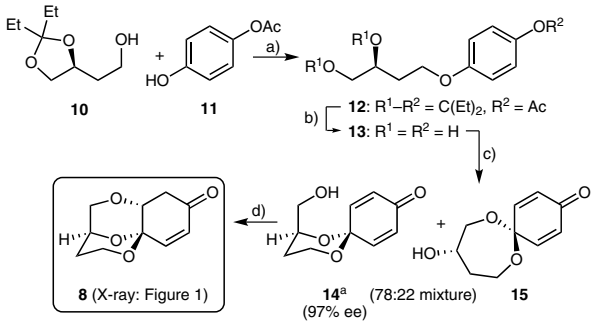
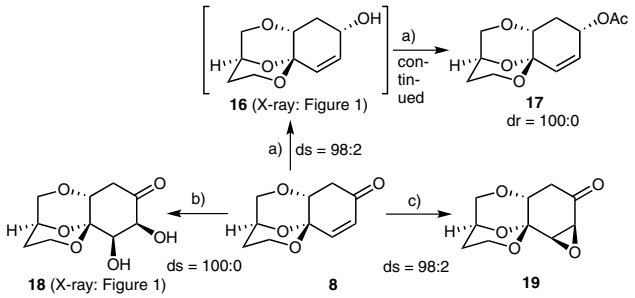


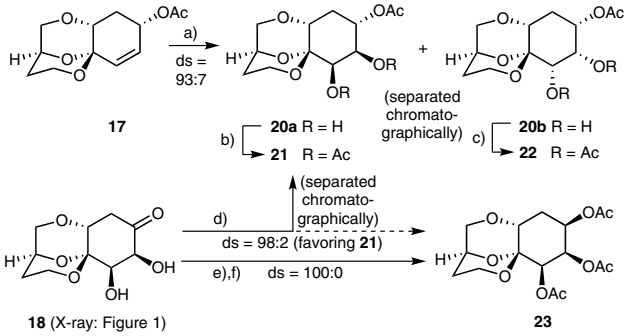
Scheme 2 Synthesis of the unsubstituted tricyclic cyclohexenone **8**. *Reagents and conditions*: (a) **10**[12] (1.0 equiv), **11**[14] (1.1 equiv), Ph_3P (1.1 equiv), DEAD (1.1 equiv), CH_2Cl_2, r.t., 4 h, 91%; (b) Amberlyst-15 (cat.), MeOH, r.t., 20 h, 92%; (c) $PhI(O_2CCF_3)_2$ (1.1 equiv), $NaHCO_3$ (3.0 equiv), MeCN, r.t., 15 min, K_2CO_3 (2.2 equiv), 85%, **14**/**15** (78:22 mixture); (d) NaH (1.5 equiv), 18-crown-6 (0.5 equiv), toluene, 110 °C, 24 h, 81%. [a] The drawing of compound **14** depicts primarily constitution and configuration. Its dioxane moiety is drawn in a conformation, which relates closely to the 3D structure of compound **8** prepared therefrom. However, the major conformer of compound **8** contains a dioxane chair with an equatorial α-hydroxymethyl group. This follows from the J = 11.8 Hz coupling in the (HO)CH_2–C*H*–CH_{ax} motif; it is a *trans*-diaxial H,H coupling.

C=C bond of the tricyclic cyclohexenone **8** was dihydroxylated with exceptionally high diastereocontrol from the β-face when subjected to a citric acid mediated osmylation.[17] The tricyclic dihydroxycyclohexanone **18** resulted in 92% yield. High stereocontrol was also observed for the nucleophilic epoxidation of cyclohexenone **8** with cumene hydroperoxide and Triton-B.[18] If the reaction was β-selective, like the previous transformations, the product was the epoxycyclohexanone **19** (58% yield).



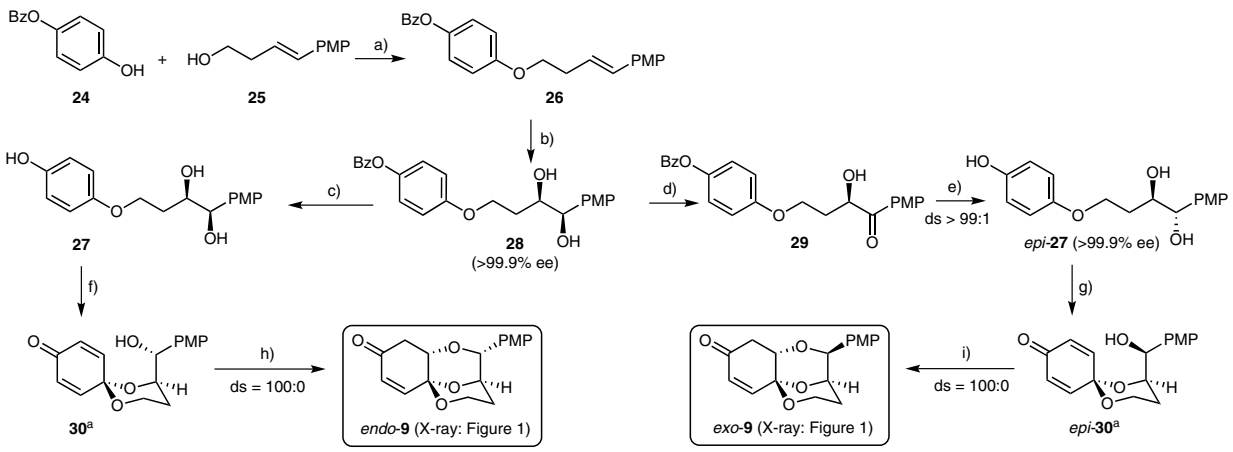
Scheme 3 C=C and C=O bond functionalizations of the cyclohexenone moiety of the unsubstituted tricyclic cyclohexenone **8**. *Reagents and conditions*: (a) $LiAlH_4$ (0.3-fold molar amount), THF, –78 °C, 1 h; Ac_2O (7.0 equiv), DMAP (10 mol%), –78 °C → r.t., 6 h, 88%; (b) $K_2OsO_2(OH)_4$ (0.5 mol%), NMO (1.2 equiv), citric acid (2.0 equiv), *t*-BuOH–H_2O (1:1), r.t., 8 h, 92%; (c) cumene hydroperoxide (2.0 equiv), $BnNMe_3^+ {}^-OH$ (cat.), THF, 0 °C, 2 d, 58%.

Scheme 4 shows stereogenic follow-up transformations of the cyclohexenyl acetate **17** and the cyclohexanediol **18**, prepared as shown in Scheme 3. The citric acid mediated osmylation[17] of cyclohexenyl acetate **17** (Scheme 4, top) delivered the diastereomeric *cis*-1,2-diols **20a** (85%) and **20b** (7%) after separation by flash chromatography on silica gel.[19] Diacetylations rendered the stereochemically homogenous triacetates **21** (95%) and **22** (90%), respectively. The former compound, i.e., **21** was identical with the triacetate obtained from the cyclohexanediol **18** by the following treatment (Scheme 4, bottom): OH-directed reduction of the C=O bond with $Me_4N^+ {}^-BH(OAc)_3$;[20] diacetylation and separation from a trace of triacetate **23** by flash chromatography[19] (*ds* = 98:2). The triacetate **23**, in turn, could be prepared from the cyclohexanediol **18** with essentially complete diastereocontrol by reversing the order of steps, that is, by a diacetylation followed by $NaBH_4$ reduction.



Scheme 4 Processing the tricyclic templates **17** and **18** from Scheme 3. *Reagents and conditions*: (a) $K_2OsO_2(OH)_4$ (5 mol%), NMO (1.3 equiv), citric acid (2.0 equiv), *t*-BuOH–H_2O (1:1), r.t., 15 h, 84.6% **20a**, 6.8% **20b** (separated by flash chromatograpy[19]); (b) Ac_2O (4.0 equiv), DMAP (20 mol%), pyridine (5.0 equiv), CH_2Cl_2, r.t., 15 h, 95%; (c) Ac_2O, pyridine, r.t., 20 h, 90%; (d) $Me_4N^+ {}^-BH(OAc)_3$ (3.0 equiv), AcOH (6.0 equiv), MeCN, r.t., 1.5 h; Ac_2O (15 equiv), DMAP (30 mol%), pyridine (18 equiv), THF, 40 °C, 20 h, 94% **21**, 1.4% **23** (separated by flash chromatography[19]); (e) same as (c) but 18 h, 71%; (f) $NaBH_4$ (three-fold molar amount), MeOH, 0 °C, 1 h; Ac_2O, pyridine, r.t., 18 h, 53%.

At this point we had gained the stereouniform cyclohexanone-based diol **18** and epoxide **19** (Scheme 3), the cyclohexene-based monoacetate **17** (Scheme 3), and the cyclohexane-based triacetates **21** and **23** (Scheme 4) in quite satisfactory manners. However, all efforts to transform these compounds to a more cyclitol-like structure met with failure. A plausible culpable was the 1,4-dioxane subunit. It stemmed from the oxa-Michael addition step (**14** → **8**, Scheme 2), had stayed since, but now refused to ring-open. We felt, however, that exactly this ring-opening was a prerequisite for having more promising attempts at hydrolyzing the ketal group in any of the mentioned 'building blocks'.[21] As a consequence we chose to modify the 1,4-dioxane moiety of the tricyclic cyclohexenone **8**, which we had studied so far; we introduced a predetermined breaking point by a *p*-methoxyphenyl (PMP) substituent. It turned the hitherto 'purely aliphatic ether' moiety into a *p*-methoxybenzyl (PMB) ether moiety. PMB ethers can be removed under a number of reaction conditions, which leave aliphatic ethers unaffected.[22] These considerations made either of the tricyclic cyclohexenone diastereomers *endo*-**9** or *exo*-**9** (Scheme 5) a viable second-generation cyclitol building block candidate for our project.



Scheme 5 Synthesis of the PMP-substituted tricyclic cyclohexenones *endo*-**9** and *exo*-**9**. *Reagents and conditions*: (a) **25**[23] (1.00 equiv), **24**[24] (1.20 equiv), Ph_3P (1.10 equiv), DIAD (1.15 equiv), THF, r.t., 12 h, 93%; (b) $K_2OsO_2(OH)_4$ (1.0 mol%), $(DHQD)_2PHAL$ (2.0 mol%), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–H_2O (1:1), 0 °C, 6 d, 94%, 99.2% ee (≥99.9% ee after crystallization); (c) KOH (1.1 equiv), MeOH, r.t., 2 h, 99%; (d) DDQ (1.07 equiv), CH_2Cl_2, r.t., 8 d, 95%, >99.9% ee; (e) $Zn(BH_4)_2$ (0.5-fold molar amount), THF, –30 °C, 14 h; NaOH (2.2 equiv), MeOH, 0 °C → r.t., 2 h, 96%, ds >99:1, >99.9% ee; (f) $PhI(O_2CCF_3)_2$ (1.05 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, 0 °C, 20 min, 82%; (g) same as (f), 79%; (h) NaH (1.4 equiv), DME, 60 °C, 90 min, 62%; (i) NaH (1.2 equiv), THF, 65 °C, 100 min, 87%. [a]The drawings of compounds **30** and *epi*-**30** depict primarily constitutions and configurations. The dioxane moieties are drawn in conformations, which relate closely to the 3D structure of compounds *endo*-**30** and *exo*-**30** prepared therefrom. However, the major conformers of compounds **30** and *epi*-**30** contain dioxane chairs with an equatorial α-hydroxybenzyl group. This follows from the J = 11.8 Hz coupling in the respective (HO)CH(PMP)–C*H*–CH_{ax} motif; it is a *trans*-diaxial H,H coupling. $(DHQD)_2PHAL$ = bis(dihydroquinidine)phthalazine-1,4-diyl diether.

Our routes to the second-generation cyclitol precursors *endo*-**9** and *exo*-**9** (Scheme 5) began with the *E*-configured homocinnamylic alcohol **25**[23] and hydroquinone monobenzoate (**24**).[24] The latter compound was alkylated by the former under Mitsunobu conditions.[13] The resulting ether **26** (93% yield) was dihydroxylated asymmetrically.[25] This rendered the *syn*-configured diol **28** in 94% yield and with 99.2% ee[26] (→ ≥99.9% ee[26] after recrystallization). It was transformed into the tricyclic cyclohexenone *endo*-**9** retaining both stereocenters, and into the epimeric cyclohexenone *exo*-**9** inverting the benzylic stereocenter.

The retention-of-configuration pathway from diol **28** to cyclohexenone *endo*-**9** comprises three steps (Scheme 5, lower left): (1) Alkaline benzoate cleavage (→ 99% hydroquinone monoether **27**); (2) oxidation with $PhI(O_2CCF_3)_2$[15] (→ 82% benzoquinone monoketal **30**[27]); (3) NaH-induced oxa-Michael cyclization (→ 62% target *endo*-**9**, *ds* = 100:0). The inversion-of-configuration pathway from diol **28** to cyclohexenone *exo*-**9** consists of five steps, which were realized in four operations (Scheme 5, lower right). We began by inverting the configuration of the benzylic stereocenter through an oxidation/reduction sequence. Other than in existing procedures[28] this was realized without protection in between. Diol **28** and DDQ[29] gave 95% α-hydroxy ketone **29** without racemization.[30] Reduction with $Zn(BH_4)_2$[31] was completely *anti*-selective[32] so that an ensuing debenzoylation provided the desired hydroquinone monoether *epi*-**27** exclusively.[33] Oxidation with $PhI(O_2CCF_3)_2$[15] gave 79% of the benzoquinone monoketal *epi*-**30**.[34] Sodium hydride induced cyclization delivered the tricycle *exo*-**9** (87%, *ds* = 100:0).

The stereostructures of the novel cyclohexenones *endo*-**9** and *exo*-**9** were ascertained by X-ray monocrystal analyses (Figure 1). Their cyclohexenone rings possess half-chair conformations. The latter are folded such that they have two quasi-equatorial oxygen substituents and one quasi-axial oxygen substituent. The heterocycles in compounds *endo*-**9** and *exo*-**9**, i.e., the 1,4-dioxane and 1,3-dioxane ('ketal') rings, have chair conformations. The same half-chair/chair/chair scaffold was contained in our first-generation tricyclic cyclohexenone **8** (Figure 1). Structurally speaking, our second-generation tricyclic cyclohexenones *endo*-**9** and *exo*-**9** differ from **8** only by their respective PMP substituent. It is axially appended to the 1,4-dioxane moiety of tricycle *endo*-**9** and equatorially in *exo*-**9**. These differential PMP orientations let us expect that C=C or C=O bond functionalizations in the tricycle *endo*-**9** would exhibit (even) higher β-selectivities than analogous reactions of the tricycles *exo*-**9** and **8**. For reasons unknown, these expectancies did not bear out fully (vide infra): usually, C=C bond functionalizations were more β-selective in scaffolds with an *exo*- rather than *endo*-PMP substituent.

The C=O and C=C bonds of the PMP-containing cyclohexenones *endo*-**9** and *exo*-**9** were turned into oxygenated stereocenters by the reactions shown in Scheme 6. In essence, these reactions exhibited similar or lesser diastereoselectivity, respectively, as the analogous reactions of the PMP-free cyclohexenone **8** (Scheme 3). Firstly, $LiAlH_4$ reductions of the carbonyl group delivered the cyclohexenols *endo*-**31** (ds >99:1) and *exo*-**31** (ds = 98:2), respectively.[35] Secondly, citric acid mediated osmylations[17] of the cyclohexenones *endo*-**9** and *exo*-**9** gave the *cis*-1,2-

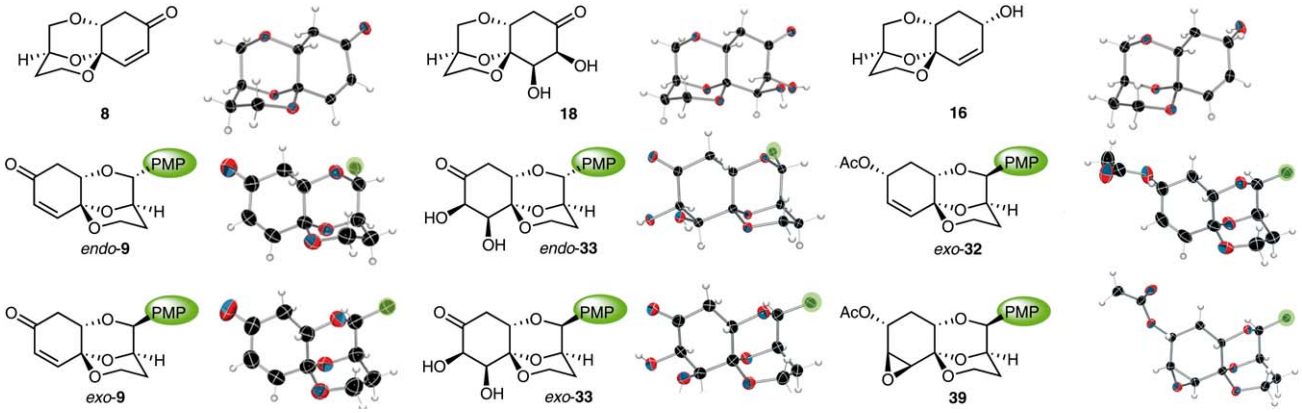
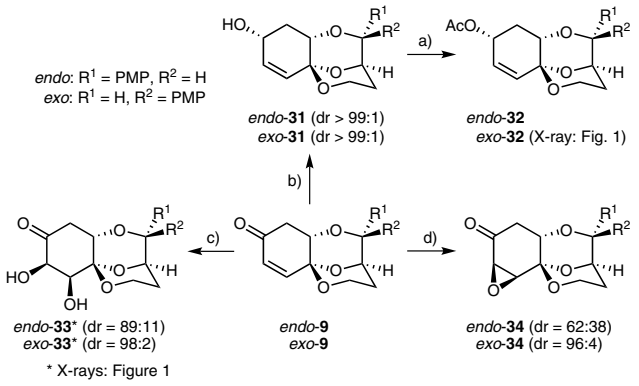


Figure 1 ORTEP plots[a] of X-ray crystal structure analyses of compounds **8** (at 100 K[45]), **16** (at 100 K[46]), **18** (at 100 K[47]), *endo*-**9** (at 294 K[48]), *exo*-**9** (at 294 K[49]), *endo*-**33** (at 100 K[50]), *exo*-**33** (at 173 K[51]), *exo*-**32** (at 173 K[52]), and **39** (at 100 K[53]). The left-hand column depicts cyclohexenones (**8**, *endo*-**9**, and *exo*-**9**), the center column dihydroxycyclohexanones (**18**, *endo*-**33**, and *exo*-**33**), and the right-hand column a cyclohexenol (**16**), a related cyclohexenyl acetate (*exo*-**32**), and a corresponding epoxycyclohexyl acetate (**39**). [a] For easier recognizability the *para*-methoxyphenyl ('PMP') rings are omitted except for their center C-1. The latter is shown in green color. Full representations of these X-ray structures are included in the Supporting Informations.

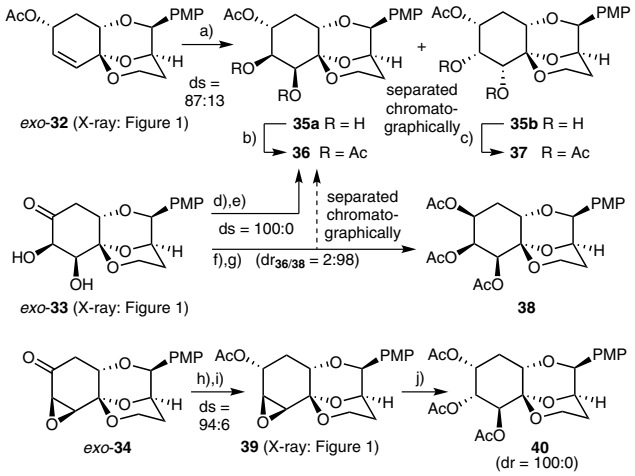
diol *endo*-**33** as an inseparable 89:11 mixture with a minor diastereomer (90% combined yield) and the pure *cis*-1,2-diol *exo*-**33** (92%) after purification by flash chromatography,[19] respectively. Thirdly, nucleophilic epoxidation of cyclohexenones *endo*-**9** and *exo*-**9** with H_2O_2/DBU[36] furnished the epoxycyclohexanone *endo*-**34** in an inseparable 62:38 mixture with its diastereomer (49% combined yield) and the epoxycyclohexanone *exo*-**34** (81%) with *ds* = 96:4, respectively.



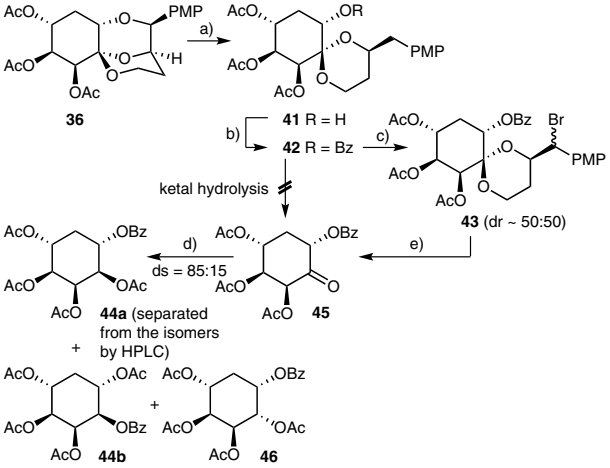
Scheme 6 C=C and C=O bond functionalizations of the cyclohexenone moiety of the PMP-substituted tricyclic cyclohexenones *endo*-**9** and *exo*-**9**. *Reagents and conditions*: (a) for *endo*-**32**: Ac_2O (2.0 equiv), DMAP (10 mol%), pyridine (3.0 equiv), CH_2Cl_2, r.t., 6 h, 97%; for *exo*-**32**: same as above but 12 h, 100%; (b) for *endo*-**31**: $LiAlH_4$ (0.3-fold molar amount), THF, –78 °C, 30 min, 99%; for *exo*-**31**: same as above but 45 min, 100%, 98:2 mixture with the diastereomer (dr >99:1 after recrystallization from Et_2O); (c) for *endo*-**33**: $K_2OsO_2(OH)_4$ (1.2 mol%), citric acid (2.0 equiv), NMO (1.5 equiv), MeCN–*t*-BuOH–H_2O (4:1:1), r.t., 3 d, 90% of the 89:11 mixture with the diastereomer; for *exo*-**33**: $K_2OsO_2(OH)_4$ (0.5 mol%), citric acid (2.0 equiv), NMO (1.5 equiv), *t*-BuOH–H_2O (1:1), r.t., 30 h, 92% pure *exo*-**33** after flash chromatography;[19] (d) for *endo*-**34**: H_2O_2 (8.0 equiv), DBU (3.0 equiv), THF, r.t., 15 h, 49%, 62:38 mixture with the diastereomer; for *exo*-**34**: H_2O_2 (3.0 equiv), DBU (1.0 equiv), THF, r.t., 2 h, 81% of the 96:4 mixture with the diastereomer (dr >99:1 after recrystallization).

Scheme 7 shows the subsequent introduction of other stereogenic centers into the cyclohexenyl acetate *exo*-**32**, the cyclohexanediol *exo*-**33**, and the epoxycyclohexanone *exo*-**34** (all prepared as shown in Scheme 6). The cyclohexenyl acetate *exo*-**32** was *cis*-dihydroxylated by Sharpless' OsO_4–NMO–citric acid procedure.[17] The 1,2-diols **35a** and **35b** resulted in a 87:13 ratio. They were separated by flash chromatography[19] and acetylated, which provided the corresponding triacetates **36**[37] and **37**. A 100% diastereoselective route to the triacetate **36**[37] was the triacetoxyborohydride reduction[20] of the C=O-containing cyclohexanediol *exo*-**33**. Yet another triacetate **38** was accessed with excellent stereocontrol (*ds* = 98:2), too. To this end, the C=O-containing cyclohexanediol *exo*-**33** was diacetylated and the resulting diacetoxy ketone reduced by $LiAlH(Ot\text{-}Bu)_3$. Finally, we also prepared the not yet mentioned triacetate **40** in a highly stereocontrolled manner. Starting with a Luche reduction[38] of the epoxycyclohexanone *exo*-**34** we obtained the epoxycyclohexanol with *ds* = 94:6. An esterification followed by purification by flash chromatography[19] afforded the epoxycyclohexyl acetate **39** as a single diastereomer. Ring-opening of the epoxide moiety in 30:1 toluene/H_2O in the presence of $BF_3{\cdot}OEt_2$[39] delivered two diaxial diols[40] exclusively (not depicted in Scheme 7). The diacetylation of these diols resulted in the already mentioned triacetate **40**.[40]

Scheme 8 presents a proof-of-concept sequence. It showcases how we degraded the tricyclic triacetate **36** to the monocyclic cyclitol derivative **44a** (along with two isomers). Substrate **36** was chosen arbitrarily from our sizable collection of tricyclic templates. In step one we cleaved its PMB–O bond by treatment with Et_3SiH in F_3CCO_2H.[41] This broke the 1,4-dioxane moiety of substrate **36** open in 94% yield. Thereby a transformation had been turned into practice, for which we had found no solution with respect to the PMP-free substrate **21** (Scheme



Scheme 7 Processing the tricyclic templates *exo*-**32**, *exo*-**33**, and *exo*-**34** from Scheme 6. *Reagents and conditions*: (a) $K_2OsO_2(OH)_4$ (5.0 mol%), citric acid (2.0 equiv), NMO (1.5 equiv), H_2O–*t*-BuOH–MeCN (2:2:1), r.t., 2 d, 85% **35a**, 13% **35b** (separated by flash chromatography[19]); (b) Ac_2O (4.0 equiv), DMAP (20 mol%), pyridine (8.0 equiv), CH_2Cl_2, r.t., 15 h, 99%; (c) same as (b), 99%; (d) $Me_4N^+ {}^-BH(OAc)_3$ (4.0 equiv), AcOH (8.0 equiv), MeCN, r.t., 2 h, 100%; (e) Ac_2O (10 equiv), DMAP (30 mol%), pyridine (10 equiv), THF, r.t., 16 h, 98%; (f) AcCl (4.0 equiv), DMAP (20 mol%), pyridine (5.4 equiv), CH_2Cl_2, r.t., 20 h, 89%; (g) LiAlH(O*t*-Bu)$_3$ (2.0 equiv), THF, –30 °C, 15 h, → r.t. within 4 h; Ac_2O (18 equiv), DMAP (15 mol%), pyridine (20 equiv), THF, r.t., 3 d, 96% **38**, 2% **36** (separated by flash chromatography[19]); (h) $NaBH_4$ (1.0-fold molar amount), $CeCl_3$ (1.0 equiv), THF–MeOH (1:1), –78 °C → 0 °C, 3 h; (i) Ac_2O (2.0 equiv), DMAP (15 mol%), pyridine (3.0 equiv), CH_2Cl_2, r.t., 2 h, 88% (over the 2 steps) pure **39** after flash chromatography;[19] (j) $BF_3{\cdot}OEt_2$ (1.1 equiv), toluene–H_2O (30:1), 0 °C → r.t., 6 h; Ac_2O (10 equiv), DMAP (20 mol%), pyridine (15 equiv), CH_2Cl_2, r.t., 15 h, 82%.



Scheme 8 Synthesis of the asymmetrically esterified *neo*-quercitol **44a** after ether cleavage and ketal fragmentation of the tricyclic template **36** from Scheme 7. *Reagents and conditions*: (a) Et_3SiH (5 equiv), CF_3CO_2H, r.t., 3 h, 94%; (b) PhCOCl (1.5 equiv), DMAP (15 mol%), pyridine, r.t., 15 h, 98%; (c) NBS (1.05 equiv), AIBN (20 mol%), CCl_4, reflux, *hν* (150 W tungsten lamp), 3 h, 71%; (d) LiAlH(O*t*-Bu)$_3$ (2.0 equiv), THF, r.t., 1 h; isolation of crude product, Ac_2O (≥8 equiv), pyridine (≥12 equiv), DMAP (≥30 mol%), CH_2Cl_2, r.t., 30 min, 96% of a 77:8:15 mixture **44a**/**44b**/**46**; **44a** was separated from its isomers by HPLC; (e) Zn (10 equiv), THF, r.t., 15 h, 27%.

4). The product of this ionic hydrogenolysis was the hydroxy ketal **41**. Benzoylation gave the ester **42** in near-quantitative yield. The ketal moiety in this compound, however, was inert towards acid-mediated hydrolysis. Therefore, we gave up on releasing the desired cyclohexanone **45** from the ester **42** in a single step.

A two-step detour route to the cyclohexanone **45** was feasible, though. It began with a benzylic bromination of substrate **42** with NBS–AIBN.[42] This furnished 71% of a 1:1 mixture of the diastereomeric bromides **43**. A solution of this mixture in anhydrous THF was treated with 10 equivalents of Zn powder (pretreated with Me_3SiCl) at room temperature for 15 hours. Via the respective alkylzinc bromide as a plausible intermediate, its decay by a β-elimination, and the decomposition of the resulting hemiketal the cyclohexanone tetraester **45** was formed in 27% yield. Its keto group was reduced chemoselectively in 96% yield employing LiAlH(O*t*-Bu)$_3$. A 85:15 preference for an α-attack was deduced from an outcome, which was complicated by some benzoate migration[43] in the major diastereomer of the initially formed alkoxide. After acetylating the crude product mixture, the interference of this benzoyl shift had diverted some of the desired product **44a** to the regioisomer **44b** (82% combined yield). The minor diastereomer of the reduction product suffered no such 'diversion' through acyl group migration.[43] Our workup procedure advanced it to the corresponding acetate **46** (14% yield). Our final products **44a** (which was separated by HPLC from its isomers and thereby isolated pure) and **44b** represent unsymmetrically peracylated *neo*-quercitols. Compound **46** is a peracylated (–)-*gala*-quercitol. Their preparation from the tricyclic cyclohexenone *exo*-**9** via the tricyclic triacetate **36** is the first demonstration of the viability of our approach to cyclitols.

The present study describes the synthesis of three tricyclic cyclohexenone templates (**8**, *endo*-**9**, and *exo*-**9**). They are designed as novel intermediates en route to synthetic conduritols (**1**), quercitols (**2**), and inositols (**3**). The four-step sequence disclosed in Scheme 8 details how the tricyclic triacetate **36**, which was made from template *exo*-**9** in three steps (Schemes 6 and 7), was transformed into the quercitol peresters **44a**, **44b**, and **46**. If the sequence of Scheme 8 can be improved and generalized it will be applicable for the selective syntheses of both unprotected and protected cyclitols. It is conceivable that the synthetic strategy delineated here can be extended to producing carbasugars.[44]

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References and Notes

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(22) For example, DDQ/H_2O, $(NH_4)_2Ce(NO_3)_6/H_2O$, $Me_2S/MgBr_2{\cdot}OEt_2$, NaI/$CeCl_3$, Na/NH_3, H_2/Pd(C) or $Et_3SiH/BF_3{\cdot}OEt_2$: Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; Wiley-Interscience: Hoboken, **2007**, 4th ed. 23–30,120–135.

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(27) The oxidation of the diol **27** delivered, besides the six-membered-ring ketal **30**, the isomeric seven-membered-ring ketal (8%; not depicted in Scheme 5), i.e. a PMP-substituted analogue of the seven-membered-ring ketal **15**. It was separated by flash chromatography on silica gel (ref. 19).

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(34) The oxidation of the diol *epi*-**27** delivered, besides the six-membered-ring ketal *epi*-**30**, the isomeric seven-membered-ring ketal (10%; not depicted in Scheme 5), i.e. another (ref. 27) PMP-substituted analogue of the seven-membered-ring ketal **15**. It was separated by flash chromatography on silica gel (ref. 19).

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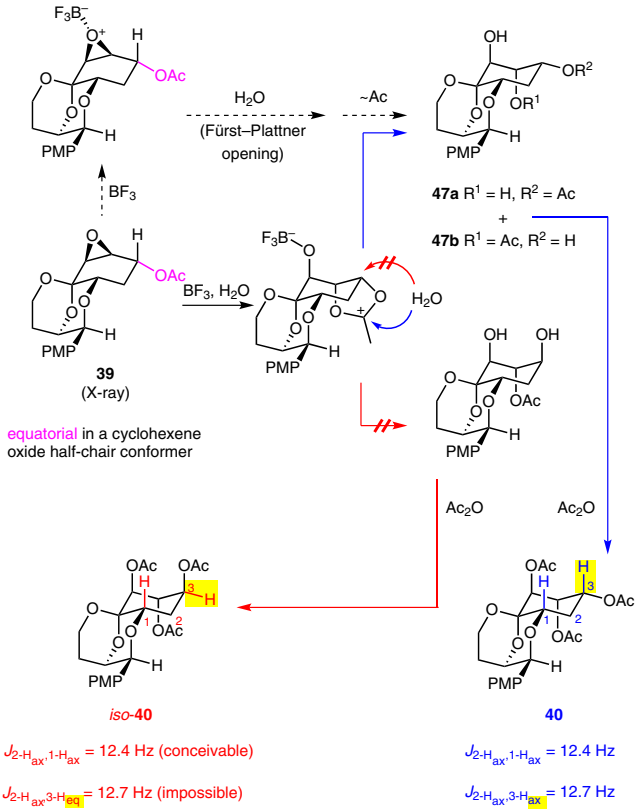

Scheme 9

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(46) The crystallographic data of the tricyclic cyclohexenol **16** are contained in CCDC 987666 (ref. 54).

(47) The crystallographic data of the tricyclic dihydroxy-cyclohexanone **18** are contained in CCDC 987665 (ref. 54).

(48) The crystallographic data of the tricyclic cyclohexenone *endo*-**9** are contained in CCDC 987667 (ref. 54).

(49) The crystallographic data of the tricyclic cyclohexenone *exo*-**9** are contained in CCDC 987668 (ref. 54).

(50) The crystallographic data of the tricyclic dihydroxy-cyclohexanone *endo*-**33** are contained in CCDC 987669 (ref. 54).

(51) The crystallographic data of the tricyclic dihydroxy-cyclohexanone *exo*-**33** are contained in CCDC 987670 (ref. 54).

(52) The crystallographic data of the tricyclic cyclohexenyl acetate *exo*-**32** are contained in CCDC 987671 (ref. 54).

(53) The crystallographic data of the tricyclic epoxycyclohexyl acetate **39** are contained in CCDC 987672 (ref. 54).

(54) These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via the link www.ccdc.cam.ac.uk/data_request/cif.

