Pergamon

*Tetrahedron: Asymmetry*, Vol. 8, No. 4, pp. 559–577, 1997

Printed in Great Britain

PII: S0957-4166(96)00540-X

0957-4166/97 $17.00 + 0.00

# Diastereoselectivity of the reactions of organometallic reagents with protected D- and L-erythrulose 1,3-*O*-ethylidene acetals

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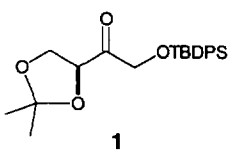
***Abstract:*** 1,3-*O*-Ethylidene acetals of D- and L-erythrulose bearing various protecting groups on the 4-OH group have been prepared using D-glucose as the starting material. The stereo-selectivity of the additions of several organometallic reagents to the carbonyl group of these compounds has then been investigated. In contrast to previously studied erythrulose derivatives, the type of protecting group does not play a significant role in the stereocontrol of the process. Theoretical calculations have been performed in order to find an explanation of this behaviour. © 1997 Elsevier Science Ltd. All rights reserved.

Since some time, we are interested in the nature of the factors which control the stereoselectivity in nucleophillic additions to heterosubstituted double bonds. As a part of this topic, we have recently disclosed on our results in the investigation of the stereoselectivity of organometallic additions to 1-*O*-silylated 3,4-isopropylidene- and 3,4-di-*O*-benzyl-L-erythrulose derivatives, **1** and **2**, respectively.[1] These compounds were allowed to react with a range of organometallic reagents. High diastereoselectivities (>9:1) were observed mainly for reactions of Grignard reagents with **2**,[1b] and were attributed to the intervention of chelation mechanisms. The predominant stereoisomer **3** thus obtained had the *R* configuration in the newly formed stereogenic carbon (C-2). This configuration corresponds to the addition to the *si* face of the carbonyl group:

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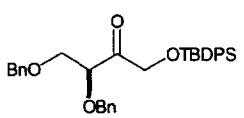


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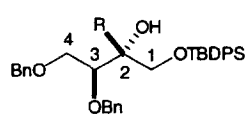


**3**

Among the different reaction conditions we assayed, the only ones clearly favouring the alternative *2S* stereoisomer (9:91), formed by attack to the *re* face, meant the use of a great excess of *neat* MeTi(O*i*Pr)$_3$ with **1** at room temperature for 2 days.[1a] These conditions, however, were not convenient from the practical point of view. We then considered other erythrulose derivatives with different molecular shapes, which could perhaps display the desired diastereofacial preference. Among these alternative derivatives we have selected those of general formula **5**, which are easily prepared from ethylidene acetal **4**.[2,3] Addition of organometallic reagents to the carbonyl group of L-erythruloses **5** should give mixtures of stereoisomers **6/7** (Scheme 1), the relative proportion of which being possibly subjected to modulation by changes in the nature of the protecting group R.

Nucleophilic additions to 1,3-dioxan-5-ones, the heterocyclic system of **5**, have been previously investigated. Jochims *et al.* studied the reaction of 2-phenyl-1,3-dioxan-5-one **8b** and its 1,3-ditiane analogue **8c** with $LiAlH_4$ and various Grignard reagents.[4] They found that acetal **8b** underwent nucleophillic additions to the carbonyl group almost exclusively from the axial side, allowing the formation of equatorial alcohols **9b**. In contrast, the sulfur analogue **7c** displayed just the opposite stereopreference, nucleophillic attacks taking place mainly from the equatorial direction to yield **10c**.

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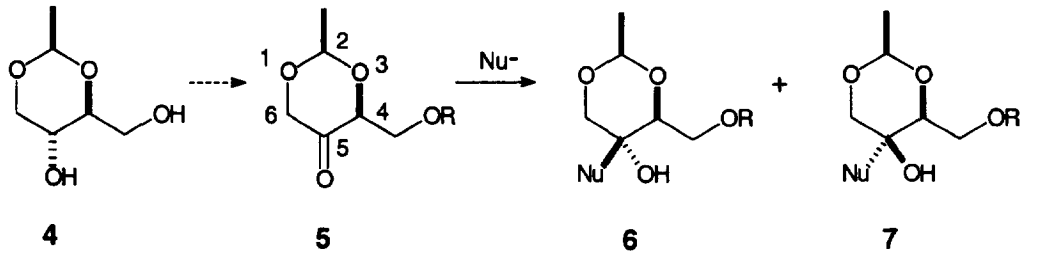
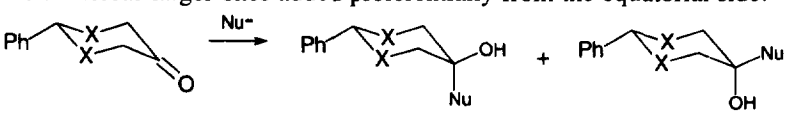



4 5 6 7

**Scheme 1.**

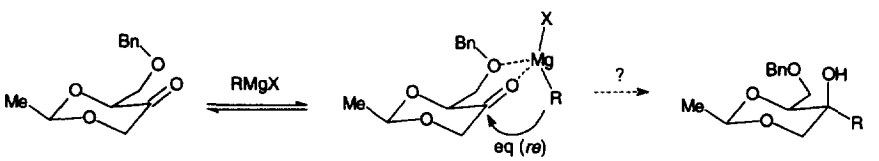
In both cases, the size of the nucleophile was not a relevant factor, small and bulky reagents behaving in essentially the same way. It is noteworthy that 4-phenylcyclohexanone **8a**, the carbocyclic analogue of the aforementioned compounds, showed an intermediate behaviour: small nucleophiles preferred the axial approach whereas larger ones added preferentially from the equatorial side:




**8a** X = $CH_2$ **9a** **10a**
**8b** X = O **9b** **10b**
**8c** X = S **9c** **10c**

The authors explained these results on the basis of a competition between the steric hidrance to axial attack, imposed mainly by the axial substituents in β position ('steric approach control'),[5] and the stereoelectronic barrier to the equatorial approach, due to the development of a torsional strain between the forming C–Nu bond and C–H or C–C bonds proximal to the carbonyl group.[6] The last model, proposed initially by Felkin,[6a,b] received theoretical refinement by Anh[6c] and later by Houk *et al.*[7] For dioxanone **8b**, axial attack is practically unhindered because of the absence of substituents in β-position. Since the aforementioned torsional barrier is still present,[7,8] this explains why **8b** reacts with nucleophiles with a high predominance of axial attack.

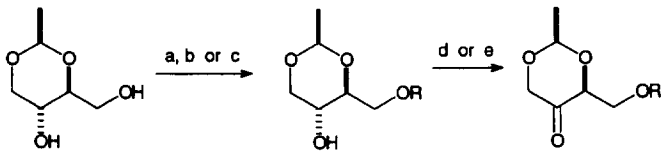
In the case of 1,3-dioxan-5-ones **5**, this particular stereopreference would yield in principle as the major diastereoisomer that formed from the addition to the *si* face of the carbonyl group, *i.e.* the same configuration already obtained in nucleophillic additions to **1** and **2**. We reasoned, however, that the presence of an additional α-$CH_2OR$ group might introduce a chelation point, which would possibly invert the diastereofacial bias inherent to the dioxanone system. The formation of a bicyclic chelate involving the carbonyl and $CH_2OR$ oxygen atoms should give rise to a preferential attack from the convex side of the complex, which corresponds to the equatorial face (*re*) of the C=O bond (Scheme 2). This outcome is particularly expected for R=Bn (benzyl), a chelation-promoting protecting group.[9] We then prepared dioxanones **5** with three types of protecting groups, R=Bn, TBDPS (*tert*-butyldiphenylsilyl) and Tr (triphenylmethyl, trityl). The last two bulky groups were expected to impede chelation,[9] thus reinforcing the axial stereopreference of the carbonyl group in **5**.




**Scheme 2.**

The requisite dioxanones were obtained from diol **4**, 1,3-*O*-ethylidene-L-erythritol, easily prepared from D-glucose in three steps.[2] Monosilylation and monotritylation of **4** were performed by standard methods (Scheme 3).[10] Efficient monobenzylation was only possible through the use of the

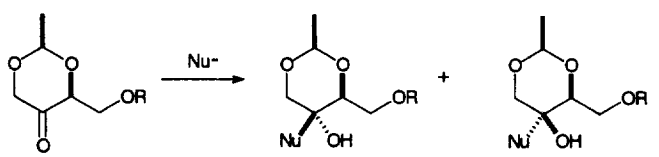
intermediate di-*n*-butylstannylidene acetal.[11] Oxidation of **11a–c** to the corresponding ketones was performed with Dess–Martin periodinane[12] except for **5c**, which was obtained with acceptable yields only under the conditions indicated in Scheme 3.[14]




**4** **11a** R=TBDPS **5a**
**11b** R=Tr **5b**
**11c** R=Bn **5c**

**Scheme 3. Reaction conditions**. a) Ref. 2 (for **11a**). b) TrCl, $Et_3N$, DMAP, $CH_2Cl_2$, room temp., 88% (for **11b**). c) $Bu_2SnO$, Tol, Δ, 18 h, then BnBr, $nBu_4N^+I^-$, 70°C, 18 h, 55% (for **11c**). d) Dess–Martin (**5a**, 87%; **5b**, 82%). e) $CrO_3$, py, Celite, 4Å-MS, $CH_2Cl_2$, 0°C, 1 h, 58% (**5c**).

Nucleophilic additions of a range of organometallic reagents to ketones **5a–5c** were then performed. The results of these reactions (Scheme 4) are indicated in Table 1.




**5a** R=TBDPS **6a** **7a**
**5b** R=Tr **6b** **7b**
**5c** R=Bn **6c** **7c**

**Scheme 4.**

One of the main conclusions to be drawn from Table 1 is that **5a** and **5b** display almost identical results towards all organometallic reagents assayed. This is interesting from the practical point of view, as trityl chloride is a much cheaper reagent than *t*-butyldiphenylsilyl chloride. From the mechanistic point of view, the results of the reactions of these two ketones with Grignard reagents are not surprising, if one takes into account the previous precedent.[4] As both bulky protecting groups are expected to prevent binding of metal ions with the ether oxygen atom,[9] chelation mechanisms may be excluded. The acetal methyl and the $CH_2OR$ group are expected to occupy equatorial positions in a chair conformation of the dioxanone ring, an assumption supported by NMR analysis.[16] The $CH_2OR$ group therefore behaves as an inert spectator which will not influence the steric course of the reaction. In consequence, nucleophillic attacks from the axial (*si*) side are predicted.[4] This is that observed in practice with methyl and ethylmagnesium halides, which displayed the highest diastereoisomeric ratios (>95:5 means that the minor stereoisomer was not observed by NMR). We do not know, however, the reasons of the much lower diastereoselectivity observed in the case of the vinyl and ethynyl magnesium halides, which even show opposite preferences. This may be due to a completely different aggregation state of the two latter reagents or perhaps to a competition between alternative mechanistic paths (see below). It is worth mentioning here that the diastereofacial preference shown by methyl and ethylmagnesium halides turned out to be again that previously observed in acyclic erythrulose derivatives, *i.e.* attack to the *si* face of the carbonyl group.[1] The other organometallic reagents showed rather disappointing results. The only exception was tetramethylzirconium,[17] which showed a fair diastereoselectivity in its reaction with **5a** and, most interestingly for our purposes, added to the *re* face of the carbonyl group. The reasons of this behaviour are also unknown.

**Table 1**. Nucleophilic additions of organometallic reagents to L-erythrulose derivatives **5a–c**[a,1,15,26,27]

| Entry | Ketone | Reagent | Solvent | T (°C) / t (h) | Yield (%) | 6 / 7[b] |
|---|---|---|---|---|---|---|
| 1 | **5a** | MeLi | $Et_2O$ | -78 / 1 | 65 | 40 : 60 |
| 2 | **5a** | MeMgBr | $Et_2O$ | -78 / 1 | 80 | >95 : 5 |
| 3 | **5a** | EtMgBr | $Et_2O$ | -78 / 1 | 73 | >95 : 5 |
| 4 | **5a** | $CH_2$=CHMgBr | $Et_2O$ | -78 / 1 | 72 | 30 : 70 |
| 5 | **5a** | HC≡CMgBr | $Et_2O$ | 0 / 2 | 77 | 70 : 30 |
| 6 | **5a** | $Me_2CuLi$ | $Et_2O$ | -40 → 0 / 2 | 54 | 60 : 40 |
| 7 | **5a** | $MeTi(OiPr)_3$ | $Et_2O$ | 25 / 60 | 68 | 70 : 30 |
| 8 | **5a** | $Me_3Al$ | $C_6H_6$ | 25 / 1 | 60 | 78 : 22 |
| 9 | **5a** | $Me_4Zr$ | THF | -20 / 1.5 | 68 | 20 : 80 |
| 10 | **5b** | MeLi | $Et_2O$ | -78 / 1 | 89 | 45 : 55 |
| 11 | **5b** | MeMgBr | $Et_2O$ | -78 / 1 | 80 | >95 : 5 |
| 12 | **5b** | EtMgBr | $Et_2O$ | -78 / 1 | 69 | >95 : 5 |
| 13 | **5b** | $CH_2$=CHMgBr | $Et_2O$ | -78 / 1 | 69 | ~50 : 50 |
| 14 | **5b** | HC≡CMgBr | $Et_2O$ | 0 / 2 | 78 | 70 : 30 |
| 15 | **5c** | MeLi | $Et_2O$ | -78 / 3 | [c] | ~50 : 50 |
| 16 | **5c** | MeMgBr | $Et_2O$ | -78 / 1 | [c] | 85 : 15 |
| 17 | **5c** | EtMgBr | $Et_2O$ | -78 / 1 | [c] | 89 : 11 |
| 18 | **5c** | $CH_2$=CHMgBr | $Et_2O$ | -78 / 1 | [c] | 23 : 77 |
| 19 | **5c** | HC≡CMgBr | $Et_2O$ | 0 / 2 | [c] | ~50 : 50 |
| 20 | **5c** | $Me_2CuLi$ | $Et_2O$ | -40 → 0 / 2 | [c] | ~50 : 50 |
| 21 | **5c** | $MeTi(OiPr)_3$ | $Et_2O$ | 25 / 60 | [c] | ~70 : 30 |
| 22 | **5c** | $Me_4Zr$ | THF | -20 / 1.5 | [c] | ~50 : 50 |

[a]The configurations of the addition products were established though NOE measurements and chemical correlations.[15] [b]The diastereoisomeric ratios **6/7** were measured by means of $^1H$ and $^{13}C$ NMR and are the average values of three experiments. [c]Incomplete reaction: the product was by NMR analysis a mixture of addition products and partially epimerized starting material (overall yield 60-80%).

The results observed with O-benzylated ketone **5c** and Grignard reagents deserve some comment. We had anticipated that chelation of the metal with the carbonyl and the $CH_2OR$ oxygen atoms (Scheme 2) would possibly cause a preferential attack from the equatorial, and perhaps less hindered, side. As Table 1 shows, this expectation was not borne in practice. Ketone **5c** behaved in essentially the same way as **5a** and **5b**, although with a somewhat lower stereoselectivity. Moreover, reactions of **5c** with all organometallic reagents assayed had low yields and were never complete, even after prolonged reaction times. We do not attribute these results to a particular lack of reactivity of the carbonyl group of **5c** but rather to a pronounced tendency of this product to undergo proton abstraction (H-4 or H-6). This converts the ketone into the corresponding metal enolate which then, after work-up, reverts back to the parent compound (and in part to its C-4 epimer). Furthermore, the $\Delta^4$-enolate

**Table 2.** HF/3-21G calculated total (a.u.) and relative energies (kcal/mol) for MeMgCl addition to ketone **5** (R=Me) after prior chelate formation

| | E (a.u.) | ΔE (kcal/mol) |
|---|---|---|
| MeMgCl + **5** (R=Me) | -1263.552967 | 0 |
| **C1a** | -1263.650029 | -60.91 |
| **C1e** | -1263.647650 | -59.41 |
| **TS1a** | -1263.617696 | -40.62 |
| **TS1e** | -1263.614287 | -38.48 |

may also undergo to some extent extrusion of the OBn group, which explains the relatively low yields obtained. In fact, enolization was also observed in ketones **5a** and **5b** but to a lesser extent (≤15%).

The stereochemical behaviour of **5c** may be interpreted in such a way as to assume that no chelation at all takes place, the same results being thus expected as for **5a** or **5b**. However, no reasons for this behaviour are apparent. We then had recourse to theoretical calculations in order to find a possible explanation. With the aim of simplifying these calculations, the OBn of compound **5c** was replaced by a OMe group. Methyl magnesium chloride was selected as a simple model reagent. We first determined the most stable conformation of the model molecule (**5**, R=Me, Scheme 1) by molecular mechanics methods.[18] As expected, this was found to be the chair-like form with the methyl and $CH_2OMe$ groups accomodated in equatorial orientations[16] (see Scheme 2). In this conformation, the spatial proximity of the carbonyl and $CH_2OMe$ oxygen atoms allows chelate formation with the magnesium atom of the Grignard reagent. Subsequently, an extensive exploration of the potential energy surface by means of *ab initio* calculations at the HF/3-21G level[19] rendered two magnesium chelate complexes, **C1a** and **C1e**, which differ in the spatial orientation of the methyl and chlorine ligands around the magnesium atom. Their formation is quite exothermic (their energies are about 60 kcal/mol lower than the sum of those of the isolated ketone and Grignard reagent, see Table 2), and takes place reversibly without any noticeable energy barrier.[20] Their optimized conformations are represented in Figure 1. The magnesium atom is coordinated to the lone pairs of the carbonyl and methoxyl oxygen atoms and forms a puckered six-membered ring. Similar structures have been found for related chelates using X-ray methods[21] and theoretical calculations.[22]

Under assumption that each of these chelates would then react through intramolecular, rate-limiting 1,3-transfer of the methyl group from magnesium to carbon, *ab initio* methods at the aforementioned level predicted two transition structures **TS1a** and **TS1e**, the chelate conformation being maintained throughout the reaction path. Selected geometric parameters are displayed in Figure 1. Table 2 further presents the total and relative energies for the stationary points on the two reaction channels[23] and shows that even the calculated transition structures are lower in energy than the initial system (isolated ketone+Grignard reagent). This is clearly due to the strong stabilization generated by chelate formation. The energetically more favourable pathway corresponds to transition state **TS1a**, where the methyl group adds to the carbonyl carbon from the axial side. This particular geometry avoids the torsional strain present in the alternative transition structure **TS1e**, in agreement with Felkin–Anh's and Houk's models for nucleophilic attack on cyclohexanones.[6–8,24] Therefore, chelate formation, if present to any extent, does not change the inherent bias of 1,3-dioxan-5-ones for axial nucleophilic attacks, which is thus always observed independently of the nature of R in the α-$CH_2OR$ side chain.

During our efforts to obtain ketones **5a–c** by oxidation of alcohols **11a–c**, we noticed that in some conditions, most particularly with the Swern method, variable amounts of a second ketone were formed. These turned out to be the C-4 epimers **12a–c**, formed because of the basic conditions of these reagents.[13] We thought that a comparison of the stereoselectivity of ketones **12a–c** with those of **5a–c** was worth investigating. Compounds **12**, which are D-erythrulose derivatives, might be also

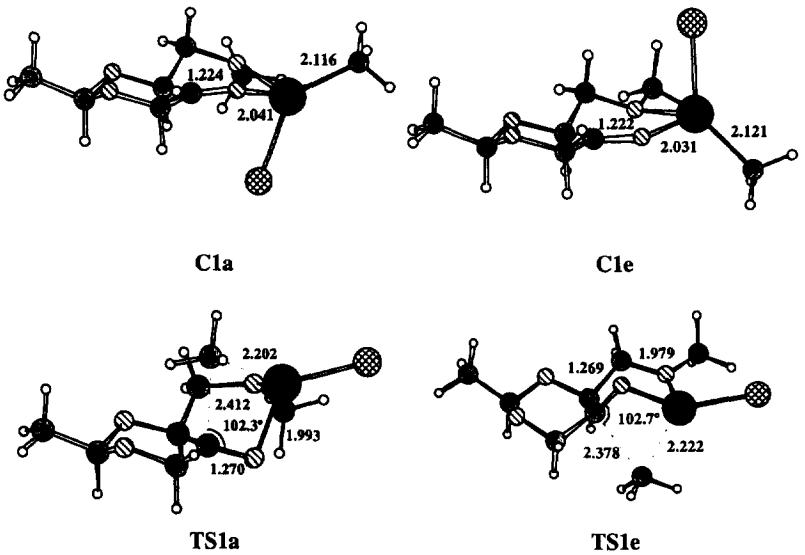
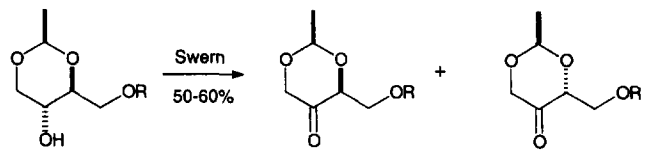



**Figure 1.** HF/3-21G optimized $CH_3MgCl$/5 (R=Me) chelates (**C1a** and **C1e**) and calculated transition structures (**TS1a** and **TS1e**) for intramolecular magnesium-to-carbon 1,3-methyl transfer.

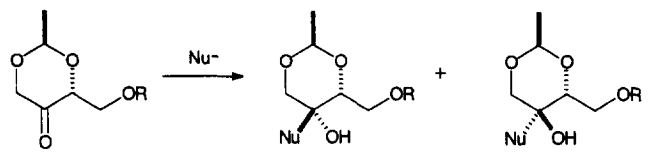
obtainable in a similar way to **5**, but starting from another sugar (*e.g.* D-galactose). However, since only a preliminary comparison with ketones **5** was pursued, we obtained them simply by oxidation of alcohols **11** under conditions favouring epimerization of the initially formed **5** (Scheme 5). Mixtures of **5** and **12** were obtained and separated by chromatography (Scheme 5).




| | | |
|---|---|---|
| **11a** R=TBDPS | **5a** | **12a** |
| **11b** R=Tr | **5b** | **12b** |
| **11c** R=Bn | **5c** | **12c** |

**Scheme 5.**

Organometallic additions to ketones **12** were then investigated (Scheme 6). The results are shown in Table 3.




| | | |
|---|---|---|
| **12a** R=TBDPS | **13a** | **14a** |
| **12b** R=Tr | **13b** | **14b** |
| **12c** R=Bn | **13c** | **14c** |

**Scheme 6.**

Table 3 shows that the epimeric ketones **12a–c** display again a clear preference to undergo nucleophilic attack from the *si* side of the carbonyl group. Still more strongly than in the previous

**Table 3.** Nucleophilic additions of organometallic reagents to D-erythrulose derivatives **12a–c**[a,1,15,26,27]

| Entry | Ketone | Reagent | Yield (%) | **13 / 14**[b] |
|---|---|---|---|---|
| 1 | **12a** | MeLi | 60 | 95 : 5 |
| 2 | **12a** | MeMgBr | 65 | 95 : 5 |
| 3 | **12a** | EtMgBr | 64 | 90 : 10 |
| 4 | **12b** | MeLi | 78 | 95 : 5 |
| 5 | **12b** | MeMgBr | 93 | 95 : 5 |
| 6 | **12b** | EtMgBr | 70 | 95 : 5 |
| 7 | **12c** | MeLi | [c] | >95 : 5 |
| 8 | **12c** | MeMgBr | [c] | >95 : 5 |
| 9 | **12c** | EtMgBr | [c] | 95 : 5 |

[a]All reactions were conducted in $Et_2O$ at −78 °C for 1 h (longer times did not improve the yields). The configurations of the addition products were established though NOE measurements and chemical correlations.[15] [b]The diastereoisomeric ratios **13/14** were measured by means of both $^1H$ and $^{13}C$ NMR and are the average values of three experiments. [c] Incomplete reaction: the product was by NMR analysis a mixture of addition products and partially epimerized starting material (overall yield 60-80%).

case, these ketones showed a visible tendency to undergo enolization during the reaction. Here again, we carried out theoretical calculations with these compounds with the aim of explaining the sense of diastereocontrol. The simplified ketone **12** (R=Me, see Scheme 5) and methyl magnesium chloride were used as model compounds for the calculations. According to molecular mechanics,[18] ketone **12** (R=Me) displays a main conformation which resembles a slightly distorted chair with an axial $CH_2OMe$ group. This conclusion was supported by NMR analysis.[16] Since chelation cannot take place in a conformation of this type, we assumed a prior monodentate complexation between the magnesium and the carbonyl oxygen atoms, with the fourth coordination point at the magnesium being occupied by a solvent molecule. Subsequent 1,3-methyl transfer from magnesium to carbon may take place from either an axial or an equatorial direction, yielding either **13** or **14**, respectively (Scheme 6).

An extensive exploration of the potential energy surface for this process by means of *ab initio* methods at the aforementioned level yielded the two respective transition structures, **TS2a** and **TS2e**, which correspond to these attacks. Figure 2 shows their optimized geometries with inclusion of some selected geometric parameters. Table 4 presents the total and relative energies for the stationary points on the two reaction channels. Transition structure **TS2a** is, as in the previous case, less energetic than the initial ketone+Grignard reagent system due to the stabilization associated with complex formation. Here again, the energetically more favourable reaction pathway (**TS2a**) corresponds to 1,3-methyl transfer from the magnesium atom to the carbonyl group alongside the axial direction. This geometry avoids the torsional strain present in the alternative transition structure **TS2e**, in agreement with Felkin-Anh's and Houk's models.[6–8,24] Axial attack therefore takes always place with any one of the three R protecting groups.

As a summary of all facts disclosed above, we may conclude that Grignard additions to the carbonyl group of 1,3-dioxan-5-ones are strongly dominated by the tendency to avoid torsional strains in the transition states, which leads to a marked preference for axial attacks. Introduction of chelation points in the vicinity of the carbonyl group does not cause essential changes in this preference.

## Experimental

NMR spectra were measured in $CDCl_3$ solution at 22°C (Varian Unity 400 and Gemini 200). Mass spectra were run by the electron impact mode (70 eV) on a VG AutoSpec mass spectrometer. IR

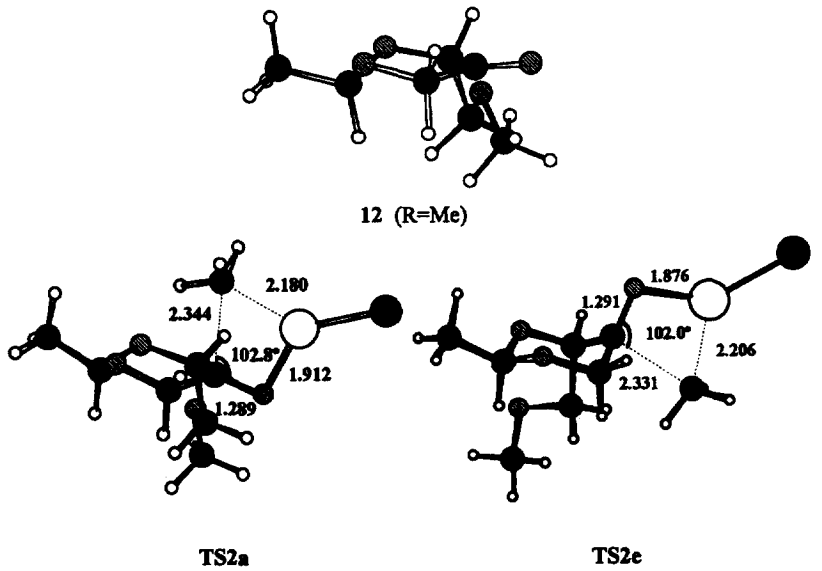



**Figure 2**. Optimized conformation of ketone **12** (R=Me) and calculated transition structures (HF/3-21G) **TS2a/TS2e** for magnesium-to-carbon 1,3-methyl transfer within its complex with MeMgCl.

**Table 4**. 3HF/3-21G calculated total (a.u.) and relative energies (kcal/mol) for MeMgCl addition to ketone **12** (R=Me) after prior complexation

| | E (a.u.) | ΔE (kcal/mol) |
|---|---|---|
| MeMgCl + **12** (R=Me) | -1263.548095 | 0 |
| **C2a** | -1263.605027 | -35.73 |
| **C2e** | -1263.601060 | -33.24 |
| **TS2a** | -1263.563811 | -9.86 |
| **TS2e** | -1263.543838 | 2.67 |

spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 22°C. Reactions which required an inert atmosphere were carried under argon (Ar) with flame-dried glassware. Commercial reagents (Aldrich or Fluka) were used as received. THF was freshly distilled under Ar from sodium-benzophenone ketyl. Benzene was distilled under Ar from sodium wire. Dichloromethane was distilled from $P_2O_5$ and stored over 4Å molecular sieves (4Å-MS). DMSO was dried and stored over 4Å-MS. Triethylamine was distilled from $CaH_2$. Trityl chloride (TrCl) was crystallized from isooctane prior to use. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, extraction with the indicated solvent, additional washing with 5% aq $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aq HCl (if bases had been utilized), then again with brine, drying over anhydrous $Na_2SO_4$ or $MgSO_4$ and elimination of the solvent *in vacuo*. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 50–200 μ) with the indicated eluent. All obtained products gave satisfactory microanalytical data (C, H, ±0.5%).

*(2R,4S,5R)-2-Methyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-ol (**11a**)*

Obtained as previously described.[3]

*(2R,4S,5R)-2-Methyl-4-(trityloxymethyl)-1,3-dioxan-5-ol (**11b**)*

A solution of diol **4**[2] (3.70 g, 25 mmol) in dry $CH_2Cl_2$ (80 ml) was treated sequentially under Ar with triethylamine (5.6 ml, 40 mmol), DMAP (48 mg, 0.4 mmol) and TrCl (8.36 g, 30 mmol). The resulting solution was stirred at room temperature for 1 h. Work-up ($CH_2Cl_2$) and column chromatography (hexane/EtOAc 9:1) afforded **11b** (8.60 g, 88%) as a white solid: mp 148–150°C, $[\alpha]_D$ +35 ($CHCl_3$, *c* 2); IR $\nu_{max}$ $cm^{-1}$: 3450 (br, OH), 3060, 3020, 1491, 1449, 1408, 1218, 1082, 791, 758, 707; EIMS, *m/z* (% rel. int.): 390.1841 ($M^+$, 3), 313 ($M^+-Ph$, 7), 243 ($Ph_3C^+$, 100), 183 (15), 165 (28), 105 (10). Calc. for $C_{25}H_{26}O_4$, M=390.1831; $^1H$ NMR (400 MHz): δ 7.45–7.40 (6H, *m*, aromatic), 7.35–7.20 (9H, *m*, aromatic), 4.66 (1H, *q*, J=5 Hz, H-2), 4.12 (1H, *dd*, J=11, 5 Hz, H-6eq), 3.65 (1H, *br ddd*, J=10, 10, 5 Hz, H-5), 3.62 (1H, *m*, H-4), 3.54 (1H, *dd*, J=9, 4.5 Hz, C*H*$_2$OTr), 3.40 (1H, *dd*, J=11, 10 Hz, H-6ax), 3.28 (1H, *dd*, J=9, 7 Hz, C*H*$_2$OTr), 3.00 (1H, *br d*, J=1.5 Hz, OH), 1.28 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (100 MHz): δ 143.2, 128.5, 128.0, 127.3 (aromatic), 98.8 (C-2), 87.7 (*C*Ph$_3$), 78.3 (C-4), 70.0 (C-6), 66.0 (*C*H$_2$OTr), 65.5 (C-5), 20.4 (Me).

*(2R,4S,5R)-2-Methyl-4-(benzyloxymethyl)-1,3-dioxan-5-ol (**11c**)*

A solution of diol **4**[2] (7.41 g, 50 mmol) in dry toluene (150 ml) containing activated 4Å-MS was treated under Ar with $Bu_2SnO$ (12.70 g, ca: 51 mmol). The solution was heated at reflux for 18 h and then cooled to 70°C. Benzyl bromide (12 ml, ca. 100 mmol) and $n$Bu$_4N^+I^-$ (3.7 g, ca. 10 mmol) were then added to the solution, which was further heated at the same temperature for 18 h. The reaction mixture was then filtered through Celite and the solvent was removed *in vacuo*. Column chromatography of the residue (hexane/EtOAc 19:1 to eliminate tin impurities, then 9:1 and 7:3) furnished **11c** (6.55 g, 55%) as a colourless oil: $[\alpha]_D$ −0.5 ($CHCl_3$, *c* 3.9); IR $\nu_{max}$ $cm^{-1}$: 3450 (br, OH), 3031, 1496, 1454, 1408, 1370, 1319, 1230, 1058, 952, 864, 833, 738; EIMS, *m/z* (% rel. int.): 238.1196 ($M^+$, 7), 194 (3), 177 (12), 176 (15), 135 (24), 133 (26), 117 (14), 107 (23), 105 (25), 91 (100). Calc. for $C_{13}H_{18}O_4$, M=238.1205; $^1H$ NMR (400 MHz): δ 7.35–7.25 (5H, *m*, aromatic), 4.64 (1H, *q*, J=5 Hz, H-2), 4.59, 4.55 (2H, AB system, J=12 Hz, benzyl C*H*$_2$), 4.09 (1H, *dd*, J=10.5, 5.2 Hz, H-6eq), 3.73 (1H, *dd*, J=10, 5.2 Hz, C*H*$_2$OBn), 3.66 (1H, *dd*, J=10, 5.212 Hz, C*H*$_2$OBn), 3.66 (1H, *m*, H-5), 3.56 (1H, *dt*, J=9, 5.2 Hz, H-4), 3.36 (1H, *t*, J=10.5 Hz, H-6ax), 2.95 (1H, *d*, J=3 Hz, OH), 1.32 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (100 MHz): δ 137.3, 128.4, 127.9, 127.8 (aromatic), 98.8 (C-2), 78.7 (C-4), 73.7 (benzyl *C*H$_2$), 71.1 (*C*H$_2$OBn), 70.1 (C-6), 64.4 (C-5), 20.4 (Me).

*(2R,4S)-2-Methyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-one (**5a**)*

A solution of alcohol **11a** (7.73 g, 20 mmol) in dry $CH_2Cl_2$ (250 ml) was treated under Ar with Dess–Martin periodinane[12] (12.72 g, 30 mmol). The resulting solution was stirred at room temperature for 1 h. After this time, the reaction mixture was diluted with EtOAc and treated with an aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, with further stirring for 10 min. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1) yielded **5a** (6.69 g, 87%) as a colourless oil: $[\alpha]_D$ −51 ($CHCl_3$, *c* 4.6); IR $\nu_{max}$ $cm^{-1}$: 3072, 3050, 1738 (ketone C=O), 1589, 1473, 1428, 1410, 1391, 1362, 1261, 1113, 978, 940, 872, 824, 741, 702; EIMS, *m/z* (% rel. int.): 384.1739 ($M^+$, 0.5), 383 (1.5), 327 ($M^+-t$Bu, 63), 297 (40), 283 (77), 267 (78), 255 ($Ph_2$tBuSiO$^+$, 65), 241 (54), 225 (100), 211 (27), 199 ($Ph_2SiOH^+$, 50), 183 (96), 181 (45), 177 (78), 163 (97), 135 (30), 115 (49), 105 (90). Calc. for $C_{22}H_{28}O_4Si$, M=384.1756; $^1H$ NMR (400 MHz): δ 7.75–7.65 (4H, *m*, aromatic), 7.50–7.30 (6H, *m*, aromatic), 5.12 (1H, *q*, J=5 Hz, H-2), 4.38 (1H, *d*, J=18 Hz, H-6eq), 4.33 (1H, *m*, H-4), 4.28 (1H, *dd*, J=18, 1 Hz, H-6ax), 4.07 (1H, *dd*, J=11, 4.2 Hz, C*H*$_2$OSi), 3.97 (1H, *dd*, J=11, 2.5 Hz, C*H*$_2$OSi), 1.47 (3H, *d*, J=5 Hz, Me–C2), 1.03 (9H, *s*, *t*Bu); $^{13}C$ NMR (100 MHz): δ 205.5 (C-5), 135.8, 135.6, 133.3, 133.1, 129.7, 127.7, 127.6 (aromatic), 97.1 (C-2), 83.6 (C-4), 72.8 (C-6), 63.7 (*C*H$_2$OSi), 26.7, 19.3 (*t*BuSi), 20.6 (Me–C2).

*(2R,4S)-2-Methyl-4-(trityloxymethyl)-1,3-dioxan-5-one (**5b**)*

Obtained by oxidation of **11b** (7.81 g, 20 mmol) with Dess–Martin periodinane under the same conditions as above. Work-up and column chromatography (hexane/EtOAc 9:1) afforded **5b** (6.37 g, 82%) as a white solid: mp 116–118°C, $[\alpha]_D$ −49.5 ($CHCl_3$, *c* 3.6); IR $\nu_{max}$ $cm^{-1}$: 3055, 1737 (ketone C=O), 1491, 1448, 1374, 1266, 1142, 1118, 1033, 959, 905, 703; EIMS, *m/z* (% rel. int.): 388.1683 ($M^+$, 3), 344 (2), 311 ($M^+$−Ph, 48), 244 (100), 243 ($Ph_3C^+$, 96), 183 (55), 165 (97), 105 (70). Calc. for $C_{25}H_{24}O_4$, M=388.1674; $^1H$ NMR (400 MHz): δ 7.45–7.40 (6H, *m*, aromatic), 7.35–7.25 (9H, *m*, aromatic), 5.15 (1H, *q*, J=5 Hz, H-2), 4.43 (1H, *d*, J=18 Hz, H-6eq), 4.38 (1H, *m*, H-4), 4.28 (1H, *dd*, J=18, 1 Hz, H-6ax), 3.54 (1H, *dd*, J=10, 2.5 Hz, C*H*$_2$OTr), 3.39 (1H, *dd*, J=10, 5 Hz, C*H*$_2$OTr), 1.52 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (100 MHz): δ 205.1 (C-5), 143.7, 128.6, 128.0, 127.0 (aromatic), 97.3 (C-2), 86.7 (*C*Ph$_3$), 82.3 (C-4), 72.7 (C-6), 63.7 (*C*H$_2$OTr), 20.6 (Me–C2).

*(2R,4S)-2-Methyl-4-(benzyloxymethyl)-1,3-dioxan-5-one (**5c**)*

A suspension of Celite (40 g) in dry $CH_2Cl_2$ (150 ml) was treated under Ar with pyridine (22 ml), followed by addition of activated 4Å-MS (ca. 20 g). The resulting mixture was then cooled to 0°C. Solid $CrO_3$ (12 g, 0.12 mol) was then added in small portions to the mixture, followed by stirring in the ice bad for 30 min. After this time, a solution of **11c** (4.76 g, 20 mmol) in dry $CH_2Cl_2$ (35 ml) was added, and the stirring was continued for 45 min. The reaction mixture was then diluted with $Et_2O$ (100 ml), further stirred for 10 min. and filtered through Celite. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1 and 7:3) provided **5c** (2.74 g, 58%) as a colourless oil: $[\alpha]_D$ −36 ($CHCl_3$, *c* 3.8); IR $\nu_{max}$ $cm^{-1}$: 1730 (ketone C=O), 1601, 1496, 1453, 1410, 1368, 1315, 1273, 1207, 1113, 949, 866, 744, 700; FAB HRMS: 237.1117 (M+$H^+$). Calc. for $C_{13}H_{17}O_4$, M=237.1126; $^1H$ NMR (400 MHz): δ 7.35–7.25 (5H, *m*, aromatic), 5.13 (1H, *q*, J=5 Hz, H-2), 4.60 (2H, *s*, benzyl C*H*$_2$), 4.44 (1H, *ddd*, J=5.5, 2.5, 1 Hz, H-4), 4.36 (1H, *d*, J=18 Hz, H-6eq), 4.27 (1H, *dd*, J=18, 1 Hz, H-6ax), 3.87 (1H, *dd*, J=11, 2.5 Hz, C*H*$_2$OBn), 3.81 (1H, *dd*, J=11, 5.5 Hz, C*H*$_2$OBn), 1.48 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (100 MHz): δ 204.2 (C-5), 137.7, 128.4, 127.8, 127.7 (aromatic), 97.6 (C-2), 82.7 (C-4), 73.7 (benzyl *C*H$_2$), 72.5 (C-6), 68.6 (*C*H$_2$OBn), 20.5 (Me–C2).

*(2R,4R)-2-Methyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-one (**12a**)*

Dry DMSO (5.7 ml, 80 mmol) was added under Ar at −60°C to a solution of oxalyl chloride (3.5 ml, 40 mmol) in dry $CH_2Cl_2$ (100 ml). After stirring at this temperature for 2 min., a solution of **11a** (7.73 g, 20 mmol) in dry $CH_2Cl_2$ (60 ml) was added dropwise. Stirring was continued for 15 min., then triethylamine (22.5 ml, 160 mmol) was added with further stirring for 10 min. at the same temperature. The cooling bad was removed and the reaction mixture was stirred at room temp. for 3–4 h. Work-up ($CH_2Cl_2$) furnished in 50–60% overall yield a ca. 1:1 mixture of **5a** and **12a** (both yield and epimeric ratio may vary depending on minor variations in the reaction conditions), which were separated by column chromatography (hexane/EtOAc 9:1). **12a**: colourless oil, $[\alpha]_D$ +82 ($CHCl_3$, *c* 1); IR $\nu_{max}$ $cm^{-1}$: 3071, 3050, 1737 (ketone C=O), 1463, 1427, 1408, 1145, 1112, 1076, 972, 928, 862, 822, 741, 702; EIMS, *m/z* (% rel. int.): 384.1747 ($M^+$, 0.5), 327 ($M^+$−*t*Bu, 17), 297 (12), 283 (26), 267 (33), 255 ($Ph_2$*t*BuSi$O^+$, 22), 253 (56), 241 (24), 225 (20), 199 ($Ph_2SiOH^+$, 50), 183 (39), 181 (45), 177 (28), 163 (37), 135 (14), 115 (18), 105 (39). Calc. for $C_{22}H_{28}O_4Si$, M=384.1756; $^1H$ NMR (400 MHz): δ 7.70–7.60 (4H, *m*, aromatic), 7.50–7.30 (6H, *m*, aromatic), 5.67 (1H, *q*, J=5 Hz, H-2), 4.44 (1H, *d*, J=18 Hz, H-6eq), 4.33 (1H, *m*, H-4), 4.33 (1H, *d*, J=18 Hz, H-6ax), 4.11 (1H, *dd*, J=11, 3 Hz, C*H*$_2$OSi), 3.95 (1H, *dd*, J=11, 2.5 Hz, C*H*$_2$OSi), 1.44 (3H, *d*, J=5 Hz, Me–C2), 1.03 (9H, *s*, *t*Bu); $^{13}C$ NMR (100 MHz): δ 206.2 (C-5), 135.6, 135.5, 132.7, 132.3, 130.0, 129.9, 127.9, 127.8 (aromatic), 96.9 (C-2), 81.1 (C-4), 73.9 (C-6), 66.6 (*C*H$_2$OSi), 26.7, 19.2 (*t*BuSi), 20.6 (Me–C2).

*(2R,4R)-2-Methyl-4-(trityloxymethyl)-1,3-dioxan-5-one (**12b**)*

Obtained under the same conditions described above for **12a**. Work-up provided in 50–60% overall yield a ca. 1:1 mixture of **5b** and **12b** (both yield and epimeric ratio may vary depending on minor

variations in the reaction conditions), which were separated by column chromatography (hexane/EtOAc 9:1). **12b**: colourless oil, $[\alpha]_D$ +51 ($CHCl_3$, *c* 2.6); IR $\nu_{max}$ $cm^{-1}$: 3059, 1737 (ketone C=O), 1597, 1491, 1448, 1408, 1265, 1153, 1099, 909, 736, 703; EIMS, *m/z* (% rel. int.): 388.1661 ($M^+$, 1), 344 (1), 311 ($M^+-Ph$, 14), 260 ($Ph_3COH^+$, 77), 244 (99), 243 ($Ph_3C^+$, 65), 183 (73), 165 (100), 154 (42), 105 (86), 77 (59). Calc. for $C_{25}H_{24}O_4$, M=388.1674; $^1H$ NMR (200 MHz): δ 7.45–7.40 (6H, *m*, aromatic), 7.35–7.25 (9H, *m*, aromatic), 5.72 (1H, *q*, J=5 Hz, H-2), 4.47 (2H, *br s*, H-6ax, H-6eq), 4.44 (1H, *br dd*, J=4, 2.5 Hz, H-4), 3.65 (1H, *dd*, J=10, 4 Hz, $CH_2OTr$), 3.50 (1H, *dd*, J=10, 2.5 Hz, $CH_2OTr$), 1.51 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (50 MHz): δ 205.8 (C-5), 143.4, 128.6, 128.0, 127.3 (aromatic), 96.5 (C-2), 87.5 ($CPh_3$), 80.0 (C-4), 73.5 (C-6), 66.1 ($CH_2OTr$), 20.7 (Me–C2).

*(2R,4R)-2-Methyl-4-(benzyloxymethyl)-1,3-dioxan-5-one (**12c**)*

Obtained under the same conditions described above for **12a**. Work-up ($CH_2Cl_2$) provided in 50–60% overall yield a ca. 1:1 mixture of **5c** and **12c** (both yield and epimeric ratio may vary depending on minor variations in the reaction conditions), which were separated by column chromatography (hexane/EtOAc 9:1). **12c**: colourless oil, $[\alpha]_D$ +57 ($CHCl_3$, *c* 2); IR $\nu_{max}$ $cm^{-1}$: 3032, 1737 (ketone C=O), 1641, 1496, 1452, 1409, 1361, 1253, 1214, 1146, 1102, 1077, 1046, 991, 942, 862, 739, 700; FAB HRMS: 237.1131 ($M+H^+$). Calc. for $C_{13}H_{17}O_4$, M=237.1126; $^1H$ NMR (400 MHz): δ 7.40–7.25 (5H, *m*, aromatic), 5.50 (1H, *q*, J=5 Hz, H-2), 4.52 (2H, *br s*, benzyl $CH_2$), 4.42 (1H, *dd*, J=3.5, 2.5 Hz, H-4), 4.37 (1H, *d*, J=18 Hz, H-6eq), 4.27 (1H, *dd*, J=18, 1 Hz, H-6ax), 3.90 (1H, *dd*, J=10, 3.5 Hz, $CH_2OBn$), 3.81 (1H, *dd*, J=10, 2.5 Hz, $CH_2OBn$), 1.41 (3H, *d*, J=5 Hz, Me–C2); $^{13}C$ NMR (100 MHz): δ 205.9 (C-5), 137.5, 128.4, 127.8, 127.5 (aromatic), 96.5 (C-2), 79.4 (C-4), 73.7 (benzyl $CH_2$), 73.3 (C-6), 72.1 ($CH_2OBn$), 20.5 (Me–C2).

*General experimental procedures for additions of organometallic reagents to ketones **5a–c** and **12a–c***

For indications of substrate, solvent, temperature and yield, reference is always given to Tables 1 and 2. Exclusion of oxygen and moisture is assumed in all cases.

*Method A (for MeLi, Grignard reagents and $Me_3Al$)*

A solution of the appropriate ketone (1 mmol) in the indicated solvent (4 ml) is cooled to the indicated temperature. The required organometallic reagent (3 mmol) is then added dropwise, and the reaction mixture is stirred for the indicated time. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 4:1) yielded the desired product with the indicated yield and diastereoisomeric composition.

*Method B (for $Me_2CuLi$)*

CuI (228.5 mg, 1.2 mmol) was flame-dried under Ar until appearance of a yellowish colour. After cooling to 0°C, $Et_2O$ (3.5 ml) was added followed by MeLi (1.6 M in hexanes, 1.57 ml, 2.5 mmol). The solution was then cooled to −65°C and treated dropwise with a solution of the appropriate ketone (0.4 mmol) in $Et_2O$ (2 ml). The reaction mixture was warmed up to −40°C and stirred for 1 h, then warmed up to 0°C and stirred again for 1 h. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1) yielded the desired product with the indicated yield and diastereoisomeric composition.

*Method C (for $MeTi(OiPr)_3$)*

A solution of $ClTi(OiPr)_3$ (1M in hexanes, 7 ml, 7 mmol) was treated at −50°C with MeLi (1.6 M in $Et_2O$, 4.4 ml, 7 mmol). The cooling bad was removed and the mixture was stirred at room temperature for 2 h. After this, the obtained reagent solution was filtered under Ar with careful exclusion of moisture and poured directly into the flask containing the appropriate ketone (0.45 mmol). The solvent was then eliminated *in vacuo* and the oily mixture was stirred at room temperature for 60 h. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 4:1) afforded the desired product with the indicated yield and diastereoisomeric composition.

*Method D (for $Me_4Zr$)*

A suspension of $ZrCl_4$ (233 mg, 1 mmol) in THF (1.5 ml) was treated at −20°C with MeLi (1.6 M in hexanes, 2.5 ml, 4 mmol). The mixture was then stirred at the same temperature for 20 min. After this, a solution of the appropriate ketone (0.5 mmol) in THF (3 ml) was added dropwise. The reaction mixture was stirred at −20°C for 90 min. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1) afforded the desired product with the indicated yield and diastereoisomeric composition.

*(2R,4S,5R)-2,5-Dimethyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-ol (**15**)*

Formed by reaction of **5a** with methylmagnesium bromide (Table 1): colourless oil, $[\alpha]_D$ +14 ($CHCl_3$, *c* 3.5); IR $\nu_{max}$ $cm^{-1}$: 3460 (br, OH), 3072, 3050, 1471, 1428, 1362, 1112, 976, 948, 823, 740, 702; EIMS, *m/z* (% rel. int.): 400.2073 ($M^+$, 0.5), 343 ($M^+-t$Bu, 1), 299 (26), 269 ($Ph_2tBuSiOCH_2^+$, 15), 241 (37), 221 (66), 199 ($Ph_2SiOH^+$, 100), 191 ($t$BuPhSiOCH$_2^+$, 25), 163 (32), 139 (16). Calc. for $C_{23}H_{32}O_4Si$, M=400.2069; $^1$H NMR (400 MHz): δ 7.75–7.65 (4H, *m*, aromatic), 7.50–7.35 (6H, *m*, aromatic), 4.68 (1H, *q*, J=5 Hz, H-2), 3.85–3.70 (4H, non-first-order *m*, H-4, H-6eq, C$H_2$OSi), 3.53 (1H, *br d*, J=11 Hz, H-6ax), 3.40 (1H, *br s*, OH), 1.41 (3H, *s*, Me–C5), 1.28 (3H, *d*, J=5 Hz, Me–C2), 1.09 (9H, *s*, $t$Bu); $^{13}$C NMR (100 MHz): δ 135.6, 135.5, 132.3, 132.2, 130.1, 130.0, 127.9 (aromatic), 99.4 (C-2), 80.1 (C-4), 76.2 (C-6), 66.5 (C-5), 63.9 (C$H_2$OSi), 26.8, 19.1 ($t$BuSi), 20.5 (Me–C2), 20.1 (Me–C5).

*(2R,4S,5R)-2,5-Dimethyl-4-(hydroxymethyl)-1,3-dioxan-5-ol (**16**)*

A) By desilylation of **15**: a solution of **15** (400.6 mg, 1 mmol) in dry THF (25 ml) was treated with solid tetra-*n*-butylammonium fluoride trihydrate (331 mg, 1.05 mmol) and stirred at room temp. for 30 min. After adding water (1 ml), the solvent was totally eliminated *in vacuo*. Column chromatography of the residue (hexane/EtOAc 9:1, then 1:2) provided **16** (149 mg, 92%). B) By detritylation[25] of **18**: a 1.8 M solution of trifluoroacetic acid/trifluoroacetic anhydride was prepared by dissolving these reagents in the appropriate amount of dry $CH_2Cl_2$. Compound **18** (162 mg, 0.4 mmol) was then dissolved under Ar in dry $CH_2Cl_2$ (1 ml) and treated dropwise at room temperature with the aforementioned solution (0.65 ml, ca. 3 equiv). The reaction mixture turned yellow and was then cooled to 0°C, followed by addition of triethylamine (0.5 ml, 3.6 mmol). After stirring for 5 min, the reaction mixture was poured into MeOH (10 ml). Stirring was continued for 30 min. at room temp. After removal of all solvents *in vacuo*, the residue was chromatographed (hexane/EtOAc 9:1, then 1:2) to yield **16** (54 mg, 83%): colourless oil, $[\alpha]_D$ +5.4 ($CHCl_3$, *c* 1.1); IR $\nu_{max}$ $cm^{-1}$: 3400 (br, OH), 1468, 1449, 1410, 1381, 1259, 1127, 1034, 975, 942, 861, 757; EIMS, *m/z* (% rel. int.): 161.0792 ($M^+$−H, 7), 147 ($M^+$−Me, 4), 131 ($M^+-CH_2OH$, 17), 101 (81), 58 (100). Calc. for $C_7H_{13}O_4$, M=161.0813; $^1$H NMR (400 MHz): δ 4.70 (1H, *q*, J=5 Hz, H-2), 3.85–3.70 (2H, *m*, C$H_2$OH), 3.69 (1H, *d*, J=10.7 Hz, H-6eq), 3.58 (1H, *dd*, J=7, 5.5 Hz, H-4), 3.45 (1H, *br d*, J=10.7 Hz, H-6ax), 2.45 (1H, *br s*, OH), 2.35 (1H, *br s*, OH), 1.33 (3H, *d*, J=5 Hz, Me–C2), 1.32 (3H, *s*, Me–C5); $^{13}$C NMR (100 MHz): δ 99.5 (C-2), 82.2 (C-4), 76.8 (C-6), 66.1 (C-5), 61.5 (C$H_2$OH), 20.5 (Me–C2), 19.9 (Me–C5).

*(2R,4S,5R)-2,5-Dimethyl-4-(benzyloxymethyl)-1,3-dioxan-5-ol (**17**)*

A) By monobenzylation of **16**: an 80% suspension of NaH in mineral oil (72 mg, ca. 2.4 mmol of sodium hydride) was washed three times under Ar with dry hexane. Dry THF (2 ml) was then added, followed by a solution of **16** (194 mg, ca. 1.2 mmol) in dry THF (10 ml). The solution was stirred at room temp. for 30 min. Benzyl bromide (284 µl, 2.4 mmol) and $n$Bu$_4$N$^+$I$^-$ (22 mg, 0.06 mmol) were then sequentially added. The reaction mixture was stirred at room temp. for 90 min. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1) furnished **17** (256 mg, 84%) as a colourless oil: $[\alpha]_D$ +20.5 ($CHCl_3$, *c* 1.8); IR $\nu_{max}$ $cm^{-1}$: 3450 (br, OH), 3031, 1454, 1404, 1376, 1111, 976, 950, 865, 739, 700; FAB HRMS: 253.1434 (M+H$^+$). Calc. for $C_{14}H_{21}O_4$, M=253.1439; $^1$H NMR (400 MHz): δ 7.40–7.30 (5H, *m*, aromatic), 4.68 (1H, *q*, J=5 Hz, H-2), 4.58, 4.53 (2H, AB system, J=12 Hz, benzyl C$H_2$), 3.73 (1H, *dd*, J=7.5, 6.5 Hz, H-4), 3.71 (1H, *d*, J=11 Hz, H-6eq), 3.62 (2H,

*d*, J=7 Hz, C*H*$_2$OBn), 3.47 (1H, *dd*, J=11, 1 Hz, H-6ax), 2.90 (1H, *br s*, OH), 1.31 (3H, *s*, Me–C5), 1.30 (3H, *d*, J=5 Hz, Me–C2); $^{13}$C NMR (100 MHz): δ 137.1, 128.5, 128.1, 128.0 (aromatic), 99.4 (C-2), 79.5 (C-4), 76.3 (C-6), 73.9 (benzyl *C*H$_2$), 69.4 (*C*H$_2$OBn), 66.1 (C-5), 20.5 (Me–C2), 19.9 (Me–C5). B) By reaction of **5c** with methylmagnesium bromide (Table 1): the NMR data of the major product formed in this reaction were identical with those of pure **17** reported above.

*(2R,4S,5R)-2,5-Dimethyl-4-(trityloxymethyl)-1,3-dioxan-5-ol (**18**)*

Formed by reaction of **5b** with methylmagnesium bromide (Table 1): colourless oil, [α]$_D$ +4.7 ($CHCl_3$, *c* 5.1); IR $\nu_{max}$ cm$^{-1}$: 3530 (br, OH), 3054, 1491, 1449, 1420, 1265, 1121, 1059, 978, 954, 869; EIMS, *m/z*: 404.1995 (M+H$^+$). Calc. for $C_{26}H_{28}O_4$, M=404. 1987; $^1$H NMR (400 MHz): 7.50–7.40 (6H, *m*, aromatic), 7.35–7.20 (9H, *m*, aromatic), 4.69 (1H, *q*, J=5 Hz, H-2), 3.82 (1H, *dd*, J=9, 5.2 Hz, H-4), 3.71 (1H, *d*, J=11 Hz, H-6eq), 3.53 (1H, *dd*, J=9, 5.2 Hz, C*H*$_2$OTr), 3.51 (1H, *d*, J=11 Hz, H-6ax), 3.25 (1H, *br s*, OH), 3.10 (1H, *t*, J=9 Hz, C*H*$_2$OTr), 1.26 (3H, *d*, J=5 Hz, Me–C2), 1.10 (3H, *s*, Me–C5); $^{13}$C NMR (100 MHz): δ 143.1, 128.4, 128.1, 127.3 (aromatic), 99.4 (C-2), 88.0 (*C*Ph$_3$), 79.6 (C-4), 76.1 (C-6), 66.3 (C-5), 63.6 (*C*H$_2$OTr), 20.5 (Me–C2), 19.9 (Me–C5).

*(2R,3S)-4-O-Benzyl-2-methylbutane-1,2,3,4-tetraol (**19**)*

A solution of **17** (202 mg, 0.8 mmol), *p*-toluenesulphonic acid hydrate (15 mg, 0.08 mmol) and 1,2-ethanedithiol (0.67 ml, 8 mmol) in dry $CHCl_3$ (6 ml) was heated at reflux for 3 h. Work-up ($CH_2Cl_2$) and column chromatography (hexane/EtOAc 1:1, then EtOAc) provided **19** (134 mg, 74%): colourless oil, [α]$_D$ −8.2 ($CHCl_3$, *c* 1.5); IR $\nu_{max}$ cm$^{-1}$: 3420 (br, OH), 1452, 1360, 1259, 1050, 900, 875, 736; FABMS: 227.1278 (M+H$^+$). Calc. for $C_{12}H_{19}O_4$, M=227.1283; $^1$H NMR (400 MHz): δ 7.40–7.30 (5H, *m*, aromatic), 4.56 (2H, *s*, benzyl C*H*$_2$), 3.78 (1H, *dd*, J=6.5, 4.5 Hz, H-3), 3.69 (1H, *dd*, J=9.5, 4.5 Hz, H-4), 3.66 (1H, *d*, J=11 Hz, H-1), 3.59 (1H, *dd*, J=9.5, 6.5 Hz, H-4′), 3.43 (1H, *d*, J=11 Hz, H-1′), 1.14 (3H, *s*, Me); $^{13}$C NMR (100 MHz): 137.3, 128.6, 128.0, 127.9 (aromatic), 74.0 (C-3), 73.8 (benzyl *C*H$_2$), 73.5 (C-2), 70.8 (C-4), 67.7 (C-1), 20.4 (Me).

*(2R,3S)-1,3,4-Tri-O-benzyl-2-methylbutane-1,2,3,4-tetraol (**20**)*

Triol **19** (113 mg, 0.5 mmol) was benzylated as described above for **16**→**17**. Work-up ($Et_2O$) and column chromatography (hexane/EtOAc 9:1) provided 160 mg (79%) of **20** as a colourless oil: [α]$_D$ +10.2 ($CHCl_3$, *c* 6); IR $\nu_{max}$ cm$^{-1}$: 3440 (br, OH), 3088, 3064, 3030, 1454, 1265, 1097, 1028, 909, 736, 700; FABMS: 407.2223 (M+H$^+$). Calc. for $C_{26}H_{31}O_4$, M=407.2222; $^1$H NMR (200 MHz): δ 7.45–7.30 (15H, *m*, aromatic), 4.86, 4.59 (2H, AB system J=11.5 Hz, benzyl C*H*$_2$), 4.56 (2H, *s*, benzyl C*H*$_2$), 4.52 (2H, *s*, benzyl C*H*$_2$), 3.93 (1H, *dd*, J=9, 2.5 Hz, H-3), 3.79 (1H, *dd*, J=9, 6.5 Hz, H-4), 3.72 (1H, *dd*, J=9, 6.5 Hz, H-4′), 3.62 (1H, *d*, J=9 Hz, H-1), 3.31 (1H, *d*, J=9 Hz, H-1′), 1.17 (3H, *s*, Me); $^{13}$C NMR (50 MHz): 138.8, 138.2, 138.0, 128.4, 128.3, 127.8, 127.7, 127.5, (aromatic), 80.5 (C-3), 74.9 (C-1), 73.7, 73.6, 73.4 (benzyl *C*H$_2$+C-2), 71.3 (C-4), 19.7 (Me).

*(2R,4S,5R)-5-Ethyl-2-methyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-ol (**21**)*

Formed by reaction of **5a** with ethylmagnesium bromide (Table 1): colourless oil, [α]$_D$ −5.6 ($CHCl_3$, *c* 2.5); IR $\nu_{max}$ cm$^{-1}$: 3440 (br, OH), 3072, 1462, 1428, 1402, 1113, 998, 823, 739, 702; EIMS, *m/z* (% rel. int.): 414.2214 (M$^+$, 0.5), 413 (1), 313 (24), 283 (15), 241 (34), 235 (68), 205 (21), 199 (Ph$_2$SiOH$^+$, 100), 163 (28), 139 (16). Calc. for $C_{24}H_{34}O_4Si$, M=414.2226; $^1$H NMR (400 MHz): δ 7.75–7.65 (4H, *m*, aromatic), 7.50–7.35 (6H, *m*, aromatic), 4.70 (1H, *q*, J=5 Hz, H-2), 4.02 (1H, *d*, J=11 Hz, H-6eq), 3.85–3.75 (3H, non-first-order *m*, H-4, C*H*$_2$OSi), 3.33 (1H, *dd*, J=11, 1 Hz, H-6ax), 3.15 (1H, *br s*, OH), 1.97 (1H, *sext*, J=7.5 Hz, C*H*$_2$Me), 1.57 (1H, *sext*, J=7.5 Hz, C*H*$_2$Me), 1.26 (3H, *d*, J=5 Hz, Me–C2), 1.08 (9H, *s*, *t*Bu), 1.03 (3H, *t*, J=7.5 Hz, CH$_2$*Me*); $^{13}$C NMR (100 MHz): δ 135.6, 135.5, 132.2, 130.1, 130.0, 127.9 (aromatic), 99.5 (C-2), 80.8 (C-4), 71.2 (C-6), 68.0 (C-5), 63.5 (*C*H$_2$OSi), 26.8, 19.1 (*t*BuSi), 23.4 (*C*H$_2$Me), 20.5 (Me–C2), 6.8 (CH$_2$*Me*).

*(2R,4S,5R)-5-Ethyl-2-methyl-4-(hydroxymethyl)-1,3-dioxan-5-ol (22)*

A) By desilylation of **21**: as described above for **15→16** (85% yield). B) By detritylation of **24**: as described above for **18→16** (72% yield): colourless oil, $[\alpha]_D$ −13 ($CHCl_3$, *c* 5.6); IR $\nu_{max}$ $cm^{-1}$: 3420 (br, OH), 1451, 1409, 1264, 1129, 1042, 909, 734; FABMS: 177.1116 ($M+H^+$). Calc. for $C_8H_{17}O_4$, M=177.1126; $^1H$ NMR (200 MHz): δ 4.73 (1H, *q*, J=5 Hz, H-2), 3.99 (1H, *d*, J=11 Hz, H-6eq), 3.90–3.60 (3H, *m*, H-4, $CH_2OH$), 3.25 (1H, *br d*, J=11 Hz, H-6ax), 2.95 (1H, *br s*, OH), 1.97 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.44 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.33 (3H, *d*, J=5 Hz, Me–C2), 0.97 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (50 MHz): δ 99.7 (C-2), 83.5 (C-4), 71.7 (C-6), 67.7 (C-5), 60.9 ($CH_2OH$), 23.3 ($CH_2Me$), 20.5 (Me–C2), 6.8 ($CH_2Me$).

*(2R,4S,5R)-5-Ethyl-2-methyl-4-(benzyloxymethyl)-1,3-dioxan-5-ol (23)*

A) By monobenzylation of **22**: as described above for **16→17** (95% yield): colourless oil: $[\alpha]_D$ −2.1 ($CHCl_3$, *c* 1.4); IR $\nu_{max}$ $cm^{-1}$: 3500 (br, OH), 3054, 1454, 1406, 1266, 1108, 952, 897, 865, 739; FABMS: 267.1603 ($M+H^+$). Calc. for $C_{15}H_{23}O_4$, M=267.1596; $^1H$ NMR (400 MHz): δ 7.40–7.30 (5H, *m*, aromatic), 4.70 (1H, *q*, J=5 Hz, H-2), 4.56, 4.52 (2H, AB system, J=12 Hz, benzyl $CH_2$), 3.99 (1H, *d*, J=11.2 Hz, H-6eq), 3.79 (1H, *dd*, J=8, 6.2 Hz, H-4), 3.66 (1H, *dd*, J=9, 8 Hz, $CH_2OBn$), 3.60 (1H, *dd*, J=9, 6.2 Hz, $CH_2OBn$), 3.26 (1H, *dd*, J=11.2, 1.5 Hz, H-6ax), 2.65 (1H, *br s*, OH), 1.94 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.40 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.30 (3H, *d*, J=5 Hz, Me–C2), 0.96 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): δ 137.1, 128.5, 128.0, 127.9 (aromatic), 99.5 (C-2), 80.3 (C-4), 73.9 (benzyl $CH_2$), 71.3 (C-6), 69.0 ($CH_2OBn$), 67.6 (C-5), 23.3 ($CH_2Me$), 20.5 (Me–C2), 6.7 ($CH_2Me$). B) By reaction of **5c** with ethylmagnesium bromide (Table 1): the NMR data of the major product formed in this reaction were identical with those of pure **23** reported above.

*(2R,4S,5R)-5-Ethyl-2-methyl-4-(trityloxymethyl)-1,3-dioxan-5-ol (24)*

Formed by reaction of **5b** with ethylmagnesium bromide (Table 1): colourless oil, $[\alpha]_D$ −3.6 ($CHCl_3$, *c* 5.5); IR $\nu_{max}$ $cm^{-1}$: 3530 (br, OH), 3059, 3032, 1597, 1499, 1401, 1223 1125, 1001, 899, 765, 746, 706; EIMS, *m/z* (% rel. int.): 418.2133 ($M^+$, 0.5), 341 ($M^+-Ph$, 1.5), 243 ($Ph_3C^+$, 100), 165 (24), 115 (10). Calc. for $C_{27}H_{30}O_4$, M=418.2144; $^1H$ NMR (400 MHz): δ 7.50–7.40 (6H, *m*, aromatic), 7.35–7.20 (9H, *m*, aromatic), 4.72 (1H, *q*, J=5 Hz, H-2), 4.00 (1H, *d*, J=11.3 Hz, H-6eq), 3.89 (1H, *dd*, J=9.2, 5.2 Hz, H-4), 3.53 (1H, *dd*, J=9.2, 5.2 Hz, $CH_2OTr$), 3.30 (1H, *dd*, J=11.3, 1 Hz, H-6ax), 3.15 (1H, *t*, J=9.2, Hz, $CH_2OTr$), 2.95 (1H, *br s*, OH), 1.73 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.26 (3H, *d*, J=5 Hz, Me–C2), 1.06 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 0.87 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): δ 143.1, 128.4, 128.1, 127.8, 127.3 (aromatic), 99.5 (C-2), 88.0 ($CPh_3$), 80.5 (C-4), 71.1 (C-6), 67.8 (C-5), 63.1 ($CH_2OTr$), 23.1 ($CH_2Me$), 20.5 (Me–C2), 6.7 ($CH_2Me$).

*(2R,3S)-4-O-Benzyl-2-ethylbutane-1,2,3,4-tetraol (25)*

From **23** by acetal cleavage as described above for **17→19** (53% yield): colourless oil, $[\alpha]_D$ −11.5 ($CHCl_3$, *c* 0.34); IR $\nu_{max}$ $cm^{-1}$: 3420 (br, OH), 1643, 1454, 1065, 891, 736, 700; EIMS, *m/z* (% rel. int.): 209.1193 ($M^+-CH_2OH$, 3), 179 (8), 107 (10), 91 (100). Calc. for $M^+-CH_2OH$ ($C_{12}H_{17}O_3$), M=209.1177; $^1H$ NMR (200 MHz): δ 7.35–7.20 (5H, *m*, aromatic), 4.56, 4.52 (2H, AB system, J=12 Hz, benzyl $CH_2$), 3.90–3.40 (5H, *m*, H-1, H-1′, H-3, H-4, H-4′), 1.70–1.50 (2H, *m*, $CH_2Me$), 0.88 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (50 MHz): 137.5, 128.6, 128.1, 127.9 (aromatic), 75.3 (C-2), 73.7 (benzyl $CH_2$), 73.5 (C-3), 71.0 (C-4), 65.5 (C-1), 26.3 ($CH_2Me$), 7.4 (Me).

*(2R,3S)-1,3,4-Tri-O-benzyl-2-ethylbutane-1,2,3,4-tetraol (26)*

Triol **25** was benzylated as described above for **16→17** (83% yield): colourless oil, $[\alpha]_D$ +9 ($CHCl_3$, *c* 2.6); IR $\nu_{max}$ $cm^{-1}$: 3500 (br, OH), 3088, 3065, 3030, 1588, 1454, 1111, 1028, 736, 700; EIMS, *m/z* (% rel. int.): 299.1674 ($M^+-CH_2OBn$, 14), 281 ($M^+-CH_2OBn-H_2O$, 11), 223 (16), 205 (20), 188 (24), 181 (96), 177 (100), 134 (22), 115 (33), 91 (74), 65 (29). Calc. for $M^+-CH_2OBn$ ($C_{19}H_{23}O_3$), M=299.1647; $^1H$ NMR (400 MHz): δ 7.45–7.25 (15H, *m*, aromatic), 4.86, 4.58 (2H, AB system, J=11.5 Hz, benzyl $CH_2$), 4.54, 4.51 (2H, AB system, J=12 Hz, benzyl $CH_2$), 4.49, 4.46 (2H, AB

system, J=12 Hz, benzyl $CH_2$), 3.88 (1H, *dd*, J=10, 3 Hz, H-4), 3.79 (1H, *dd*, J=6.5, 3 Hz, H-3), 3.71 (1H, *dd*. J=10, 6.5 Hz, H-4′), 3.54 (1H, *d*, J=9 Hz, H-1), 3.40 (1H, *d*, J=9 Hz, H-1′), 2.85 (1H, *br s*, OH), 1.75–1.60 (2H, *m*, $CH_2$Me), 0.89 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}$C NMR (100 MHz): 138.8, 138.2, 138.1, 128.4, 128.3, 128.2, 127.7, 127.5 (aromatic), 81.0 (C-3), 75.3 (C-2), 73.7, 73.5, 73.4 (benzyl $CH_2$), 72.0 (C-1), 71.2 (C-4), 26.1 ($CH_2$Me), 7.4 (Me).

*(2R,4R,5R)-2,5-Dimethyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-ol (27)*

Formed by reaction of **12a** with methylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +8.8 ($CHCl_3$, *c* 5.5); IR $\nu_{max}$ cm$^{-1}$: 3450 (br, OH), 3071, 1472, 1427, 1404, 1390, 1361, 1112, 822, 739, 702; EIMS, *m/z* (% rel. int.): 400.2063 ($M^+$, 0.5), 399 (0.5), 299 (91), 269 ($Ph_2tBuSiOCH_2^+$, 58), 241 (94), 221 (56), 199 ($Ph_2SiOH^+$, 78), 191 ($t$BuPhSiOCH$_2^+$, 100), 183 (46), 163 (94), 139 (386), 135 (42). Calc. for $C_{23}H_{32}O_4Si$, M=400.2069; $^1$H NMR (400 MHz): δ 7.75–7.65 (4H, *m*, aromatic), 7.50–7.35 (6H, *m*, aromatic), 5.08 (1H, *q*, J=5.5 Hz, H-2), 4.12 (1H, *dd*, J=11, 5.5 Hz, $CH_2$OSi), 3.88 (1H, *dd*, J=11, 5.5 Hz, $CH_2$OSi), 3.78 (1H, *t*, J=5.5 Hz, H-4), 3.66, 3.60 (2H, AB system, J=11.5 Hz, H-6eq, H-6ax), 3.35 (1H, *br s*, OH), 1.30 (3H, *d*, J=5.5 Hz, Me–C2), 1.29 (3H, *s*, Me–C5), 1.06 (9H, *s*, $t$Bu); $^{13}$C NMR (100 MHz): δ 135.6, 132.7, 132.6, 130.0, 129.9, 127.8 (aromatic), 94.1 (C-2), 76.9 (C-4), 70.8 (C-6), 67.4 (C-5), 63.0 ($CH_2$OSi), 26.8, 19.1 ($t$BuSi), 23.9 (Me–C5), 18.2 (Me–C2).

*(2R,4R,5R)-2,5-Dimethyl-4-(hydroxymethyl)-1,3-dioxan-5-ol (28)*

A) By desilylation of **27**: as described above for **15**→**16** (96% yield). B) By detritylation of **30**: as described above for **18**→**16** (76% yield): colourless oil, $[\alpha]_D$ +17 ($CHCl_3$, *c* 0.8); IR $\nu_{max}$ cm$^{-1}$: 3580 (br, OH), 1421, 1265, 1084, 909, 737; EIMS, *m/z* (% rel. int.): 161.0820 ($M^+$−H, 2), 147 ($M^+$−Me, 14), 131 ($M^+$−$CH_2OH$, 47), 101 (91), 87 (51), 58 (100). Calc. for $C_7H_{13}O_4$, M=161.0813; $^1$H NMR (400 MHz): δ 5.19 (1H, *q*, J=5.5 Hz, H-2), 3.90 (2H, *br d*, J=5.5 Hz, $CH_2$OH), 3.77 (1H, *t*, J=5.5 Hz, H-4), 3.68, 3.55 (1H, AB system, J=11.5 Hz, H-6ax, H-6eq), 3.35 (1H, *br s*, OH), 1.37 (3H, *d*, J=5.5 Hz, Me–C2), 1.26 (3H, *s*, Me–C5); $^{13}$C NMR (100 MHz): δ 94.2 (C-2), 76.3 (C-4), 69.9 (C-6), 67.6 (C-5), 60.9 ($CH_2$OH), 22.8 (Me–C5), 17.3 (Me–C2).

*(2R,4R,5R)-2,5-Dimethyl-4-(benzyloxymethyl)-1,3-dioxan-5-ol (29)*

A) By monobenzylation of **28**: as described above for **16**→**17** (76% yield). B) By reaction of **12c** with methylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +15.5 ($CHCl_3$, *c* 1.6); IR $\nu_{max}$ cm$^{-1}$: 3410 (br, OH), 3054, 1453, 1441, 1406, 1265, 1114, 896, 738, 704; FAB HRMS: 253.1437 (M+H$^+$). Calc. for $C_{14}H_{21}O_4$, M=253.1439; $^1$H NMR (400 MHz): δ 7.40–7.25 (5H, *m*, aromatic), 5.17 (1H, *q*, J=5.5 Hz, H-2), 4.57, 4.55 (2H, AB system, J=12 Hz, benzyl $CH_2$), 3.90 (2H, *m*, H-4, $CH_2$OBn), 3.74 (1H, *dd*, J=11.5, 6.5 Hz, $CH_2$OBn), 3.68, 3.61 (2H, AB system, J=11.5 Hz, H-6eq, H-6ax), 3.05 (1H, *br s*, OH), 1.36 (3H, *d*, J=5.5 Hz, Me–C2), 1.28 (3H, *s*, Me–C5); $^{13}$C NMR (100 MHz): δ 137.5, 128.5, 127.9, 127.8 (aromatic), 94.2 (C-2), 76.0 (C-4), 73.6 (benzyl $CH_2$), 70.7 (C-6), 69.2 ($CH_2$OBn), 67.1 (C-5), 23.6 (Me–C5), 18.1 (Me–C2).

*(2R,4R,5R)-2,5-Dimethyl-4-(trityloxymethyl)-1,3-dioxan-5-ol (30)*

Formed by reaction of **12b** with methylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +5.5 ($CHCl_3$, *c* 1.9); IR $\nu_{max}$ cm$^{-1}$: 3420 (br, OH), 1550, 1447, 1406, 1217, 1149, 1103, 1076, 1045, 991, 942, 761, 705; EIMS, *m/z* (% rel. int.): 404.1995 ($M^+$, 0.5), 327 ($M^+$−Ph, 3), 259 (14), 243 ($Ph_3C^+$, 71), 228 (14), 215 (11), 183 (24), 165 (100), 161 (55), 131 (16), 105 (33), 101 (30), 77 (16), 58 (26). Calc. for $C_{26}H_{28}O_4$, M=404.1987; $^1$H NMR (400 MHz): δ 7.50–7.40 (6H, *m*, aromatic), 7.35–7.20 (9H, *m*, aromatic), 5.07 (1H, *q*, J=5.5 Hz, H-2), 3.87 (1H, *t*, J=5.5 Hz, H-4), 3.60 (1H, *d*, J=12 Hz, H-6eq), 3.55 (1H, *dd*, J=10.5, 5.5 Hz, $CH_2$OTr), 3.47 (1H, *dd*, J=10.5, 5.5 Hz, $CH_2$OTr), 3.46 (1H, *d*, J=12 Hz, H-6ax), 3.00 (1H, *br s*, OH), 1.35 (3H, *d*, J=5.5 Hz, Me–C2), 1.22 (3H, *s*, Me–C5); $^{13}$C NMR (100 MHz): δ 143.5, 128.6, 128.0, 127.2 (aromatic), 94.0 (C-2), 87.5 ($CPh_3$), 76.3 (C-4), 70.6 (C-6), 67.1 (C-5), 62.2 ($CH_2$OTr), 23.8 (Me–C5), 18.2 (Me–C2).

*(2R,3R)-4-O-Benzyl-2-methylbutane-1,2,3,4-tetraol (31)*

From **29** by acetal cleavage as described above for **17**→**19** (60% yield): colourless oil, $[\alpha]_D$ +6.4 ($CHCl_3$, *c* 1.1); IR $\nu_{max}$ $cm^{-1}$: 3380 (br, OH), 1454, 1370, 1258, 1051; FABMS: 227.1280 ($M+H^+$). Calc. for $C_{12}H_{19}O_4$, M=227.1283; $^1H$ NMR (200 MHz): δ 7.40–7.25 (5H, *m*, aromatic), 4.56 (2H, *br s*, benzyl $CH_2$), 3.80–3.40 (5H, *br m*, H-1, H-1′, H-3, H-4, H-4′), 1.10 (3H, *s*, Me); $^{13}C$ NMR (50 MHz): 137.5, 128.6, 128.1, 128.0 (aromatic), 74.3 (C-3), 73.8 (benzyl $CH_2$), 73.1 (C-2), 70.9 (C-4), 69.0 (C-1), 20.6 (Me).

*(2R,3R)-1,3,4-Tri-O-benzyl-2-methylbutane-1,2,3,4-tetraol (32)*

Triol **31** was benzylated as described above for **16**→**17** (80% yield): colourless oil, $[\alpha]_D$ −2.6 ($CHCl_3$, *c* 0.4); IR $\nu_{max}$ $cm^{-1}$: 3580 (br, OH), 3054, 1421, 1265, 1096, 909, 737; FABMS: 407.2208 ($M+H^+$). Calc. for $C_{26}H_{31}O_4$, M=407.2222; $^1H$ NMR (200 MHz): δ 7.45–7.25 (15H, *m*, aromatic), 4.86, 4.60 (2H, AB system J=11.5 Hz, benzyl $CH_2$), 4.55 (2H, *s*, benzyl $CH_2$), 4.52 (2H, *s*, benzyl $CH_2$), 3.90–3.65 (3H, *m*, H-3, H-4, H-4′), 3.53 (1H, *d*, J=9 Hz, H-1), 3.39 (1H, *d*, J=9 Hz, H-1′), 3.00 (1H, *br s*, OH), 1.25 (3H, *s*, Me); $^{13}C$ NMR (50 MHz): 138.6, 138.3, 138.1, 128.5, 128.4, 128.0, 127.7 (aromatic), 80.9 (C-3), 74.8 (C-1), 73.8, 73.5, 73.4 (benzyl $CH_2$+C-2), 70.7 (C-4), 22.0 (Me).

*(2R,4R,5R)-5-Ethyl-2-methyl-4-(t-butyldiphenylsilyloxymethyl)-1,3-dioxan-5-ol (33)*

Formed by reaction of **12a** with ethylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +14.5 ($CHCl_3$, *c* 4); IR $\nu_{max}$ $cm^{-1}$: 3480 (br, OH), 3054, 1463, 1427, 1265, 1145, 1112, 909, 737, 704; EIMS, *m/z* (% rel. int.): 414.2230 ($M^+$, 0.5), 413 (0.5), 313 (54), 283 (22), 241 (44), 235 (100), 205 (23), 199 ($Ph_2SiOH^+$, 87), 163 (18), 139 (8). Calc. for $C_{24}H_{34}O_4Si$, M=414.2226; $^1H$ NMR (400 MHz): δ 7.75–7.65 (4H, *m*, aromatic), 7.50–7.35 (6H, *m*, aromatic), 4.97 (1H, *q*, J=5 Hz, H-2), 4.22 (1H, *dd*, J=10.7, 5.5 Hz, $CH_2OSi$), 3.93 (1H, *dd*, J=10.7, 5.5 Hz, $CH_2OSi$), 3.86 (1H, *t*, J=5.5 Hz, H-4), 3.75, 3.67 (2H, AB system, J=11.5 Hz, H-6eq, H-6ax), 1.79 (2H, *m*, $CH_2Me$), 1.25 (3H, *d*, J=5 Hz, Me–C2), 1.07 (9H, *s*, *t*Bu), 0.95 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): δ 135.6, 132.6, 132.5, 130.0, 127.9, 127.8 (aromatic), 94.0 (C-2), 75.7 (C-4), 69.2 (C-6), 68.9 (C-5), 62.8 ($CH_2OSi$), 26.8, 19.1 (*t*BuSi), 29.6 ($CH_2Me$), 19.5 (Me–C2), 6.9 ($CH_2Me$).

*(2R,4R,5R)-5-Ethyl-2-methyl-4-(hydroxymethyl)-1,3-dioxan-5-ol (34)*

A) By desilylation of **33**: as described above for **15**→**16** (80% yield). B) By detritylation of **36**: as described above for **18**→**16** (95% yield): colourless oil, $[\alpha]_D$ +17.5 ($CHCl_3$, *c* 0.7); IR $\nu_{max}$ $cm^{-1}$: 3600 (br, OH), 1421, 1409, 1265, 1101, 1046, 896, 738; FAB HRMS: 177.1122 ($M+H^+$). Calc. for $C_8H_{17}O_4$, M=177.1126; $^1H$ NMR (400 MHz): δ 5.17 (1H, *q*, J=5.5 Hz, H-2), 3.95 (2H, *br d*, J=5.5 Hz, $CH_2OH$), 3.85 (1H, *t*, J=5.5 Hz, H-4), 3.77 (1H, *d*, J=11.5 Hz, H-6eq), 3.60 (1H, *d*, J=11.5 Hz, H-6ax), 2.55 (1H, *br s*, OH), 2.25 (1H, *br s*, OH), 1.80–1.65 (2H, *m*, $CH_2Me$), 1.37 (3H, *d*, J=5.5 Hz, Me–C2), 0.95 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): δ 94.0 (C-2), 75.4 (C-4), 69.5 (C-5), 68.1 (C-6), 60.8 ($CH_2OH$), 28.7 ($CH_2Me$), 18.1 (Me–C2), 6.7 ($CH_2Me$).

*(2R,4R,5R)-5-Ethyl-2-methyl-4-(benzyloxymethyl)-1,3-dioxan-5-ol (35)*

A) By monobenzylation of **34**: as described above for **16**→**17** (63% yield). B) By reaction of **12c** with ethylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +18.5 ($CHCl_3$, *c* 1.6); IR $\nu_{max}$ $cm^{-1}$: 3560 (br, OH), 3054, 1421, 1265, 1145, 1100, 896, 738; FABMS: 267.1606 ($M+H^+$). Calc. for $C_{15}H_{23}O_4$, M=267.1596; $^1H$ NMR (400 MHz): δ 7.40–7.30 (5H, *m*, aromatic), 5.08 (1H, *q*, J=5.5 Hz, H-2), 4.58, 4.54 (2H, AB system, J=12 Hz, benzyl $CH_2$), 3.94 (2H, *m*, H-4, $CH_2OBn$), 3.79 (1H, *dd*, J=12, 7 Hz, $CH_2OBn$), 3.75, 3.64 (2H, AB system, J=11.2 Hz, H-6eq, H-6ax), 2.90 (1H, *br s*, OH), 1.94 (2H, *q*, J=7.5 Hz, $CH_2Me$), 1.32 (3H, *d*, J=5.5 Hz, Me–C2), 0.93 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): δ 137.4, 128.5, 128.0, 127.8 (aromatic), 94.1 (C-2), 74.9 (C-4), 73.7 (benzyl $CH_2$), 69.1 (C-6, $CH_2OBn$), 68.7 (C-5), 29.3 ($CH_2Me$), 19.1 (Me–C2), 6.8 ($CH_2Me$).

*(2R,4R,5R)-5-Ethyl-2-methyl-4-(trityloxymethyl)-1,3-dioxan-5-ol (36)*

Formed by reaction of **12b** with ethylmagnesium bromide (Table 2): colourless oil, $[\alpha]_D$ +5 ($CHCl_3$, *c* 2.8); IR $\nu_{max}$ $cm^{-1}$: 3460 (br, OH), 1459, 1375, 1245, 1047, 939, 917, 899, 847, 739; EIMS, *m/z* (% rel. int.): 341.1761 ($M^+-Ph$, 2), 244 (100), 243 ($Ph_3C^+$, 99), 175 (34), 165 (73), 145 (22), 115 (24), 72 (21), 57 (32). Calc. for $C_{21}H_{25}O_4$, M=341.1752; $^1H$ NMR (400 MHz): δ 7.50–7.40 (6H, *m*, aromatic), 7.35–7.20 (9H, *m*, aromatic), 4.94 (1H, *q*, J=5.5 Hz, H-2), 3.95 (1H, *t*, J=5.5 Hz, H-4),. 3.67 (1H, *d*, J=11.5 Hz, H-6eq), 3.60 (1H, *dd*, J=10, 5.5 Hz, $CH_2OTr$), 3.52 (1H, *dd*, J=10, 5.5 Hz, $CH_2OTr$), 3.44 (1H, *d*, J=11.5 Hz, H-6ax), 2.85 (1H, *br s*, OH), 1.75 (2H, *m*, $CH_2Me$), 1.30 (3H, *d*, J=5.5 Hz, Me–C2), 0.91 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (50 MHz): δ 143.4, 128.6, 128.0, 127.2 (aromatic), 93.8 (C-2), 87.6 ($CPh_3$), 75.5 (C-4), 68.8 (C-6), 68.6 (C-5), 62.0 ($CH_2OTr$), 29.4 ($CH_2Me$), 19.3 (Me–C2), 6.8 ($CH_2Me$).

*(2R,3R)-4-O-Benzyl-2-ethylbutane-1,2,3,4-tetraol (37)*

From **35** by acetal cleavage as described above for **17→19** (53% yield): colourless oil, $[\alpha]_D$ +6.5 ($CHCl_3$, *c* 1.5); IR $\nu_{max}$ $cm^{-1}$: 3420 (br, OH), 1642, 1454, 1259, 1064, 891, 736, 700; EIMS, *m/z* (% rel. int.): 209.1174 ($M^+-CH_2OH$, 6), 107 (11), 91 (100). Calc. for $C_{12}H_{17}O_3$, M=209.1177; $^1H$ NMR (400 MHz): δ 7.40–7.25 (5H, *m*, aromatic), 4.56, 4.54 (2H, AB system, J=12 Hz, benzyl $CH_2$), 3.85 (1H, *br t*, J=3.5 Hz, H-3), 3.75–3.65 (3H, *br m*, H-1, H-4, H-4′), 3.53 (1H, *br d*, J=11.5 Hz, H-1′), 3.10 (1H, *br s*, OH), 2.90 (1H, *br s*, OH), 1.60 (1H, *sext*, J=7.5 Hz, $CH_2Me$), 1.40 (1H, *m*, $CH_2Me$), 0.89 (3H, *t*, J=7.5 Hz, $CH_2Me$); $^{13}C$ NMR (100 MHz): 137.3, 128.6, 128.1, 127.9 (aromatic), 74.4 (C-2), 73.8 (benzyl $CH_2$), 73.6 (C-3), 70.6 (C-4), 66.1 (C-1), 26.9 ($CH_2Me$), 7.5 ($CH_2Me$).

*(2R,3R)-1,3,4-Tri-O-benzyl-2-ethylbutane-1,2,3,4-tetraol (38)*

Triol **37** was benzylated as described above for **16→17** (83% yield): colourless oil, $[\alpha]_D$ −9.3 ($CHCl_3$, *c* 0.1); IR $\nu_{max}$ $cm^{-1}$: 3550 (br, OH), 3054, 1588, 1453, 1421, 1266, 1096, 911, 737; EIMS, *m/z* (% rel. int.): 299.1660 ($M^+-CH_2OBn$, 14), 281. ($M^+-CH_2OBn-H_2O$, 3), 243 (7), 223 (6), 181 (39), 177 (24), 115 (6), 91 (100), 65 (7). Calc. for $C_{19}H_{23}O_3$, M=299.1647; $^1H$ NMR (400 MHz): δ 7.35–7.20 (15H, *m*, aromatic), 4.82 (1H, *d*, J=11.5 Hz, benzyl $CH_2$), 4.55 (1H, *d*, J=11.5 Hz, benzyl $CH_2$), 4.53, 4.50 (2H, AB system, J=12 Hz, benzyl $CH_2$), 4.47 (2H, *s*, benzyl $CH_2$), 3.84 (1H, *dd*, J=10, 3 Hz, H-4), 3.76 (1H, *dd*, J=6, 3 Hz, H-3), 3.69 (1H, *dd*, J=10, 6 Hz, H-4′), 3.45 (2H, *s*, H-1, H-1′), 2.80 (1H, *br s*, OH), 1.60 (2H, *m*, $CH_2Me$), 0.88 (3H, *t*, J=7.5 Hz, *Me*); $^{13}C$ NMR (100 MHz): 138.7, 138.1, 128.4, 128.3, 127.9, 127.7, 127.6 (aromatic), 80.4 (C-3), 75.5 (C-2), 73.7, 73.5, 73.4 (benzyl $CH_2$), 71.7 (C-1), 70.8 (C-4), 26.9 ($CH_2Me$), 7.4 (Me).

**Acknowledgements**

The authors thank the Spanish Ministry of Education and Science (DGICYT projects PB2-0745) and BANCAJA (project B-10-CE) for financial support of this research.

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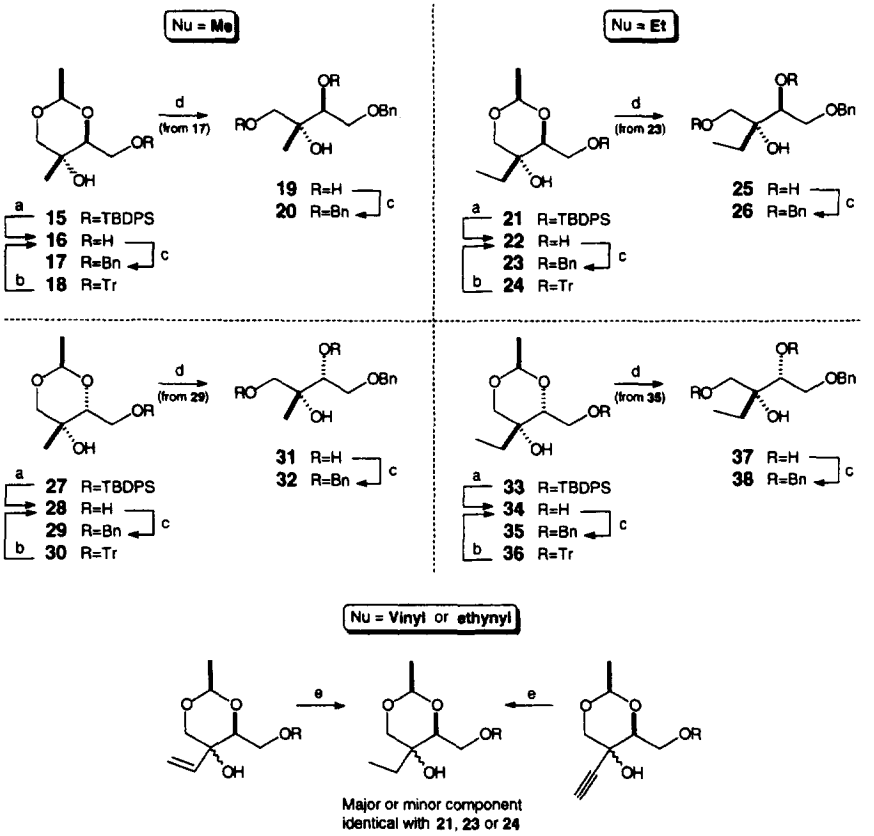


**Reaction conditions.** a) TBAF, THF, room temp., 30 min. b) TFA, TFAA, room temp., then $Et_3N$, MeOH. c) NaH, BnBr, THF, room temp. d) 1,2-ethanedithiol, TsOH, $CHCl_3$, reflux. e) $H_2$, 5% Pd/C, EtOAc, room temp.


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15. For the establishment of configurations, the chemical correlations depicted below were performed. Since only addition products with Nu=Me and Et and 5*R* configuration were obtained in a high stereoisomeric purity (≥95% de), these are given specific numbers in the Scheme above (**15–18**, **21–24**, **27–30** and **33–36**). Compounds **15–18** and **21–24** were then correlated as described below with compounds **20** and **26** of known absolute configuration.[1,26,27] Addition products with Nu=vinyl and ethynyl, which were mixtures of two stereoisomers, were hydrogenated to the corresponding C-ethyl products. Either the major (ethynyl) or the minor (vinyl) component

of the mixture of hydrogenated products was found identical with one of compounds **21**, **23** or **24**. Compounds **27–30** and **33–36** were correlated with compounds **32** and **38**. The absolute configurations of the two latter compounds were deduced from the fact that they were neither identical nor enantiomeric to, respectively, **20** and **26**.

16. In ketones **5a–c**, clear NOEs (8%) were observed between H-2 and H-4 (heterocycle numbering), which must therefore be axial. In ketones **12a–c**, however, NOEs were detected between H-2 and the $CH_2OR$ hydrogens.
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*(Received in UK 5 December 1996)*