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Desymmetrisation and ring opening of cyclohexa-1,4-dienes. An access to highly functionalised cyclic and acyclic systems

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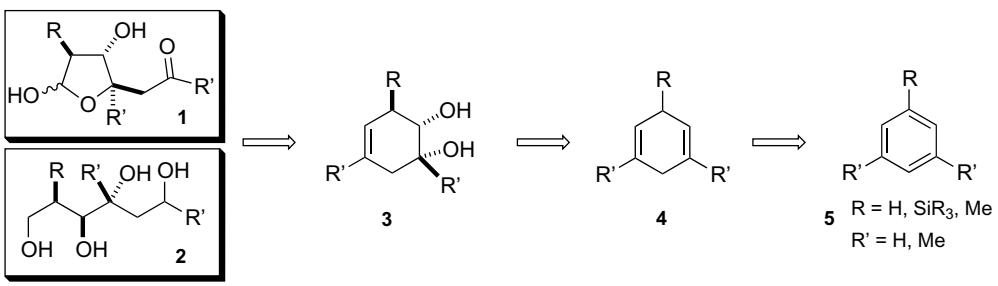
Abstract—Acyclic and cyclic synthons are readily available in three steps starting from substituted arenes. Birch reduction of the latter followed by desymmetrisation through Sharpless AD reaction then ozonolysis thus afforded five-membered ring lactols and acyclic polyols with good to excellent stereocontrol in high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Total synthesis of complex natural products possessing arrays of contiguous stereocentres such as polyketide-derived natural products in the polyether macrolide and polyene families still continue to be a matter of strong interest. Acyclic stereocontrol has been used extensively in this respect to set up chains with adjacent stereogenic centres, having the correct relative configurations. Diastereo- and enantioselective addition of nucleophiles to carbonyl groups and additions of electrophiles to double bonds are amongst the most efficient methods for this purpose.[1] Functionalisation then ring opening of a cyclic precursor may however offer a very attractive alternative to acyclic stereocontrol.[2] Conformational preferences, particularly in six-membered ring systems, have thus allowed the elaboration of highly substituted rings possessing several contiguous stereogenic centres in a very stereocontrolled manner. Such a strategy pioneered by Corey and Woodward to access macrocyclic polypropionate subunits has since been recognised as a valuable method for the synthesis of other natural products.[3] Once the stereogenic centres have been created, ring opening can be carried out through various methods depending on the remaining functionalities and the substitution pattern on the ring. Ozonolysis and Baeyer–Villiger reactions are often used in this context due to their mildness and high level of selectivity.[4] Recently, transition metal complexes have also been shown to mediate efficiently ring-opening processes.[5] We report here on a novel approach towards acyclic and cyclic synthons using this concept as applied to highly functionalised cyclohexene rings.

We recently described a very straightforward method to access, in a limited number of steps, five- and six-membered rings having multiple stereocentres.[6] Our approach was based on a sequence involving a Birch reduction of arylsilane precursors followed by a desymmetrisation of the silylcyclohexa-1,4-dienes using Sharpless asymmetric dihydroxylation (AD reaction) or amino-hydroxylation (AA reaction). The resulting diols or amino-alcohols were then elaborated further to provide conduritols, carba-sugars as well as carba-*C*-



Scheme 1.

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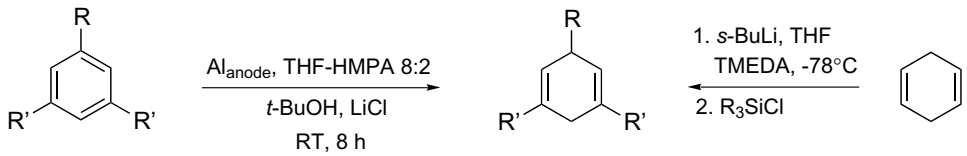
disaccharides with complete diastereocontrol and good levels of enantioselectivity. We report here on an extension of this strategy to the synthesis of cyclic and acyclic synthons such as **1** and **2** possessing several contiguous stereocentres starting form readily available arenes **5** (Scheme 1). The desymmetrisation of dienes **4** will be carried out using the powerful Sharpless AD reaction,[7] the diols **3** being then opened through ozonolysis. A careful control of the work-up conditions[4c–e] after ozonolysis will then ensure the introduction of useful functionalities such as diols or lactols.

Dienes **7a–d** were prepared through electrochemical Birch reduction of arenes **6a–d**[6f,8] or metallation–silylation of cyclohexa-1,4-diene.[9] Birch reduction of **6a–c** gave the corresponding dienes **7a–c** in 80–94% yields. In contrast, the arylsilane **6d** led to large amounts of over-reduction in the same conditions and was thus better prepared through metallation and silylation[9] with the suitable chlorosilane (Scheme 2).

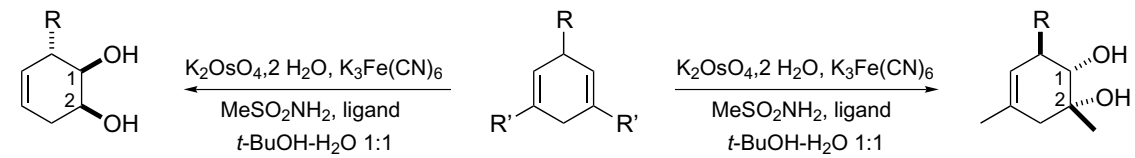
Dienes **7a–d** were then subjected to the Sharpless dihydroxylation conditions to afford the corresponding diols **8a–d** with yields and stereoselectivities depending on the nature of the substrates and the ligands (Scheme 3, Table 1). As already reported from our previous studies,[6] the silicon group efficiently controlled the diastereofacial selectivity, the approach of the osmium reagent occurring exclusively *anti* relative to the silicon group (Table 1, entries 6–8). Not surprisingly, the methyl group as in **7a** led to a much lower level of diastereocontrol, also favouring the *anti* diol **8a**[10] (entries 1–4). Importantly, the nature of the Sharpless ligand had a profound effect not only on the enantioselectivity but also on the diastereofacial selectivity of the



6a, R = Me, R' = Me
6b, R = H, R' = Me
6c, R = $SiMe_2t$-Bu, R' = H
6d, R = Si(*i*-Pr)$_3$, R' = H

7a, R = Me, R' = Me (94%)
7b, R = H, R' = Me (80%)
7c, R = $SiMe_2t$-Bu, R' = H (93%)
7d, R = Si(*i*-Pr)$_3$, R' = H (93%)

Scheme 2.



8c, R = $SiMe_2t$-Bu
8d, R = Si(*i*-Pr)$_3$

7a, R = Me, R' = Me
7b, R = H, R' = Me
7c, R = $SiMe_2t$-Bu, R' = H
7d, R = Si(*i*-Pr)$_3$, R' = H

8a, R = Me
8b, R = H

Scheme 3.

Table 1. Sharpless asymmetric dihydroxylation of dienes **7a–d** (Scheme 3)

Entry	Diene	Conditions	Ligand	d.e. (%)[a]	e.e. (%) major[b]	e.e. (%) minor[b]	Config.	Yield (%)
1	**7a**	10°C, 8 h	Quinuclidine	88	–	–	–	37
2	**7a**	10°C, 14 h	$(DHQD)_2PHAL$	40	70	18	1*R*,2*S*[d]	55
3	**7a**	10°C, 16 h	$(DHQ)_2PHAL$	60	60	60	1*S*,2*R*[d]	52
4	**7a**	10°C, 24 h	$(DHQ)_2AQN$	70	30	32	1*S*,2*R*[d]	40
5	**7b**	0°C, 72 h	Quinuclidine	–	–	–	–	61
6	**7c**	0°C, 4 h	$(DHQ)_2PYR$	>98	50	–	1*S*,2*S*[e]	87
7	**7d**	0°C, 4 h	Quinuclidine	>98	–	–	–	100[f]
8	**7d**	0°C, 4 h	$(DHQ)_2PYR$	>98	40[c]	–	1*S*,2*S*[e]	100[f]

[a] Estimated from the ^1H NMR of the crude reaction mixture.
[b] Determined by HPLC analysis on a Chiralcel OD® column (hexane–*i*-PrOH 97:3).
[c] Measured using ^1H and ^{19}F NMR of the corresponding Mosher's esters.
[d] Assumed configurations at C-1 and C-2 based on Sharpless quadrant device[7a,b] (see Fig. 1).
[e] See Ref. 6.
[f] Total yield of the mixture **8d**/tetrol (see text).

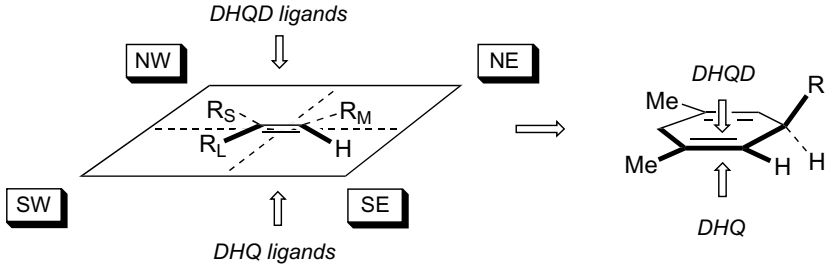
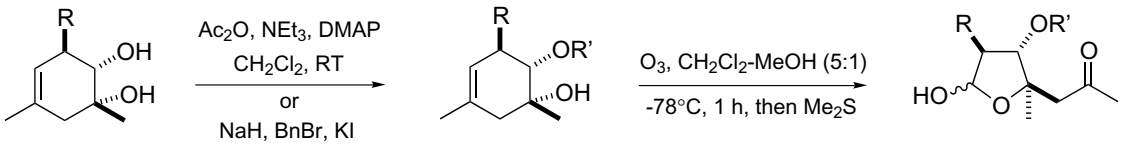


Figure 1. Quadrant method for rationalisation of AD enantiofacial selectivity.[7a,b]

process. Achiral quinuclidine was found to be the most efficient ligand in term of diastereocontrol leading to **8a** with 88% d.e. (entry 1). A relatively high enantioselectivity but poor diastereoselectivity in favour of the major isomer **8a** was obtained with commercially available $(DHQD)_2PHAL$ (entry 2).[11] With this ligand, the minor isomer was obtained with a poor enantioselectivity. Conversely, $(DHQ)_2AQN$[12] led to better diastereocontrol but to low enantiocontrol for both diastereomers (entry 4). $(DHQ)_2PHAL$ was found to be a good compromise, with 60% d.e. and 60% e.e. for both diastereomers (entry 3). It is also worthy of note that the successful ligand for the dihydroxylation of dienylsilanes (i.e. $(DHQ)_2PYR$, entries 6 and 8) was totally inefficient for non-silylated analogues and did not afford any product with diene **7a**. Finally, we noticed that TIPS(i-Pr_3Si)-diene **7d** behaved differently from its analogues (entries 7 and 8). Large amounts of a tetrol (isolated as its bis-acetonide)[13] resulting from a double dihydroxylation were observed during desymmetrisation of **7d**.[14] While a 6:4 ratio of **8d**/tetrol was obtained when quinuclidine was used as a ligand (entry 7), an 8:2 ratio was obtained with $(DHQ)_2PYR$ (entry 8). The larger amount of tetrol observed with **7d** compared to its analogues could be attributed both to its much larger size[6f] and to its more important lipophilicity. The much lower amount of tetrol detected with other dienes (i.e. **7a**–**c**) may thus be due to the highly polar nature of the tetrols in these cases which remain in the aqueous layer after work-up.[15]

Selective monoacetylation and monobenzylation of diols **8a**,**b**, using standard protocols, were then carried out, affording the alcohols **9a**–**c** in high yields. Ozonolysis of the latter were then performed in a CH_2Cl_2–MeOH mixture at low temperature leading after reductive work-up with Me_2S to the desired lactols **10a**–**c**[16] with the stereochemistry as shown (Scheme 4).[17] Similarly, protection of the diols **8c**,**d** as reported[6f] gave the corresponding acetonides **11a**,**b** which were submitted to the ozonolysis. Considering that a silyl group might be too good a leaving group when located α to an aldehyde function,[18] a reductive work-up with $NaBH_4$ was first carried out after the ozonolysis. It was thus found that ozonolysis of **11a**,**b** led, after reduction of the ozonide, to the corresponding diols **12** (85% yield from **11a**) and **13**[19] (30% overall yield from **7d**, three steps) (Scheme 5). We were also pleased to observe that free hydroxy groups in **13** could be differentiated, thus allowing further manipulations of these intermediates. Mesylate **14** was thus prepared in 55% yield from **13**, demonstrating that the presence of the bulky TIPS

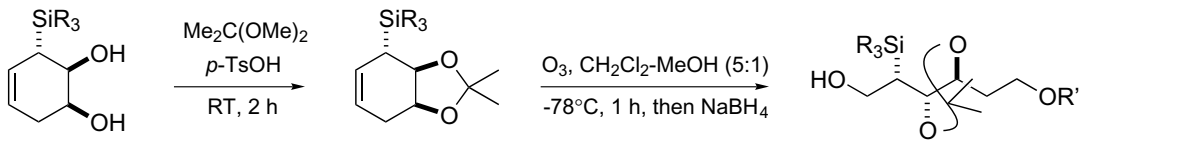


8a, R = Me
8b, R = H

9a, R = Me, R' = Ac (93%)
9b, R = Me, R' = Bn (99%)
9c, R = H, R' = Ac (94%)

10a, R = Me, R' = Ac (76%)
10b, R = Me, R' = Bn (73%)
10c, R = H, R' = Ac (32%)

Scheme 4.

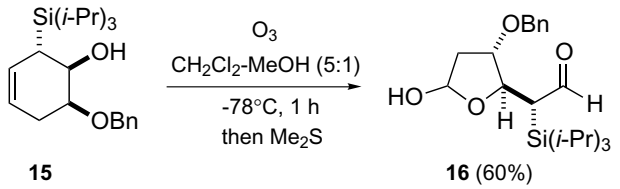


8c, SiR_3 = $SiMe_2t$-Bu
8d, SiR_3 = Si(i-Pr)$_3$

11a
11b

12, SiR_3 = $SiMe_2t$-Bu, R' = H
13, SiR_3 = Si(i-Pr)$_3$, R' = H
14, SiR_3 = Si(i-Pr)$_3$, R' = Ms
MsCl, Pyr.
0°C (55%)

Scheme 5.



Scheme 6.

group efficiently prevents the formation of the mesylate β to silicon.

Finally, based on the above observation, it was decided to use purposely the unique steric bulk of the TIPS group to prepare fragile α-silylaldehydes.[18,20] These aldehydes are valuable intermediates which can be converted stereoselectively into allylsilanes through Wittig reactions[21a] or into β-hydroxysilanes through addition of organometallic reagents.[21b] Selective monobenzylation of the diol **8d**, away from the TIPS group, thus led to the alcohol **15** (40%) which was submitted to the ozonolysis (Scheme 6). Reductive work-up with Me_2S as above furnished the lactol **16** in 60% yield as one diastereomer having the required α-silylaldehyde moiety.

As a summary, we have described here a short, general and stereocontrolled access to highly functionalised cyclic and acyclic intermediates, using a Birch reduction–dihydroxylation–ozonolysis sequence starting from simple arenes. As shown with lactols **10a–c**, otherwise difficult to control quaternary stereogenic centres can be installed stereoselectively in only four steps from inexpensive aromatic substrates. Application of this methodology to the synthesis of naturally occurring tetrahydrofurans is now underway.

Acknowledgements

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10. Compound **8a** was readily separated from the minor diastereomer through crystallisation.
11. Assumption on the absolute configuration of **8a** was based on Sharpless mnemonic device[7a,b] and is consistent with results obtained recently during AD reaction on related dienes, see: Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *118*, 11038–11053.
12. Eecker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448–450.
13. ^{1}H NMR of the bis-acetonide protected tetrol showed that it is *meso*, indicating that the second dihydroxylation also took place *anti* relative to the silicon group. The bis-acetonide could not be separated from the monoacetonide **11b** and was thus isolated after the ozonolysis of **11b** (Scheme 5).
14. This may indicate that a kinetic amplification operates during the dihydroxylation process. A careful investigation of the possible implication of this phenomenon in our desymmetrisation process is currently underway. For a closely related example of kinetic amplification, see:

Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529.
15. We had observed similar formation of tetrols with other dienylsilanes, but in very low amount (Angelaud, R. Ph.D. Thesis, Lausanne, 1997).
16. The lactols **10a–c** were obtained as a mixture of diastereomers (lactol centre), respectively: 6:4 for **10a**; 7:3 for **10b** and 6:4 for **10c**, as estimated from the ^{1}H NMR of the crude reaction mixtures.
17. The relative configuration of **10a** (and consequently of **10b**) was determined from NOE experiments performed on the corresponding lactone. This also allowed us to determine unambiguously the relative configuration of **8a**.
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19. The protection–ozonolysis sequence was carried out on the mixture **8d**/tetrol.[13]
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