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Note

Double asymmetric induction in the catalytic osmylation of some α,β-unsaturated octuronic acid derivatives*†

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The *syn*, vicinal bishydroxylation of olefins with osmium tetraoxide is among the most selective and reliable of organic transformations[2], and the introduction of catalytic processes[3] has greatly increased the usefulness of such transformations, particularly in the synthesis of higher-carbon sugars[4]. The stereochemical outcome of the osmylation of unsaturated sugar derivatives usually complies with Kishi's empirical rule[5], which predicts that the relative stereochemistry between the pre-existing hydroxyl or alkoxyl group at the adjacent stereocentre and the newly introduced hydroxyl group of the major product will be *erythro*. A successful ascent of the sugar series depends, to a large extent, on achieving high diastereofacial selectivity in the osmylation reaction.

Based on the known preference of allylic systems to adopt an eclipsed conformation[6], and assuming that this conformational preference is expressed in the transition state, the stereochemical outcome of the osmylation was formulated[5] as arising from preferential attack of osmium tetraoxide on the face of the olefinic linkage opposite to that of the pre-existing hydroxyl or alkoxyl group at the adjacent stereocentre when the molecule adopts the sterically least-compressed conformation **1A**. However, the Kishi model **1A**[5] poses certain problems with conjugate esters, most notably the non-compliance[4,5] of many (*Z*)-conjugate esters with the empirical formulation, and there is also increasing theoretical[7,8] and experimental evidence[1,7,9] to indicate that the "alkoxy-inside" conformation **1B**[10], which undergoes stereoselective osmylation from the less hindered face on the olefinic linkage, provides a better model for osmylations involving (*E*)-conjugate esters. Whilst both models lead to identical qualitative predictions, the ensuing discussion is centred on the "alkoxy-inside" conformation **1B** for the (*E*)-conjugate esters **6**, **9**, and **12**. This departure from the Kishi model[5] used in our preliminary communication[11] is taken in the light of new evidence[1,9] that reveals the "alkoxy-inside" conformation **1B** to be the favoured crystallographic ground-state

* Dedicated to Professor Leslie Hough in the year of his 65th birthday.
† Higher-carbon Sugars, Part 15. For Part 14, see ref. 1.
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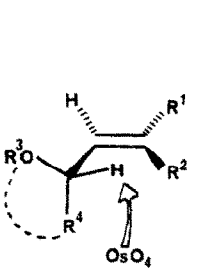
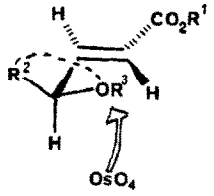
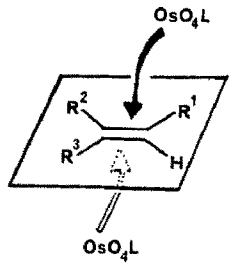


1A



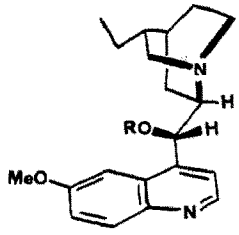
1B

L = dihydroquinidine ester 3

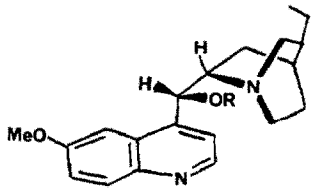


L = dihydroquinine ester 4

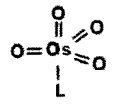
2



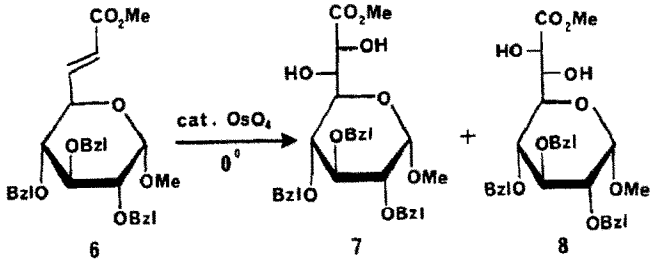
3 R = p-ClC$_6$H$_4$CO



4



5 L = 3 or 4

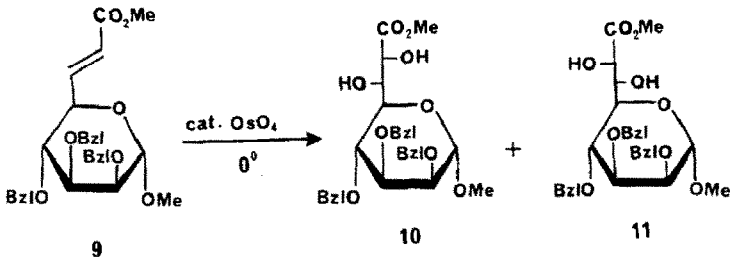


6 7 8

	ratio 7:8
OsO_4 only	10.3 : 1
OsO_4 + 3	1.34:1
OsO_4 + 4	20.5 : 1

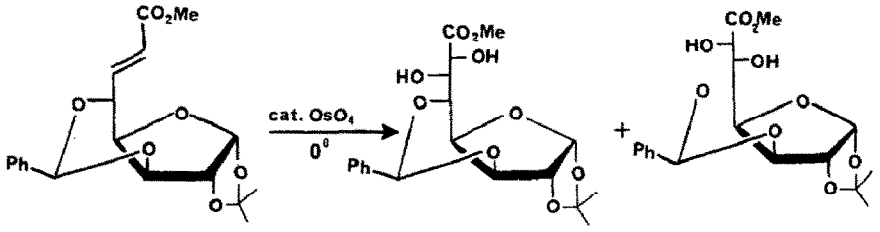
conformation of related (*E*)-conjugate esters. A more detailed discussion of this point appears in ref. 1.

Sharpless and co-workers[12,13] have recently produced a face-selection model **2** for the *catalytic* asymmetric osmylation of prochiral olefins, using either dihydroquinidine *p*-chlorobenzoate (**3**) or dihydroquinine *p*-chlorobenzoate (**4**) as the chiral ligand in the osmylating agent **5**[13]. Although not enantiomers, the cinchona alkaloid derivatives **3** and **4** behave as though they were in this system and, importantly, participate in a rate-accelerated process[12]. By combining the models **1B**[10] and **2**[12], there is every likeli-



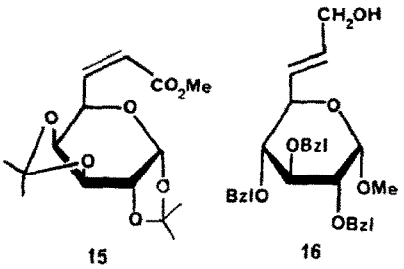
9 10 11

	ratio 10:11
OsO_4 only	7.4: 1
OsO_4 + 3	3.45:1
OsO_4 + 4	15.9 : 1

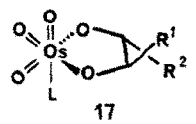


12 13 14

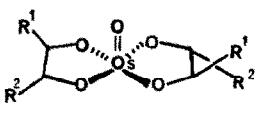
	ratio 13:14
OsO_4 only	1: 2.15
OsO_4 + 3	1 : 5.3
OsO_4 + 4	1 : 1.6



15 16



17



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hood of the inherent diastereofacial selectivity of the chiral allylic system **1B** being enhanced in the presence of **4**, whereas it would diminish with **3** as the chiral ligand in the osmylating agent **5**. In keeping with this notion, the diastereofacial selectivities of several α,β-unsaturated uronic acid derivatives used in the synthesis of higher-carbon sugars[14] were significantly improved when the "matching" osmylation reaction[15] was

used. Several carbohydrate-based allylic alcohols were similarly examined, but the results were unsatisfactory (see later).

Unlike a previous report[16], we found that catalytic asymmetric osmylation[12] in the presence of the appropriate alkaloid ester worked well for (*E*)-conjugate esters such as **6**, **9**, and **12**. Both (*E*)-octenopyranosiduronate derivatives **6** (ref. 14) and **9** (ref. 14) showed enhanced diastereofacial selectivities when catalytic osmylation was carried out at 0° in the presence of the "matching" dihydroquinine ester **4**, whereas there was a significant decrease in their diastereofacial selectivities in the presence of the "mismatching" dihydroquinidine ester **3***. For each set of results, the stereoisomer (**7**, **10**, and **13**) predicted by Kishi's empirical rule[5] is given first. Likewise, the diastereofacial selectivity of the (*E*)-octenofuranuronate **12**[14], which preferentially undergoes catalytic osmylation in an anti-Kishi sense, more than doubled in the presence of the "matching" dihydroquinidine ester **3**. The ratio, 1:5.3, of **13** to **14** obtained using the catalytic procedure[12] still falls a little short of that (1:7.2) obtained by stoichiometric asymmetric osmylation of **12** (see Experimental for details), which provides a measure of the highest diastereofacial selectivity that can be reached or approached by the catalytic procedure[12,13]; the diastereoisomeric excess (d.e.) corresponding to these ratios is 68 and 76%, respectively.

By contrast, there was little change in the anti-Kishi selectivity[17] of the (*Z*)-octenopyranuronate derivative **15** towards catalytic osmylation in the presence of either **3** or **4** under our experimental conditions. It is significant that osmylations of (*Z*)-conjugate esters often exhibit[16] poor stereoselectivities in the corresponding stoichiometric procedure and provide[4,5] most of the exceptions to Kishi's empirical rule[5].

It is important for a successful result that the reaction mixture retains a yellow–orange hue [the colour of **5** (ref. 13)] throughout the experiments where all the reactants, including the unsaturated substrate, are present at the start. The early appearance of a blackish tint, as was the case in the catalytic asymmetric osmylation of the octenopyranose derivative **16** (ref. 18) and other related allylic alcohols, signals the onset of a second cycle initiated by the formation of a bisglycolate **18** from the pivotal osmium (VIII) trioxoglycolate complex **17** (ref. 13) by reaction with more unsaturated substrate. Since the second cycle turns over at a much lower rate, the amount of osmium catalyst available for the first and more facial-selective cycle is severely depleted. Slow addition of the unsaturated substrate often produces much better results in such cases[13]. The success achieved with the conjugate octuronic acid derivatives **6**, **9**, and **12**, without the need to resort to slow addition, is doubtless connected with the dampening of the reactivity of the olefinic linkage towards electrophiles brought about by the electron-withdrawing ester group.

* In the experimental procedure used, all the reactants, including the (*E*)-conjugate ester, were present at the start. However, slow addition of the unsaturated substrate often produces better results[13].

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Bruker AM300/WB spectrometer operating at 300 MHz. Other general methods used are described in ref. 14, which also contains details of the identification of the osmylation products mentioned in the text.

General procedure for catalytic asymmetric osmylation. — To a well-stirred and cooled (0°) solution of the (*E*)-conjugate ester (0.55 mmol), *N*-methylmorpholine *N*-oxide monohydrate (0.67 mmol, 1.2 equiv.), and either **3** or **4** (0.15 mmol, 0.27 equiv.) in acetone–water (5.2:1 v/v, 1.55 mL) was added 0.055M osmium tetraoxide in toluene (0.1 mL, 0.01 equiv.), whereafter the reaction mixture was stirred for 4–6 h at 0° and then kept overnight in a refrigerator (0–4°) before being processed in the usual way[14,17]. The ratios of the osmylation products were determined by 300-MHz ^{1}H-n.m.r. spectroscopy (see ref. 14 for details) on the crude reaction mixtures prior to chromatography, which furnished the products in combined yields of $\geq$90%. For a useful comparison with the original osmylation procedure[14], the foregoing procedure resulted in an increase in the d.e. of **7** from 82 to 91%, that of **10** from 76 to 88%, and that of **14** from 36.5 to 68%.

General procedure for stoichiometric asymmetric osmylation. — To a stirred and cooled (0°) solution of osmium tetraoxide (0.4 mmol) and either **3** or **4** (0.4 mmol) in acetone–water (5:1 v/v, 4 mL) was added the (*E*)-conjugate ester (0.4 mmol), whereafter the reaction mixture was stirred at 0° until t.l.c. (see ref. 14 for appropriate solvent systems) indicated that no starting material remained. After the addition of saturated aqueous sodium metabisulphite (2 mL) and solid sodium metabisulphite (0.2 g), the mixture was stirred at room temperature for 1.5 h and then dispersed in dichloromethane (100 mL). The organic solution was separated and washed with saturated aqueous sodium metabisulphite (10 mL) and water (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The ratios of the osmylation products were determined by 300-MHz ^{1}H-n.m.r. spectroscopy after percolation of the crude products in an appropriate solvent system (see ref. 14) through a short column of silica gel. Recoveries of the combined osmylation products were $\geq$85%. The ratios obtained for the osmylation products were as follows: **7**:**8**, >50:1 (d.e. >96%); **10**:**11**, ~45:1 (d.e. ~96%); and **13**:**14**, 1:7.2 (d.e. 76%).

ACKNOWLEDGMENTS

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