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The development of strategies and methods for the synthesis of biologically active compounds

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This review describes new strategies and methodology for asymmetric and stereoselective syntheses that have been developed within the Nelson group at the University of Leeds, UK. Syntheses of *C*-substituted monosaccharides, *C*-linked disaccharide mimetics, the C_{58}–C_{71} fragment of palytoxin and an established intermediate in a total synthesis of Hemibrevetoxin B are described. The work is described within the context of related research in organic chemistry.

Introduction

Much of our research has focused on the synthesis of biologically active compounds. Our research has not been based around any particular reaction or functional group. Instead, we have concentrated on the development of new and unusual *strategies* for asymmetric and stereoselective synthesis. Accordingly, we have endeavoured to exploit the synthetic strategies that have been most appropriate to the target molecules under investigation.

In 'diversity-oriented' work,[1] we have focused on the development of complementary stereoselective reactions for the divergent synthesis of many different stereoisomers from a common precursor. A series of stereochemically diverse *C*-substituted monosaccharides was prepared in this way. With reliable methods in hand, a two-directional synthetic approach was exploited in the synthesis of some *C*-linked disaccharide mimetics.

Adam Nelson has research interests in asymmetric synthesis and chemical biology. Dr Nelson obtained a BA degree in Natural Sciences from the University of Cambridge in 1993. He undertook postgraduate studies at the same institution under the supervision of Stuart Warren and he obtained a PhD in 1996. Dr Nelson moved to a postdoctoral research fellowship with Professor E. J. Thomas at the University of Manchester and, in 1998, was appointed as a lecturer in organic chemistry at the University of Leeds. He was awarded the 2001 RSC Meldola medal and a 2002 Pfizer Academic Award in recognition of his research into stereochemical problems and natural product synthesis. He was promoted to the position of senior lecturer in 2003. Adam Nelson lives in the Pennine town of Holmfirth, Yorkshire with his wife, Julia, and his sons, James and Ben.

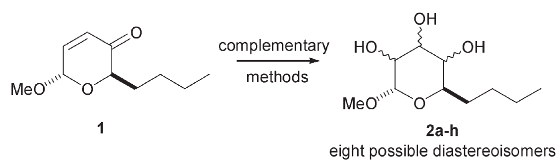
In 'target-oriented' syntheses, we have exploited both proper and improper elements of embedded symmetry. A hidden C_2 symmetry element was exploited in a two-directional synthesis of a fragment of the complex natural product, palytoxin. In addition, the hidden centre of symmetry of a fragment of Hemibrevetoxin B was exploited for the first time in natural product synthesis.

Complementary methods for the synthesis of *C*-substituted monosaccharide derivatives

The complete control of stereochemistry, that is the ability to synthesise any stereoisomer at will, is a challenging goal for the synthetic chemist. In our approach to the synthesis of *C*-substituted monosaccharide analogues, we chose to use the pyranone **1** as a template for further functionalisation (Scheme 1). There are eight possible diastereoisomeric products, **2a–h**, and our aim was to develop complementary stereoselective methods for each of these possibilities.

Alternatively, the complementary synthesis of diastereomeric target molecules can involve the use of complementary chiral reagents in an iterative sense, an approach that has been exploited in the synthesis of stereoisomeric aldoses and polyketides.[2] However, in densely functionalised systems, powerful substrate control can often lead to strong match/mismatch effects, resulting in mixtures of diastereoisomers in some cases.

We focused, therefore, on substrate-controlled methods for the stereoselective synthesis of the diastereomeric monosaccharide mimetics **2** (see Schemes 1 and 2).[3,4] As a starting point, the dihydropyrans (DHPs) **3** were dihydroxylated under Upjohn's conditions[5] (cat. OsO_4, NMO): the reactions occurred *anti*[5] to a range of pseudo-equatorial (as in **3a**) and pseudo-axial (as in **3b**) allylic OR substituents to give



Scheme 1

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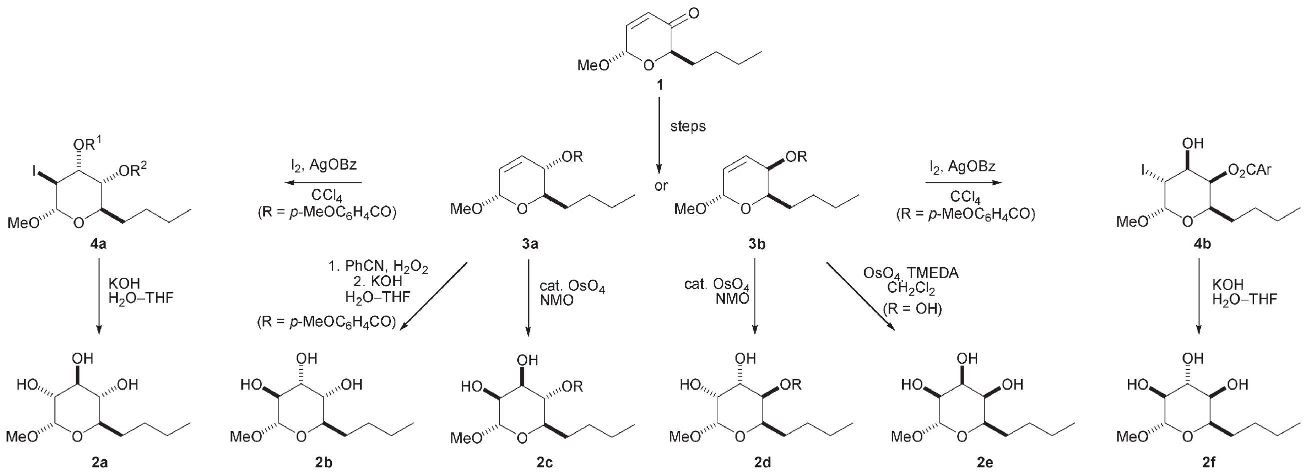
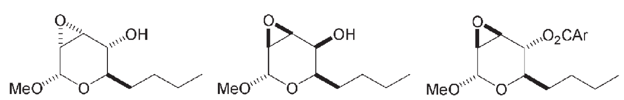


Scheme 2

diastereomeric products **2c** and **2d**.† With allylic alcohols **3b** (R = H), the sense of the diastereoselectivity of the process could be reversed by exploiting Donohoe's reaction conditions[6] (TMEDA, OsO_4, CH_2Cl_2); under these conditions, the reaction was directed by hydrogen bonding to the allylic alcohol to give the *syn* product **2e** (R = H) with $>95{:}<5$ diastereoselectivity. Unfortunately, *syn*-selective dihydroxylation of related *pseudo*-equatorial allylic alcohols (as in **3a**) was not possible under these conditions, presumably because the axial methoxy substituent prevented effective delivery of the reagent. An alternative approach to the functionalisation of the DHPs involved the hydrolysis of the corresponding epoxides, which could be generated either by hydrolysis of the iodo alcohols **4** or, more directly, by epoxidation.[3] The diastereoisomeric allylic *p*-methoxybenzoates **3** (R = *p*-$MeOC_6H_4CO$–) were treated with iodine and silver benzoate in rigorously dried carbon tetrachloride: iodonium ion formation, participation of the *p*-methoxybenzoate group and hydrolysis of the resulting dioxonium ion gave the *syn* hydroxy esters **4**.‡ We have proposed that the *syn* epoxy alcohols **5** and **6** are intermediates in the hydrolysis of these products.

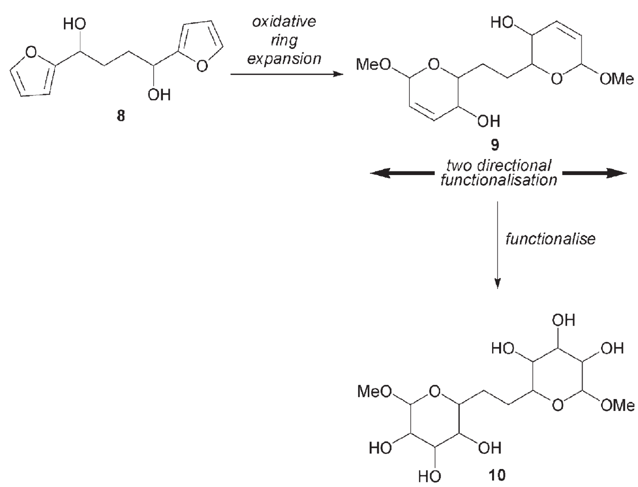


5 **6** **7**

Hence, treatment of **4b** with potassium hydroxide in water–THF gave the epoxy alcohol **6**, which was opened *trans*-diaxially[7] by hydroxide ion to give the triol **2f**. Similarly, the *anti* epoxy alcohol **7**, prepared by epoxidation of **3a**, was hydrolysed and was also opened *trans*-diaxially by hydroxide ion to give the triol **2b**. The outcome of the hydrolysis of the 80:20 mixture of regioisomeric iodo alcohols **4a** was more unusual. In this case, the *syn* epoxy alcohol **5** was proposed as an intermediate.§ *trans*-Diaxial opening of **5** would require hydroxide to attack the epoxide at the site that is β to the two oxygens of an acetal.[9] Rather than suffer this fate, the epoxide was opened (presumably *via* a higher energy, more reactive conformer) to give mainly the bis-equatorial product **2a**. Ignoring anomers, there are eight possible diastereoisomeric *C*-substituted monosaccharide mimetics **2**. The divergent nature of our synthetic approach enabled the preparation of six of these mimetics from a common intermediate by making minor variations at a relatively late stage in each synthesis. The methods developed were, in general, highly diastereoselective and complemented each other effectively.

Exploitation of desymmetrisation and two-directional approaches in the diversity-oriented and target-directed synthesis of biologically active compounds

We have exploited our reliable methods for the stereoselective functionalisation of polyhydoxylated THPs (Scheme 2) in the preparation of the *C*-linked disaccharide mimetics **10** (Scheme 3).[10]¶ We chose to introduce all of the stereogenic centres using stereoselective methods, an approach that can allow the preparation of analogues incorporating unnatural or unusual monosaccharide units. Hence, difuryl diols of the general structure **8** were oxidised to give di-DHPs **9**, which were exploited as templates for further functionalisation. Excluding anomers, there are 136 possible stereoisomers of **10** and



Scheme 3

† The tetrahydropyrans (THPSs) **2** were characterised as the corresponding triacetates.

‡ The ester **3a** gave an 80:20 mixture of the of the regioisomeric iodo alcohols **4a** (with $R^1 = H$, $R^2 = p\text{-}MeOC_6H_4CO$ and $R^1 = p\text{-}MeOC_6H_4CO$, $R^2 = H$). The compounds had the same relative configuration.

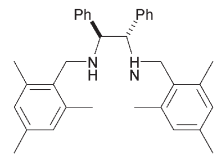
§ In a related system, we have observed the formation of a similar epoxide under milder reaction conditions.[8]

¶ The mimetics **10** were characterised as the corresponding hexa-acetates.

we have developed methods for the synthesis of nineteen of these isomers. Our approach lent itself to a two-directional[11] synthetic strategy, which has significantly reduced the number of synthetic steps required. Previous syntheses of *C*-linked disaccharides have used at least one monosaccharide as a starting material and have usually exploited a connective reaction, such as the Kishi,[12] Ramberg-Bäcklund,[13] Wittig,[14] Henry[15] or metathesis reactions, to link the rings. There are 72 stereoisomers with the 1,4 stereochemical relationship found in the C_2-symmetrical [(*R*,*R*) or (*S*,*S*)] diol **8**. The diol (*R*,*R*)-**8** was prepared in >95% ee by asymmetric reduction of the corresponding diketone and was converted into the di-DHP templates **9**.[10a,10c] The di-DHPs were functionalised in a two-directional sense using dihydroxylation reactions (Scheme 4). As we have already seen (Scheme 2), the Upjohn and Donohoe methods were, in part, complementary. The two-directional approach was often very efficient indeed: for example, in the synthesis of **10AA**, six new stereogenic centres were introduced with almost complete stereocontrol using a reduction and a dihydroxylation reaction.

The approach is not restricted to the synthesis of C_2-symmetrical disaccharide mimetics. Using the unsymmetrical template **9c**, which has both a pseudo-axial and a pseudo-equatorial hydroxyl group, the unsymmetrical mimetics **10AB** and **10AC** were prepared. In particular, under Donohoe's reaction conditions (TMEDA, OsO_4), the di-DHP **9c** could be elaborated such that the stereochemical outcome was different in each of the rings: the reagent was directed by the pseudo-axial alcohol but reacted *anti* to the pseudo-equatorial hydroxyl group to give the mimetic **10AC** with >95:5 diastereoselectivity.

Other mimetics **10** may be prepared from the *meso* diol (*R**, *S**)-**8**. In these cases, an asymmetric synthesis could involve the desymmetrisation of a highly functionalised *meso* template such as **11** or **12** (Scheme 5). However, important asymmetric reactions such as the Sharpless dihydroxylation[16] and epoxidation[17] reactions are not well-suited to the enantioselective functionalisation of cyclohex-2-enols. We found that the OsO_4·**15** complex[18] was an effective reagent for desymmetrisation in these cases.



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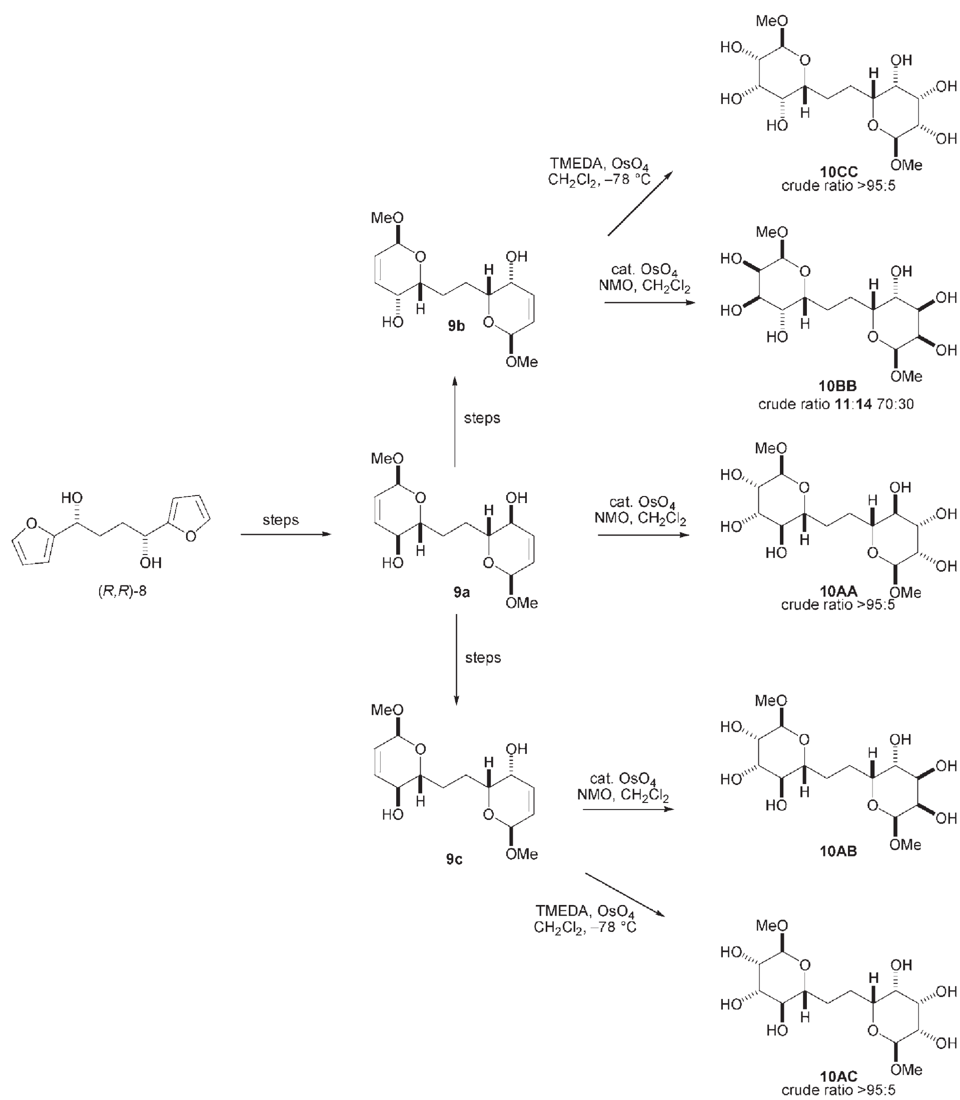
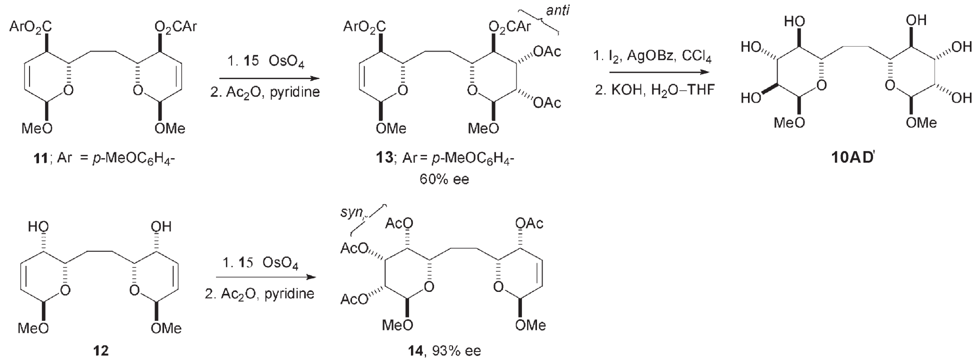
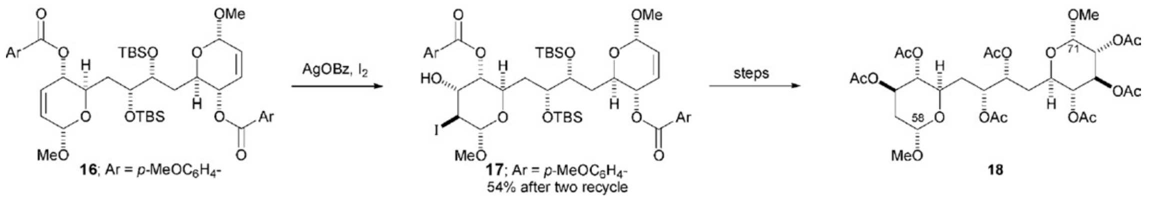
For example, treatment of **11** with OsO_4·**15** at −20 °C gave the corresponding desymmetrised diol as a single diastereoisomer in 84% yield and with 60% ee; acetylation gave **13**.[10b,19] The natural diastereoselectivity—reaction *anti* to



Scheme 4



Scheme 5



Scheme 6

the allylic *p*-methoxybenzoyl group—could be reversed by delivery of the reagent to the reacting double bond.[10b,19] Hence, reaction of **12** (with its two pseudo-axial alcohols) with OsO_4·**15** was highly *syn*-selective and gave, after peracetylation, the tetraacetate **14** with 93% ee (87% yield based on recovered starting material). We believe that the diastereoselectivity stemmed from hydrogen bonding of the reagent to the pseudo-axial hydroxyl group and that this reaction was the first example of a directed asymmetric dihydroxylation.

The remaining DHP of **13** was primed for further functionalisation. Hence, Prévost reaction of **13** and hydrolysis with potassium hydroxide solution gave, by analogy with the formation of **4a** (Scheme 2), the allolactose mimetic **10AD'**.[10b–c] We have shown that this mimetic may have affinity for the *lac* repressor protein, LacI, which is similar to that of allolactose itself.

We have also exploited our methods for the stereoselective functionalisation of polyhydroxylated THPs in target-directed synthesis (Scheme 6).[8] The homotopic termini of the C_2-symmetric di-DHP **16** were differentiated statistically using a Prévost reaction; a 54% yield of the iodo alcohol **17** was obtained after two recycles of the recovered starting material. Further steps, including another Prévost reaction to functionalise the other ring, gave the C_{58}–C_{71} fragment of palytoxin (**18**).[8]

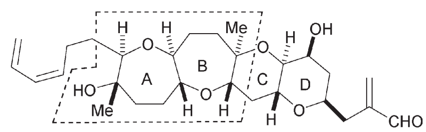
Extension of desymmetrisation to centrosymmetric molecules: preparation of a key intermediate in a total synthesis of Hemibrevetoxin B

A strong theme of our research has been the development of new and unusual synthetic strategies. Desymmetrisation is one of the most powerful strategies for asymmetric synthesis.[20] The approach generally involves the functionalisation of a *meso*[21] substrate with an internal mirror plane. Chiral reagents may, in principle, differentiate between enantiotopic groups in such a substrate. Provided that the chiral reagent can differentiate effectively between the enantiotopic sides of the substrate, a product is produced in quantitative yield and with high enantiomeric excess.

Examples of two such desymmetrisation processes were described earlier (Scheme 5). For example, the chiral complex **15**·OsO_4 reacted with the *meso* di-DHP **12** to give, after acetylation, the tetraacetate **14** with 93% ee.[18] In other words, the chiral reagent exhibited *ca.* 97:3 selectivity in its differentiation between the enantiotopic DHPs of **12** (Scheme 7).

In fact, a desymmetrisation reaction could be applied to a substrate with *any* improper element of embedded symmetry.[22] For example, the diepoxide **19** is not chiral because it has an embedded centre of symmetry. The epoxides of **19** are, therefore, enantiotopic and may distinguished by a chiral reagent. Selective hydrolysis of just one of the enantiotopic epoxide groups would destroy the centre of symmetry and would yield the diol **20** in high yield and as a single enantiomer.

Although many biologically active molecules have embedded centrosymmetric fragments, this hidden symmetry has rarely been exploited in synthesis. The AB ring system of Hemibrevetoxin B (**21**) is a centrosymmetric dioxepane ring and we have exploited this hidden symmetry for the first time in natural product chemistry.[23,24]



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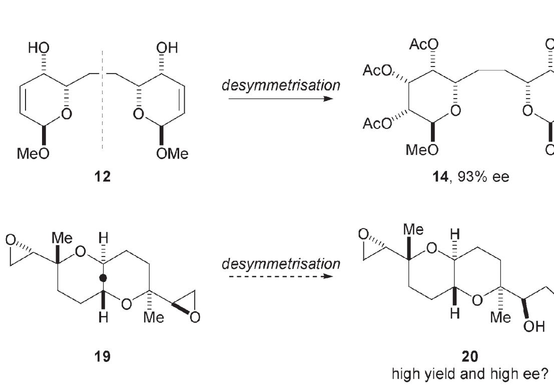
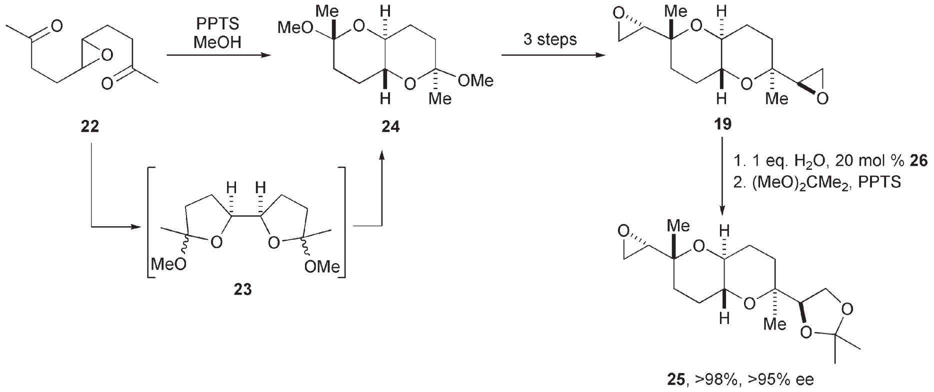


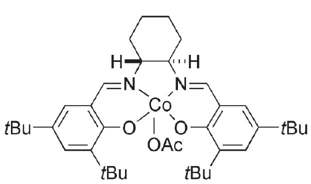
Scheme 7



Scheme 8

The centrosymmetric diepoxide **19** was prepared using the two-directional synthetic approach shown in Scheme 8. The *trans*-fused di-THP core was prepared by treatment of the epoxy diketone **22** with PPTS in methanol. Initially, the reaction proceeded under kinetic control: ring-opening of the epoxide gave the diacetal **23** in which the configuration of the ring junction of **24** had been established. Thereafter, thermodynamic control prevailed: equilibration of **23** controlled the regiochemistry of the ring system and the configuration of the anomeric centres and an 85% yield of the fused bicyclic diacetal **24** was obtained. The centrosymmetric diacetal **24** was elaborated two-directionally to give, in three steps, the centrosymmetric diepoxide **19**.

The key step of the synthesis was the desymmetrisation of a centrosymmetric molecule.[22] Like desymmetrisations of molecules with an internal mirror plane,[20] the strategy can, in principle, yield enantiomerically pure products in quantitative yield. Jacobsen epoxide hydrolysis[25] of the diepoxide **19**, catalysed by the complex **26**, proceeded with high enantiotopic group selectivity to yield, after protection, the epoxide **25** in $>98\%$ yield and $>95\%$ ee.[24] The epoxide **25** was prepared in eight steps and 34% overall yield, a sequence that compared extremely favourably with its earlier synthesis (22 steps, 14% overall yield). Subsequently, Overman *et al.* have exploited the centrosymmetric core of Psycholeine[26] in its synthesis, though their synthesis involved the desymmetrisation of a molecule with an internal mirror plane followed by rearrangement to give the centrosymmetric core of the natural product. Other examples of desymmetrisations of centrosymmetric molecules have been reported: a [4 + 4] photodimer,[27] a lactide,[28] a diketone[29] and a diol[30] have all been desymmetrised effectively.



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Conclusions and outlook

A strong theme of the work described in this review has been the exploitation of efficient synthetic strategies. Complementary methods for the stereoselective synthesis of polyhydroxylated THPs have been described, which were exploited, in conjunction with a two-directional synthetic approach,[11] in the preparation of *C*-linked disaccharide mimetics[10] and the C_{58}–C_{71} fragment of palytoxin.[8] It is clear that diversity-oriented synthesis[1] will play a critical role in the discovery of new functional molecules over the next ten years. To date, our own work has focused on the introduction of stereochemical diversity; future work will require synthetic approaches to natural product-like molecules with diverse skeletons and appended functionality.

The recognition of hidden elements of symmetry has greatly improved the efficiency of some of the syntheses described: both hidden proper[8] (*e.g.*, C_2 symmetry) and embedded improper elements of symmetry have been exploited. In particular, desymmetrisation reactions were exploited in the synthesis of a *C*-linked analogue of allolactose[10b–c] and, by desymmetrisation of a centrosymmetric molecule,[22] in the synthesis of an intermediate in a total synthesis of Hemibrevetoxin B.[24] The exploitation of symmetry can greatly improve synthetic efficiency and is, therefore, a powerful approach in the synthesis of complex target molecules. Desymmetrisation tactics have enabled embedded symmetry to be exploited many times, though the vast majority of these examples have involved *meso* precursors with an internal mirror plane. It is likely that other embedded elements of improper symmetry (including centres of symmetry) will be recognised and exploited in the future. Desymmetrisation is not restricted to target-directed syntheses and will also be exploited as a means for the introduction of stereochemical diversity into libraries of natural product-like molecules.

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