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Stereoselective allylations of erythrulose derivatives under anhydrous conditions

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Abstract—We have investigated a number of nucleophilic additions of allylating reagents to several α,α′,β-trioxygenated ketones (*O*-protected erythrulose derivatives). Reagents based on lithium, magnesium, copper and titanium gave low to medium stereoselectivities and did not display any recognizable trend in the sense of stereoselection. In contrast, reactions involving silicon and tin derivatives were highly stereoselective and gave rise to essentially a single diastereoisomer, the structure of which depended on the type of protecting group. Thus, α,β-di-*O*-benzylated derivatives experienced almost exclusive addition to the carbonyl Si side, whereas α,β-*O*,*O*-alkylidene derivatives (dioxolane acetals) yielded the opposite diastereoisomers as a result of addition to the Re side. These results suggest the intermediacy of α-chelates in the additions of silicon and tin reagents to the di-*O*-benzylated derivatives. In contrast, the opposite stereoisomers, formed in the reactions of dioxolanes, are believed to be formed through Felkin–Anh transition states, pointing again to the reluctance of acetal oxygens to participate in chelated intermediates. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Carbohydrates, particularly monosaccharides, represent one of the most convenient chiral sources in the synthesis of enantiopure compounds.[1] The ketotetrose L-(*S*)-erythrulose and its derivatives[2] of general formula **1** (R^1, R^2, R^3 = protecting groups) are useful additions to the list of chiral precursors of this type. The carbonyl group of **1** is a prominent site for the appendage of additional carbon fragments through nucleophilic addition. The selection of suitable protecting groups is important, as they exert a control on the steric course of nucleophilic additions.[3] The literature contains a great deal of studies on stereoselective additions of *C*-nucleophiles to polyoxygenated aldehydes.[4] However, the corresponding behavior of highly functionalized ketones such as **1** (Scheme 1) is less documented.[2d,5] We have recently described the stereochemical outcome of many organometallic additions to the carbonyl groups of several protected erythrulose derivatives of the type **1**.[6] The diastereoselectivity of these reactions proved strongly dependent on the type of hydroxyl protecting group. In fact, addition processes involving Grignard reagents and some specifically protected ketones **1** were particularly diastereoselective as well as extremely fast. This was attributed to the intermediacy of reactive five-membered α-chelates involving the metal, the carbonyl oxygen and the α-oxygen atoms, a conclusion supported by quantum-mechanical calculations.[7] In contrast, no conclusive evidence could be gathered to substantiate the intermediacy of six-membered β-chelates in these additions, in spite of the demonstrated existence of such chelates.[8] Since the stereoisomer predicted in this case was the same as that predicted by the Felkin–Anh model, this was chosen as the preferred explanation of the stereochemical outcome in those cases where the intermediacy of an α-chelate was excluded.

It is worth mentioning here that, among the many organometallic additions to derivatives **1** investigated, those of allylating reagents gave unsatisfactory stereoselectivities in many cases.[6a] Still, nucleophilic addition of allyl appendages to aldehydes, ketones or their imino derivatives often constitutes a convenient feature in

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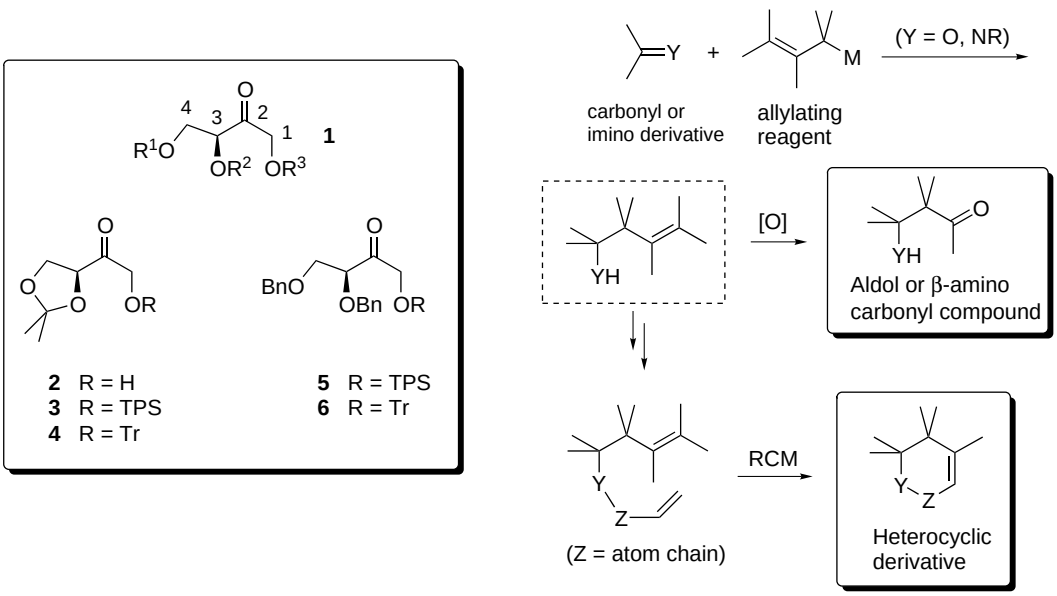
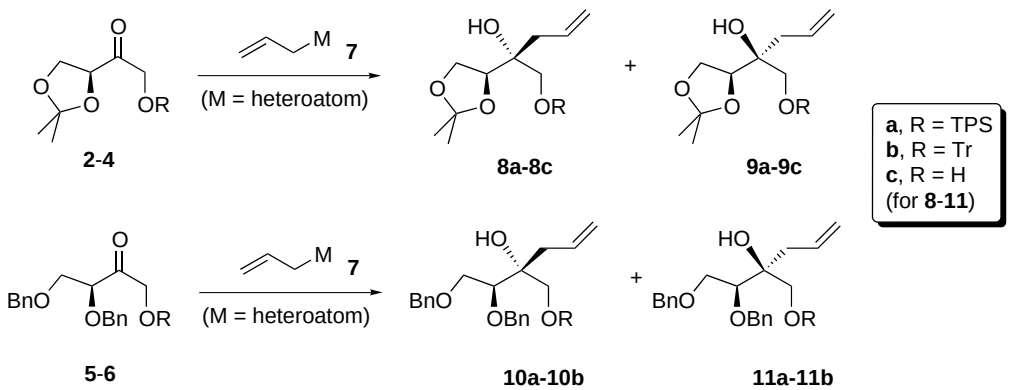
synthetic designs; the C=C bond of the allyl moiety may be later manipulated in various ways, for example, via oxidative cleavage to a functionalized fragment bearing alcohol or carbonyl groups (equivalent of aldol addition), via intramolecular ring-closing metathesis (RCM) to heterocyclic systems,[9] etc. (Scheme 1). Such strategies have proven useful in our syntheses of some naturally occurring molecules.[10] We have thus investigated in detail the influence of the allylation conditions (heteroelement and protecting group type, addition of Lewis acids, etc.) in the stereoselectivity of the reaction. The substrates selected for this purpose were L-erythrulose derivatives **2**–**6** (Scheme 1), the preparation of which has recently been reported.[6a,11] These ketones were subjected to a range of nucleophilic allylating reagents **7**[12] under various reaction conditions. Our purpose was to find reaction conditions suitable for the preparation of allylation products of either configuration in the newly generated stereogenic center (Scheme 2). Herein, we describe these results in detail.

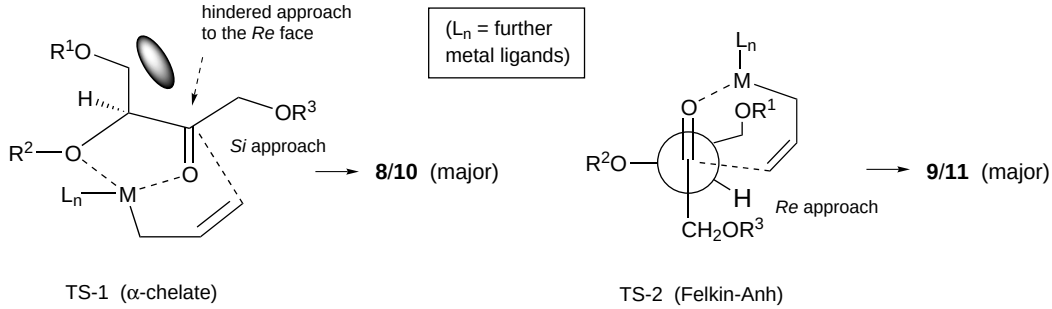
As in our previous publication,[6a] we wished to determine the extent to which the stereoselectivity of nucleophilic additions would be controlled by either Cram-type chelation mechanisms involving the various oxygen atoms or by transition states of the Felkin–Anh type.[3,13] In the case of Lewis acidic allyl heteroatomic derivatives, the transfer of the allyl moiety takes place through a cyclic, six-membered transition state of the metallo-ene type (the concomitant inversion of the allyl residue is not relevant in the case of the unsubstituted allyl moiety). As depicted in Scheme 3, the five-membered α-chelate is predicted to react from the less hindered *Si* side of the carbonyl group (TS-1), leading predominantly to stereoisomers **8** or **10**. The alternative stereoisomers **9** or **11**, derived from attack on the *Re* side, are expected to be the major products when the non-chelated Felkin–Anh transition state TS-2 is operating (on the basis of our previous experiences with protected erythruloses,[6a] we have discarded here the intermediacy of β-chelates).



Scheme 1.



Scheme 2. Addition of nucleophilic allylating reagents **7** to erythruloses **2**–**6**.



Scheme 3. Transition states during addition of Lewis acidic allyl metal reagents to erythrulose derivatives.

2. Results and discussion

As in the compounds described in our previous work, the oxygen atom of the primary hydroxyl group at C(1) in the erythrulose derivatives (e.g. **3**–**6**) was blocked using various protecting groups. We later found, however, that some allylating reagents could actually be used in the presence of the free OH group at C(1). For this reason, acetonide **2**[11] was also included in the list.

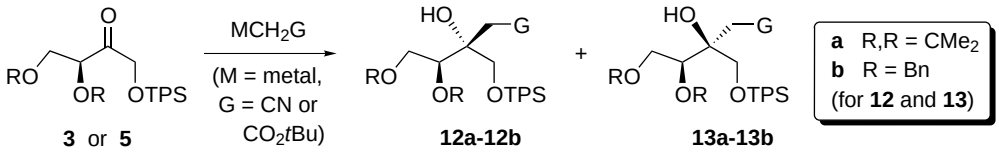
The additions of Li and Mg allyl reagents to ketones **3** and **5** were briefly mentioned in our previous report.[6a] A more detailed account is presented in Table 1. These allyl metal reagents did not give very high diastereomeric ratios in their reactions with ketones **3**–**6**. The erratic behavior of the lithium reagents toward erythrulose derivatives, either of the acetonide or of the dibenzyl type, was already noted. It seems that the lithium atom is not particularly prone to participate in α-chelates in the reactions under study; in fact, the Felkin–Anh stereoisomers **9** and **11** were the major products formed, albeit with low diastereoisomeric ratios (entries 1–4). More surprising, however, were the similarly low diastereoisomeric ratios found with Grignard reagents. Furthermore, while acetonides **3** and **4** displayed low diastereoisomeric ratios with predominance of the Felkin–Anh stereoisomer **9**, the benzylated derivatives **5** and **6** gave a slightly higher percentage of Cram's α-chelation stereoisomer **10** (entries 5–8). The latter result was particularly unexpected as non-allyl Grignard reagents had previously given very high diastereoisomeric ratios in their reactions with **5** and **6**,[6a] most likely via TS-1 (Scheme 3, M = Mg). This behavior does not extend to allylmagnesium bromide, perhaps because the non-chelated TS-2 has a decreased energy barrier and becomes thus more competitive in this case.

In relation to one of our research projects, we also investigated the aldol-type reactions of **3** and **5** with equivalents of acetate enolate. Even though an acetate appendage can also be obtained through oxidative cleavage of the double bond of an allyl moiety (Scheme 1), a stereoselective aldol reaction of this type would constitute a shorter and thus more convenient route. Enolates of *t*-butyl acetate were first selected for this purpose (Scheme 4). After investigating the influence of a number of factors (solvent, temperature, presence of additives), the best conditions in terms of yield and stereoselectivity were those indicated in the last three entries of Table 1. Additives such as HMPA or DMPU were not beneficial as they markedly reduced the reaction rate without changing the diastereoisomeric ratio to any relevant extent. Transmetalation of lithium to magnesium, zinc or titanium enolates was similarly not useful, either, as this led mainly to recovery of the starting material at −78°C or to decomposition at higher temperatures. Equally unsuccessful was the use

Table 1. Stereoselectivity in the additions of allyl lithium, allylmagnesium bromide and acetic acid enolate equivalents to erythrulose derivatives **3**–**6**[a]

Entry	Ketone	Reagent	Solvent	% Yield	**8**:**9** or **10**:**11**[b]
1	**3**	AllylLi[c]	THF/Et_2O	85	22:78
2	**4**	AllylLi[c]	THF/Et_2O	88	1:3
3	**5**	AllylLi[c]	THF/Et_2O	87	3:7
4	**6**	AllylLi[c]	THF/Et_2O	90	2:3
5	**3**	AllylMgBr	Et_2O	90	1:4
6	**4**	AllylMgBr	Et_2O	85	32:68
7	**5**	AllylMgBr	Et_2O	86	67:33
8	**6**	AllylMgBr	Et_2O	95	3:2
9	**3**	$LiCH_2CO_2tBu$	Et_2O	78	1:9[d]
10	**5**	$LiCH_2CO_2tBu$	Et_2O	95	1:4[d]
11	**5**	$LiCH_2CN$	THF	70	24:76[d]

[a] In all cases, 2.5 equiv. of the nucleophile were added at −78°C to the appropriate ketone in the indicated solvent.
[b] Determined by means of ^1H and ^{13}C NMR.
[c] Prepared according to Ref. 25.
[d] Ratio **12**:**13**, see Scheme 4 and comments in the text.



Scheme 4. Addition of acetic acid enolate equivalents to erythruloses **3** and **5**.

of the dianion of acetic acid. The lithium anion of acetonitrile gave results similar to those observed with the anion of *tert*-butyl acetate. In all cases where a reaction was observed, the Felkin–Anh stereoisomers **13a** or **13b** were the major products. However, the observed diastereoisomeric ratios were not high.

We then turned our attention to other allyl metal derivatives. Among these, titanium, copper and zinc seemed to be the metals of choice for our purposes. Four different types of titanium reagents[14] were assayed on ketones **3** and **5** (Table 2). Good yields were obtained in all cases but the degrees of diastereoselectivity were too variable (with diastereoisomeric ratios of between 1:1 and 12:88 and the Felkin–Anh isomers predominating). The allyl copper reagent[15] displayed a somewhat better degree of diastereoselection, particularly in the case of acetonide **3**. Here again, the Felkin–Anh isomer was the major compound formed. This contrasts with the reactions of the same ketones with non-allylic cuprates, in which the major products were the isomers predicted from chelation control.[6a] Finally, both ketones proved unreactive toward allyl zinc derivatives prepared either by insertion of zinc into the C–Br bond of allyl bromide,[16a,b] or by transmetalation of allylmagnesium bromide with zinc chloride in THF.[16c]

The best results in terms of stereoselectivity were eventually obtained with allyl trimethylsilane[12,17] or allyl tri-*n*-butylstannane[12] in the presence of suitable Lewis acids[4g,18] (Table 3). Reactions with allyl trimethylsilane were unsuccessful with ketones **2**–**4**: strong Lewis acids such as $TiCl_4$ or $SnCl_4$ caused the decomposition of the acetonide moiety, whereas less strong Lewis acids such as the etherates of BF_3 or $MgBr_2$ were unable to promote the reaction. With $TiCl_2(O\text{-}iso\text{-}Pr)_2$, the only result observed was electrophilic attack at the acetonide moiety with concomitant ring opening.[19] Basic catalysis met also with failure (entry 1): partial decomposition was the only result in the reaction of **2** with allyl trimethylsilane in the presence of tetra-*n*-butylammonium fluoride.[20] In contrast with these failures, ketone **5** displayed an excellent stereoselectivity in its reaction with allyl trimethylsilane in the presence of $SnCl_4$ ($TiCl_4$ was similarly effective) as the minor isomer **11a** was not detected by high-field NMR (entry 2). The stereoisomer which was formed, **10a**, was that predicted by Cram's cyclic chelation model. It is thus likely that the bidentate Lewis acid $SnCl_4$ first forms a five-membered chelate with ketone **5** (Scheme 5), and the chelate is then intermolecularly attacked by the allyl silane. The closely related ketone **6** was expected to behave in the same way, but its somewhat labile protecting group did not survive the Lewis acidic reaction conditions (entry 3).

The more reactive allyl tri-*n*-butylstannane was able to allylate either type of ketone under mild conditions. Even with the mild Lewis acid $MgBr_2{\cdot}Et_2O$ as the promoter, clean and highly stereoselective reactions were observed at –40°C. In the case of **5** and **6**, single

Table 2. Stereoselectivity in the additions of allyl copper, titanium and zinc reagents to erythrulose derivatives **3** and **5**

Entry	Ketone	Reagent	Solvent	*T* (°C)	% Yield	**8**:**9** or **10**:**11**[a]
1	**3**	$AllylTiCl_3$[b]	Toluene/Et_2O	rt	81	3:7
2	**3**	$AllylTiCl(OiPr)_2$[c]	Et_2O	−40→rt	73	27:73
3	**3**	$AllylTi(OiPr)_3$[d]	THF	rt	79	36:64
4	**3**	$AllylTi(OiPr)_4^-$[e]	THF	−10	84	32:68
5	**3**	AllylCuLi[f]	THF	−78→−40	92	6:94
6	**3**	AllylZnBr[g]	THF	–[g]	–[g]	–
7	**5**	$AllylTiCl_3$[b]	Toluene/Et_2O	rt	79	12:88
8	**5**	$AllylTiCl(OiPr)_2$[c]	Et_2O	−40→rt	91	27:73
9	**5**	$AllylTi(OiPr)_3$[d]	THF	rt	89	~1:1
10	**5**	$AllylTi(OiPr)_4^-$[e]	THF	−10	88	27:73
11	**5**	AllylCuLi[f]	THF	−78→−40	94	19:81
12	**5**	AllylZnBr[g]	THF	–[g]	–[g]	–

[a] Determined by means of ^1H and ^{13}C NMR.
[b] Prepared according to a modification of the procedure described in Ref. 14c.
[c] Prepared according to Ref. 14d.
[d] Prepared according to Ref. 14e.
[e] Prepared according to Ref. 14b.
[f] Prepared according to Ref. 15b.
[g] Prepared under various conditions according to Refs. 16a–c, but no reaction took place.

Table 3. Stereoselective additions of allyl silicon and tin reagents to erythrulose derivatives **2**–**6**[a]

Entry	Ketone	Reagent	T (°C)/t (h)	% Yield	**8**:**9** or **10**:**11**[b]
1	**2**	$AllylSiMe_3/TBAF$[c]	−78→−10/5	Dec.	–
2	**5**	$AllylSiMe_3/SnCl_4$	−78→−40/6	80	>19:1
3	**6**	$AllylSiMe_3/SnCl_4$	−78→−40/6	–[d]	–
4	**2**	$AllylSnBu_3/MgBr_2$[e]	−78→−40/4	60	<1:19
5	**3**	$AllylSnBu_3/MgBr_2$[e]	−78→−40/4	80	<1:19
6	**3**	$AllylSnBu_3/LiClO_4$[f]	25/72	86	3:7
7	**4**	$AllylSnBu_3/MgBr_2$[e]	−78→−40/4	85	<1:19
8	**5**	$AllylSnBu_3/MgBr_2$[e]	−78→−40/4	80	>19:1
9	**6**	$AllylSnBu_3/MgBr_2$[e]	−78→−40/4	85	>19:1

[a] In all cases except entry 1, 1.2 equiv. of the organometallic reagent was added to a mixture of the appropriate ketone and the Lewis acid (1.2 equiv.) in dry CH_2Cl_2.

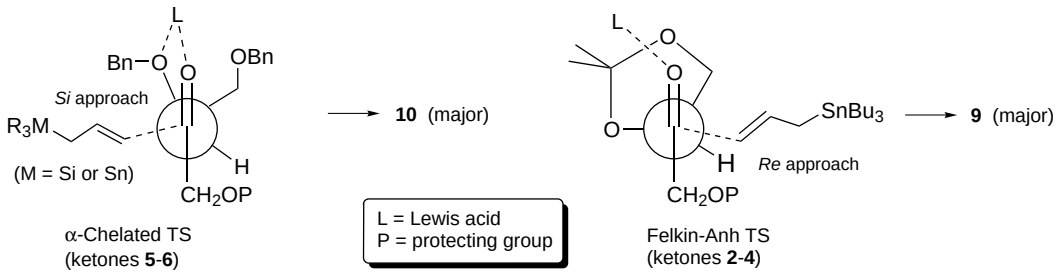
[b] Determined by means of ^1H and ^{13}C NMR (d.r.>19:1 or <1:19 means that NMR signals from the minor isomer were not visible).

[c] TBAF and $allylSiMe_3$ (1.4 equiv. each) were added in dry THF to ketone **2** at the indicated temperature.

[d] Cleavage of the trityl group took place.

[e] The monodentate Lewis acid $BF_3{\cdot}Et_2O$ not only gave inferior yields and d.r.s, but also caused cleavage of the trityl protecting group in ketones **4** and **6**. Strong Lewis acids ($TiCl_4$, $SnCl_4$) caused decomposition of the acetonide moiety in ketones **2**–**4**.

[f] Solvent was either Et_2O or CH_2Cl_2.

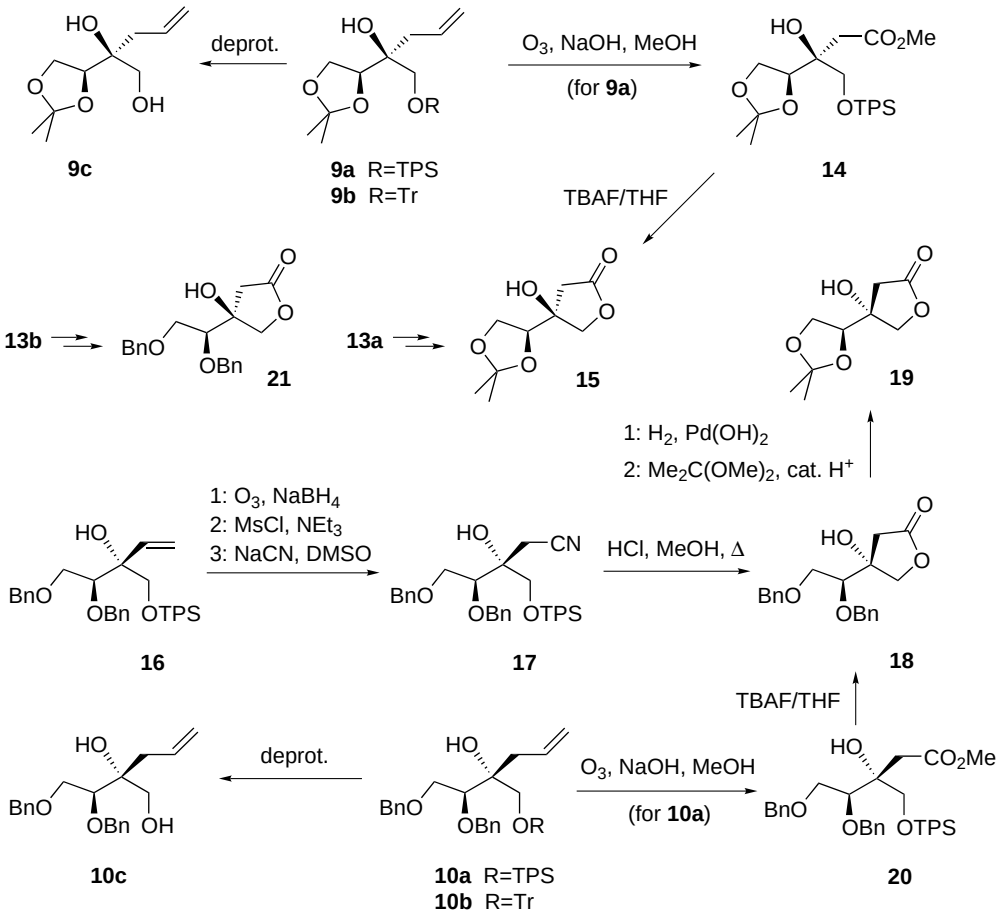


Scheme 5. Transition states in Lewis acid promoted addition of allyl silanes/stannanes to erythrulose derivatives.

stereoisomers were obtained (**10a** and **10b**, respectively) with the configuration corresponding to that predicted by Cram's cyclic chelation model (entries 8 and 9). Here again, the mechanistic model of Scheme 5 may be applied. It is worth mentioning that the monodentate Lewis acid $BF_3{\cdot}Et_2O$, which cannot form chelates, gave poorer results in terms of both yield and stereoselectivity.

On the basis of these findings, we were surprised by the results observed in the reactions of the allylstannane with acetonides **2**–**4** (entries 4, 5 and 7). Ketones **3** and **4**, which have a very bulky protecting group at the OH at C(1), gave rise to only one diastereoisomer in each case, **9a** and **9b**, which are those predicted by the Felkin–Anh model (Scheme 5). The same result was observed when the Lewis acid $MgBr_2{\cdot}Et_2O$ was replaced by $TiCl_2(O\text{-}iso\text{-}Pr)_2$.[19] Interestingly, ketone **2**, bearing an unprotected C(1) hydroxyl group, gave rise to the Felkin–Anh diastereoisomer **9c**. In an attempt to invert the stereochemical bias of the acetonide-protected erythruloses, we also used $LiClO_4$ as the Lewis acid[18a–c] in either Et_2O or CH_2Cl_2 as the solvent. Unfortunately, the reactions were poorly selective and very slow even at room temperature.

The configurations of the diastereoisomers formed in the aforementioned reactions have been established with the aid of unambiguous chemical correlations (Scheme 6). Compound **9a**, obtained from **3** and allyl tri-*n*-butylstannane (Table 3, entry 5) was converted in two steps into lactone **15** via β-hydroxy ester **14**. The NMR data of **15** were similar, although not identical, to those of lactone **19**, obtained as described below. The known compound **16**,[6a] prepared by reaction of ketone **5** with vinyl magnesium bromide, was transformed in four steps into lactone **18** via cyanohydrin **17**. The absolute configuration of **18** was confirmed by means of X-ray diffraction analysis.[21] Lactone **18** was also obtained from allylation product **10a**, a fact which establishes the configuration of the new stereogenic center formed in the allylations of **5** (Table 3, entries 2 and 8). Two simple reactions on **18** transformed it into lactone **19**, not identical with **15**, as commented above. Finally, the configurations of the other products of the allylation of ketones **2**–**4** and **5**–**6** were established through cleavage of the protecting group to yield in all cases the same diols, **9c** and **10c**, respectively. The configurations of the products formed in the aldol reaction of **5** with the carbanion of acetonitrile (Scheme 4) were established by comparison of their NMR data with those of **17**, which turned out to be identical with the minor component of the mixture. Likewise, the mixture of stereoisomers formed in the aldol reactions with acetic ester enolates were converted by reaction with TBAF into a mixture of the stereoisomeric lactones **15** (major) and **19** (minor) in the case of **3**, and lactone **18** (minor) and its stereoisomer **21** (major) in the case of **5**.



Scheme 6. Chemical correlations between allylation products.

Consideration of the overall results in Tables 1–3 leads to some general conclusions. The chelation isomers (Cram) **8**/**10** are formed with a very high diastereoisomeric ratio with allyl silane or stannane and the *O*-benzylated ketones **5** and **6** in the presence of a bidentate Lewis acid.[4g,18] It is thus likely that α-chelates are formed in these cases and there is a great deal of experimental evidence[3,13] for their intermediacy in carbonyl additions. In contrast, the Felkin–Anh isomers **9**/**11** were formed with a very high diastereoisomeric ratio only in acetonides **2**–**4**, where the intermediacy of an α-chelate would not have been otherwise excluded in principle. These results should be now viewed in light of previous observations on nucleophilic additions to 2,3-*O*-isopropylidene glyceraldehyde and its 2,3-di-*O*-benzyl analogue.[22] In all of the cases examined, the acetonide was clearly the less diastereoselective compound, with the major stereoisomer being the opposite of that predicted by the α-chelation model. In order to explain this, it has been proposed[22a] that glyceraldehyde acetonide reacts mainly under non-chelation control because of: (a) a too high chelate energy content due to appreciable ring strain and to non-bonded interactions of the acetonide geminal methyl groups with metal ligands (cf. TS-1 in Scheme 3), and/or (b) a depressed donor ability of the acetonide α-oxygen atom owing to the mutual electron-withdrawing inductive effect by the other oxygen atom. Of these explanations, the second one seems more likely to us in view of existing experimental evidence.[23] It is also worth mentioning that even ketone **2** with an unprotected OH at C(1) reacts very stereoselectively under these conditions. This reinforces our view of the absence of chelation with acetonides, as it has been shown that α,α′-oxygenated ketones often display low diastereoselectivities in cases where chelation at both sides of the carbonyl group is possible.[24]

3. Conclusions

In summary, we have been able to perform highly stereoselective nucleophilic allylations of α,α′,β-trioxygenated ketones of the type described above. Either of the two possible diastereoisomeric tertiary alcohols were obtained by means of a simple change in the type of protecting group. When the α-oxygen atom bears substituents (e.g. benzyl) which do not prevent the formation of Cram-type five-membered chelates, nucleophilic attack will take place from the less hindered face of the carbonyl group, leading in most cases to very high stereoselectivities. If these conditions are not met (e.g. insufficient Lewis basicity of the α-oxygen atom on steric and/or electronic grounds, absence or insufficient acidity of bidentate Lewis acids, including the heteroatom in the allylating reagent), the Felkin–Anh stereoisomer will normally predominate albeit to an extremely variable and non-predictable extent.

4. Experimental

4.1. General methods

^{1}H NMR spectra (400 or 500 MHz) and ^{13}C NMR spectra (100 or 125 MHz) were measured at 22°C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ7.25 for ^{1}H NMR data and the triplet centered at 77.00 ppm for ^{13}C NMR data). Unambiguous assignments of ^{1}H and ^{13}C NMR signals were made with a combination of spin decoupling, DEPT and HMQC experiments. Mass spectra were run in a VG AutoSpec mass spectrometer using either the electron impact mode (EIMS, 70 eV), the chemical ionization mode (CIMS, with CH_4 as the carrier gas) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix). Samples for IR spectral measurements were prepared as oily films on NaCl plates (oils) or KBr pellets (solids). Optical rotations were measured at 22°C. The diastereoisomeric composition was determined by means of high-field ^{1}H and ^{13}C NMR of the crude reaction mixture just prior to chromatography.

Column chromatography (CC) was performed on silica gel Süd-Chemie AG (60–200 μm). Experiments which required an inert atmosphere were carried out under dry argon (Ar) in a flame-dried glassware. THF and Et_2O were freshly distilled from sodium/benzophenone ketyl and were transferred via syringe. Toluene was freshly distilled from sodium wire. Methylene chloride was distilled from P_2O_5 and stored over 4 Å molecular sieves. Commercially available reagents (Aldrich or Fluka) were used as received. If not detailed otherwise, the work-up of the reactions was consistently performed in the following manner: the reaction mixture was poured into brine and extracted twice with solvent (Et_2O, CH_2Cl_2 or EtOAc), the organic layer was washed with diluted aq. NH_4Cl and then washed again with brine, the organic layer was dried over anhydrous $MgSO_4$ or Na_2SO_4, and the solvent was eliminated with a rotary evaporator at aspirator pressure. The starting ketones **2**–**6** were prepared according to described procedures.[6a,11]

4.2. General experimental procedures for allylations of ketones 2–6

All synthetic operations were performed under careful exclusion of oxygen and moisture. All solvents used in synthetic operations were dried according to the aforementioned procedures. Yields and diastereoisomeric compositions are indicated in Tables 1–3.

4.3. Addition of allyl lithium[25]

Lithium wire (125 mg, 18 mmol) was cut and washed with hexane and THF. Further THF (2 ml) was added followed by rapid stirring and cooling to −15°C. A solution of allyl phenyl ether (206 μl, 1.5 mmol) in Et_2O (2 ml) was then added via syringe. Stirring was then continued for 15 min at the same temp., wherein a pale bluish-green color appeared. After further stirring for 15–20 min at room temp., the solution turned dark red. The mixture was then re-cooled to −78°C and allowed to stand. An aliquot of this solution (3.5 ml) was carefully taken with a syringe and added dropwise to a solution of the appropriate ketone (0.5 mmol) in THF (5 ml) at the same temperature. The reaction mixture was then stirred for 1 h. Work-up (CH_2Cl_2) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product.

4.4. Addition of allyl magnesium bromide

A solution of the appropriate ketone (1 mmol) in Et_2O (10 ml) was cooled to −78°C. A solution of allyl magnesium bromide (1 M commercial solution in Et_2O, 2.5 ml) was then added dropwise at the same temp., and the reaction mixture was stirred for 1 h. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product.

4.5. Addition of allyl titanium reagents[14]

4.5.1. AllylTiCl$_3$. A solution of titanium tetrachloride in toluene (1 M, 2.7 ml, 2.7 mmol) was added dropwise at 0°C to a solution of allyl magnesium chloride in Et_2O (1 M, 13.5 ml, 13.5 mmol). The solution was then diluted with dry toluene (30 ml) and stirred, wherein it turned dark blue. An aliquot of this solution (0.6 ml) was added dropwise at 0°C to a solution of the appropriate ketone (0.2 mmol) in dry toluene (2 ml). After removal of the cooling bath, the mixture was stirred overnight at room temp. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product, together with 70% of recovered starting material. Chemical yields are based on recovered material.

4.5.2. AllylTiCl(*O*-*iso*-Pr)$_2$. Titanium tetra-*iso*-propoxide (4.43 ml, 15 mmol) and allyl bromide (1.3 ml, 15 mmol) were dissolved in Et_2O (10 ml), cooled to –40°C and treated at this temp. with a solution of *iso*-propyl magnesium chloride in Et_2O (2 M, 15 ml, 30 mmol). After stirring at –40°C for 1 h, a solution of the appropriate ketone (1 mmol) in Et_2O was added. The stirring was continued for 30 min at –40°C and then overnight at room temp. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product.

4.5.3. AllylTi(*O*-*iso*-Pr)$_3$. A solution of chlorotitanium tri-*iso*-propoxide in hexanes (1 M, 10 ml, 10 mmol) was treated at −78°C with allyl magnesium bromide (1 M in THF, 10 ml, 10 mmol). After stirring for 30 min at the same temp., the appropriate ketone (1 mmol) dissolved in THF (10 ml) was added dropwise. After stirring for 30 min, the cooling bath was removed and the mixture was stirred overnight at room temp. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) afforded the desired allylation product.

4.5.4. AllylTi(*O-iso*-Pr)$_4^-$. A solution of allyl magnesium chloride in THF (1 M, 18 ml, 18 mmol) was treated at −78°C with titanium tetra-*iso*-propoxide (5.9 ml, 20 mmol). The formation of the orange 'ate' complex was complete after stirring for 30 min at the same temp. The appropriate ketone (1 mmol) dissolved in THF (10 ml) was then added dropwise, the temperature was increased to −10°C and the mixture was stirred for 5 h at this temperature. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) afforded the desired allylation product.

4.6. Addition of allyl copper reagent[15]

A mixture of CuI (400 mg, 2.10 mmol) and anhydrous LiCl (89 mg, 2.10 mmol) was gently heated under Ar. After cooling at room temp., THF (2 ml) was added. The mixture was stirred for 5 min and cooled to −78°C. A solution of allyl lithium, freshly prepared by reaction of MeLi (1.6 M in hexanes, 1.25 ml, 2 mmol) with allyl tri-*n*-butyltin (0.62 ml, 2 mmol) at −78°C, was added to the CuCl/LiCl solution at the same temp. The mixture was then stirred for 30 min, wherein it turned dark brown. The appropriate ketone (0.7 mmol) dissolved in THF (2 ml) was then added dropwise, and the temperature was slowly increased to −40°C. The reaction mixture was stirred overnight at this temperature. Work-up (Et_2O) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product.

4.7. Addition of allyl zinc reagents

The allylzinc reagents were prepared as described in the literature by: (a) insertion of Rieke Zn into the C–Br bond of allyl bromide,[16a] followed by reaction in anhydrous THF at −78°C (4 h). (b) in situ generation by reaction of Zn with allyl bromide under Barbier conditions,[16b] including sonication, followed by reaction in anhydrous THF at room temp. (6 h). (c) Transmetallation of zinc chloride with allyl magnesium chloride,[16c] followed by reaction in anhydrous THF at room temp. (6 h). In none of these conditions could a reaction be observed.

4.8. Addition of allyl silane and allyl stannane in the presence of Lewis acids

Molecular sieves (4 Å) were added at room temp. to a solution of the appropriate ketone (1 mmol) in CH_2Cl_2 (2 ml). The solution was then stirred for 10 min at room temp. and cooled to −78°C. The appropriate Lewis acid (1.2 mmol) dissolved in CH_2Cl_2 (2 ml) was then added dropwise at the same temperature. The stirring was continued for 10 min, followed by addition of a solution of allyl trimethyl silane or allyl tri-*n*-butyl stannane (1.2 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was then stirred for about 6 h (allyl silane) or 4 h (allyl stannane) (TLC monitoring). During this time the temperature was slowly increased to −40°C. Work-up (CH_2Cl_2) and column chromatography (hexane/EtOAc mixtures) yielded the desired allylation product. With $TiCl_2(OiPr)_2$ as the Lewis acid, the reaction was conducted for 5 h at −10°C. With $LiClO_4$, the reaction was conducted for 72 h at room temperature (in this case, Et_2O and CH_2Cl_2 gave essentially the same result).

4.9. Addition of acetonitrile and *tert*-butyl acetate enolates

This was completed as previously described.[6a]

4.10. Desilylation of 9a and 10a to 9c and 10c, respectively

A solution of **9a** (440 mg, 1 mmol) in dry THF (5 ml) was treated with solid tetra-*n*-butylammonium fluoride hydrate (288 mg, 1.1 mmol) and stirred under Ar at room temp. for 30 min. After adding water (1 ml), the volatiles were totally eliminated in vacuo. CC of the residue (hexane/EtOAc 9:1, then 7:3) provided **9c** (170 mg, 84%). The same procedure was used to convert **10a** to **10c** (90%).

4.11. Detritylation of 9b and 10b to 9c and 10c, respectively

Method A. 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.[26] Compound **9b** (178 mg, 0.4 mmol) was then dissolved in dry CH_2Cl_2 (2 ml) and treated dropwise at room temperature under Ar with 0.65 ml of the aforementioned solution (ca. 1.2 mmol). 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 7:3) to yield **9c** (65 mg, 80%). Method B. Compound **10b** (292 mg, 0.5 mmol) was dissolved in a 1:1 MeOH/THF mixture (5 ml) and treated with conc. HCl (0.1 ml). The mixture was then stirred at room temp. for 18 h. After addition of solid Na_2CO_3 (210 mg, 2 mmol), the mixture was stirred for further 5 min and evaporated in vacuo. CC of the residue on silica gel (hexane–EtOAc 9:1, then 7:3) furnished **10c** (140 mg, 82%).

4.12. Ozonolysis of 9a in basic medium to yield methyl ester 14

A solution of alcohol **9a** (220 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) was cooled to −78°C and treated with methanolic NaOH (2.5 M, 1 ml). Ozone (O_2/O_3) was then bubbled through the solution for 30 min. After eliminating the residual ozone by bubbling Ar through the solution, the reaction mixture was worked up (CH_2Cl_2) and chromatographed on silica gel (hexane–EtOAc 8:2) to afford ester **14** (196 mg, 83%). The same procedure was used to convert **10a** to **20** (80%).

4.13. Desilylation of 14 with concomitant ring closure to lactone 15

A solution of ester **14** (472 mg, 1 mmol) in dry THF (5 ml) was treated with solid tetra-*n*-butylammonium fluoride hydrate (288 mg, 1.1 mmol) and stirred under Ar at room temp. for 45 min. After eliminating the volatiles at reduced pressure, CC of the residue on silica gel (hexane/EtOAc 8:2, then 7:3) provided lactone **15** (136 mg, 67%). The same procedure was used to convert ester **20** to lactone **18** (64%).

4.14. Conversion of vinyl carbinol 16 to nitrile 17

A solution of vinyl carbinol **16**[6a] (567 mg, 1 mmol) in dry CH_2Cl_2 (10 ml) was cooled to −78°C. Ozone (O_2/O_3) was then bubbled through the solution for 45 min. After eliminating the residual ozone by bubbling Ar through the reaction mixture, a solution of $NaBH_4$ (190 mg, 5 mmol) in EtOH (5 ml) was added dropwise with subsequent removal of the cooling bath. After reaching room temperature, the reaction mixture was stirred for further 2 h and worked up (CH_2Cl_2) to furnish a crude diol, which was directly subjected to mesylation.

The diol obtained above was dissolved in dry CH_2Cl_2 (5 ml), cooled to −30°C and treated under Ar with mesyl chloride (78 μl, 1 mmol), triethyl amine (210 μl, 1.5 mmol) and DMAP (122 mg, 1 mmol). The reaction mixture was stirred for 2 h at −30°C, then for 5 h at 0°C. Work-up (CH_2Cl_2) gave a crude mesylate which was used in the next reaction.

A solution of the crude mesylate and NaCN (122 mg, 2.5 mmol) in dry DMSO (5 ml) was heated at 55° for 18 h. After cooling to room temp., the reaction mixture was poured onto brine and extracted with EtOAc. The organic layer was back-washed with brine and dried on anhydrous Na_2SO_4. After solvent removal, the residue was chromatographed on silica gel (hexane–EtOAc 7:3) to yield nitrile **17** (348 mg, 60% overall from **16**).

4.15. Hydrolysis of 17 to lactone 18

Nitrile **17** (290 mg, 0.5 mmol) was dissolved in a MeOH/conc. HCl 5:1 mixture (8 ml) and heated under reflux for 2 h. After cooling to room temp. and removal of most volatiles in vacuo, the reaction mixture was worked up (EtOAc). CC of the residue on silica gel (hexane–EtOAc 9:1, then 7:3) provided lactone **18** (154 mg, 90%).

4.16. Conversion of lactone 18 to lactone 19

The hydrogenation catalyst 20% $Pd(OH)_2$/C (50 mg) was suspended in EtOH (5 ml) and stirred for 10 min under an H_2 atmosphere. The substrate (103 mg, 0.3 mmol) was dissolved in EtOH (5 ml) and added via syringe to the catalyst suspension. The reaction mixture was then stirred for 24 h at room temp. After this time (TLC monitoring), the mixture was filtered through Celite, the reaction flask and the Celite were washed two times with EtOH, and the organic layers were concentrated to dryness at reduced pressure. This gave a crude triol which was used in the next reaction.

The triol obtained above was dissolved in dry acetone (2 ml) and treated with anhydrous $CuSO_4$ (32 mg, 0.2 mmol).[27] After adding *p*-toluenesulphonic acid (5 mg), the solution was stirred under Ar for 24 h at room temp. (TLC monitoring). Work-up (CH_2Cl_2) and CC on silica gel (hexane–EtOAc 8.2 and then 1:1) furnished lactone **19** (36 mg, 60% overall from **18**).

4.17. Conversion of the stereoisomeric mixtures 12/13a and 12/13b (G=COO*t*Bu) into lactones 15/19 and 18/21, respectively

The mixtures of esters **12**/**13a** and **12/13b** (1 mmol in each case) was treated with TBAF (1.1 mmol) in dry THF as described above for the conversion **14→15**. In the case of **12**/**13a**, this yielded a mixture of lactones **15** (major) and **19** (minor). In the case of **12**/**13b**, this yielded a mixture of lactones **18** and **21**, from which the major lactone **21** could be isolated in 65% yield by crystallization from hexane–EtOAc.

4.18. (2*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-pentene-1,2-diol 9a

Oil, $[\alpha]_D=+2.8$ (*c* 4; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3550 (br, OH), 3065, 2936, 2853, 2846, 1464, 1432, 1375, 1216, 1106, 1065, 920, 820, 740; ^1H NMR (400 MHz) δ 7.65 (4H, m, aromatic), 7.40 (6H, m, aromatic), 5.84 (1H, ddt, $J=17$, 10.5, 7.5 Hz, H-4), 5.08 (1H, br d, $J=17$ Hz, H-5_t), 5.07 (1H, br d, $J=10.5$ Hz, H-5_c), 4.23 (1H, t, $J=7$ Hz, H-4′), 3.90 (2H, m, H-$5'_a$, H-$5'_b$), 3.63, 3.49 (2H, AB system, $J=10.5$ Hz, H-1_a/H-1_b), 2.42 (2H, m, H-3_a, H-3_b), 1.40, 1.36 (2×s, 3H each, acetonide methyls), 1.07 (9H, s, *t*BuSi); ^{13}C NMR (100 MHz) δ 135.6, 135.5, 132.8, 132.7, 129.9, 129.8, 127.8, 127.7, 127.6 (aromatic), 133.3 (C-4), 118.4 (C-5), 108.9 (C-2′), 78.2 (C-4′), 73.5 (C-2), 66.0 (C-1), 64.6 (C-5′), 38.8 (C-3), 26.9 (SiC*Me*$_3$), 26.3, 25.1 (acetonide methyls), 19.3 (Si*C*Me$_3$); CIMS, *m*/*z* (% rel. int.) 441. 2467 $[M+H]^+$ (16), 383 $[M-t\text{Bu}]^+$ (74), 247 (100), 101 (90). Calcd for $C_{26}H_{37}O_4Si$, $M=441.2461$. Anal. calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found, C, 70.60; H, 8.42%.

4.19. (2*S*)-1-*O*-Trityl-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-pentene-1,2-diol 9b

Oil, $[\alpha]_D=-7.1$ (*c* 6.6; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3400 (br, OH), 2985, 2932, 1595, 1472, 1221, 1069, 753, 700; ^1H NMR (400 MHz) δ 7.50–7.20 (15H, m, aromatic), 5.61 (1H, ddt, $J=17.2$, 10.5, 7.5 Hz, H-4), 5.02 (1H, br dd, $J=17.2$, 2 Hz, H-5_t), 4.96 (1H, br dd, $J=10.5$, 2 Hz, H-5_c), 4.38 (1H, dd, $J=8$, 6.3 Hz, H-4′), 4.00 (1H, dd, $J=8$, 6.3 Hz, H-$5'_a$), 3.91 (1H, t, $J=8$ Hz, H-$5'_b$), 3.19, 3.00 (2H, AB system, $J=8.8$ Hz, H-1_a/H-1_b), 2.35 (1H, br dd, $J=13.8$, 7.7 Hz, H-3_a), 2.19 (1H, dd, $J=13.8$, 7 Hz, H-3_b), 1.41, 1.37 (2×s, 3H each, acetonide methyls); ^{13}C NMR (100 MHz) δ 143.7, 128.7, 127.7, 127.1 (aromatic), 132.3 (C-4), 118.7 (C-5), 108.9 (C-2′), 86.7 (*C*Ph$_3$), 78.1 (C-4′), 73.1 (C-2), 65.3

(C-1), 64.5 (C-5′), 38.3 (C-3), 26.4, 25.6 (acetonide methyls); CIMS, m/z (% rel. int.) 445.2387 $[M+H]^+$ (0.5), 271 (65), 244 (100). Calcd for $C_{29}H_{33}O_4$, $M=$ 445.2379. Anal. calcd for $C_{29}H_{32}O_4$: C, 78.35; H, 7.26. Found, C, 78.60; H, 7.40%.

4.20. (2*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-pentene-1,2-diol 9c

Oil, $[\alpha]_D=+7.1$ (c 4.8; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 3076, 2985, 2935, 1376, 1257, 1217, 1157, 1064, 920, 858; ^1H NMR (500 MHz) δ 5.82 (1H, ddt, $J=17$, 10.3, 7 Hz, H-4), 5.12 (1H, br d, $J=10.3$ Hz, 1H, H-5_c), 5.11 (1H, br d, $J=17$ Hz, H-5_t), 4.10 (1H, t, 7 Hz, H-4′), 4.00 (2H, d, $J=7$ Hz, H-$5'_a$, H-$5'_b$), 3.72, 3.52 (2H, AB system, $J=11.2$ Hz, H-1_a/H-1_b), 2.70 (1H, br s, OH), 2.50 (1H, br s, OH), 2.28 (1H, dd, $J=14$, 7 Hz, H-3_a), 2.13 (1H, dd, $J=14$, 7 Hz, H-3_b), 1.42, 1.35 (2×s, 3H each, acetonide methyls); ^{13}C NMR (125 MHz) δ 132.3 (C-4), 119.0 (C-5), 109.4 (C-2′), 80.2 (C-4′), 72.3 (C-2), 67.3 (C-1), 64.7 (C-5′), 38.9 (C-3), 26.2, 25.4 (acetonide methyls); EIMS, m/z (% rel. int.) 187.0960 $[M-CH_3]^+$ (6), 171 $[M-CH_2OH]^+$ (4), 101 (100). Calcd for $C_{10}H_{18}O_4-CH_3$, $M=187.0970$. Anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found, C, 59.60; H, 9.06%.

4.21. (2*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(1*S*)-1,2-bis-(benzyloxy)ethyl]-4-pentene-1,2-diol 10a

Oil, $[\alpha]_D=-2.4$ (c 11.8; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3550 (br, OH), 3069, 2931, 2859, 1457, 1428, 1391, 1364, 1266, 1108, 918, 821, 740; ^1H NMR (500 MHz) δ 7.65 (4H, m, aromatic), 7.40–7.20 (16H, br m, aromatic), 5.85 (1H, ddt, $J=16.5$, 11, 6 Hz, H-4), 5.03 (1H, br d, $J=11$ Hz, H-5_c), 5.02 (1H, br d, $J=16.5$ Hz, H-5_t), 4.90, 4.58 (2H, AB system, $J=11.5$ Hz, OCH_2Ph), 4.51, 4.48 (2H, AB system, $J=12$ Hz, OCH_2Ph), 3.90 (1H, dd, $J=10$, 2 Hz, H-$2'_a$), 3.82 (1H, dd, $J=6$, 2 Hz, H-1′), 3.73 (1H, dd, $J=10$, 6 Hz, H-$2'_b$), 3.69, 3.61 (2H, AB system, $J=10$ Hz, H-1_a/H-1_b), 2.90 (1H, br s, OH), 2.40 (2H, m, H-3_a, H-3_b), 1.07 (9H, s, *t*BuSi); ^{13}C NMR (125 MHz) δ 138.8, 138.2, 135.7, 133.0, 129.8, 128.4, 128.2, 127.7, 127.6 (aromatic), 133.6 (C-4), 117.8 (C-5), 81.0 (C-1′), 75.6 (C-2), 73.6, 73.5 (2×OCH_2Ph), 71.3 (C-1), 66.1 (C-2′), 38.1 (C-3), 27.0 (SiCMe_3), 19.3 (SiCMe_3); CIMS, m/z (% rel. int.) 581.3079 $[M+H^+]$ (1), 107 (100). Calcd for $C_{37}H_{45}O_4Si$, $M=581.3087$. Anal. calcd for $C_{37}H_{44}O_4Si$: C, 76.51; H, 7.64. Found, C, 76.77; H, 7.78%.

4.22. (2*R*)-1-*O*-Trityl-2-[(1*S*)-1,2-bis(benzyloxy)ethyl]-4-pentene-1,2-diol 10b

Oil, $[\alpha]_D=-2.4$ (c 11.4; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3550 (br, OH), 3062, 3030, 2873, 1491, 1449, 1364, 1214, 1078, 915, 743, 700; ^1H NMR (500 MHz) δ 7.50–7.25 (25H, br m, aromatic), 5.82 (1H, ddt, $J=$ 17.2, 10.2, 7 Hz, H-4), 5.05 (2H, br m, H-5_c, H-5_t), 4.90, 4.60 (2H, AB system, $J=11.5$ Hz, OCH_2Ph), 4.47, 4.45 (2H, AB system, $J=12$ Hz, OCH_2Ph), 3.87 (1H, dd, $J=6$, 3 Hz, H-1′), 3.82 (1H, dd, $J=10.4$, 3 Hz, H-$2'_a$), 3.63 (1H, dd, $J=10.4$, 6 Hz, H-$2'_b$), 3.30, 3.17 (2H, AB system, $J=9.5$ Hz, H-1_a/H-1_b), 3.00 (1H, br s, OH), 2.50 (1H, br m, H-3_a, H-3_b); ^{13}C NMR (125 MHz) δ 143.7, 138.7, 138.1, 128.8, 128.3, 128.2, 127.7, 127.6, 127.4, 127.0 (aromatic), 133.6 (C-4), 117.8 (C-5), 86.8 (CPh_3), 80.8 (C-1′), 75.5 (C-2), 73.4 (2×OCH_2Ph), 70.8 (C-1), 65.5 (C-2′), 38.8 (C-3); EIMS, m/z (% rel. int.) 493.2377 $[M-Bn]^+$ (1), 333 (12), 244 (100). Calcd for $C_{40}H_{40}O_4$-Bn, $M=493.2378$. Anal. calcd for $C_{40}H_{40}O_4$: C, 82.16; H, 6.89. Found, C, 82.00; H, 7.01%.

4.23. (2*R*)-2-[(1*S*)-1,2-Bis(benzyloxy)ethyl]-4-pentene-1,2-diol 10c

Oil, $[\alpha]_D=+24.7$ (c 2.2; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3430 (br, OH), 2928, 2873, 1720, 1453, 1096, 1068; ^1H NMR (500 MHz) δ 7.40–7.25 (10H, m, aromatic), 5.90 (1H, ddt, $J=17.5$, 10, 7 Hz, H-4), 5.12 (1H, br d, $J=10$ Hz, H-5_c), 5.10 (1H, br d, $J=17.5$ Hz, H-5_t), 4.78, 4.62 (2H, AB system, $J=11.5$ Hz, OCH_2Ph), 4.58 (2H, s, OCH_2Ph), 3.84 (1H, dd, $J=10$, 5 Hz, H-$2'_a$), 3.74 (1H, t, $J=5$ Hz, H-1′), 3.70–3.65 (2H, m, H-$2'_b$, H-1_a), 3.53 (1H, dd, $J=11.5$, 5 Hz, H-1_b), 3.10 (1H, br s, 2-OH), 2.50 (1H, t, $J=6$ Hz, 1-OH), 2.41 (1H, dd, $J=14$, 7.5 Hz, H-3_a), 2.32 (1H, dd, $J=14$, 7.5 Hz, H-3_b); ^{13}C NMR (125 MHz) δ 138.1, 137.4, 128.6, 128.5, 128.0, 127.9, 127.8 (aromatic), 133.4 (C-5), 118.3 (C-6), 80.6 (C-2), 75.2 (C-3), 73.8, 73.5 (2×OCH_2Ph), 69.1 (CH_2OH), 65.9 (C-1), 38.6 (C-4); FAB MS, m/z 343.1923 $[M+H^+]$. Calcd for $C_{21}H_{27}O_4$, $M=343.1909$. Anal. calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found, C, 73.58; H, 7.80%.

4.24. Methyl (3*S*)-4-(*tert*-butyldiphenylsilyloxy)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxybutanoate 14

Oil, $[\alpha]_D=-9.2$ (c 0.35; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3490 (br, OH), 3072, 3049, 2933, 2891, 2858, 1739 (ester C=O), 1473, 1428, 1371, 1210, 1100, 1070, 1008, 858, 825, 742, 703; ^1H NMR (500 MHz) δ 7.70 (4H, br m, aromatic), 7.50–7.40 (6H, br m, aromatic), 4.35 (1H, dd, $J=7.5$, 6.5 Hz, H-4′), 4.05 (1H, dd, $J=8$, 6.5 Hz, H-$5'_a$), 3.98 (1H, dd, $J=8$, 7.5 Hz, H-$5'_b$), 3.74, 3.72 (2H, AB system, $J=10$ Hz, H-4_a/H-4_b), 3.70 (3H, s, OMe), 3.60 (1H, br s, OH), 2.75, 2.66 (2H, AB system, $J=15$ Hz, H-2_a/H-2_b), 1.41, 1.40 (2×3H, 2×s, acetonide *Me*), 1.10 (9H, s, Me_3CSi); ^{13}C NMR (125 MHz) δ 172.1 (C=O), 135.6, 132.8, 132.7, 129.8, 127.9, 127.7 (aromatic), 109.1 (C-2′), 78.4 (C-4′), 73.2 (C-3), 66.5 (C-4), 64.6 (C-5′), 51.8 (OMe), 36.9 (C-3), 26.7 (Me_3CSi), 26.1, 25.1 (acetonide *Me*), 19.2 (Me_3CSi); FAB MS, m/z (% rel. int.) 473.2368 $[M+H^+]$ (1), 415 (100). Calcd for $C_{26}H_{37}O_6Si$, $M=473.2359$. Anal. calcd for $C_{26}H_{36}O_6Si$: C, 66.07; H, 7.68. Found, C, 66.20; H, 7.81%.

4.25. (4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-hydroxytetrahydrofuran-2-one 15

White needles, mp 69–70°C (from hexane–Et_2O), $[\alpha]_D=$ -35.4 (c 1.4; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 2988, 2933, 1775 (lactone C=O), 1462, 1377, 1263, 1210, 1157, 1111, 1067, 1033, 852; ^1H NMR (400 MHz) δ 4.33, 4.22 (2H, AB system, $J=10$ Hz, H-5_a/H-5_b), 4.18 (1H, dd, $J=7$, 6 Hz, H-4′), 4.03 (1H, dd, $J=8.8$, 7

Hz, H-5′$_a$), 3.84 (1H, dd, J=8.8, 6 Hz, H-5′$_b$), 3.20 (1H, br s, OH), 2.64, 2.47 (2H, AB system, J=17.5 Hz, H-3$_a$/H-3$_b$), 1.42, 1.32 (2×s, 3H each, acetonide methyls); ^{13}C NMR (100 MHz) δ 175.4 (C-2), 110.3 (C-2′), 77.7 (C-4′), 76.6 (C-4+C-5), 64.8 (C-5′), 38.6 (C-3), 26.2, 24.5 (acetonide methyls); CIMS, m/z (% rel. int.) 203.0919 [M+H$^+$] (97), 187 [M$^+$−Me] (52), 145 (100), 127 (82). Calcd for $C_9H_{15}O_5$, M=203.0919. Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found, C, 53.69; H, 7.00%.

4.26. (3*R*,4*S*)-4,5-Bis(benzyloxy)-3-(*tert*-butyldiphenylsilyloxymethyl)-3-hydroxypentanenitrile 17

Oil, $[\alpha]_D$=+6.7 (c 4.2; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 3066, 3033, 2932, 2860, 2250 (C≡N), 1459, 1426, 1364, 1265, 1208, 1107, 1027, 820, 740, 701; ^{1}H NMR (400 MHz) δ 7.60 (4H, br m, aromatic), 7.50–7.20 (16H, br m, aromatic), 4.74, 4.48 (2H, AB system, J=11.5 Hz, OCH_2Ph), 4.42, 4.40 (2H, AB system, J=12 Hz, OCH_2Ph), 3.80–3.70 (2H, m, H-4/H-5$_a$), 3.76, 3.66 (2H, AB system, J=10.5 Hz, TPSOCH_2), 3.60 (1H, dd, J=10.5, 4 Hz, H-5$_b$), 3.45 (1H, br s, OH), 2.82, 2.64 (2H, AB system, J=16.5 Hz, H-2$_a$/2$_b$), 1.06 (9H, s, Me_3CSi); ^{13}C NMR (100 MHz) δ 143.6, 138.7, 138.0, 128.8, 128.3, 128.2, 127.7, 127.6, 127.4, 127.0 (aromatic), 133.5 (C-4), 117.8 (C-5), 86.8 (CPh$_3$), 80.8 (C-1′), 75.5 (C-2), 73.4 (2×OCH_2Ph), 70.8 (C-1), 65.4 (C-2′), 38.7 (C-3); EIMS, m/z (% rel. int.) 579.2811 [M]$^+$ (1), 536 (10), 522 [M$^+$−tBu] (100). Calcd for $C_{36}H_{41}NO_4Si$, M=579.2804. Anal. calcd for $C_{36}H_{41}NO_4Si$: C, 74.57; H, 7.13. Found, C, 74.33; H, 7.17%.

4.27. (4*R*)-4-[(1*S*)-1,2-Bis(benzyloxy)ethyl]-4-hydroxytetrahydrofuran-2-one 18

White needles, mp 90–91°C (from hexane–EtOAc), $[\alpha]_D$=+46.5 (c 2; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 3064, 3031, 2870, 1780 (lactone C=O), 1496, 1454, 1398, 1367, 1253, 1179, 1095, 1027, 911, 817, 736; ^{1}H NMR (400 MHz) δ 7.40–7.20 (10H, m, aromatic), 4.70, 4.49 (2H, AB system, J=12 Hz, OCH_2Ph), 4.52 (2H, s, OCH_2Ph), 4.26 (1H, dd, J=9.9, 1.5 Hz, H-5$_a$), 4.11 (1H, d, J=9.9 Hz, H-5$_b$), 3.72 (1H, dd, J=10, 4 Hz, H-2′$_a$), 3.65 (1H, dd, J=10, 6.8 Hz, H-2′$_b$), 3.58 (1H, dd, J=6.8, 4 Hz, H-1′), 3.30 (1H, d, J=1.5 Hz, OH), 2.70, 2.49 (2H, AB system, J=17.5 Hz, H-3$_a$/H-3$_b$); ^{13}C NMR (100 MHz) δ 175.3 (C-2), 136.9, 136.8, 128.7, 128.4, 128.2, 127.8 (aromatic), 79.0 (C-4), 77.7 (C-1′), 75.9 (C-5), 73.9, 72.7 (2×OCH_2Ph), 68.2 (C-2′), 39.8 (C-3); FAB MS, m/z 343.1557 [M+H]$^+$. Calcd for $C_{20}H_{23}O_5$, M=343.1545. Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found, C, 70.34; H, 6.30%.

4.28. (4*R*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-hydroxytetrahydrofuran-2-one 19

Oil, $[\alpha]_D$=+9.1 (c 1.5; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 2989, 2938, 2901, 1776 (lactone C=O), 1384, 1374, 1209, 1159, 1033, 851; ^{1}H NMR (400 MHz) δ 4.26, 4.18 (2H, AB system, J=10 Hz, H-5$_a$/H-5$_b$), 4.17 (1H, dd, J=6.8, 6 Hz, H-4′), 4.07 (1H, dd, J=8.5, 6.8 Hz, H-5′$_a$), 3.84 (1H, dd, J=8.5, 6 Hz, H-5′$_b$), 2.79, 2.57 (2H, AB system, J=17.8 Hz, H-3$_a$/H-3$_b$), 2.60 (1H, br s, OH), 1.45, 1.36 (2×s, 3H each, acetonide methyls); ^{13}C NMR (100 MHz) δ 171.9 (C-2), 110.3 (C-2′), 77.5 (C-4′), 75.3 (C-4+C-5), 65.0 (C-5′), 39.2 (C-3), 26.2, 24.5 (acetonide methyls); CIMS, m/z (% rel. int.) 203.0922 [M+H$^+$] (54), 185 [M+H$^+$−H$_2$O] (100). Calcd for $C_9H_{15}O_5$, M=203.0919. Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found, C, 53.40; H, 7.05%.

4.29. Methyl (3*R*,4*S*)-4,5-bis(benzyloxy)-3-(*tert*-butyldiphenylsilyloxymethyl)-3-hydroxypentanoate 20

Oil, $[\alpha]_D$=+7.5 (c 2.2; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3470 (br, OH), 3065, 3031, 2932, 2859, 1732 (ester C=O), 1453, 1430, 1392, 1342, 1259, 1205, 1109, 1024, 822, 740, 702; ^{1}H NMR (500 MHz) δ 7.65 (4H, br m, aromatic), 7.45–7.20 (16H, br m, aromatic), 4.86, 4.56 (2H, AB system, J=11.5 Hz, OCH_2Ph), 4.51, 4.49 (2H, AB system, J=12 Hz, OCH_2Ph), 4.00–3.70 (5H, br m, H-4, H-5$_a$, H-5$_b$, TPSOCH_2), 3.49 (3H, s, OMe), 2.74, 2.60 (2H, AB system, J=15 Hz, H-2$_a$/H-2$_b$); ^{13}C NMR (125 MHz) δ 172.8 (C=O), 138.7, 138.0, 135.7, 129.8, 128.3, 127.9, 127.7, 127.6, 127.4 (aromatic), 80.3 (C-4), 75.6 (C-3), 73.5 (2×OCH_2Ph), 70.7 (C-5), 67.2 (TPSOCH_2), 51.5 (OMe), 38.0 (C-2), 27.0 (Me_3CSi), 19.3 (Me$_3$CSi); CIMS, m/z (% rel. int.) 613.2990 [M+H$^+$] (7), 337 (82), 199 (100). Calcd for $C_{37}H_{45}O_6Si$, M=613.2985. Anal. calcd for $C_{37}H_{44}O_6Si$: C, 72.52; H, 7.24. Found, C, 72.63; H, 7.39%.

4.30. (4*S*)-4-[(1*S*)-1,2-Di(benzyloxy)ethyl]-4-hydroxytetrahydrofuran-2-one 21

White needles, mp 77–78°C (from hexane–EtOAc), $[\alpha]_D$=+26.7 (c 3.4; $CHCl_3$); IR ν_{max} (NaCl) cm^{-1}: 3450 (br, OH), 3031, 2923, 2869, 1779 (lactone C=O), 1454, 1368, 1264, 1180, 1094, 1023, 740; ^{1}H NMR (400 MHz) δ 7.40–7.25 (10H, m, aromatic), 4.70, 4.49 (2H, AB system, J=11.7 Hz, OCH_2Ph), 4.53 (2H, s, OCH_2Ph), 4.21, 4.19 (2H, AB system, J=10.2 Hz, H-5$_a$/H-5$_b$), 3.75–3.60 (3H, m, H-1′, H-2′$_a$, H-2′$_b$), 3.30 (1H, d, J=1Hz, OH), 2.71 (1H, dd, J=17.5, 1 Hz, H-3$_a$), 2.41 (1H, d, J=17.5 Hz, H-3$_b$); ^{13}C NMR (100 MHz) δ 175.4 (C-2), 137.0, 136.9, 128.6, 128.2, 128.1, 127.9 (aromatic), 78.8 (C-4), 78.2 (C-1′), 77.2 (C-5), 73.9, 72.5 (2×OCH_2Ph), 68.2 (C-2′), 39.2 (C-3); CIMS, m/z (% rel. int.) 343.1537 [M+H]$^+$ (21), 91 (100). Calcd for $C_{20}H_{23}O_5$, M=343.1545. Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found, C, 70.04; H, 6.29%.

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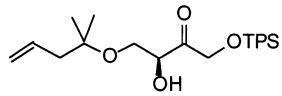
19. This Lewis acid was prepared according to the procedure described in Ref. 14b, p. 258. With ketone **3** and allyl trimethylsilane, the only product isolated after 5 h in CH_2Cl_2 at −10°C was alcohol **i** (63%). With ketone **3** and allyl tri-*n*-butylstannane, the only product isolated after 5 h in CH_2Cl_2 at −10°C was **9a** (77%).



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