ChemComm
FEATURE ARTICLE

Parlaying C–O chirality into C–C chirality: improving the cost/benefit ratio of carbohydrate templates

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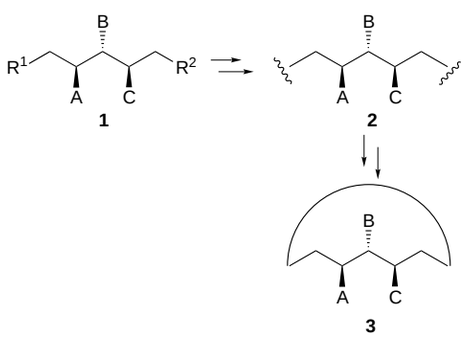
Use of sugars as chirons for complex carbocyclic targets requires that C–O chirality be transmuted into C–C chirality. The cost/benefit ratio in such syntheses is one index of efficiency. For example, the process involving oxidation of a secondary alcohol followed by methylenation and hydrogenation gives, at best, a 1 : 1 ratio. The aim of lowering this ratio has been a feature of our synthetic studies, some of which are described in this article. Among other things, the studies show that the stereochemistry of pendant, off-template mixed acetals can direct the stereo- and regioselectivity choices (*e.g.* 5-*exo-trig versus* 6-*exo-trig*) in radical cyclization reactions.

The term 'chirality transfer'[1] is generally used[2] in the context of the transformation profiled generically in Scheme 1, whereby a chiron[3] **1** is used to furnish a chiral fragment **2**, which is subsequently embedded in the target molecule **3**. The literature[4] is rich in examples of this basic strategy particularly with macrolide syntheses where the 'visual dialogue'[3] between the C–OH bonds of the starting sugar and the polyhydroxylic target is apt. In such examples chirality transfer refers to a prefabricated building block,[2] *e.g.* **2**, that is utilized convergently. However, the term may also refer to the process by which one type of asymmetry is transmuted into another, *e.g.* **4** → **5** or **5** → **6** (Scheme 2). The latter examples are abstracted from Stork's synthesis of prostaglandin $F_{2\alpha}$, notable for the fact that all of the sugar's C–OH bonds were utilized for some type of stereocontrol.[4] This study provided an excellent example of how to make optimum use of a sugar's many C–OH chiral centres.

Unfortunately this standard was not met in many syntheses that were to follow, as may be illustrated by the examples in Schemes 3 and 4, taken from the published work of one of the authors.[5,6]

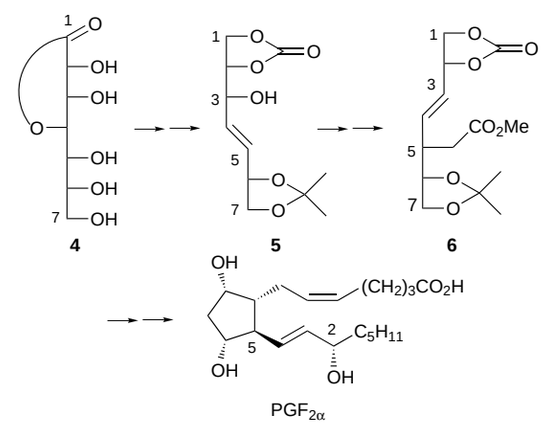
Thus in a synthesis of frontalin enantiomers (Scheme 3), ketone **8a** was used to give diastereoisomers **8b**, **c**, each of which was processed to furnish optically pure (*R*)- and (*S*)-**9**, which were then elaborated into (+)- and (−)-frontalin, respectively. In this exercise, the cost/benefit ratio is 4 : 1, based on the number of chiral centres lost and gained in going from the hexose to **9**.



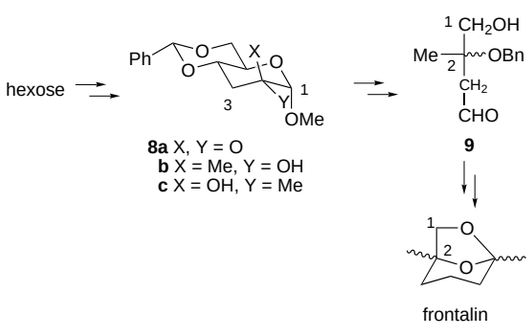
Scheme 1

This synthesis had merit in being enantiodivergent, as was also true for the chrysanthemic acid syntheses in Scheme 4; however, with the latter the cost/benefit ratio was improved to 2 : 1.

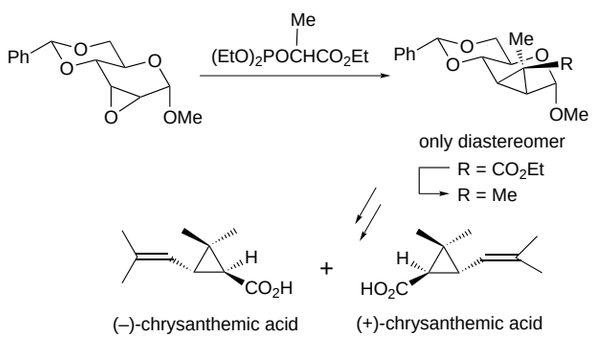
Ultimately, the case studies in Schemes 3 and 4 return to the challenge posed by Stork's prostaglandin synthesis (Scheme 2),



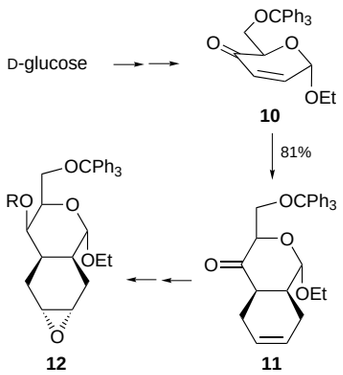
Scheme 2



Scheme 3



Scheme 4



Scheme 5

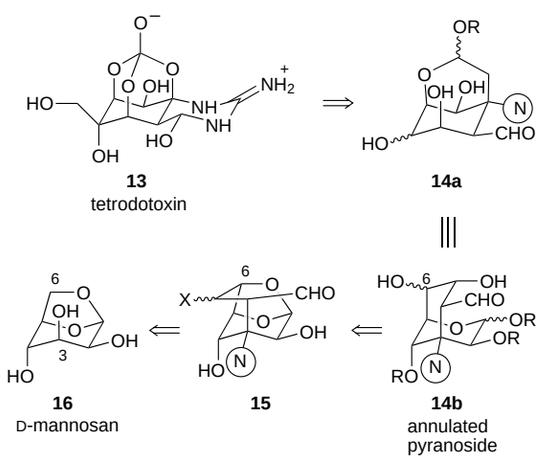
namely the problem of parlaying C–O into C–C stereochemistry.

En route to the well investigated α-enone **10**[7] (Scheme 5), three of the four chiral centres of D-glucose are 'destroyed', but because additions to **10** are facially selective, and the resulting adducts, *e.g.* **11**, are conformationally inflexible,[8] future transformations are highly diastereoselective.[9,10] As a result the cost/benefit ratio can sometimes be over compensated. In the case of **12**, for example, the ratio is 4 : 6 (ignoring the anomeric centre).

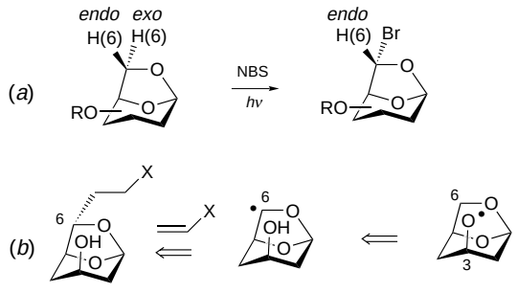
The indirect conversion of C–O into C–C chirality, as reported in Scheme 5, may be ascribed to the unique topographical features of enone **10**. However, with other substrates the prospect may not be as felicitous. In this article we give an account of some recent studies on the application of free radical methods for addressing the problem of C–O to C–C chirality transfer in connection with our program on converting carbohydrates into densely functionalized carbocycles.[11,12]

C–O to C–C chirality transfer *via* serial 1,5-hydrogen transfer/intermolecular radical addition: the carbocyclic core of tetrodotoxin

Tetrodotoxin (TTX), **13**[13] occupies a unique place in natural products chemistry and efforts in our laboratory towards its synthesis employ the retrosynthetic plan summarized in Scheme 6.[14] The bicyclic entity **14a**, when displayed as in **14b**, emphasizes the relationship to an annulated pyranoside. Retron **15** indicates the need for a functionalized two-carbon bridge between C-3 and C-6 of an anhydropyranoside and further 'visual dialogue'[3] leads to commercially available D-mannosan **16** (1,6-anhydro-β-D-mannopyranose).



Scheme 6



Scheme 7

Retron **15** requires a functionalized branch at C-6. This requirement is facilitated by the unusual $^1C_4$ conformation of 1,6-anhydro sugars which enables remarkably reactions as exemplified by the elegant site-, regio- and stereo-selective bromination described by Ferrier and Furneaux[15] [Scheme 7(*a*)]. Thus hydrogen abstraction and subsequent bromination both take place from the less hindered *exo* face of the dioxabicyclo[3.2.1]octane system.

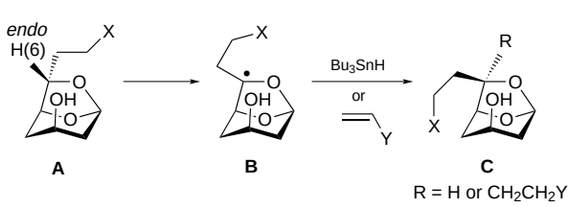
Could these facile stereodirecting capabilities of 1,6-anhydro sugars be of service to us? As expressed retrosynthetically in Scheme 7, we could conceivably employ the enthalpy driven C–O → C–OH 1,5-hydrogen transfer process, which is the basis of the original Barton reaction for functionalizing a remote angular methyl group.[16] Thus an axial C(3)–O radical should generate a carbon-centred radical at C(6), which should trap an external alkene from the less hindered *exo* face[17] [Scheme 7(*b*)].

However, in the context of the TTX plan in Scheme 6, retron **15** requires the C(6)-substituent to be *endo* oriented. This requirement could be met by taking advantage of a highly remarkable facet of our strategy, *viz*. (i) that it is *endo*-H(6) which is transferred, and (ii) that the process is amenable to iteration. Therefore an alkyl substituent, stereoselectively introduced at C(6) (**A**, Scheme 8) still presents an *endo* H(6) for transfer leading to the planar π-radical (**B**, Scheme 8).

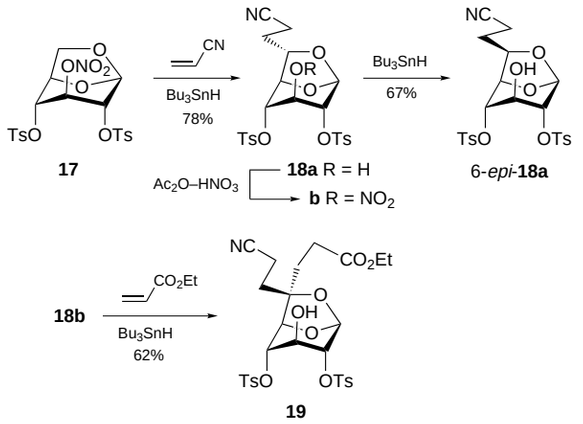
The latter radical could, in its turn, react from the *exo* face again with Bu_3SnH, *e.g.* **B** → **C** (R = H). Alternatively, we could take advantage of the nucleophilic character of the stabilized α-oxygenated radical[17] to foster reaction with electron-deficient alkenes. The method would then permit complete control in the creation of a secondary or tertiary branch at C-6, with either *R* or *S* orientation.

The design of this strategy was facilitated by studies in our laboratory which had shown that alkoxy radicals could be conveniently generated by reaction of nitrate esters with tri-*n*-butyltin hydride.[18] Accordingly, reaction of **17** with tri-*n*-butyltin hydride in the presence of acrylonitrile led to **18a**[19] (Scheme 9), and iteration of the process led to nitrate ester **18b** which on treatment with tri-*n*-butyltin hydride afforded 6-*epi*-**18a**.

On the other hand, a second branch at C-6 could be introduced stereoselectively by reaction of **18b** with tri-*n*-butyltin hydride in the presence of the appropriate radical trap, ethyl acrylate in the case of **19**.[19]



Scheme 8



Scheme 9

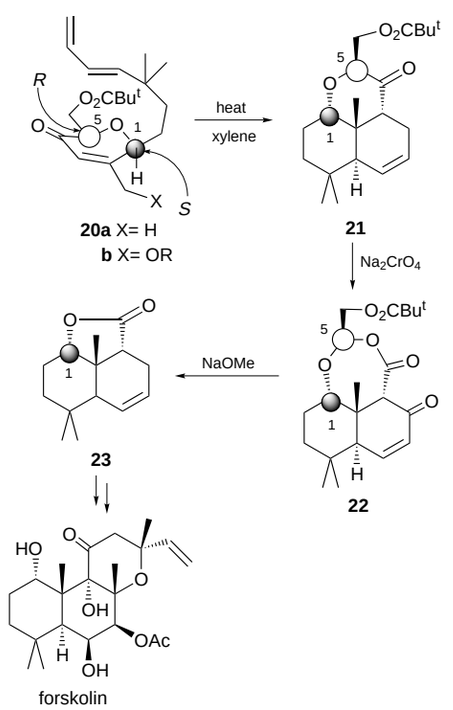
In this exercise the cost/benefit ratio is a highly rewarding 0 : 1 and it is noteworthy that the C(3)–OH is recovered unprotected after each operation.

C–O to C–C chirality transfer *via* serial radical reactions on glycals: preliminary studies for the decalin portion of azadirachtin

Carbohydrate based Diels–Alder strategies are specially useful in the preparation of carbocyclic natural products, and it is in that context that α-enones were investigated in our laboratories.[11] Thus intermolecular Diels–Alder reactions (see Scheme 5) led to an early synthesis of actinobolin.[20]

We have also reported a relay synthesis of forskolin which features an intramolecular Diels–Alder (IMDA) reaction as the key step, wherein the trienic enoce **20a** was used to furnish the *trans*-decalin precursor **21**[21](Scheme 10). Further functionalization employed simultaneous Baeyer–Villiger and allylic oxidations leading to **22**. Treatment of this acetal lactone with mild base provided **23**, which had served as a forskolin precursor in the laboratories of Ziegler[22] and Rúveda.[23]

However, the potential of this strategy was undermined by the many steps leading to **20a** from D-glucose. In particular,



Scheme 10

introduction of the vinyl methyl residue proved to be especially demanding. This challenge, together with cognizance that the C(10) alkyl residue of clerodane terpenoids, such as azadirachtin, is frequently oxygenated, compelled us to consider appropriately functionalized synthons such as **20b**.

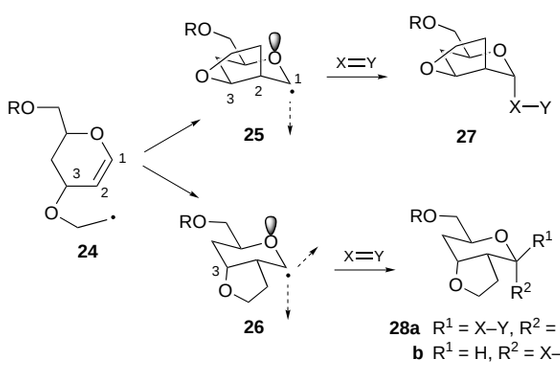
Our retrosynthetic analysis made use of the observation that, *en route* to decalin **23**, the chiral information at C(5) of enone **20a** was discarded (Scheme 10). The only essential chiral centre was therefore C(1). Thus either a D or an L sugar could be used as the starting material provided that the resulting stereogenic centre at C(1) would be *S*. This realization greatly simplified the synthetic planning because *S* chirality is found in β-D-*C*-glycosides as well as their α-L counterparts. The latter, in which the anomeric substituent is (normally) axially oriented, can be readily accessed through an anomeric radical.

Besides this conceptual viability it was also of help to note that the functionalization of C(6) of the sugars was also irrelevant. Therefore L-rhamnal (a 6-deoxy L-sugar) could be used as the starting material, thus adding economical viability to the synthetic approach (compare: L-rhamnose, 1 kg = £280; L-glucose, 1 kg = £16 400).

The need for a carbon branch at C(2) suggested that our recently developed strategy for serial radical reaction on glycals could be pressed into service (Scheme 11).[24] In this strategy, modelled after the Stork–Sher method,[25] serial radical reactions of C(3)-tethered glycals, *e.g.* **24**, leads to intermediate anomeric radicals *e.g.* **25** and **26**, which trap suitable reactants, *e.g.* X=Y, to afford *C*-glycosides *e.g.* **27** and **28**, respectively. We had also shown that the degree of stereocontrol depends on the interplay of 'shape selectivity'[25] (*vide infra*) and the radical anomeric effect.[26] When both are congruent, as in **25** → **27**, stereoselectivity is exquisite; however when both forces are in opposition, as in **26** → **28a,b**, lower preference in favour of 'shape selectivity' is observed.[24*a*]

Selected examples illustrating the scope and viability of this procedure are shown in Table 1.[24*b*] The sequence takes place with complete stereoselectivity at the anomeric carbon for the formation of α-*C*-glycosides (entries 1–5, 7–9). However, the protocol is less exclusive in the case of β-*C*-glycosides since anomeric mixtures are obtained (see entry 6), Notably the procedure allows for introduction of one- or two-carbon branches at C(2), according to precedents from Stork and coworkers,[25] Nishiyama *et al.*[27] and Tamao *et al.*[28]

Implementation of the protocol for the decalin moiety (Scheme 12), takes advantage of the O(3) bond of **31** for installing carbon branches at C(1) and C(2). The latter stereocentre is 'destroyed' in going from **40** → **41**, but this event is inconsequential because it is the surviving stereogenic centre at C(1) that dictates stereoselectivity on the IMDA process, wherein three new chiral centres are created in **42b**.[29,30] The overall cost/benefit ratio in terms of C–O to C–C chirality transfer is 2 : 2 for the radical process, and increases to 3 : 4 if the IMDA process is included.

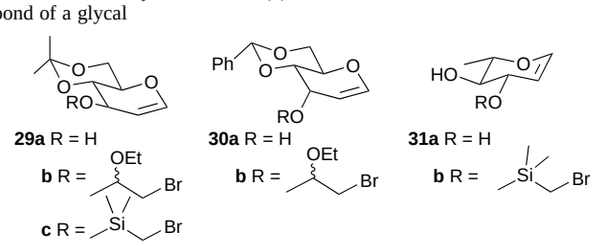


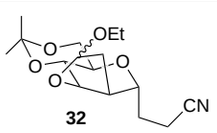
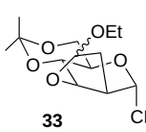
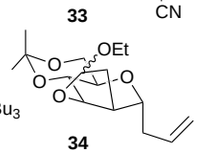
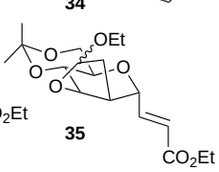
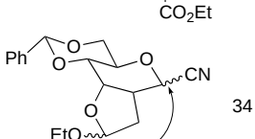
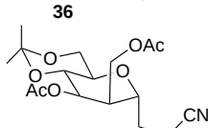
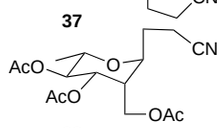
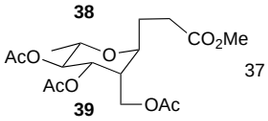
Scheme 11

C–O to C–C chirality transfer *via* serial radical reactions on hex-2-enopyranosides: the cyclohexane fragment of reserpine

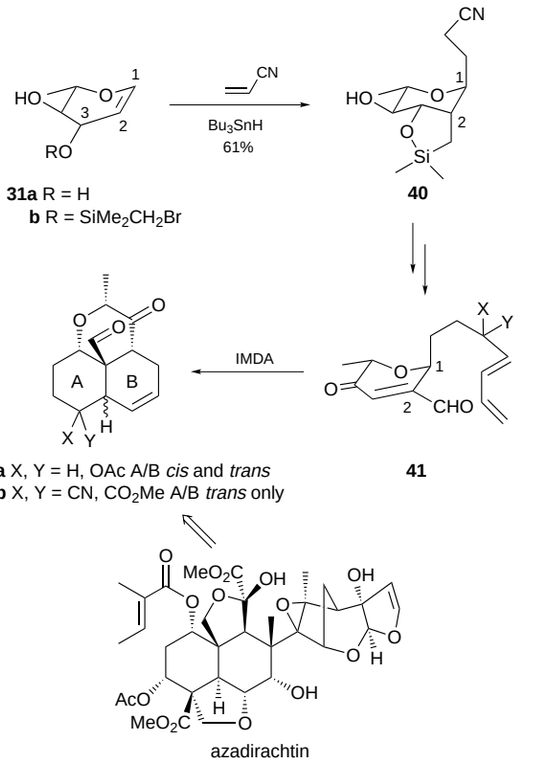
Reserpine, [Scheme 13(*a*)], a prominent member of the yohimbine family of indole alkaloids, possesses a pentacyclic skeleton which contains six chiral centres.[31] Woodward's landmark synthesis featured the richly functionalized E-ring intermediate **43** [Scheme 13(*b*)].[32] This densely functionalized cyclohexane which by itself accounts for five of the six chiral centres was especially appealing to us.

Table 1 Radical cyclization of C(3) tethered radicals onto the $\Delta^{1,2}$ double bond of a glycal



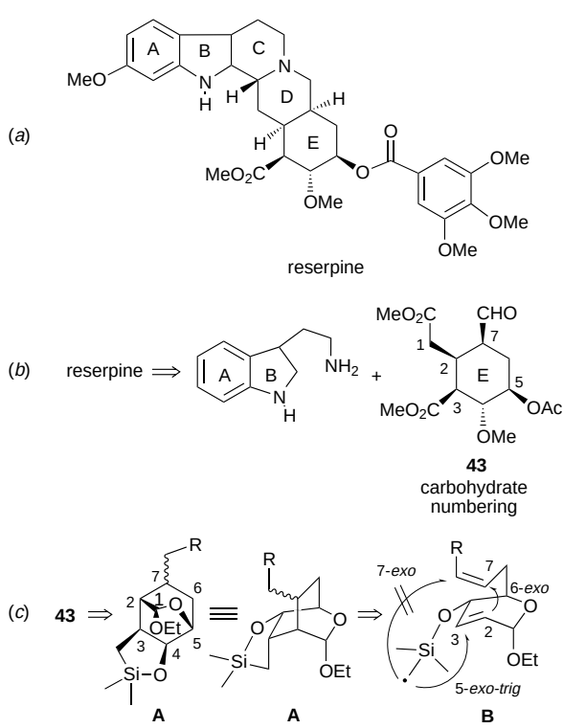
Entry	Substrate	Reaction conditions[a]	Radical trap	Product	Yield (%)
1	**29b**	A	CN	 **32**	75
2	**29b**	B	CN	**32**	78
3	**29b**	B	C=N–Bu^t	 **33**	76
4	**29b**	C	SnBu$_3$	 **34**	68
5	**29b**	D	Bu$_3$Sn, CO$_2$Et	 **35**	63
6	**30b**	B	C=N–Bu^t	 (5:1) β:α mixture **36**	34
7	**29c**	E	CN	 **37**	61
8	**31b**	E	CN	 **38**	32
9	**31b**	E	CO$_2$Me	 **39**	37

[a] For reaction conditions see ref. 24(*b*).

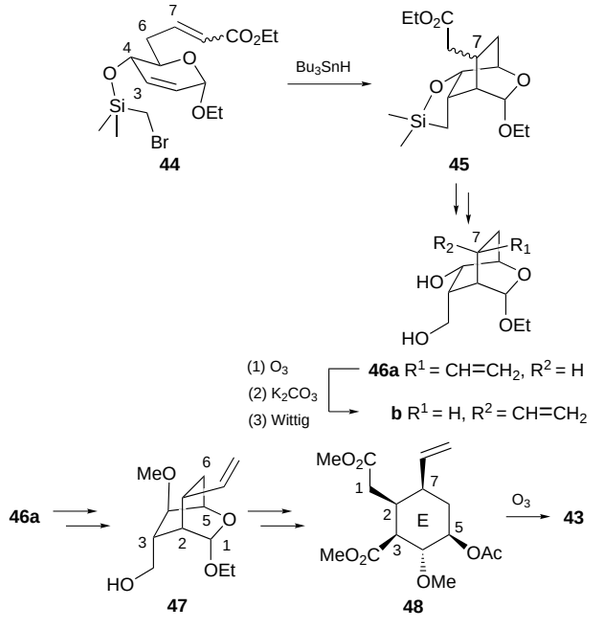


Scheme 12

Our strategy for this project was based on the correlation of a tricyclic cage **A**, with **43** [Scheme 13(*c*)].[33] Intermediate **A**, which already fulfills all functional and stereochemical requirements, could be accessed by serial radical cyclizations of a dienic pyranoside **B**. The latter contains two unsaturated sites, but the 5-*exo* mode should prevail over the 7-*exo* alternative, thereby presenting the resulting C(2) radical to C(7) for 6-*exo* cyclization. A C–O bond, this time at C(4), is once again key to



Scheme 13

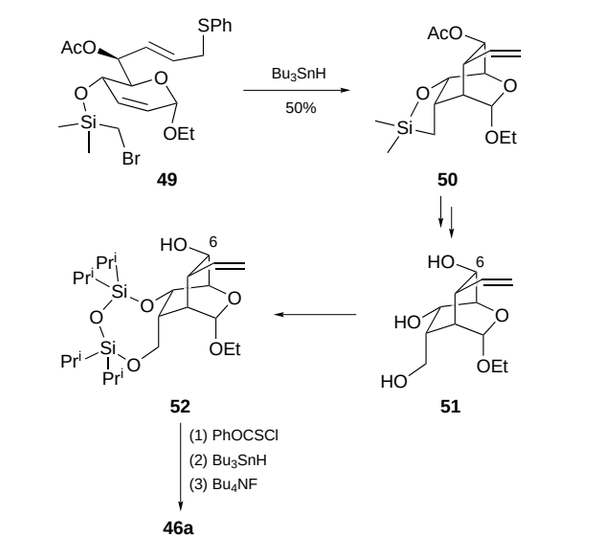


Scheme 14

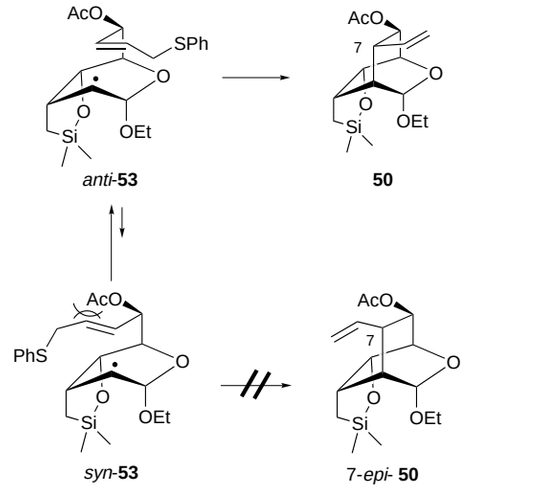
the plan, since it directs the stereochemical outcome in the formation of two [C(3), C(2)] of the three new stereogenic centres.

The strategy was first tested on pyranoside diene **44**[34] (Scheme 14), which furnished a mixture of caged compounds **45**. Oxidation of the silicon bridge in **45**, according to Tamao *et al.*,[28] gave a diol which was protected. Processing of the ethoxycarbonyl group into a vinyl moiety paved the way to epimers **46a,b**, which were readily separated. 'Unwanted' **46b** was transformed into **46a** (see Scheme 14), which could then be processed, *via* **47**, into **48**. Cyclohexane **48** is a masked precursor of Woodward's intermediate, in that the pendant vinyl residue at C(7) is retrosynthetically correlated with the aldehyde group of **43**.

Although the above mentioned strategy worked well, we were dissatisfied, because virtually no stereocontrol had been exerted over the C(7) vinyl residue. We therefore explored a parallel route in which a C–O bond at C(6) could be used to dictate the developing orientation at C(7).[35] Accordingly, radical cyclization of **49** (Scheme 15) led stereoselectively to **50** from which triol **51** was readily obtained. Selective protection



Scheme 15



Scheme 16

of the hydroxy groups paved the way for C(6) deoxygenation, furnishing **46a**.

The stereochemical model, based on the release of 1,3-allylic strain[36] (*e.g.* **53** → **50**, Scheme 16), therefore worked well and represents an additional mode of C–O to C–C chirality transfer.

The overall result, in terms of C–O to C–C chirality transfer, is 2 : 2 for the first synthetic route, and it increases to 2 : 3 if the oxygenated substituent at C(6) is incorporated.

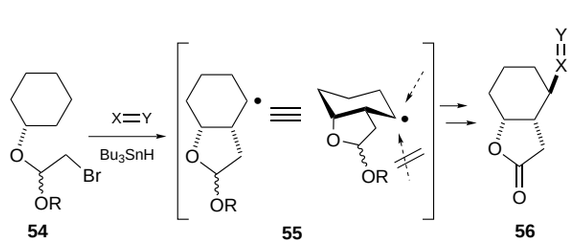
C–O to C–C chirality transfer. Effects of the 'irrelevant' configuration at the anomeric centre of mixed haloacetals on the chemo- and stereo-selectivity of serial radical reactions.

Much of the chemistry utilized in the two preceding sections has relied on Stork's bicyclic radical **55**[25] (Scheme 17) which shows remarkable 'shape selectivity' in promoting reactions that occur *anti* to the fused five-membered ring. The latter, in turn, is formed by 5-*exo*-*trig* radical cyclization of haloacetals **54**. The configuration at the anomeric centre of these structures has always been considered as irrelevant,[25] a fact which is not surprising since the concept was developed in the context of the corresponding lactones **56**.

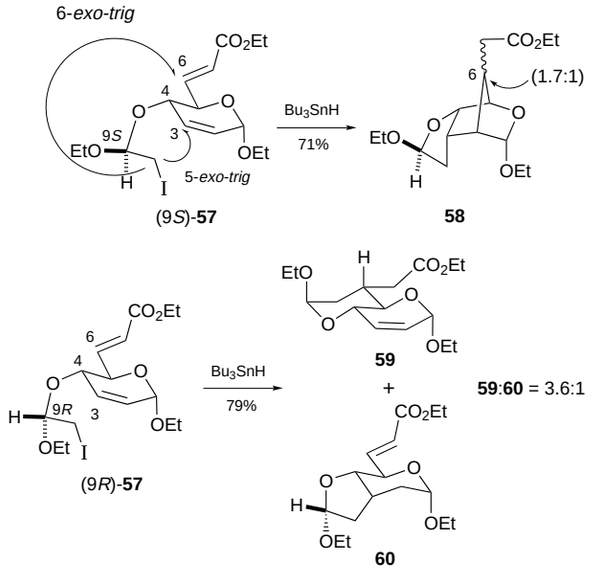
However, in the course of our exploratory studies,[37] we were intrigued by the suspicion that the configuration at the anomeric centre of the haloacetals was defining the stereoselectivity of the radical reaction. Accordingly, it was desirable to examine the reactions of diastereopure isomers.

The *R* and *S* haloacetals **57**[38] were chosen for this study because radical cyclization could take place at C(3) or at C(6). Interestingly, (9*S*)-**57** furnished exclusively tricyclic compounds **58** (Scheme 18), while (9*R*)-**57** gave rise to a mixture of regioisomeric bicyclic compounds **59** and **60**, with no evidence of a tricyclic product.

The opposite regioselectivity preferences observed for the epimers **57** may be rationalized by invoking intermediates, in which the ethoxy group enjoys an anomeric effect as in **A** and **C**, (Scheme 19). These gain precedence over those alternatives



Scheme 17



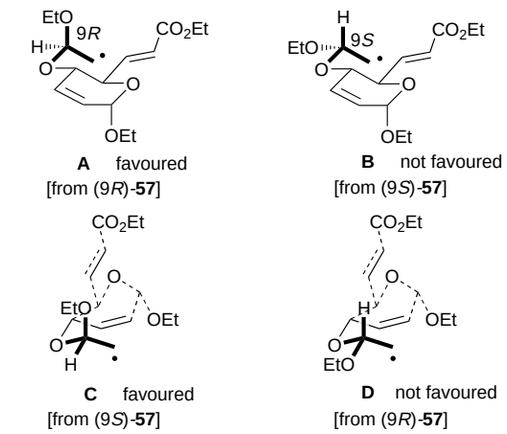
Scheme 18

where the ethoxy group occupies the more sterically advantageous pseudo-equatorial position, *e.g.* **B** and **C** (Scheme 19), as would be the case in the classical Beckwith–Schiesser model for 5-*exo-trig* ring closure of substituted hexenyl radicals.[39,40]

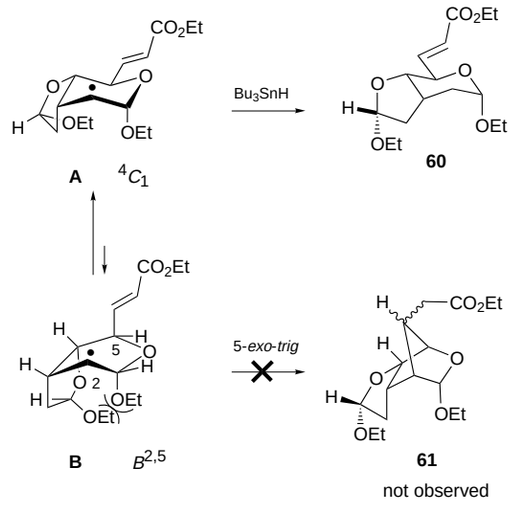
It is clear that in order for the second cyclization [C(2) to C(6)] to take place, the radical at C(2) must change conformation from a $^4C_1$ chair (**A**, Scheme 20), which enjoys an anomeric effect, to a $B^{2,5}$ boat (**B**, Scheme 20), which does not, and where all the substituents reside in pseudo-axial orientations. The fact that the double-cyclization product, **61**, is not obtained from (9*R*)-**57** [*cf.* (9*S*)-**57**, Scheme 18] may be associated with an additional destabilizing steric interaction between the two anomeric ethoxy groups in the required $B^{2,5}$ conformation as shown in Scheme 20.

In analysing the stereoelectronic factors depicted in Scheme 11, it was noted (see Table 1) that selectivity for the installation of an anomeric branch varied from complete (*i.e.* **25** → **27**) to selective (*ca.* 5–3 : 1) (*i.e.* **26** → **28a,b**).[24a] In light of the results in Schemes 18–20, it seemed wise to reexamine the reaction of **30b** (Scheme 21). In the presence of *tert*-butyl isocyanide,[24b] sequential cyclization–intermolecular radical trapping led to a *ca.* 5 : 1 mixture of epimeric cyanides **36a,b**, each one being itself a mixture of epimeric acetals.

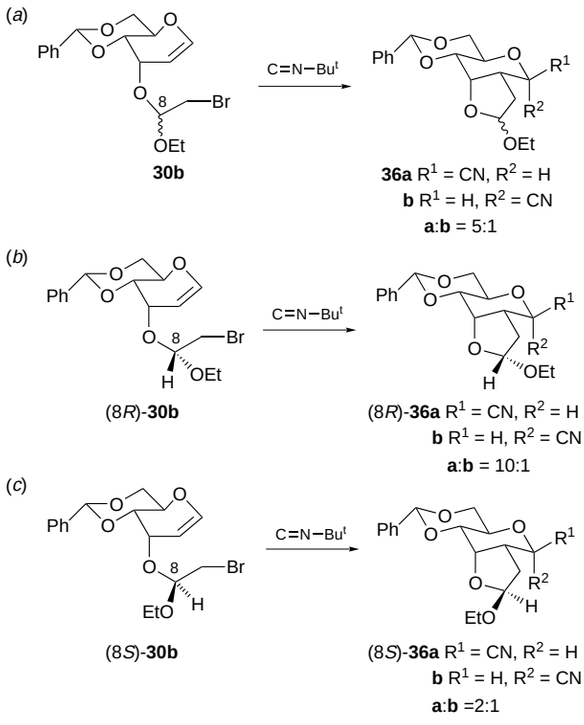
It was therefore justifiable to study each isomer. Remarkably, each showed distinctly different behaviour (Scheme 21), for which Stork's carbocyclic series (Scheme 18) did not provide a precedent.[25] Obviously the radical anomeric effect is responsible for the high percentage of α-*C*-glycoside (8*S*)-**36b** obtained on the cyclization of (8*S*)-**30b**. On the other hand, in the cyclization of (8*R*)-**30b**, the presence of an *endo*-oriented ethoxy substituent efficiently shields the α-face and overrides the radical anomeric effect (see **62**, Scheme 22).



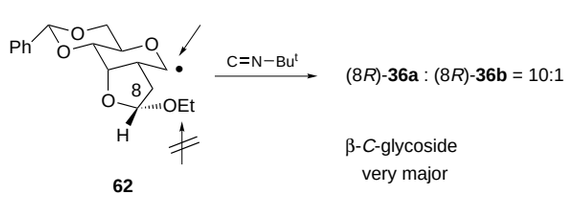
Scheme 19



Scheme 20



Scheme 21



Scheme 22

Summary

We have presented a view on stereoselective radical transformations in which C–O bonds play a leading role on inducing C–C bond stereochemistry. One of the starting sugar's several C–O bonds has been used to induce C–C chirality for a variety of synthetic targets. Owing to their wealth of oxygen atoms, carbohydrates have been the substrates of choice for these transformations. However, from the last two examples it is clear that even 'imported' oxygen atoms can have a dramatic influence on newly formed C–C bonds.

Acknowledgments

J. C. L is grateful to the Consejo Superior de Investigaciones Cientificas (C.S.I.C) and Consejeria de Educacion, Comunidad Autonoma de Madrid for financial support. These studies were made possible by grants from the National Science Foundation (CHE 892003 and 9311356) and National Institutes of Health (GM 51237).

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Footnotes and References

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