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Asymmetrized tris(hydroxymethyl)methane as a precursor of N- and O-containing 6-membered heterocycles through ring-closing metathesis†

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A novel synthetic application of asymmetrized tris(hydroxymethyl)methane (THYM*) **1**, obtained in both enantiomeric forms in high e.e. *via* a chemoenzymatic procedure, is described. Starting from the common precursor **3**, N- and O-containing 6-membered heterocycles have been prepared exploiting ring-closing metathesis as the key step. Possible elaborations of the double bond in **6** and **28** have been explored and, in the case of **28**, conversion into the glycosidase inhibitor isofagomine **53** has been achieved.

Introduction

The synthesis of O- and N- containing heterocycles in enantiopure form is still an important goal for organic chemists, since compounds bearing this basic structure can be exploited as precursors of important biologically active molecules. Among them, polyhydroxylated non-aromatic heterocycles have been often used as enzyme inhibitors (in particular against glycosidases and glycosyltransferases).[1,2] This inhibition is of great importance for the development of compounds displaying therapeutic activity against inflammatory diseases,[2] diabetes,[3] viral infections such as HIV[4] and influenza,[5] and cancer (both in the stimulation of immune system against tumoural cell proliferation and in contrasting metastasis formation).[6] While O-heterocycles can be exploited for the preparation of modified sugars, functionalized N-containing cyclic compounds can be converted into iminosugars, a family of small molecules that mimic the cyclic alkoxycarbenium-like transition state occurring during the glycosidic bond cleavage.

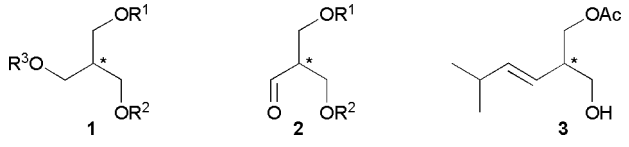
An impressive number of syntheses of these derivatives has been reported in recent years. In these synthetic approaches, various methods have been employed for the formation of the heterocyclic ring, including lactamization,[7] Mitsunobu's cyclization,[8] isoxazoline elaboration,[9] intramolecular amidomercuration[10] (for N-heterocycles) and hetero Diels–Alder reactions[11] for O-heterocycles.

However, one of the most useful methods for generating partially saturated heterocycles with different ring sizes is ring-closing metathesis (RCM), since the *endo* double bond resulting from the cyclization step can be functionalized in many different ways, with high diastereoselection in some cases. Through this procedure[12] 5-,[13,14] 6-,[14,15] 7-[16,17] and even 8-membered[16,18] partially saturated N-heterocycles are readily availabe. Tandem stereoselective ring-opening metathesis – ring-closing metathesis (ROM–RCM) has been employed for 6-membered ring formation during the synthesis of swainsonine analogues.[19] Finally, RCM has been also successfully applied to the synthesis of 5-,[20,21] 6-,[21,22] and 7-membered partially saturated O-heterocycles.[20]

Many of the glycomimetics of this type prepared so far have not been branched: the carbon atoms have all been included in the ring and the hydroxy groups have all been directly bonded to the ring. However, branched analogues, where at least one of the hydroxy groups is on a side arm, are very interesting, as demonstrated by the biological activity of some natural members of this class. Branched derivatives are clearly more difficult to prepare in enantiomerically pure form, since they can not be easily derived from natural sugars. The synthesis of branched N- or O-heterocycles in enantiomerically pure form through RCM requires an optically active acyclic precursor. We have previously described a new polyfunctionalized branched chiral building block, asymmetrized tris(hydroxymethyl)methane **1** (THYM*),[23] that is particularly well suited for the preparation of several acyclic polyoxygenated compounds. In this paper we will describe its use, in conjunction with RCM, in the efficient assembly of branched N- or O-heterocycles that can be in turn employed in the synthesis of polyhydroxylated glycomimetics.

Results and discussion

In this project we planned to use monoacetate **3** as chiral building block (Scheme 1). This compound is a synthetic equivalent of asymmetrized tris(hydroxymethyl)methane **1** (THYM*) or of the corresponding aldehyde, bis(hydroxymethyl)acetaldehyde **2** (BHYMA*). Both enantiomers of monoacetate **3** can be produced on a multigram scale, by two complementary chemoenzymatic procedures: the *R* enantiomer in 98% e.e. by monoacylation of the corresponding diol catalyzed by lipase from porcine pancreas (PPL) supported on Celite,[24] and the *S* enantiomer in 97% e.e. by monohydrolysis of the corresponding diacetate catalyzed by commercially available PPL.[25]



Scheme 1

In actual fact, the double bond of **3** behaves as a masked aldehyde, since this group can be restored through a stereoconservative ozonolysis/reduction, and can be further reduced to the corresponding alcohol. THYM* and BHYMA* have been previously submitted to several transformations involving: a) the substitution of one oxygenated moiety with a suitable nucleophile without the formation of new stereocentres;[23] b) the stereoselective functionalization of one or two branches with the creation of new stereogenic centres;[23] c) the stereoselective elaboration, which has also been performed intramolecularly,[26] of suitable alkenes obtained after olefination of BHYMA*.[23] In all these applications the double bond of **3** was always cleaved by ozonolysis/reduction. Now we report a new application of **3**,

† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/ob/b5/b502952j/

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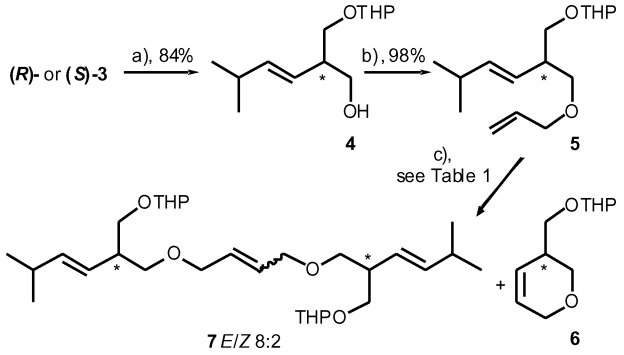
in which the double bond is not oxidatively cleaved, but, on the contrary, used as a functional group for RCM, to give both 2,3-dihydropyrans and 1,2,3,6-tetrahydropyridines.[27,28] The second double bond needed for RCM is introduced on one of the two hydroxymethyl side arms by nucleophilic substitution.[28]

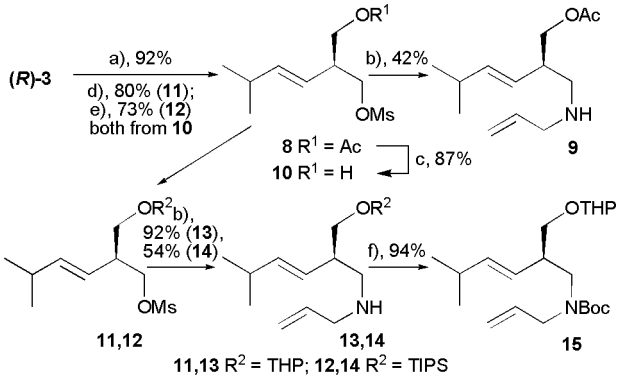
As a first goal we studied the independent transformation of both enantiomers of **3** into **6** (Scheme 2). The introduction of an allyl group onto an oxygen requires the formation of an alkoxide.[29] These conditions are, however, not compatible with the acetyl group. Therefore, the better-suited THP group was employed. High-yielding protection–deprotection furnished the two enantiomers of **4**, which were uneventfully converted into the allyl ethers **5**. RCM on **5**, performed in the presence of 5% Grubbs' first-generation catalyst, required careful monitoring of the reaction conditions, as shown in Table 1, since the formation of **7** (as an 8 : 2 *E* : *Z* mixture), arising from an intermolecular process, is in some cases significant. The amount of **7** cannot be suppressed by high dilution conditions (entries 2 and 3), carried out by the slow addition of the catalyst through a syringe pump. While RCM usually involves two terminal double bonds, in this case a terminal alkene and a substituted alkene are implicated. The higher steric requirements of the intramolecular reaction, makes the intermolecular reaction between two terminal olefins a competitive process even under high dilution. However, by simply changing the solvent from benzene to CH_2Cl_2, this side reaction was nearly completely suppressed.



Scheme 2 *Reagents and conditions*: (a) (i) DHP, *p*-TSA, CH_2Cl_2, 0 °C; (ii) KOH, MeOH, 0 °C; (b) allyl bromide, NaH, DMF, rt.

The analogous N-heterocycles were synthesized following two strategies, differing in the order of introduction of the allyl moiety and the carbamate protecting group. Initially the more expeditious route depicted in Scheme 3 was explored. Nucleophilic displacement on mesylates **8**, **11** and **12**, by means of allylamine both as the solvent and reagent, was successful only if performed at 80 °C in a sealed tube, giving the desired secondary amine in good yield only when THP was used as the O-protecting group. However, in view of further synthetic elaborations, we wanted to develop an efficient protocol able to produce a small library of differently O-protected starting materials for RCM. For this reason we turned our attention to the second strategy, shown in Scheme 4.

The nucleophilic displacement with sodium azide on mesylate **8** gave the desired azide **16** in excellent yield. The attempts



Scheme 3 *Reagents and conditions*: (a) MsCl, Et_3N, CH_2Cl_2, −30 °C; (b) allylamine, 80 °C; (c) KOH, MeOH, 0 °C; (d) DHP, *p*-TSA, CH_2Cl_2, 0 °C; (e) TIPS-Cl, imidazole, DMF, rt; (f) Boc_2O, 1,2-dichloroethane, reflux.

to convert this compound directly into the *O*-acetyl derivative of **21** failed: during the Staudinger reduction of the azide an intramolecular acyl transfer took place to give acetamide **17**. Most likely, this transfer occurs during the hydrolysis of the intermediate iminophosphorane, as previously experienced by us with similar compounds.[30] However, after hydrolyzing the acetate by means of *Pseudomonas cepacia* lipase,[31] the conversion of the azide **18** into **21** occurred cleanly, using a modified literature procedure[32] that involved trapping of the intermediate amino alcohol with Boc-ON.[33] From this intermediate, three differently protected dienes (**15**, **24** and **25**) have been prepared by protection followed by allylation. The allylation of the carbamate was quite troublesome, with the yields strictly depending upon the nature of the O-protecting group. Compound **15** was obtained in an unexpectedly low yield,[34] while the moderate yield for **24** is in part due to the competitive intramolecular silyl migration from oxygen to nitrogen with concomitant O-allylation, following a behaviour previously observed on other THYM* derivatives. This competitive process was indeed completely suppressed when the bulkier TIPS protecting group was employed.

Compound **15** was also prepared by introducing the THP protecting group prior to azide reduction (Scheme 4). In conclusion, **15** has been obtained following three different routes (taking into account also the one depicted in Scheme 3), equivalent in terms of steps. Among them, the one described in Scheme 3 turned out to be the best, because of the low yield for the allylation of carbamate **20**.

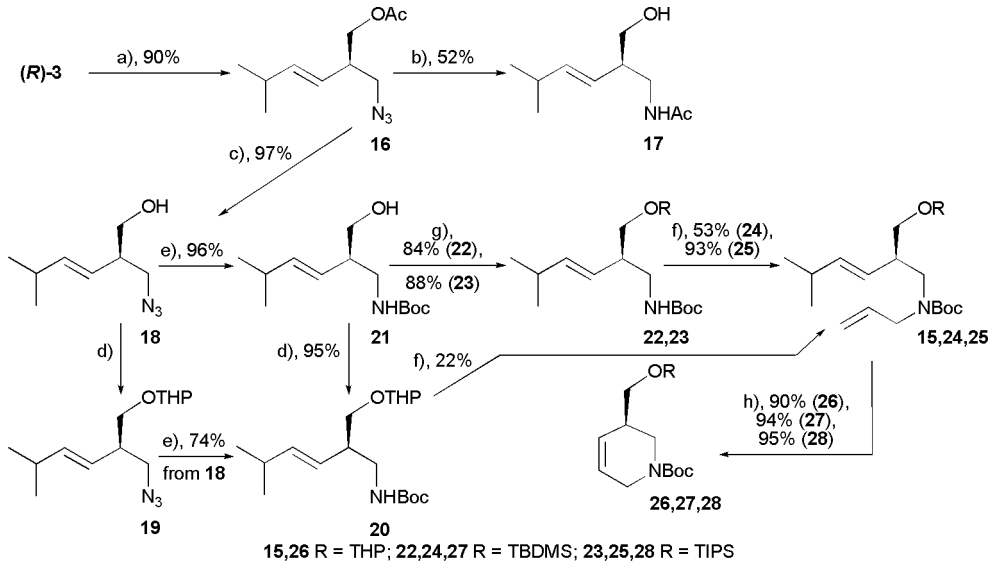
With an analysis of the influence of both the O- and N-protecting groups on the RCM reaction in mind, we also synthesized an analogue of **25**, compound **31** (Scheme 5). This was obtained from **18** by the same sequence, but with somewhat lower overall yield.

The four O-protected carbamates **15**, **24**, **25** and **31** were then submitted to RCM in the presence of first-generation Grubbs' catalyst, under the conditions found optimal for **5**. Boc-protected olefins reacted smoothly to give the corresponding tetrahydropyridines in excellent yield, thus suggesting in this case a negligible influence of the branched unsaturated moiety

Table 1 Ring-closing metathesis on **5**, using 5% Grubbs' first-generation catalyst

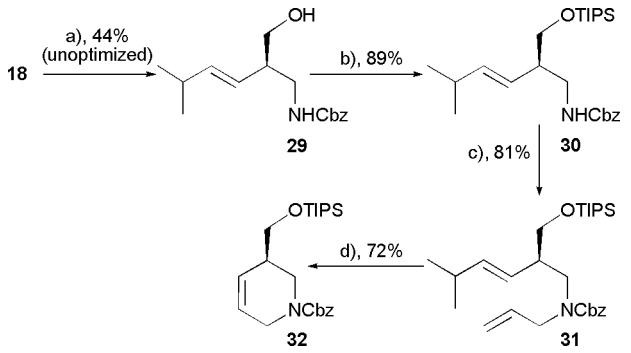
Entry	Solvent	Concentration of **5**/M	Temperature/°C	Yield of **6** (%)	Yield of **7** (%)
1	Benzene	0.020	50	44	6.5
2	Benzene	0.034[a]	40 → 50	77	10
3	Benzene	0.034[a]	60	57	5.3
4	1,2-Dichloroethane	0.019	50	74	2.8
5	CH_2Cl_2	0.020	reflux	80	trace

[a] Catalyst added through a syringe pump over a period of 6–7 h.



Scheme 4 *Reagents and conditions*: (a) (i) MsCl, Et_3N, CH_2Cl_2, −30 °C; (ii) NaN_3, DMF, 50 °C; (b) PPh_3, THF–H_2O, 55 °C; (c) PCL, THF–H_2O 1 : 3, pH 7, rt; (d) DHP, *p*-TSA, CH_2Cl_2, 0 °C; (e) (i) PPh_3, THF–H_2O, rt; (ii) Boc-ON, Et_3N, rt; (f) allyl bromide, NaH, DMF, rt; (g) $R^1{}_2R^2SiCl$, imidazole, rt [R^1 = Me, R^2 = *t*Bu (**22**), $R^1 = R^2$ = *i*Pr (**23**)]; (h) Grubbs' catalyst, 0.028 M (**26**), 0.014 M (**27**) or 0.036 M (**28**) in CH_2Cl_2, reflux.

during the cyclization process. In contrast to the O-containing dienes, in no cases could we detect acyclic derivatives analogous to **7**, and this fact allowed us to work, for preparative purposes, using more concentrated solutions. Finally, we were surprised by the different behaviour of the Cbz-protected diene, which was transformed into **32** in only moderate yield (Scheme 5), thus indicating an influence of the N-protecting group on the outcome of the reaction. An important feature of this reaction is the procedure necessary for elimination of the Ru derivatives responsible for the deeply coloured crude mixture. Several reported methods have been tested to remove these coloured impurities [including treatment with $Pb(OAc)_4$,[35] Me_2SO, and Ph_3PO[36]]; the most efficient additive in our case was shown to be triphenylphosphine oxide.

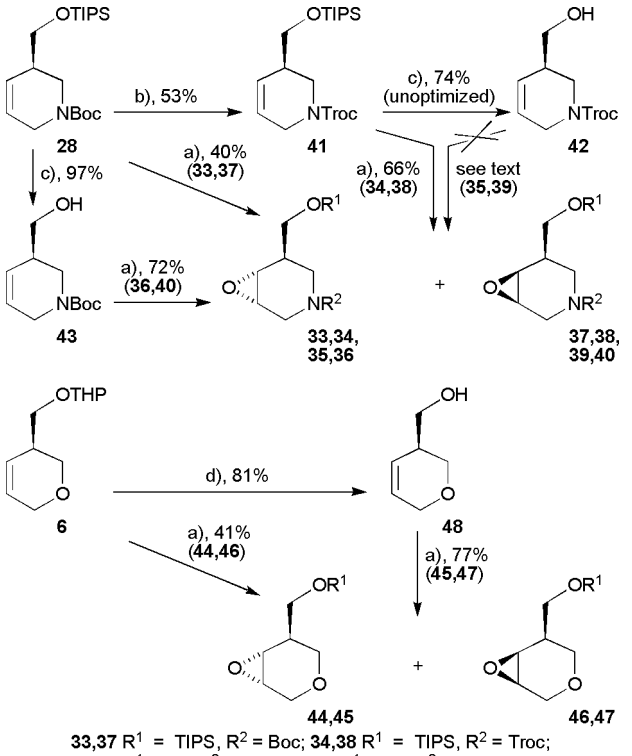


Scheme 5 *Reagents and conditions*: (a) (i) PPh_3, THF–H_2O, rt; (ii) BnOCOCl, pH 10, rt; (b) TIPS-Cl, imidazole, DMF, rt; (c) allyl bromide, NaH, DMF, rt; (d) Grubbs' catalyst, 0.010 M, CH_2Cl_2, reflux.

Although several unsaturated six-membered oxygen and nitrogen heterocycles have been built up by a RCM reaction, our strategy is, to the best of our knowledge, the only one using a chemoenzymatic strategy, involving an asymmetrization reaction for the preparation of the acyclic precursor.[37] This allows also the synthesis of both enantiomers by two possible pathways: a) starting from *R*- or *S*-**3**, readily accessible as described above, or b) exploiting the "enantiodivergency" of either *R*- or *S*-**3**, a property arising from the presence of two differentiated hydroxymethyl groups that are, however, synthetically equivalent and can be manipulated independently to establish at will the absolute configuration of the stereogenic centre.

Both synthons **6** and **28**, obtained in an overall yield of 66% (4 steps) and 64% (8 steps) from **3**, respectively, can be envisaged as starting materials for more funtionalized heterocycles, due to the presence of the double bond and a pre-existing stereocentre.

As a first attempt at functionalization, we studied the epoxidation of both N- and O-heterocycles, choosing **28** as the model substrate (Scheme 6). The reaction, performed under usual peracid conditions, was rather slow, requiring at least rt in order to start, with several additions of oxidant necessary in order to obtain a complete conversion of the alkene into the epoxide. However, we found that the best, though modest, results in terms of yield, reproducibility and d.r. could be achieved when operating in refluxing CH_2Cl_2 (entry 1, Table 2), while higher boiling solvents such as 1,2-dichloroethane were



Scheme 6 *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2, reflux, (b) (i) CF_3CO_2H, CH_2Cl_2, 0 °C; (ii) Troc-Cl, H_2O, pH 10, rt; (c) *n*-Bu_4NF, THF, rt; (d) MeOH, *p*-TSA, rt.

Table 2 Epoxidation of N- and O-containing cyclic alkenes

Entry	Alkene	Reagent	Solvent	Temperature/°C	Time/h	Products	Yield (% *anti* + *syn*)	D.r.
1	**28**	*m*-CPBA	CH_2Cl_2	reflux	5	**33**,**37**	40	58 : 42[a]
2	**28**	NaClO, Jacobsen catalyst [(*R*,*R*)- or (*S*,*S*)-]	CH_2Cl_2	rt	24	**33**,**37**	trace	—
3	**28**	*m*-CPBA, NMO, Jacobsen catalyst [(*R*,*R*)- or (*S*,*S*)-]	CH_2Cl_2	−78 °C → rt	22	**33**,**37**	18	—
4	**41**	*m*-CPBA	CH_2Cl_2	reflux	5.5	**34**,**38**	66	53 : 47[b]
5	**42**	*t*-BuOOH/VO(acac)$_2$	CH_2Cl_2	rt	24	**35**,**39**	—	—
6	**43**	*t*-BuOOH/VO(acac)$_2$	CH_2Cl_2	rt	24	**36**,**40**	—	—
7	**43**	*m*-CPBA	CH_2Cl_2	reflux	5.5	**36**,**40**	72	75 : 25[c]
8	**6**	*m*-CPBA	CH_2Cl_2	reflux	6	**44**,**46**	41	50 : 50[a]
9	**48**	*m*-CPBA	CH_2Cl_2	reflux	5	**45**,**47**	77	72 : 28[c]

[a] By ^{13}C NMR. [b] By ^{1}H NMR. [c] By GC-MS.

less satisfactory. The low stereoselectivity confirms previous results on similar compounds reported by Bols,[38] thus proving a negligible influence of the bulky O-protecting group on directing the attack of *m*-CPBA.

In order to improve this reaction we turned our attention to the employment of both enantiomers of a Mn(III)-based Jacobsen catalyst, using hypochlorite as a stoichiometric oxidant,[39] hoping to observe a different stereoselectivity depending upon the absolute configuration of the catalyst. In this case the reaction was also very slow, whatever the amount of oxidant employed, and only traces of product were obtained. When a more efficient oxidant system (*m*-CPBA/*N*-methylmorpholine-*N*-oxide) was used,[40] an improved but always unsatisfactory yield was obtained.

The results for the epoxidation of **28**, in terms of yield, were in contrast with literature data, which could be attributed to the (possibly) low thermal stability of *N*-Boc derivatives in the presence of peracids.[41] To support this hypothesis we converted **28** into 2,2,2-trichloroethylcarbamate **41**, a derivative very similar to the one described by Bols (with a TIPS instead of a TBDPS group).[38] In this case an improved yield was observed (entry 4), but the results were hardly reproducible, and moreover the reaction was almost completely non-stereoselective.

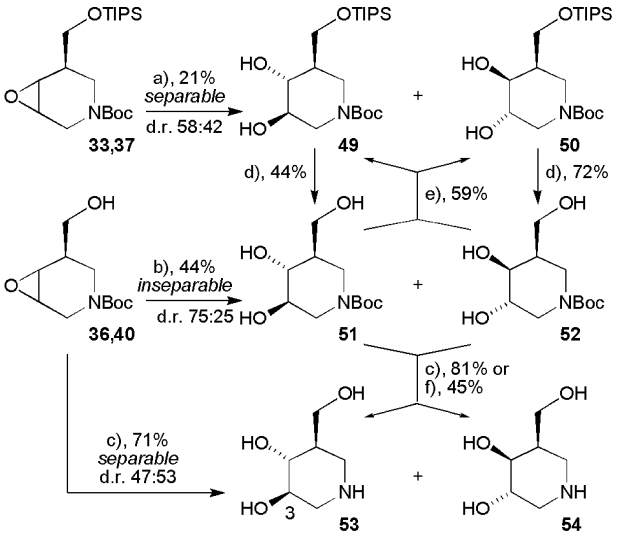
Working on the unprotected alcohol **43**, we reasoned that the *syn*-stereoisomer could be favoured using the *t*-BuOOH/VO(acac)$_2$ system, as a consequence of a possible cyclic transition state involving vanadium, *t*-BuOOH, the primary alcoholic function and the olefin. Indeed, this strategy has been successfully applied to other THYM*-derived alkenes.[42] However, in this case this approach failed: either starting from **42** or **43**, a low reactivity was observed; using forcing reaction conditions, only decomposition of starting material was obtained.

Finally, the best results, also in terms of d.r., were obtained on the unprotected homoallylic alcohol **43** (entry 7).[43] In all cases we were unable to separate the diastereomeric epoxides by chromatography, and for this reason we could not assign the relative configuration to the prevailing isomer (which was always the same), although the *anti*-epoxide seems to be the most likely (*vide infra*).

A behaviour similar to the pair **28**,**43** was observed when **6** and **48** were submitted to epoxidation by means of *m*-CPBA. While the THP-protected compound **6** was converted into **44**,**46** in moderate yield and without stereoselection (entry 8), the free alcohol **48** gave **45**,**47** in quite good yield and with a 72 : 28 diastereomeric ratio (entry 9); however, we were again unable to separate the diastereoisomers of the O-derivatives.

As a matter of fact, both types of heterocycles showed a low reactivity when treated with peracids, which is in contrast with the usual behaviour of olefins, and this reactivity seems not to depend upon the nature of the heteroatom. A more important influence on the yield and the d.r. can be attributed to the presence or absence of an O-protecting group. The only conclusion allowed by the collected data is that the stereoselectivity can not be attributed to steric effects.

As a possible application of our building blocks, we checked the possibility to transform the nitrogen derivatives into two diastereomeric iminosugars, namely isofagomine **53**[44] and its 'gulo' analogue **54**.[45] For this purpose we had to hydrolyze the oxirane ring and to remove the carbamate. For the first goal, both acidic and basic conditions were tested. The acidic hydrolysis was tested on both **33**,**37**, and **36**,**40**, and turned out to be not very satisfactory in terms of yield. In both cases, the diastereomeric ratio of the resulting diols was identical to that of the starting epoxides. Thus we presume that the reaction is regioselective and stereospecific (*anti* opening). A reasonable assumption is that water attacks the less crowded C_3 atom. In this hypothesis the major starting epoxides should be *anti*. However, since we were not able to perform the reaction on the diastereomerically pure oxiranes, we cannot definitely prove that each isomer affords a single diol. Diols **49** (major) and **50** (minor) were readily separated. On the contrary, separation of triols **51** (major) and **52** (minor) was not possible.[46] The chemical correlations depicted in Scheme 7 demonstrated that the major isomers **49** and **51** have the same relative configuration.



Scheme 7 *Reagents and conditions*: (a) 2.3% aq. $HClO_4$, reflux; (b) 3% $HClO_4$ in Me_2CO, rt; (c) 1% aq. KOH, reflux; (d) *n*-Bu_4NF, THF, rt; (e) TIPS-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (f) AcOEt–HCl (3 M), 2 : 1, rt.

Thanks to the better overall yield (from **28**) and the higher diastereomeric ratio, acidic opening of epoxyalcohols **36**,**40** is to be preferred for the synthesis of isofagomine **53**.

Regarding the mixture of triols **51**,**52** deriving from hydrolysis of **36**,**40**, the Boc group was removed under different conditions, affording the final compounds **53** and **54**, again with the

same diastereomeric ratio of the starting expoxides. At this step the diastereomers were separated by chromatography and independently fully characterized and compared with the literature data, which allowed the unambigous assignment of relative and absolute configuration. In particular, the optical rotatory power of **53** is consistent with literature data,[38,47] and this fact demonstrated that the whole sequence proceeded from THYM* without racemization.

Other methods for epoxide opening under mild conditions, highly employed in the field of sugars (such as water in the presence of sodium acetate[48] or benzoate[49]), were shown to be ineffective, while prolonged reaction time induced only extensive decomposition of starting material. On the contrary, when the the mixture of **36**,**40** was treated in aqueous alkali, a reproducible one-pot transformation into **53** and **54** in good yields was realized. However, in this case an unexpected reversal of diastereoselectivity was observed, with compound **54**, having the same relative stereochemistry of **50** or **52**, prevailing.[50] These experimental data demonstrated that under basic conditions the oxirane opening is most likely to be a non-regioselective process. This base-catalysed process is therefore to be preferred for the synthesis of the 'gulo' isomer.

Conclusions

In conclusion, we have demonstrated the possibility to transform THYM*, a building block easy to obtain on a multigram scale, into a series of heterocycles, differing by the nature of the heteroatom and by the ring size, which can be decided when preparing the acyclic precursor. After RCM, the endocyclic double bond can be exploited for different functionalizations, including epoxidations followed by oxirane opening by means of different nucleophiles, dihydroxylations followed by transformation into cyclic sulfates, and so on. By this strategy, a large variety of iminosugars and artificial sugars should be accessible.

Moreover, one or both oxygen arms of THYM* can be sequentially elaborated through diastereoselective procedures to give a series of dienes suited for RCM, allowing a new entry to carbasugars. Our results in this field will be reported in due course.

Experimental

NMR spectra were taken in $CDCl_3$ at 200 MHz (^{1}H) and 50 MHz (^{13}C) (unless otherwise stated), using TMS as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignment in ^{1}H NMR spectra was also made with the aid of double resonance experiments. Peak assignment in ^{13}C NMR spectra was made with the aid of DEPT experiments. GC-MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and an ionization chamber temperature of about 170 °C. Unless otherwise indicated, analyses were performed with a constant He flow of 0.9 ml min^{-1}, init. temp. 100 °C, init. time 2 min, rate 20 °C min^{-1}, final temp. 260 °C, final time 4 min, inj. temp. 250 °C, det. temp. 280 °C. R_t values are in min. IR spectra were measured in $CHCl_3$ solution with a Perkin–Elmer 881 instrument. $[\alpha]_D$ values were determined on a Jasco DIP 181 polarimeter, in $CHCl_3$ (containing 0.75–1% EtOH) solution. TLC analyses were carried out on silica gel plates, which were developed by the following detection methods: **A**) UV; **B**) dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming; **C**) dipping into a solution of 4% aq. $KMnO_4$ and warming; **D**) dipping into a solution of *p*-anisaldehyde (5.5 ml) in H_2SO_4 (7.5 ml), AcOH (2.2 ml) and EtOH (500 ml) and warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using "flash" methodology. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted thrice with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere, while RCM reactions were performed under ultra-pure argon. Lipase from *Pseudomonas cepacia* was a kind gift from Amano P, while PPL was purchased from Sigma and supported on celite following our procedure.

Note: in this section, only selected experimental data are reported. An exhaustive report is available as electronic supplementary information.†

General procedure for RCM under optimized conditions

Argon was bubbled into a solution of the desired diene [**5** (0.020 M), **15** (0.028 M), **24** (0.014 M), **25** (0.036 M), **31** (0.010 M)] in dry CH_2Cl_2 for 15 min. Then Grubbs' first-generation catalyst (5% mmol with respect to substrate) was added and the reaction was refluxed until complete (1–2.5 h). After cooling to rt, triphenylphosphine oxide (50 molar equiv. with respect to catalyst) was added and the mixture was stirred overnight. After solvent removal under reduced pressure, the crude was directly chromatographed with the appropriate eluent.

(3*S*)- and (3*R*)-3-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]-3,6-dihydro-2*H*-pyran 6. Prepared starting from both enantiomers of **5**. Chromatography with PE–Et_2O 8 : 2 → 7 : 3 gave **6** [(*S*)- from (*S*)-**5** and (*R*)- from (*R*)-**5**] as a yellow oil in 80% yield. R_f 0.41 (PE–Et_2O 7 : 3, **B**). Anal. found C, 66.45; H, 9.20. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15. $[\alpha]_D$ (2*S*-**6**) = + 79.9 ($CHCl_3$, *c* 1.22); $[\alpha]_D$ (2*R*-**6**) = −78.8 ($CHCl_3$, *c* 1.30). IR: ν_{max} 2946, 2865, 1351, 1118, 1073, 1022. GC-MS: R_t 5.10; *m*/*z* 169 (M^+ − 29, 0.084), 86 (5.6), 85 (100), 69 (5.8), 67 (20), 57 (8.9), 55 (8.2), 43 (12), 41 (20). ^{1}H NMR: 1.43–1.88 [6H, m, 3 C*H*$_2$ of THP]; 2.47 [1H, centre of m, C*H*CH$_2$OTHP]; 3.30–3.91 [6H, m, C*H*$_2$OTHP, OCHOC*H*$_2$, C*H*$_2$OCHCH$_2$OTHP]; 4.10–4.12 [2H, m, =CHC*H*$_2$O]; 4.57–4.63 [1H, m, OC*H*O]; 5.72–5.85 [2H, m, C*H*=C*H*]. ^{13}C NMR: 19.34 and 19.64 [CH$_2$*C*H$_2$(CH$_2$)$_2$O]; 25.44 [(CH$_2$)$_2$*C*H$_2$CH$_2$O]; 30.57 [*C*H$_2$(CH$_2$)$_3$O]; 35.36 and 36.60 [*C*HCH$_2$OTHP]; 62.02 and 62.44, 65.59 and 65.57, 66.26 and 66.61, 68.04 and 68.32 [4C, *C*H$_2$O]; 98.47 and 99.40 [O*C*HO]; 125.32 and 125.41, 127.86 [2C, *C*=*C*].

Compound 7 from intermolecular metathesis. Obtained, as an 8 : 2 *E* : *Z* mixture, during RCM of diene **5**. The yield depended upon the reaction conditions (trace–10%) R_f 0.36 (PE–Et_2O 7 : 3, **B**). IR: ν_{max} 2927, 2854, 1455, 1363, 1190, 1119, 1019, 974. GC-MS: compound unsuitable for this analysis. ^{1}H NMR: 0.97 [12H, d, (C*H*$_3$)$_2$CH, *J* 6.6]; 1.28–1.87 [12H, m, 3 C*H*$_2$ of THP]; 2.58 [2H, octet, (CH$_3$)$_2$C*H*, *J* 6.7]; 2.55 [2H, centre of m, C*H*CH$_2$OTHP]; 3.35–3.91 [8H, m, C*H*$_2$OTHP and C*H*$_2$OCH$_2$CH=]; 3.97 [4H, d, OC*H*$_2$CH=CHC*H*$_2$O (*E*), *J* 3.8]; 4.04 [4H, d, OC*H*$_2$CH=CHC*H*$_2$O (*Z*), *J* 4.4]; 4.59 [2H, broad t, OC*H*O, *J* 3.0]; 5.32 and 5.52 [4H, ddd and dd, C*H*=C*H*–*i*Pr, *J* 2.6, 7.8, 15.8 and 6.2, 15.6]; 5.68 [2H, broad t, OCH$_2$C*H*=C*H*CH$_2$O (*Z*), *J* 3.9]; 5.78 [2H, broad s, OCH$_2$C*H*=C*H*CH$_2$O (*E*)]. ^{13}C NMR: 19.34 [2C, CH$_2$*C*H$_2$(CH$_2$)$_2$O]; 22.52 and 22.58 [4C, CH(*C*H$_3$)$_2$]; 25.55 [2C, (CH$_2$)$_2$*C*H$_2$CH$_2$O]; 30.61 [2C, *C*H$_2$(CH$_2$)$_3$O]; 31.19 [2C, *C*H(CH$_3$)$_2$]; 42.95 [2C, *C*HCH$_2$OTHP]; 61.92, 68.19 and 68.33 [4C, *C*H$_2$OTHP and (CH$_2$)$_3$*C*H$_2$O]; 71.04 and 71.35 [4C, *C*H$_2$O*C*H$_2$CH=]; 98.70 [2C, O*C*HO]; 125.46 and 139.74 [4C, *C*H=*C*H–*i*Pr]; 129.29 [2C, OCH$_2$*C*H=*C*HCH$_2$O].

(*R*)-3-[(Tetrahydro-2*H*-pyran-2-yloxy)methyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 26. Prepared starting from **15**. Chromatography with PE–Et_2O 7 : 3 gave **26** as a yellow oil in 90% yield. R_f 0.40 (PE–Et_2O 7 : 3, **B**). Anal. found C, 64.80; H, 9.25; N, 4.60. $C_{16}H_{27}NO_4$ requires C, 64.62; H, 9.15; N, 4.71. $[\alpha]_D$ = −55.0 ($CHCl_3$, *c* 0.84). IR: ν_{max} 2943, 1675, 1365, 1192, 1119. GC-MS: R_t 7.92; *m*/*z* 242 (M^+ − 55, 0.079), 157 (16), 156 (19), 141 (6.4), 140 (18), 139 (19), 138 (7.5),

127 (18), 112 (28), 97 (8.2), 96 (16), 95 (11), 94 (19), 86 (5.7), 85 (96), 82 (9.0), 80 (9.5), 68 (15), 67 (30), 57 (100), 56 (7.2), 55 (9.5), 43 (16), 42 (5.3), 41 (47), 39 (9.4). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 0.83–1.90 [6H, m, 3 CH_2 of THP]; 1.43 [9H, s, OC(CH_3)$_3$]; 2.45 [1H, centre of m, CHCH$_2$OTHP]; 2.97–3.80 [6H, m, CH_2OTHP, OCHOCH_2, CH_2NCHCH$_2$O]; 3.82–3.83 [2H, m, =CHCH_2N]; 4.57–4.60 [1H, m, OCHO]; 5.69–5.82 [2H, m, CH=CH]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 18.37 and 18.48 [CH$_2$CH$_2$(CH$_2$)$_2$O]; 24.43 [(CH$_2$)$_2$CH$_2$CH$_2$O]; 27.47 [3C, OC(CH$_3$)$_3$]; 29.66 [CH$_2$(CH$_2$)$_3$O]; 34.95 and 35.28 [CHCH$_2$OTHP]; 41.89 and 42.09, 42.59 [2C, CH$_2$NCH$_2$]; 60.55 and 60.88, 67.29 and 67.64 [2C, CH$_2$O]; 78.04 [OC(CH$_3$)$_3$]; 97.37 and 98.14 [OCHO]; 125.05 and 125.14, 125.65 [2C, C=C]; 153.66 [CO].

(*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 27. Prepared starting from **24**. Chromatography with PE–CH$_2$Cl$_2$ 1 : 1 → CH$_2$Cl$_2$ and then Et$_2$O gave **27** as a yellow oil in 94% yield. R_f 0.18 (PE–Et$_2$O 97 : 3, **B**). Anal. found C, 62.60; H, 10.05; N, 4.35. $C_{17}H_{33}NO_3Si$ requires C, 62.34; H, 10.16; N, 4.28. $[\alpha]_D = -34.5$ (CHCl$_3$, *c* 1.42). IR: ν_{max} 2928, 2427, 1682, 1414, 1194, 1104. GC-MS: R_t 7.29; *m*/*z* 270 (M$^+$ − 57, 0.24), 215 (15), 214 (100), 170 (16), 105 (7.5), 96 (6.5), 95 (5.2), 94 (6.3), 89 (20), 88 (6.3), 75 (27), 73 (25), 67 (8.0), 57 (42), 41 (10). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 0.06 and 0.08 [6H, 2 s, Si(CH_3)$_2$*t*Bu]; 0.91 [9H, s, SiMe$_2$C(CH_3)$_3$]; 1.43 [9H, s, OC(CH_3)$_3$]; 2.32 [1H, centre of m, (CH$_3$)$_2$CH]; 3.28 and 3.55 [2H, AB part of ABX system, CH_2O, J_{AB} 13.0, J_{AX} 6.2, J_{BX} 4.3]; 3.38–3.55 [2H, m, CH_2NCHCH$_2$O]; 3.81 [2H, broad s, NCH_2CH=]; 5.67–5.80 [2H, m, CH=CH]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): −6.12 [2C, Si(*C*H$_3$)$_2$C(CH$_3$)$_3$]; 17.24 [Si(CH$_3$)$_2$*C*(CH$_3$)$_3$]; 25.31 [3C, Si(CH$_3$)$_2$C(*C*H$_3$)$_3$]; 27.54 [3C, OC(*C*H$_3$)$_3$]; 37.50 [*C*HCH$_2$O]; 41.87 and 42.67 [2C, *C*H$_2$N*C*H$_2$CH=CH]; 62.52 [*C*H$_2$OSi]; 78.06 [*C*(CH$_3$)$_3$]; 125.18 and 125.2 [2C, *C*=*C*]; 153.73 [*C*O].

(*R*)-3-[(Triisopropylsilyloxy)methyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 28. Prepared starting from **25**. Chromatography with PE–Et$_2$O 98 : 2 → 9 : 1 gave **28** as a yellow oil in 95% yield. R_f 0.36 (PE–Et$_2$O 95 : 5, **B**, **C**). Anal. found C, 64.75; H, 10.80; N, 3.65. $C_{20}H_{39}NO_3Si$ requires C, 64.99; H, 10.64; N, 3.79. $[\alpha]_D = -27.7$ (CHCl$_3$, *c* 1.15). IR: ν_{max} 2938, 2865, 1679, 1159, 1110. GC-MS: R_t 8.81; *m*/*z* 312 (M$^+$ − 57, 0.73), 272 (5.8), 271 (20), 270 (100), 226 (13), 182 (5.4), 145 (5.4), 131 (12), 119 (7.2), 103 (12), 75 (21), 73 (7.0), 67 (9.5), 61 (11), 59 (15), 57 (44), 45 (7.5), 41 (22). ^{1}H NMR (300 MHz, DMSO-d_6; temp. = 100 °C): 1.04–1.11 [21H, m, TIPS]; 1.42 [9H, s, OC(CH_3)$_3$]; 2.37 [1H, centre of m, CHCH$_2$O]; 3.30 and 3.58 [2H, AB part of ABX system, CH_2O, J_{AB} 13.0, J_{AX} 6.3, J_{BX} 8.2]; 3.51–3.70 [2H, m, CH_2NCHCH$_2$O]; 3.73–3.89 [2H, m, NCH_2CH=]; 5.70–5.80 [2H, m, CH=;CH]. ^{13}C NMR (300 MHz, DMSO-d_6; temp. = 100 °C): 11.02 [3C, Si(*C*H(CH$_3$)$_2$)$_3$]; 17.14 [6C, Si(CH(*C*H$_3$)$_2$)$_3$]; 27.50 [3C, OC(*C*H$_3$)$_3$]; 37.73 [*C*HCH$_2$O]; 41.97 and 42.65 [2C, *C*H$_2$N*C*H$_2$CH=CH]; 64.06 [*C*H$_2$OSi]; 78.03 [*C*(CH$_3$)$_3$]; 125.13 and 125.54 [2C, *C*=*C*]; 153.75 [*C*O].

(*R*)-3-[(Triisopropylsilyloxy)methyl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester 32. Prepared starting from **31**. Chromatography with PE–Et$_2$O 9 : 1 → 8 : 2 gave **32** as a yellow oil in 73% yield. R_f 0.43 (PE–Et$_2$O 8 : 2, **A**, **B**). Anal. found C, 68.60; H, 9.15; N, 3.60. $C_{23}H_{37}NO_3Si$ requires C, 68.44; H, 9.24; N, 3.47. $[\alpha]_D = -47.4$ (CHCl$_3$, *c* 1.94). IR: ν_{max} 2941, 2862, 1685, 1431, 1192, 1107. GC-MS: R_t 11.14; *m*/*z* 360 (M$^+$ − 43, 10), 317 (6), 316 (22), 182 (7), 100 (6), 92 (9), 91 100), 75 (6), 65 (7), 59 (5). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 1.06 [21H, apparent s, TIPS]; 2.40 [1H, centre of m, CHCH$_2$O]; 3.37 and 3.70 [2H, AB part of ABX system, CH_2O, J_{AB} 13.0, J_{AX} 6.6, J_{BX} 4.9]; 3.32–3.75 [2H, m, CH_2NCHCH$_2$O]; 3.78–4.01 [2H, m, NCH_2CH=]; 5.09 and 5.13 [2H, AB system, CH_2OPh, *J* 12.6]; 5.67–5.84 [2H, m, CH=CH]; 7.31–7.38 [5H, m, aromatics]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 11.00 [3C, Si(*C*H(CH$_3$)$_2$)$_3$]; 17.10 [6C, Si(CH(*C*H$_3$)$_2$)$_3$]; 37.56 [*C*HCH$_2$O]; 42.10 and 42.78 [2C, *C*H$_2$N*C*H$_2$CH=CH]; 64.00 and 65.60 [2C, *C*H$_2$OSi and *C*H$_2$OPh]; 124.76 and 125.62 [2C, *C*=*C*]; 126.69, 126.98 and 127.60 [5C, *C*H of Ph]; 136.46 [*ipso*-C of Ph]; 154.28 [*C*O].

General procedure for the epoxidation of RCM-derived products

A solution of the alkene (1.00 mmol) in dry CH$_2$Cl$_2$ (8 ml) was cooled to 0 °C and treated with *m*-CPBA (1.50 mmol). After 5 min the solution was refluxed for the required time (5–6 h). Usually, after about 2 h, a further addition of peracid was required in order for the reaction to go to completion. After cooling the reaction mixture to 0 °C, Me$_2$S (1 molar equiv. with respect to the acid employed) was added. This was followed by the addition of sat. aq. NaHCO$_3$ solution (15 ml). The biphasic system was vigorously stirred at rt for 15 min and then extracted with ether.

(1*S*,5*R*,6*R*)- and (1*R*,5*R*,6*S*)-5-[(Triisopropylsilyloxy)methyl]-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic acid *tert*-butyl ester 33 and 37. This diastereomeric mixture was prepared starting from **28**. Chromatography with PE–Et$_2$O 9 : 1 → 7 : 3 gave **33**,**37** as an inseparable 58 : 42 (^{13}C NMR) diastereomeric mixture (as a pale yellow oil) in 40% yield. R_f 0.55 (PE–Et$_2$O 7 : 3, **B**, **C**). IR: ν_{max} 2939, 2864, 1673, 1367, 1252, 1115. GC-MS: R_t 9.50; *m*/*z* 328 (M$^+$ − 57, 0.25), 312 (6.0), 288 (5.8), 287 (20), 286 (100), 256 (9.2), 242 (26), 131 (6.3), 119 (6.8), 103 (6.6), 94 (5.6), 75 (9.2), 61 (6.9), 59 (6.8), 57 (43), 56 (42), 44 (9.4), 42 (7.4), 41 (11). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 0.95–1.25 [21H, m, TIPS]; 1.40 [9H, s, OC(CH_3)$_3$]; 2.10–2.23 [1H, m, CHCH$_2$O]; 2.83–2.95 and 3.12–3.30 [2H, 2 m, 2 CH–O]; 3.40–3.90 [6H, m, CH_2OSi and CH_2NCH_2]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): [N.B.: where possible the signals in the ^{13}C NMR spectrum have been attributed to the major diastereoisomer (M) or to the minor diastereoisomer (m)] 11.00 [3C, Si(*C*H(CH$_3$)$_2$)$_3$]; 17.15 [6C, Si(CH(*C*H$_3$)$_2$)$_3$]; 27.47 [3C, OC(*C*H$_3$)$_3$]; 35.81 (m) and 36.83 (M) [*C*HCH$_2$O]; 39.23, 41.36 (M) and 41.70 (m) [2C, *C*H$_2$N*C*H$_2$]; 48.69 (m) and 49.15 (M), 50.44 (M) and 51.15 (m) [2C, 2 *C*H–O]; 62.34 (m) and 62.70 (M) [CH$_2$OSi]; 78.22 (m) and 78.23 (M) [*C*(CH$_3$)$_3$]; 153.53 (m) and 153.92 (M) [*C*O].

(1*S*,5*R*,6*R*)- and (1*R*,5*R*,6*S*)-5-[(Triisopropylsilyloxy)methyl]-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylic acid 2,2,2-trichloroethyl ester 34 and 38. This diastereomeric mixture was prepared starting from **41**. Chromatography with PE–Et$_2$O 95 : 5 → 7 : 3 gave **34**,**38** as an inseparable 53 : 47 (^{1}H NMR) diastereomeric mixture (as a pale yellow oil) in 66% yield. R_f 0.29 (PE–Et$_2$O 9 : 1, **B**, **C**). IR: ν_{max} 2920, 2860, 1710, 1601, 1193, 1123. GC-MS: R_t 11.17; *m*/*z* 418 [M$^+$ − 43 (2 ^{36}Cl and 1 ^{35}Cl, 21)], 416 [M$^+$ − 43 (3 ^{35}Cl, 20)], 388 (12), 386 (12), 312 (8.6), 272 (9.3), 270 (28), 268 (29), 234 (7.7), 232 (23), 230 (22), 222 (5.2), 220 (9.8), 218 (6.0), 211 (14), 199 (6.5), 157 (16), 145 (8.2), 139 (5.8), 138 (11), 137 (11), 135 (12), 133 (38), 131 (56), 129 (14), 127 (8.4), 123 (5.0), 121 (14), 120 (10), 119 (83), 115 (26), 114 (5.0), 113 (9.4), 111 (8.6), 108 (6.6), 103 (26), 101 (11), 99 (15), 98 (6.3), 97 (20), 96 (8.3), 95 (33), 94 (28), 93 (14), 89 (5.8), 88 (5.0), 87 (18), 85 (6.9), 83 (7.3), 82 (12), 81 (6.0), 80 (16), 79 (5.3), 77 (11), 75 (46), 73 (21), 71 (6.7), 69 (7.7), 67 (13), 63 (5.2), 61 (43), 60 (6.3), 59 (45), 57 (6.8), 56 (59), 55 (16), 54 (6.6), 53 (5.0), 45 (25), 44 (12), 43 (23), 42 (30), 41 (26), 39 (6.9). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 0.95–1.25 [21H, m, TIPS]; 2.20–2.35 [1H, m, CHCH$_2$O]; 3.06–3.39 [2H, m, 2 CH–O]; 3.57–4.07 [6H, m, CH_2OSi and CH_2NCH_2]; 4.78 and 4.83, 4.80 and 4.82 [2H, 2 AB system, CO$_2$CH_2, *J* 12.3 and 12.3]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): [N.B.: where possible the signals in the ^{13}C NMR spectrum have been attributed to the major diastereoisomer (M) or to the minor diastereoisomer (m)] 11.00 [3C, Si(*C*H(CH$_3$)$_2$)$_3$]; 17.17 [6C, Si(CH(*C*H$_3$)$_2$)$_3$]; 35.66 (m) and 36.68 (M) [*C*HCH$_2$O]; 39.59, 41.75 (m) and

42.07 (M) [2C, CH_2NCH_2]; 48.47 (m) and 48.93 (M), 50.42 (M) and 51.17 (m) [2C, 2 *C*H–O]; 62.38 (m) and 62.67 (M) [CH_2OSi]; 73.97 [CO_2CH_2]; 95.68 [CCl_3]; 152.48 [*C*O].

(1*S*,5*R*,6*R*)- and (1*R*,5*R*,6*S*)-5-Hydroxymethyl-7-oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid *tert*-butyl ester 36 and 40. This diastereomeric mixture was prepared starting from **43**. Chromatography with Et_2O gave **36**,**40** as an inseparable 75 : 25 (GC-MS) diastereomeric mixture (as a pale yellow oil) in 72% yield. R_f 0.46 (Et_2O, **C**, **D**). IR: ν_{max} 3454, 2920, 1679, 1413, 1366, 1162, 1019. GC-MS (usual method, but init. temp. 80 °C, init. time 2 min, rate 10 °C min^{-1}): R_t 10.63 (minor); *m*/*z* 229 (M^+, 1.3), 172 (5.8), 156 (5.2), 142 (5.9), 98 (5.1), 83 (8.6), 82 (6.3), 70 (6.1), 68 (5.6), 58 (5.1), 57 (100), 56 (9.0), 55 (6.6), 43 (26), 42 (7.8), 41 (23), 39 (5.0); R_t 10.82 (major); *m*/*z* 229 (M^+, 0.32), 173 (5.0), 172 (5.5), 98 (12.8), 83 (6.3), 82 (5.6), 80 (5.5), 70 (6.0), 68 (5.9), 58 (5.3), 57 (100), 56 (8.4), 55 (5.5), 44 (5.0), 43 (21), 42 (10), 41 (24), 39 (5.2). ^{1}H NMR (DMSO-d_6; temp. = 100 °C): 1.41 [9H, s, $OC(CH_3)_3$]; 2.08 [1H, centre of m, $CHCH_2O$]; 2.77–3.91 [8H, m, 2 C*H*–O, CH_2OSi and CH_2NCH_2]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): [N.B.: where possible the signals in the ^{13}C NMR spectrum have been attributed to the major diastereoisomer (M) or to the minor one (m)] 27.53 [3C, $OC(CH_3)_3$]; 35.53 (m) and 36.61 (M) [$CHCH_2O$]; 39.21 (M) and 40.40 (m), 41.39 (M) and 41.76 (m) [2C, CH_2NCH_2]; 48.73 (m) and 49.11 (M), 50.75 (M) and 51.51 (m) [2C, 2 *C*H–O]; 60.23 (m) and 60.54 (M) [CH_2OSi]; 78.22 (m) and 78.26 (M) [$C(CH_3)_3$]; 153.62 [*C*O].

(1*S*,5*R*,6*R*)- and (1*R*,5*R*,6*S*)-5-[(tetrahydro-2*H*-pyran-2-yloxy)-methyl]-3,7-dioxabicyclo[4.1.0]heptane 44 and 46. This diastereomeric mixture was prepared starting from **6**. Chromatography with PE–Et_2O 6 : 4 gave **44**,**46** as an inseparable ≈1 : 1 (^{13}C NMR) diastereomeric mixture (as a pale yellow oil) in 41% yield. R_f 0.57 (PE–Et_2O 4 : 6, **B**). GC-MS: R_t 6.06; *m*/*z* 129 (M^+ − 85, 0.22), 101 (36), 86 (6.1), 85 (100), 84 (16), 83 (18), 69 (10), 67 (16), 57 (20), 56 (9.8), 55 (31), 43 (19), 41 (29), 39 (9.8). ^{1}H NMR: 1.43–1.90 [6H, m, 3 CH_2 of THP]; 2.28–2.49 [1H, centre of m, $CHCH_2OTHP$]; 3.15–4.08 [10H, m, 4 CH_2O, 2 C*H*–O]; 4.57–4.67 [1H, m, O*CH*O]. ^{13}C NMR: 19.40 and 19.45 [$CH_2CH_2(CH_2)_2O$]; 25.38 [$(CH_2)_2CH_2CH_2O$]; 30.51 [$CH_2(CH_2)_3O$]; 34.71, 34.78, 35.04 and 35.11 [$CHCH_2OTHP$]; 50.28, 50.69, 50.98 and 51.80 [2C, 2 *C*H–O]; 62.18, 62.35 and 62.39, 63.49, 63.53 and 63.69, 64.90 and 65.11, 65.87, 65.97, 66.04 and 66.19 [4C, 4 CH_2O]; 99.04 [O*C*HO].

(1*S*,5*S*,6*R*)- and (1*R*,5*S*,6*S*)-3,7-dioxabicyclo[4.1.0]heptan-5-ylmethanol 45 and 47. This diastereomeric mixture was prepared starting from **48**. Chromatography with Et_2O gave **45**,**47** as a 72 : 28 (GC-MS) inseparable diastereomeric mixture (as a pale yellow oil) in 77% yield. R_f 0.25 (PE–AcOEt 15 : 85, **C**). IR: ν_{max} 3450, 2954, 2889, 1243, 1135, 1109, 1022. GC-MS (usual method, but init. temp. 60 °C, init. time 2 min, rate 2 °C min^{-1} until 120 °C, then 20 °C min^{-1} until 260 °C): R_t 10.08 (minor); *m*/*z* 99 (M^+ −31, 60), 87 (7.0), 83 (12), 82 (16), 81 (14), 74 (21), 73 (20), 71 (30), 70 (15), 69 (56), 68 (5.5), 58 (29), 57 (100), 56 (25), 55 (33), 54 (9.5), 53 (17), 45 (16), 44 (29), 43 (35), 42 (11), 41 (56), 40 (6.6), 39 (28); R_t 10.38 (major); *m*/*z* 129 (M^+ − 18, 2.3), 100 (5.3), 99 (84), 87 (13), 83 (22), 82 (60), 81 (31), 74 (9.0), 73 (12), 71 (29), 70 (81), 69 (100), 68 (6.1), 66 (8.6), 58 (8.2), 57 (99), 56 (23), 55 (51), 54 (16), 53 (20), 45 (24), 44 (38), 43 (63), 42 (25), 41 (80), 40 (15), 39 (43). ^{1}H NMR: 2.05–2.34 [2H, m, $CHCH_2OH$]; 3.24–4.00 [8H, m, 3 CH_2O, 2 C*H*–O]. [N.B.: where possible the signals in the ^{13}C NMR spectrum have been attributed to the major diastereoisomer (M) or to the minor diastereoisomer (m)] ^{13}C NMR: 36.31 (M) and 36.46 (m) [$CHCH_2OH$]; 50.44, 51.09 and 51.62 [2C, 2 *C*H–O]; 61.65 (M) and 62.04 (m), 63.36 (M) and 63.92 (m), 64.86 (M) and 64.91 (m) [3C, 3 CH_2O].

(3*R*,4*R*,5*R*)- and (3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-[(triisopropyl-silyloxy)methyl]piperidine-1-carboxylic acid *tert*-butyl ester 49 and 50. The diastereomeric mixture **33**,**37** (70 mg, 181 μmol) was suspended in 2.3% aq. $HClO_4$ (3 ml) and refluxed for 1 h. The solution was neutralized with solid K_2CO_3 and, after saturation with solid NaCl, an extraction was performed with AcOEt. Chromatography with PE–Et_2O 25 : 75 gave **49** (8.9 mg, 12% yield) and **50** (6.5 mg, 9% yield) as colourless oils. Compound **49**: R_f 0.36 (PE–Et_2O 75 : 25, **C**, **D**). $[\alpha]_D$ = –9.6 ($CHCl_3$, *c* 0.73). IR: ν_{max} 3424, 2934, 2866, 1680, 1420, 1191. GC-MS: R_t 10.15 (or 18.82 with usual method, but with init. temp. 130 °C, init. time 0, rate 5 °C min^{-1} to establish d.r.); *m*/*z* 342 (M^+ − 61, 0.093), 304 (14), 260 (17), 242 (13), 112 (10), 103 (6.7), 83 (5.3), 77 (8.8), 75 (15), 73 (5.0), 61 (11), 59 (10), 58 (5.2), 57 (100), 56 (6.9), 45 (6.2), 44 (66), 43 (8.2), 42 (18), 41 (18). ^{1}H NMR (DMSO-d_6; temp. = 100 °C); 0.95–1.20 [21H, m, TIPS]; 1.41 [9H, s, $OC(CH_3)_3$]; 1.47–1.62 [1H, m, $CHCH_2O$]; 2.45 [1H, dd, H_{6ax}, *J* 12.8, 10.2]; 2.56 [1H, dd, H_{2ax}, *J* 13.2, 11.4]; 3.55–3.65 [2H, m, H_3, H_4]; 3.96 [1H, ddd, H_{6eq}, *J* 12.4, 4.8, 2.2]; 3.97–4.04 [2H, m, CH_2OSi]; 4.12 [1H, ddd, H_{2eq}, *J* 13.6, 4.4, 2.6]; 4.36 [1H, d, O*H*, *J* 4.6]; 4.61 [1H, d, O*H*, *J* 4.4]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 11.04 [3C, $Si(CH(CH_3)_2)_3$]; 17.21 [6C, $Si(CH(CH_3)_2)_3$]; 27.51 [3C, $OC(CH_3)_3$]; 44.25 [$CHCH_2O$]; 44.82 and 47.73 [2C, CH_2NCH_2]; 62.14 [CH_2OSi]; 70.66 and 73.31 [2C, 2 *C*HOH]; 78.08 [$C(CH_3)_3$]; 153.41 [*C*O]. Compound **50**: R_f 0.24 (PE–Et_2O 75 : 25, **C**, **D**). $[\alpha]_D$ = −13 ($CHCl_3$, *c* 0.77). IR: ν_{max} 3416, 2923, 2865, 1680, 1416, 1157, 1088. GC-MS: R_t 10.09 (or 18.49 with usual method, but with init. temp. 130 °C, init. time 0, rate 5 °C min^{-1} to establish d.r.); *m*/*z* 342 (M^+ − 73, 1.14), 304 (23), 261 (5.5), 260 (29), 112 (9.3), 103 (7.0), 83 (5.3), 77 (8.8), 75 (16), 73 (5.6), 72 (5.6), 61 (13), 59 (11), 58 (5.4), 57 (100), 56 (10), 45 (6.4), 44 (50), 43 (6.5), 42 (19), 41 (17). ^{1}H NMR (DMSO-d_6; temp. = 100 °C); 0.94–1.20 [21H, m, TIPS]; 1.40 [9H, s, $OC(CH_3)_3$]; 2.00–2.11 [1H, m, $CHCH_2O$]; 2.80–3.81 [8H, m, $CH_2NCH_2CHCH_2OSi$, C*H*–O]; 4.41 [2H, broad s, O*H*]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 11.04 [3C, $Si(CH(CH_3)_2)_3$]; 17.21 [6C, $Si(CH(CH_3)_2)_3$]; 27.58 [3C, $OC(CH_3)_3$]; 40.79 [$CHCH_2O$]; 44.96 and 51.52 [2C, CH_2NCH_2]; 62.05 [CH_2OSi]; 67.22 and 68.56 [2C, 2 *C*HOH]; 77.55 [$C(CH_3)_3$]; 154.48 [*C*O].

(3*R*,4*R*,5*R*)- and (3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)-piperidine-1-carboxylic acid *tert*-butyl ester 51 and 52 from 36,40. Diastereomeric mixture **36**,**40** (94 mg, 410 μmol) was dissolved in acetone (8 ml) and cooled to 0 °C. 3% aq. $HClO_4$ (90 μl) was added and the rection was stirred at rt for 31 h. The solution was neutralized with solid $NaHCO_3$ and, after saturation with solid NaCl, an extraction was performed with AcOEt. Chromatography with PE–AcOEt 2 : 8 → AcOEt–MeOH 9 : 1 gave inseparable mixture **51**,**52** (45 mg, 44% yield) as a white solid with a 75 : 25 d.r. (by ^{13}C NMR). R_f 0.43 (AcOEt–MeOH 9 : 1, **D**). GC-MS (for **51**,**52**): R_t 7.57; *m*/*z* 247 (M^+, 0.34), 243 (6.2), 190 (6.7), 154 (7.0), 112 (5.4), 98 (13), 72 (5.3), 70 (11), 60 (6.7), 59 (7.6), 58 (6.7), 57 (100), 56 (10), 55 (6.3), 45 (7.6), 44 (16), 43 (18), 42 (14), 41 (33), 39 (8.5). The following spectroscopic data have been collected on the separate diastereoisomers obtained after removal of TIPS from samples of **49** and **50** (see supplementary material†). Compound **51**: IR: ν_{max} 3404, 2958, 2851, 1673, 1235, 1091. ^{1}H NMR (DMSO-d_6; temp. = 100 °C); 1.43 [9H, s, $OC(CH_3)_3$]; 1.80–2.15 [1H, m, $CHCH_2O$]; 2.42–2.58 [2H, m, H_{6ax}, H_{2ax}]; 2.76–4.13 [6H, m, CH_2OH, H_{2eq}, H_3, H_4, H_{6eq}]; 4.33 [1H, d, O*H*, *J* 3.3]; 4.38 [1H, broad s, O*H*]; 4.57 [1H, d, O*H*, *J* 3.4]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 27.62 [3C, $OC(CH_3)_3$]; 43.85 [$CHCH_2O$]; 44.69 and 47.82 [2C, CH_2NCH_2]; 59.94 [CH_2OH]; 70.69 and 73.72 [2C, 2 *C*HOH]; 78.06 [$C(CH_3)_3$]; 153.48 [*C*O]. Compound **52**: IR: ν_{max} 3367, 2962, 2845, 1674, 1249, 1146, 1097. ^{1}H NMR (DMSO-d_6; temp. = 100 °C); 1.41 [9H, s, $OC(CH_3)_3$]; 1.92–2.06 [1H, m, $CHCH_2O$]; 2.89–3.05 [2H, m, H_{6ax}, H_{2ax}]; 3.20–3.62 [9H, m, O*H*, CH_2OH, H_{2eq}, H_3, H_4, H_{6eq}]. ^{13}C NMR (DMSO-d_6; temp. = 100 °C): 27.54 [3C, $OC(CH_3)_3$]; 43.88 [$CHCH_2O$]; 45.09 and 47.81 [2C, CH_2NCH_2]; 59.95 [CH_2OH]; 67.25 and 68.87 [2C, 2 *C*HOH]; 77.56 [$C(CH_3)_3$]; 153.49 [*C*O].

(3*R*,4*R*,5*R*)- and (3*S*,4*S*,5*R*)-5-(Hydroxymethyl)piperidine-3,4-diol 53 and 54. Method 1: By removal of Boc from **51**,**53**: a) Under acidic conditions: a solution of **51**,**52** (33 mg, 132 μmol) in AcOEt (1 ml) was treated with 3 M aq. HCl (1.5 ml) and the biphasic system was stirred at rt for 1 h. The solvent was removed by distillation under vacuum. The residue was taken up with 100 μl of Et_3N and purified by preparative thin layer chromatography (thickness of silica on the plate: 0.5 mm) using MeOH–NH_3 (1%), 7 : 3, to give **53** (6.5 mg, 33% yield) and **54** (2.4 mg, 12% yield), confirming by weight the d.r. of the starting mixture of triols. b) Under basic conditions: the diastereomeric mixture **51**,**52** (18 mg, 73 μmol) was suspended in 1% aq. KOH (1 ml) and refluxed for 12 h. Water was removed under reduced pressure and the crude was directly chromatographed with MeOH–NH_3 (1%), 7 : 3, to give **53**,**54** (8.7 mg, 81% yield) as a 75 : 25 diastereomeric mixture (by ^{13}C NMR). **Method 2:** By oxirane opening under basic conditions: the diastereomeric mixture **36**,**40** (69 mg, 300 μmol) was suspended in 1% aq. KOH (2 ml) and refluxed for 3 h. Water was removed under reduced pressure and the crude was directly chromatographed with MeOH–NH_3 (1%), 7 : 3, to give **53** (13 mg, 30% yield) and **54** (18 mg, 41% yield). Compound **53**: R_f 0.41 (MeOH–NH_3 (1%), 7 : 3, **B**). $[\alpha]_D = +18$ ($CHCl_3$, *c* 0.16).[51] Compound **54**: R_f 0.22 (MeOH–NH_3 (1%), 7 : 3, **B**). $[\alpha]_D = +22$ ($CHCl_3$, *c* 0.11).[52]

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51 Other spectroscopic data agree with those reported in ref. 47.
52 Other spectroscopic data agree with those reported in ref. 38, with the exception of the ^{13}C NMR, in which, we observed a 0.7 ppm downfield shift for all the signals with respect to the reported data.