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SELECTIVE MONO-CLAISEN REARRANGEMENT OF CARBOHYDRATE GLYCALS. A CHEMICAL CONSEQUENCE OF THE VINYLOGOUS ANOMERIC EFFECT

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ABSTRACT

The mono-Claisen rearrangement of carbohydrate glycals is demonstrated to be a synthetically useful and mechanistically significant reaction. Addition of per-*O*-acetyl glycal–*tert*-butyldimethylchlorosilane mixture to lithium diisopropylamide generated a bis (or tris)ketenesilylacetal which, upon heating, underwent smooth mono-Claisen rearrangement to provide a *C*-glycosyl compound after methylation. A second apparently similar Claisen rearrangement required significantly higher temperatures in all cases. Thus, similar hydroxy groups were differentiated without resort to selective protection. A stereoelectronic rationale based on the newly-introduced vinylogous anomeric effect (VAE) is put forth to explain the accelerated Claisen rearrangements of these glycals. Molecular orbital and resonance descriptions of the VAE are included, and the VAE is also used to rationalize ground-state conformational preferences of carbohydrate glycals. The *C*-glycosyl compounds produced by mono-Claisen rearrangement were suitable for Pd(0)-catalyzed allylic alkylations, providing an unusually facile entry into the pseudomonic acid-ring systems. A nine-step synthesis of a known precursor of pseudomonic acid C is reported.

INTRODUCTION

The aliphatic Claisen rearrangement of allyl vinyl ethers to γ,δ-unsaturated carbonyl groups has become one of the most powerful and versatile tools for stereocontrolled, carbon–carbon bond formation in organic synthesis[1]. Variations of this sigmatropic rearrangement have permitted easy access to the required allyl vinyl ethers and dramatically lowered the temperature of the transposition by modification of substituents[2]. The Ireland ester enolate–Claisen procedure is perhaps the mildest and most generally useful variant now available[3]. Indeed, the

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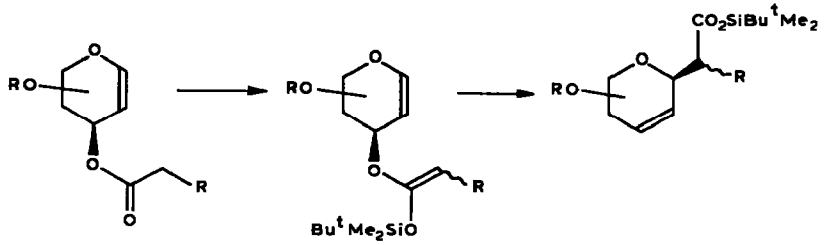


Scheme 1.

Ireland–Claisen rearrangement is almost ideal for the conversion of readily available carbohydrate glycals to biologically important *C*-glycosyl compounds (Scheme 1), and many elegant examples of the utility of this transformation have been provided by the Ireland school in both the pyran and furan series[4].

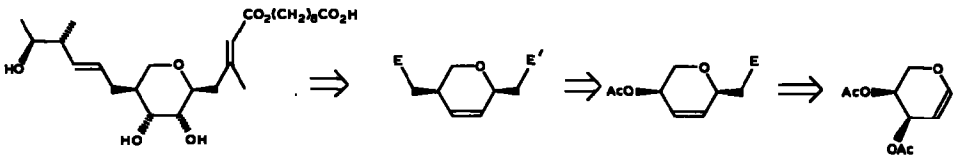
One potential drawback in the application of the Ireland–Claisen rearrangement is the (perceived) need for selective protection of the remaining hydroxyl groups in the carbohydrate as a means of rigorous chemical differentiation[4]. Such selective protection–deprotection sequences are common and lengthy, and can detract from the utility of carbohydrates as starting materials for natural products synthesis[5]. Development of reactions which differentiate between hydroxyl groups without selective protection is then an important goal in this field.

We were prompted to address this problem by a strategy for the synthesis of pseudomonic acid C (**1**) outlined in Scheme 2*. The pseudomonic acids are a relatively but small important family of antibiotics which possess the novel *C*-glycopyranosyl ring nucleus[7].

The strategy calls for the sequential transformation of the two C–OAc bonds of 3,4-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-L-*erythro*-pentenitol (**2**) into two C–C bonds in pseudomonic acid C (**1**). The first transformation (**4**→**3**) requires the retention of relative stereochemical orientation coupled with transposition of allylic regioselectivity, whereas the second step (**3**→**2**) requires the retention of both stereo- and regio-selectivity. Finally, *cis*-hydroxylation from the less-hindered face of **2** and side-chain elaboration would provide **1**. Our approach is fundamentally different from the more common method of synthesis of pseudomonic acids from carbohydrates. In this generalized approach, outlined in Scheme 3, C-2–O and C-3–O bonds derived from the carbohydrate molecule are carried through the sequence intact, while the remaining hydroxy (or hydroxymethyl) substituents are used as handles for side-chain introduction†. Although this approach may appear more straightforward on the surface, selective protection–deprotection and activation of the various hydroxy groups is required. These reactions do add to the length of the

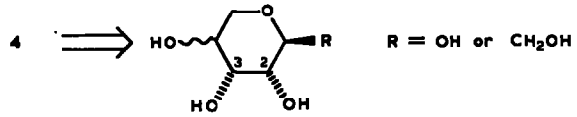
*Portions of this work have been reported in preliminary form[6].

†For racemic synthesis, see refs. 8–11. For nonracemic synthesis, see refs. 12–15. For synthetic approach, see refs. 17–18.



Scheme 2.

synthesis, even though they are frequently routine and high-yielding. We will demonstrate that the approach outlined in Scheme 2 provides a direct route from the readily available L-arabinal derivative **4** to the pseudomonic acid ring nucleus. As an added bonus, we note that D- and L-arabinose are equally inexpensive sugars, so that either enantiomeric series may be accessed.



Scheme 3.

Clearly the Ireland–Claisen rearrangement is well suited for the initial key C–O to C–C conversion (**4**→**3**) since both stereo and regio conditions are insured. However, the problem of differentiation of the two similar secondary acetates in **4** immediately arises. To avoid the problem of differentiation by protection, we have addressed the possibility of a selective mono-Claisen rearrangement of the bis(ketenesilyl)acetal derived from **4**. We now wish to report the full details of our study which show (a) that the mono-Claisen rearrangement of carbohydrate glycal polyketene acetals is a useful and general reaction; (b) that this selective Claisen rearrangement is promoted by an accelerating substituent effect of the pyran oxygen atom; (c) that this acceleration can be interpreted as a chemical consequence of the vinylogous anomeric effect (VAE); and, finally, (d) that the products of this rearrangement are suitable for further selective transformations including rapid construction of the ring nucleus of the pseudomonic acids[6].

RESULTS AND DISCUSSION

In the context of the synthetic approach to pseudomonic acid C (**1**), the selective Ireland–Claisen rearrangement was first investigated with readily available **4** (ref. 19). Generation of the bisester enolate by dropwise addition of **4** to lithium diisopropylamide (LDA), followed by silylation with *tert*-butylchlorodi-

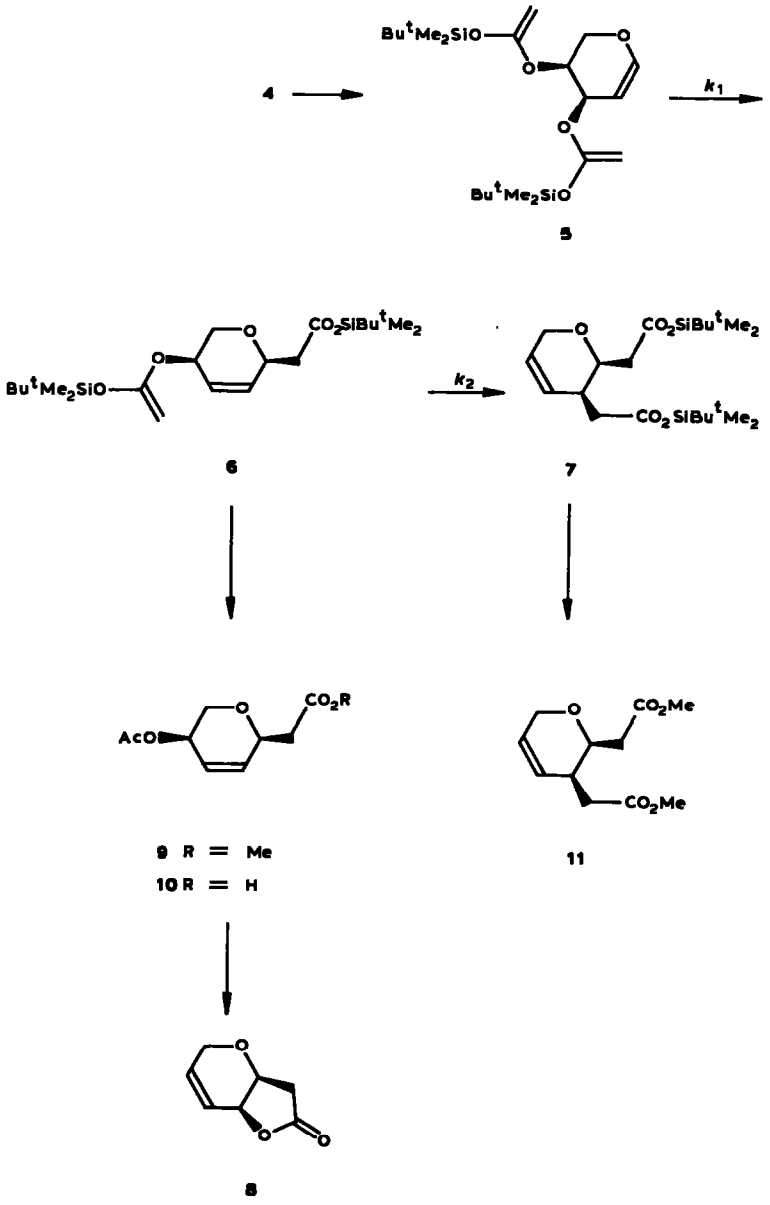
methylsilane produced a near quantitative yield of bis(silylated) material after pentane extraction. Whereas the major product (85–90%) was the bis(ketenesilyl)acetal **5**, small proportions of at least two other materials were present. Though it was strongly suspected that these were the two possible α-silyl ester ketenesilyl acetals resulting from mono *C*-silylation, the identity of the minor products was not pursued. Silylation with chlorotrimethylsilane resulted in bis(α-silyl) ester formation, and further attempts to improve the purity of the crude bis(ketenesilyl)acetal **5** by variation of the solvent, counter-ion, additive, and silylating agent were not encouraging. In general, the bis(silylated) product was rearranged without purification.

Warming of crude bis(ketenesilyl)acetal **5** for 6 h at 60° in $CDCl_3$ or C_6D_6 resulted in smooth conversion to the mono-Claisen rearrangement product **6** as indicated by ^{1}H-n.m.r. spectroscopy. In a preparative experiment, the crude rearrangement product was directly subjected to desilylation and methylation[6]. Following flash chromatography, acetate **9** was isolated in 60% yield, along with a small amount (<5%) of diester **11** resulting from the second Claisen rearrangement (**6** →**7**). A small proportion of **4** (5–7%) was also recovered. This is believed to have resulted from *C*-silylation of OAc-4, since prolonged heating at higher temperatures did not decrease the yield of this product. Alternatively, brief desilylation with potassium fluoride provides the unstable acid **10**, also in ~60% yield. Acid **10** could not be purified owing to its tendency to liberate acetic acid to form the vinyl lactone **8**. Racemic **8** is an intermediate in the Raphael synthesis[11] of pseudomonic acid C. Although **10** rearranged on standing at room temperature, the crude acid could be used immediately for subsequent transformations *(vide infra)*.

We were most pleased to discover that this selective mono-Claisen rearrangement process was practical. Indeed, the 60% yield of isolated **9** from **4** was quite satisfactory considering the number of operations in this sequence and the transformations accomplished. Note that a new carbon–carbon bond had been selectively formed and two similar secondary acetates had been differentiated in the process without resort to protection.

The tandem-Claisen product **7** was formed readily at higher temperatures. Heating of **5** in toluene at reflux, followed by desilylation–methylation as described above, provided the diester **11** in 45% yield. It is noted that such tandem-Claisen products may be synthetically useful in their own right.

We were most intrigued by this significant difference in rate between two apparently similar Claisen rearrangements. To determine the generality of the sequence outlined in the sequence **4** →**11**, the selective mono-Claisen rearrangement of related glycals was investigated. Initial attempts to doubly deprotonate 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol (**12**), according to the procedure used for **4**, met with disastrous results. Dropwise addition of **12** to lithium diisopropylamide at −78°, followed by quenching with *tert*-butylchlorodimethylsilane, provided a mixture containing bis(ketenesilyl)acetal **13** (~25%), contaminated with at least six or seven other products. Extensive variation of solvent,


4
Bu^tMe_2SiO
k_1
5
$CO_2SiBu^tMe_2$
k_2
6
7
AcO
CO_2R
9 R = Me
10 R = H
CO_2Me
11
8

temperature, silylating agent, base, or additive was not beneficial. At this time, our attention was directed to a report by Krizan and Martin[20] of the ortho-lithiation of benzonitrile with LDA in the presence of chlorotrimethylsilane. These results clearly demonstrated that quenching of LDA with the chloride was slower than deprotonation of relatively acidic protons by LDA. This technique has provided a general solution for the formation of [bis (and tris)ketene]silylacetals. Thus, dropwise addition of a mixture of both *tert*-butylchlorodimethylsilane (2 equiv.) and **12** (1 equiv.) to LDA (2 equiv.) at −78° in oxolane provided a near quantitative yield of bis(silyl)ated compound **13**. In this manner, an ester enolate is trapped by silylation immediately upon generation, and possible side-reactions are superseded. As described before, the major product (85–90%) was the bis(ketenesilyl)acetal and the minor products were believed to be mono-*C*-silylated ketenesilylacetals. All subsequently described bis(ketenesilyl)acetals were formed by this procedure. Several deprotonations entirely analogous to the method described above have been reported during the course of our work[21]. It is clear that this is a valuable technique for rapid trapping of anions.

With a procedure for bis(ketenesilyl)acetal formation in hand, a variety of Claisen substrates were prepared and rearranged. In each case, the mono-Claisen rearrangement products (**14**, **20**, **26**, and **32**) were smoothly formed after 1–4 h at 60–70° in benzene. After desilylation and methylation, the yields of purified monomethyl ester acetates **15**, **21**, **27**, and **33** ranged from 40 to 55% (overall yield from the starting glycal). Under these conditions, only trace amounts of the tandem-Claisen products (0–3%) could be isolated after methylation. Upon prolonged heating at 60–70° (several days) or heating at higher temperatures (>100°), tandem-Claisen rearrangement products were formed in all cases (**16**, **22**, **28**, and **34**). As before, these products were characterized as the methyl esters **17**, **23**, **28**, and **35**, and the overall yields of purified compounds from the starting glycal are also indicated in the scheme of structures. The yields of tandem-Claisen rearrangement products were not optimized and, in several cases, the sluggish second rearrangement was still incomplete when the reaction was stopped.

The results demonstrate the generality of the mono-Claisen process. Substrates with different configurations and substitution patterns all rearranged smoothly. It is interesting to note that the mono-Claisen rearrangement of **30** proceeded through a tris(ketenesilyl)acetal **31** to produce the ester diacetate **33**. Overall, this is a most valuable method for the direct stereocontrolled formation of *C*-glycosyl compounds from glycal acetates without protection of the hydroxy groups.

A relative-rate study of the above-described rearrangements was undertaken to ascertain the magnitude of the rate difference between the first (k_1) and second (k_2) Claisen rearrangements. Product ratios were determined by integration of appropriate resonances in the ^{1}H-n.m.r. spectra (C_6D_6), and all rates were first order over several half-lives. The results are summarized in Table I. Also collected in Table I are the rates for several model systems, derived from, cyclohexenediol (**36**), dihydropyranol (**37**), and cyclohexenol (**38**). With the important exception of

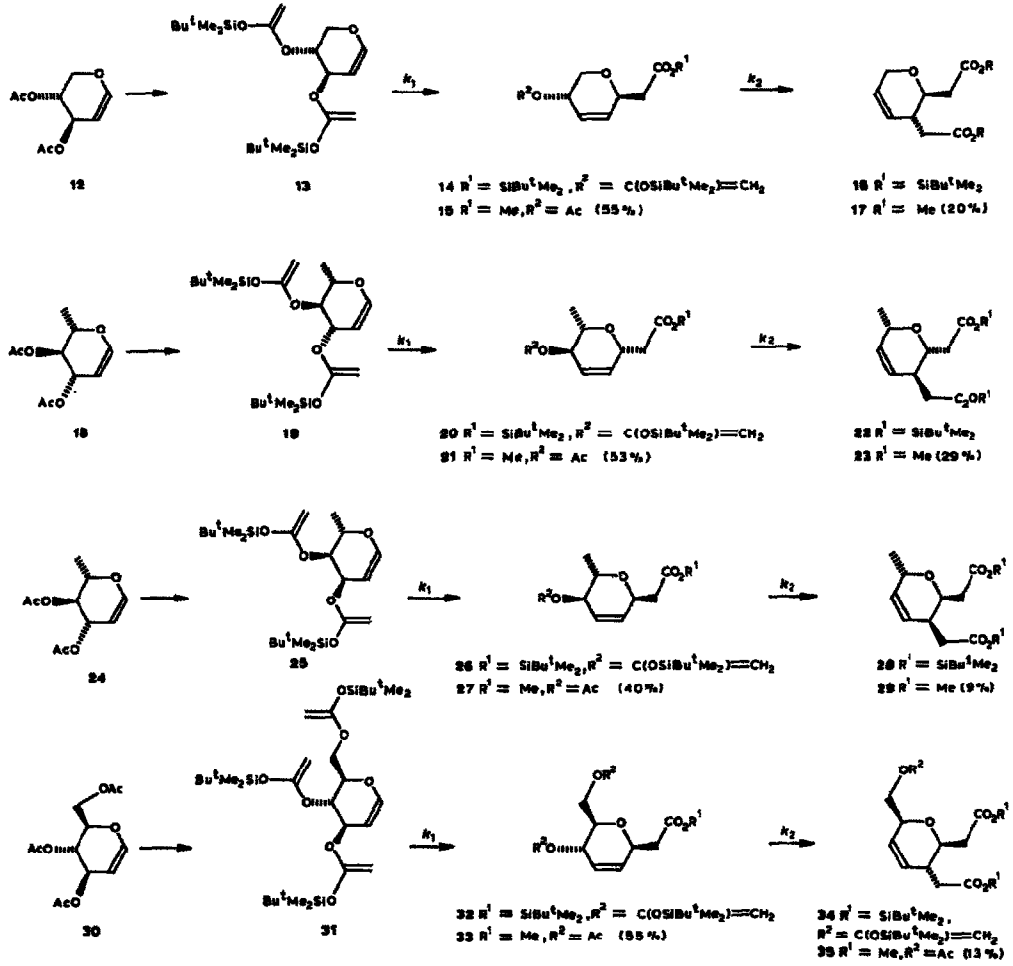

12
13
14 R¹ = SiBu^tMe₂, R² = C(OSiBu^tMe₂)=CH₂
15 R¹ = Me, R² = Ac (55%)
16 R¹ = SiBu^tMe₂
17 R¹ = Me (20%)
18
19
20 R¹ = SiBu^tMe₂, R² = C(OSiBu^tMe₂)=CH₂
21 R¹ = Me, R² = Ac (53%)
22 R¹ = SiBu^tMe₂
23 R¹ = Me (29%)
24
25
26 R¹ = SiBu^tMe₂, R² = C(OSiBu^tMe₂)=CH₂
27 R¹ = Me, R² = Ac (40%)
28 R¹ = SiBu^tMe₂
29 R¹ = Me (9%)
30
31
32 R¹ = SiBu^tMe₂, R² = C(OSiBu^tMe₂)=CH₂
33 R¹ = Me, R² = Ac (55%)
34 R¹ = SiBu^tMe₂,
R² = C(OSiBu^tMe₂)=CH₂
35 R¹ = Me, R² = Ac (13%)

TABLE I

CLAISEN RATE MEASUREMENTS OF COMPOUNDS **5, 13, 19, 25, 31, 37, 41,** AND **44**

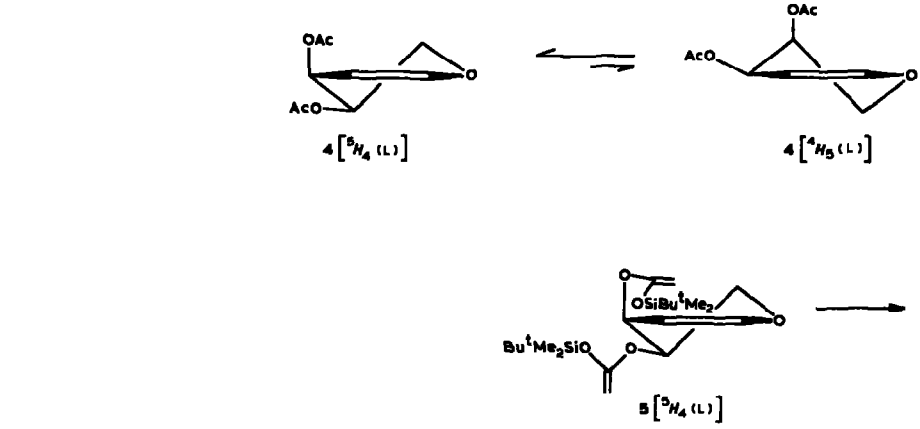
Compound	K_1 *(sec^{-1})* *(× 10^{-5})*	k_2 *(sec^{-1})* *(×10^{-6})*	*Temp. (degrees)*	k_1/k_2
5	48	25	70	20
13	68	19	60	35
19	200	3.5	60	575
25	42	8.1	60	50
31	160	7.1	60	225
37	3.3	17	65	2
41	44	[a]	60	10
44	[a]	48	60	

[a]Not applicable, see text for explanation.

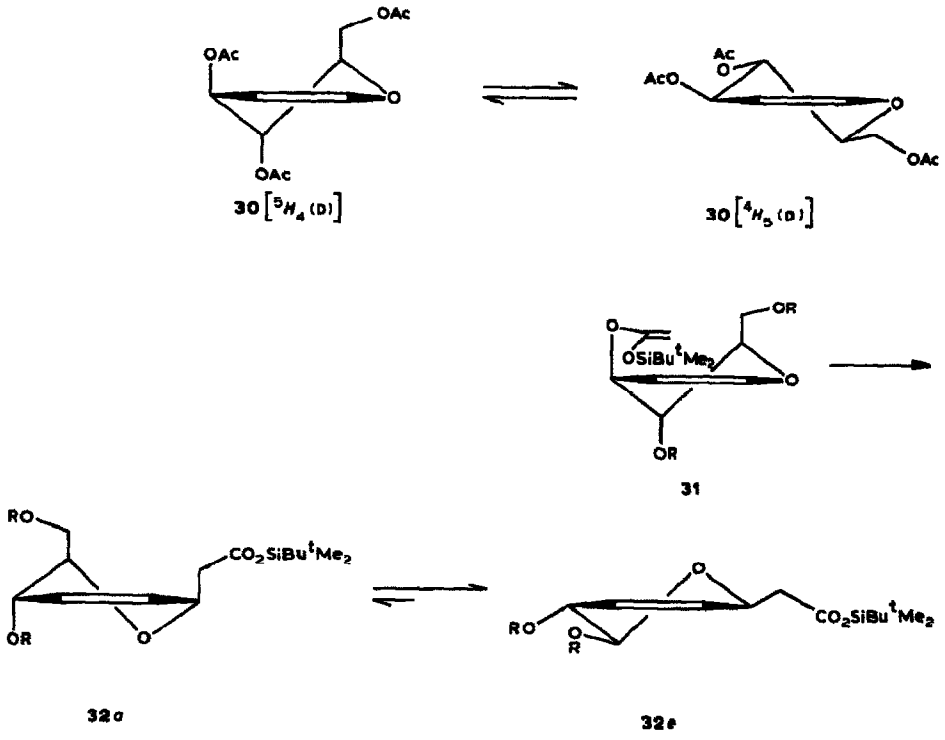
the carbocyclic analog **36**, the first Claisen rearrangement is 10–575 times faster than its partner.

We have considered three possible origins for the intriguing selectivity of these apparently similar Claisen rearrangements. The origin of the general effect $k_1 > k_2$ can be (a) conformational, (b) steric, or (c) substituent-controlled (stereoelectronic). (Of course, combinations are possible.) The importance of conformational effects is readily assessed (see Scheme 4). For proper orbital overlap in the Claisen rearrangement, the ketenesilylacetal C–O bond must attain an axial-like orientation. The L-arabinal derivative **4** is known to exist preponderantly in the $^5H_4$(L) conformation, despite the fact that the alternative $^4H_5$(L) conformation has no 1,3-diaxial-like interaction[22]. The reasons for this will be addressed shortly. According to a ^{1}H-n.m.r. coupling-constant analysis, bis(ketenesilyl)acetal **5** has a conformational preference similar to **4**. Thus, the requisite C–O bond is preponderantly axial, and a conformational problem is not encountered in the Claisen transition state proceeding to **6**. While **6** must initially be formed in conformation **6a**, it rapidly flips into conformation **6b** to minimize diaxial-like interactions. The magnitude of the vicinal and allylic coupling constants[6,10,23] of H-1 and H-4 are particularly diagnostic in this and related cases (see Experimental section). Compound **6b** is now in the conformation required for rearrangement and there is no inherent bias against the transition-state conformation of second Claisen rearrangement. Thus, the basic rate difference ($k_1 > k_2$) is not explained by conformational considerations.

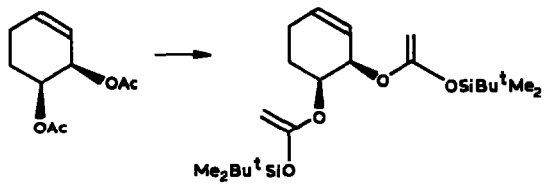
However, the importance of conformational aspects cannot be overlooked. Consider a similar analysis of the D-glucal derivative **30** (see Scheme 5) which is known to exist as a mixture of $^4H_5$(D) and $^5H_4$(D) conformers in solution. At first sight, the observation that these two conformers are comparable in energy may seem surprising. However, this will be rationalized by stereoelectronic considerations *(vide infra)*. Again, we can propose that ketenesilylacetal **31** has a similar


OAc
AcO
O
4 [$^5H_4$ (L)]
OAc
AcO
O
4 [$^4H_5$ (L)]
OSiBu^{t}Me$_2$
Bu^{t}Me$_2$SiO
O
5 [$^5H_4$ (L)]
Bu^{t}Me$_2$SiO
O
CO$_2$SiBu^{t}Me$_2$
6a
OSiBu^{t}Me$_2$
O
H-4
H-1
CO$_2$SiBu^{t}Me$_2$
6b

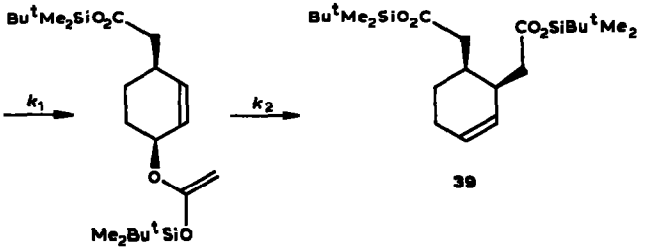
Scheme 4


OAc
OAc
OAc
O
30 [5H4 (D)]
Ac
O
AcO
O
OAc
30 [4H5 (D)]
OR
O
OSiBu^tMe2
O
OR
31
RO
CO2SiBu^tMe2
OR
O
32a
O
RO
O
R
CO2SiBu^tMe2
32e
R = O SiBu^tMe2
—C=CH2

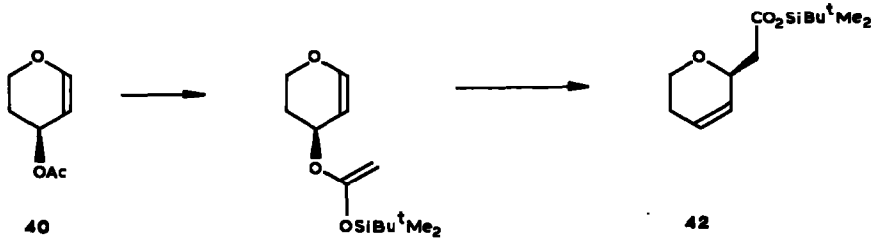
Scheme 5



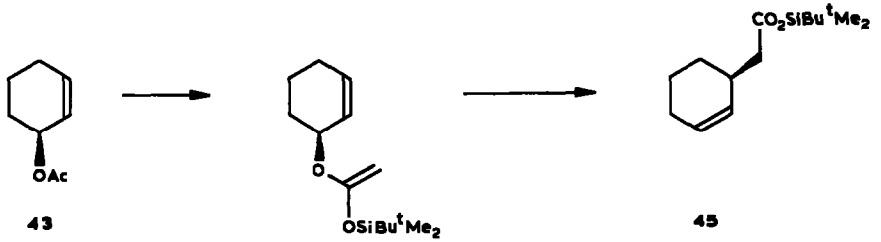
36 37



38 39



40 41 42



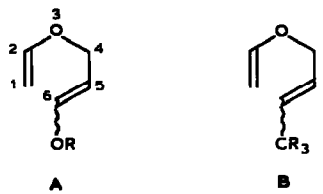
43 44 45

Scheme 6.

conformational preference to **30**. Assuming that transition-state conformational energies roughly parallel their ground-state precursors, rearrangement *via* the $^5H_4$(D) conformation of **31** should be reasonable. While the product is formed in conformation **32a**, it rapidly flips to the conformation **32e** to place all three substituents in equatorial positions. In the case of the D-glucal derivative then, there is a conformational bias against the second rearrangement according to this analysis, which correlates ground-state, conformational-energy differences to transition-state energies. While this analysis explains why the L-rhamnal and D-glucal derivatives show k_1/k_2 ratios much greater than those of the L-arabinal, D-xylal, or L-digitoxal derivatives, it is still not obvious why the underlying principle should operate. Specifically, why should **30** and **31** exist as an energetically comparable $^4H_5 \rightleftarrows {}^5H_4$(D) mixture, whereas **32** exists preferentially in the all equatorial conformation **32e**?

A steric rationale may also be put forward; perhaps the second Claisen rearrangement is more hindered than the first owing to the neighboring acetic ester side-chain. Conformational analysis (see Schemes 4 and 5) indicated that this is not likely, since the equatorially oriented CH_2CO_2R group should provide little steric hindrance to an axially entering substituent. The models outlined in Scheme 6 address this question. Assuming that this steric argument is correct, the carbocyclic analogs **37–39** might be expected to show a similar $k_1 > k_2$ preference to **5**. In fact, k_1 is only marginally greater than k_2 (Table I). In another example, the rates of rearrangement of **41** and **44** should be similar based on both steric and conformational arguments (**41** and **44** have similar conformational preferences)[24]; however, **41** rearranges at a rate one order of magnitude faster than **44** (Table I).

To summarize, the Claisen selectivity observed is not adequately explained by steric or conformational considerations. While configurations play only a minor role, conformations can be important. However, the observed conformational effects serve only to reinforce a "pre-existing" selectivity. A third obvious difference between the two Claisen rearrangements is that resulting from a substituent. The compound subject to the first Claisen rearrangement always possesses an oxygen atom in the γ-allylic position (C-6, see **A** in Scheme 7), whereas the compound subjected to the second Claisen rearrangement has a carbon atom in the



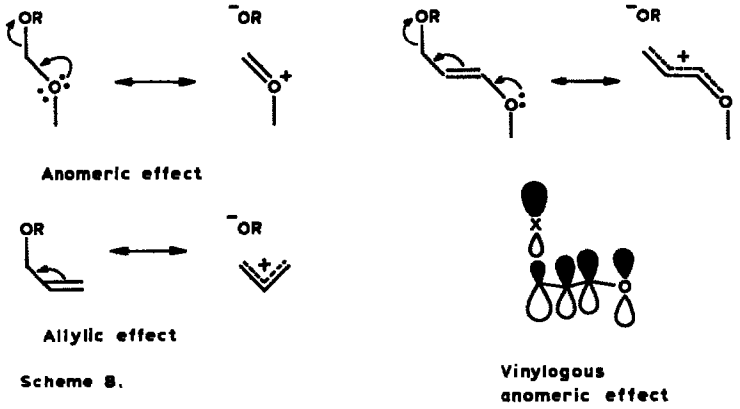
A **B**

Scheme 7

[a]Both rearrangements are strongly accelerated by the Bu^tMe_2SiO-2 substituent[3], and studies[25] in our laboratory have shown that the effect of O-6 is independent of substitution at C-2.

same position (**B** in Scheme 7). Clearly, the first Claisen rearrangement is accelerated by a substituent effect*. Thus, an electron-donating substituent in the γ-allylic position (C-6) accelerates the Claisen rearrangement. In addition to the studies outlined herein, a variety of rearrangements in acyclic systems have confirmed the generality of this statement[6,25]. The following section will provide a stereoelectronic rationale, termed the vinylogous anomeric effect, which allowed us to interpret both the known ground-state conformational preferences of sugar glycals and the origin of the accelerating effect of the electron donating oxygen atom on the Claisen rearrangement.

The vinylogous anomeric effect. — The Carpenter model has been widely used to interpret and predict substituent effects on the Claisen rearrangement[26]. This treatment calculates the difference in Huckel π-electron energy between suitable reactant and transition-state models. In the present model, an electron-donating substituent in the γ-allylic position is predicted to be decelerating. Since the basic premise of the Carpenter model seems reasonable, an overriding effect must be operating in this particular case.



Scheme 8.

We propose that the rate accelerating effect of a γ-electron-donating substituent is stereoelectronic in nature, and we introduce a rationale based on the "vinylogous anomeric effect" (VAE)[27,*] (see Scheme 8). The "anomeric effect" is well known as a guiding stereoelectronic principle in carbohydrate chemistry for interpretation of both ground-state conformational preferences, and reactivity[28,29]. In molecular orbital terms, an $n \rightarrow \sigma^*$ interaction is invoked. Alternatively, simple resonance theory permits interpretation of the anomeric effect *via* the standard "double-bond–no-bond" resonance picture. Similarly, the "allylic effect" has also been recognized as a useful principle in carbohydrate chemistry[30]. A molecular orbital diagram for the VAE invoking $\pi \rightarrow \sigma^*$ stabilization may also be con-

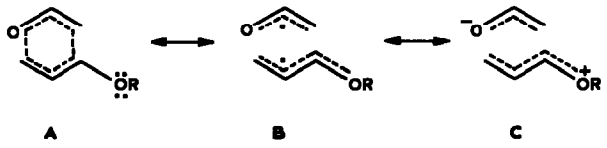
*The term "vinylogous anomeric effect" has been independently introduced, see ref. 27.

structed[31]. The simple resonance picture is also useful for the present discussion. All three "effects" are obviously related and each may be considered as an example of a more fundamental stereoelectronic principle[29]. Since an enol ether has a higher lying π-orbital (*i.e.*, better donor) than a simple olefin, the VAE should be of larger magnitude than the allylic effect[31].

Drawing an analogy of the anomeric and allylic effects, the VAE may be expected to have both conformational and chemical consequences[28,29]. From a conformational standpoint, an axial-like preference for a vinylogously anomeric C–X bond may be expected in order to provide optimum geometry for orbital interaction. Spectroscopic evidence is in good accord with this proposal and such conformational preferences have been previously recognized[22,24,27,32]. As an illustrative example, consider the ground state conformational preferences of **4** (Scheme 4) and **30** (Scheme 5). According to ^{1}H-n.m.r. coupling-constant analysis, **4** prefers the $^5H_4$(L) conformation (having the vinylogously anomeric C-4–O bond axial-like and the C-5–O bond equatorial-like) over the $^4H_5$(L) conformation (which reverses the configuration of these two substituents). While such a conformational preference may be attributed to $A_{1,2}$ strain or decreased 1,3-diaxial-like interactions in dihydropyrans relative to pyrans, we feel that the VAE is likely the most important reason. While **30** has been shown to exist in the $^4H_5$(D) conformation in the solid state[33], the ^{1}H-n.m.r. spectrum for a solution is more consistent with an ~3:2 mixture of the $^4H_5$ and $^5H_4$(D) conformers. The energetic viability of the "all axial-like" $^5H_4$(D) conformer may again be attributed to the vinylogous anomeric effect. Indeed, all cationic reactions of **30**, such as the Ferrier rearrangement[34], must proceed *via* the $^5H_4$(D) conformation. The VAE principle is readily extended to interpret conformational preferences of other glycals and related enol ethers in solution[22,24,27,32].

We turn now to the chemical consequences of the VAE. At first glance, a γ-allylic oxygen atom should retard the Claisen rearrangement, since the VAE predicts a reduction in ground-state energy relative to an unsubstituted analog. This is not the case. Since the VAE is expected to stabilize the transition state more than the ground state, a net acceleration is anticipated.

Based on elegant isotope effect studies, Gajewski and Conrad[35], and McMichael and Korver[36] have concluded that the aliphatic Claisen rearrangement has a transition state with a bond-breaking well advanced with respect to bond-making. Substituents that will facilitate bond-breaking by any means can then be expected to accelerate the Claisen rearrangement. According to the VAE, the C-3–O-4 bond is weakened relative to an unsubstituted counterpart, and its cleavage is stabilized in the transition state by the donation of electron density. Scheme 9 presents a resonance picture of the transition state which emphasizes the importance of bond-breaking. This VAE bond-breaking interpretation stresses the importance of the dipolar resonance contributor (**C**) in this Claisen rearrangement and indeed predicts that a significant, substituent-induced solvent effect may be observed. Recently, we[25], and Carpenter *et al.*[37] have observed unprecedented solvent accelera-



A B C

Scheme 9.

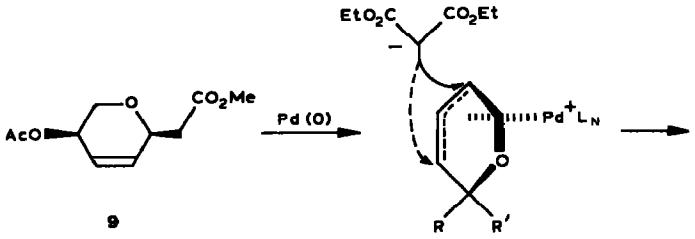
tions of related Claisen rearrangements. Note then that, in line with the anomeric effect, the VAE may impart molecules with both an increased stability and increased reactivity. Furthermore, this kinetic accelerating effect of the VAE can be compared to the kinetic anomeric effect[28] which is usually invoked for stepwise, ionic reactions. There is no reason why such effects should not operate in concerted, nonsynchronous, pericyclic reactions such as the Claisen rearrangement.

Finally, the VAE provides an explanation for the differences in relative rates (k_1/k_2) between the D-glucal **31** and the L-arabinal **5** experiments. In the first case, a much larger k_1/k_2 ratio was observed. While a 1,3-diaxial-like interaction is present in both the ground and transition state of **31**, this is largely offset by the VAE. However, the second Claisen rearrangement does not benefit from the VAE and **32** suffers 1,3-diaxial-like interactions in both the ground and transition states. Thus, the transition-state energy of the second Claisen rearrangement is raised further relative to the first.

Pseudomonic acid intermediates. — The controlled mono-Claisen rearrangement of **4** provides a direct method for introduction of the *C*-glycosyl chain of the pseudomonic acids. The remaining allylic acetate group must then serve as a handle for selective introduction of the second side-chain. Net retention of both regio- and stereo-selectivity of the allylic acetate **9** is required and, based on mechanistic considerations, a palladium-catalyzed nucleophilic displacement appeared to provide an ideal solution[38]. Such reactions with stabilized carbon-nucleophiles are well known to occur with retention of configuration *via* a double-inversion mechanism. On the other hand, regioselectivity is not determined by the precursor allylic acetate group but by steric or electronic biases (or both) in the intermediate π-allyl palladium complex.

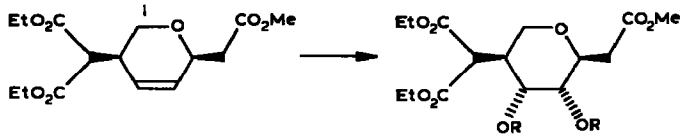
Addition of diethyl sodiomalonate to acetate **9** catalyzed by $Pd(dppe)_2$ provided essentially a single product which was readily identified as **48**. The high degree of regiocontrol may be reasonably explained by approach of the malonate reagent to the allylic position remote from the existing side-chain in the intermediate π-allyl palladium complex **46**. Catalytic osmylation[39] provided a single *cis*-diol **49** with the proper functional-group disposition for pseudomonic acid C. This diol was fully characterized by formation of both diacetate **50** and dibenzoate **51** derivatives.

The Pd(0) catalyzed displacement proved quite general. The related acetate compound **27** gave **52** as the sole isolated product in high yield. On the other hand, the D-xylal derivative **15** provided a 2:1 mixture of the regioisomers **53** and **54**. In



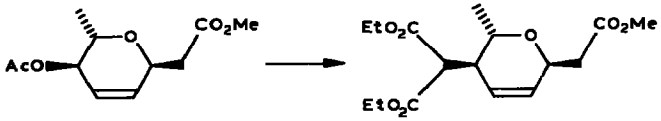
9

46 R = CH_2CO_2Me, R' = H
47 R = H, R' = CH_2CO_2Me

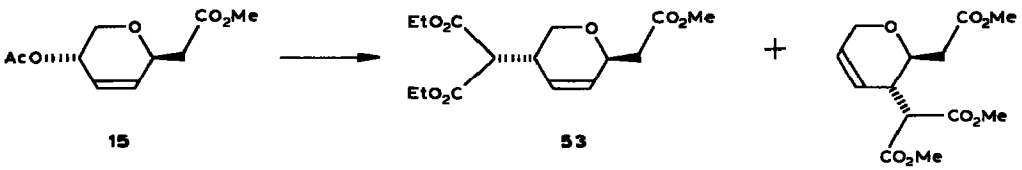


48

49 R = H
50 R = Ac
51 R = Bz



27 52

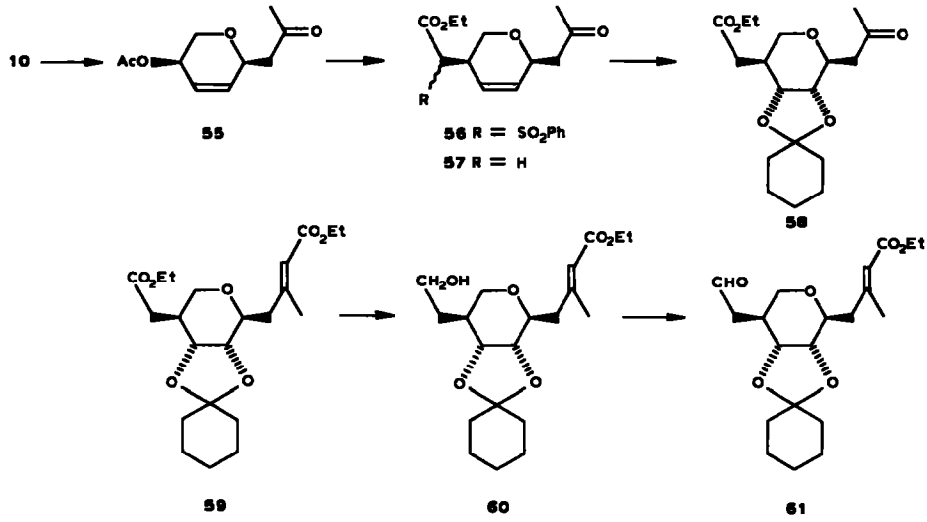


15 53 54

this case, the pendant C-2 side-chain is in position *cis* to the metal in the intermediate π-allyl palladium complex **47** and is not in a position to control the approach of an incoming nucleophile. The aforementioned regiochemical preferences are in full accord with previous observations in Pd(0)-catalyzed displacements of carbohydrate-derived allylic acetate compounds[40].

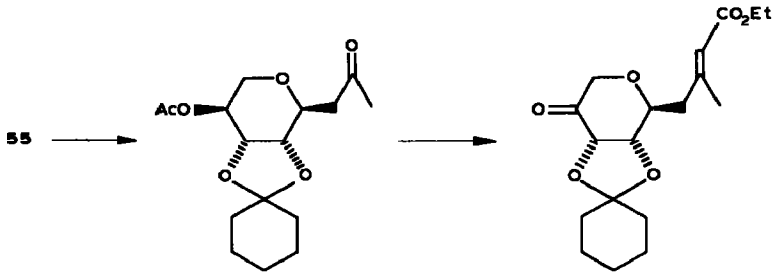
To complete the approach to pseudomonic acid C, a suitable function group differentiation was then required. Unstable acid **10** was converted directly into the methyl ketone **55** *via* a reaction of the derived acid chloride with lithium dimethyl cuprate. Alternatively, a mixed-anhydride method was also employed[41]. Palladium(0) catalyzed coupling of **55** with ethyl phenylsulfonylacetate provided **56** as a 1:1 mixture of diastereomers. Direct sodium amalgam reduction[42] of the mixture provided a single product **57** in high yield. The use of the more acidic additive sodium dihydrogenphosphate rather than the standard disodiumhydrogen phosphate was essential in this reductive desulfonylation to prevent base-catalytic side reactions, including hydrolysis and transesterification. Standard catalyzed osmylation and protection of the resultant diol as the cyclohexylidene acetal provided the ketoester **58**. After standard olefination, the *E*-olefin **59** was isolated as the major product, along with the corresponding *Z* isomer (3:1 ratio).

Finally, the two esters present in **59** were differentiated by reduction. Treatment of **59** with *in situ* generated lithium butyl(diisobutyl)aluminum hydride complex[43] (1.2 equiv.) provided a 1:1 mixture of **60** and **61** along with a small proportion of recovered **59**; it should be noted that both products resulted from the reduction of the saturated ethyl ester. Related selective reductions of saturated ketones in the presence of unsaturated ketones have previously been reported[44]. Alcohol **60** and aldehyde **61** were readily separable, and **60** was readily oxidized to **61**. Aldehyde **61** is a key intermediate in both the original Kozikowski *et al.*[8] (racemic) and Fleet *et al.*[13] (optically active) syntheses of pseudomonic acid C, and spectra



obtained from **61** compared favorably with authentic spectra kindly provided by the aforementioned authors.

For completion of the synthesis of **1**, a short sequence of olefination, ester interchange, and deprotection was required. In comparison to other syntheses, this approach is most direct and efficient. Only nine steps were required for the conversion of **4** into the highly functionalized aldehyde **61**, which means that a twelve-step, formal, total synthesis of pseudomonic acid C is at hand. Although we have not investigated further modifications, further abbreviation of the sequence of reactions is possible. Ester interchange may be omitted by use of the appropriate phosphonate in the olefination reaction[14,15], and use of a more functionalized intermediate in the palladium(0)-catalyzed alkylation might provide a more convergent approach to side-chain introduction. The latter modification might indeed be attractive owing to problems inherent[8,12–15] in the olefination of **61**. Finally, a highly functionalized intermediate **63** for the synthesis of pseudomonic acid A analogs is readily available from **55**. Hydroxylation and protection of **55** provided **62**. Subsequent olefination, acetate cleavage, and oxidation gave[16] **63** in short order.



62 **63**

In conclusion, the mono-Claisen rearrangement of carbohydrate glycals provides a facile and selective access to functionalized C-glycosyl compounds. When coupled with Pd(0)-catalyzed allylic alkylation, it results in a versatile route to the pseudomonic acid class of antibiotics. Perhaps more importantly, consideration of the selectivity observed in the sequential Claisen rearrangements has led to the introduction of the general principle of the vinylogous anomeric effect. It is expected that this principle will prove useful in the prediction and understanding of both the conformations and reactivity of carbohydrate glycals and related compounds.

EXPERIMENTAL

General methods. — Melting points and boiling points are uncorrected. Reported temperatures for Kugelrohr distillation refer to the temperature of the oven and are not true boiling points. Analytical t.l.c. was performed on Merck Silica Gel 60 F-254. Flash and medium-pressure column chromatography was performed on

Silica Gel 60 (230–400 mesh, ASTM). Preparative chromatography was also performed on a Waters Prep LC/system 500A HPLC using Prep PAK-500 silica gel cartridges. All reactions were performed under an N_2 atmosphere unless otherwise indicated. Oxolane, ethylene glycol dimethyl ether (DME), diethyl ether, and benzene were distilled from Na and benzophenone immediately before use. *N,N,N',N',N'',N''*-Hexamethylphosphoramide (HMPA), diisopropylamine, triethylamine, acetonitrile, and dichloromethane were distilled from CaH_2.

cis-[*(3,4-Dihydro-2H-pyran-3,4-diyl)bis(oxyethenylideneoxy)]bis[1,1-dimethylethyl)dimethylsilane*]. (**5**). — A stirred solution of diisopropylamine (925 μL, 6.6 mmol) in oxolane (4 mL) was cooled to 0° and treated with butyllithium (3.7 mL, 6.3 mmol, 1.7M in hexane) over several minutes. After being stirred for 10 min, the solution was cooled to −78° and 1,5-anhydro-2-deoxy-L-*erythro*-pent-1-enitol[19] (**4**) (600 mg, 3.0 mmol) in oxolane (4 mL) was added dropwise over 2–3 min. After 15 min, *tert*-butylchlorodimethylsilane (995 mg, 6.6 mmol) in HMPA (4 mL) was added. The resulting solution was stirred for an additional 1.5 h and poured into cold water–pentane. The pentane extract was washed with cold water and NaCl solutions, and dried ($MgSO_4$). Evaporation under reduced pressure gave **5** (1.28 g, 100%), yellow viscous liquid; ^{1}H-n.m.r. (C_6D_6): δ 6.15 (d, 1 H, *J* 6 Hz, H-2), 4.83 (dd, 1 H, *J* 6, 4 Hz, H-3), 4.43 (m, 1 H, H-4), 4.17 (dt, 1 H, *J* 9, 4 Hz, H-5), 4.08 (t, 1 H, *J* 9 Hz, H-6*a*), 3.83 (ddd, 1 H, *J* 9, 4, and 1 Hz, H-6*e*), 3.56 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.50 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.27 (d, 1 H, *J* 4 Hz, $=CH_2$), 3.32 (d, 1 H, *J* 4 Hz, $=CH_2$), 0.98 (s, 9 H, SiC_4H_9), 0.96 (s, 9 H, SiC_4H_9), 0.27 (s, 3 H, $SiCH_3$), 0.25 (s, 3 H, $SiCH_3$), 0.23 (s, 3 H, $SiCH_3$), and 0.21 (s, 3 H, $SiCH_3$).

*Methyl (2*R-cis*)-5-acetoxy-5,6-dihydro-2H-pyran-2-acetate* (**9**). — Ketenesilyl acetal **5** (531 mg, 1.24 mmol) was dissolved in chloroform (3 mL) and stirred for 6 h at 60°. After concentration, the residue was dissolved in HMPA (2 mL) and stirred for 12 h with water (130 μL, 7.4 mmol), KF (432 mg, 7.4 mmol), and $KHCO_3$ (745 mg, 7.4 mmol). Methyl iodide (1.23 mL) was added and the mixture stirred for an additional 12 h. Extraction with ether, followed by chromatography (1:3 ethyl acetate–hexane) afforded **9** (130 mg, 49%), clear oil; $[\alpha]_D^{25}$ −146° (*c* 0.92, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1430, 1370, 1200, 1040, and 740 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.02 (m, 2 H, H-3,4), 5.00 (m, 1 H, H-5), 4.49 (m, 1 H, H-2), 4.06 (d, 1 H, *J* 12 Hz, H-6*e*), 3.80 (dd, 1 H, *J* 12, 4 Hz, H-6*a*), 3.74 (s, 3 H, OCH_3), 2.68 (dd, 1 H, *J* 15, 7 Hz, CH_2CO_2), 2.55 (dd, 1 H, *J* 15, 5 Hz, CH_2CO_2), and 2.11 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 196, 184, 154, 142, and 141.

Anal. Calc. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.40.

*(2*R-cis*)-5-Acetoxy-5,6-dihydro-2H-pyran-2-acetic acid* (**10**). — Compound **4** (2.21 g,.11.0 mmol) was converted into the bis(ketenesilyl)acetal **5** as described above. This was dissolved in chloroform (40 mL) and stirred for 6 h at 60°. After evaporation of the chloroform solution, the residue was dissolved in acetonitrile (20 mL), and KF (3.84 g, 66 mmol), water (1.2 mL, 66 mmol), and $KHCO_3$ (6.61 g, 66 mmol) were added. The mixture was stirred for 15 h at 25° and poured into water (150 mL). The aqueous solution was washed with ether, acidified to pH 3

with 6M HCl saturated with NaCl, and extracted with ethyl acetate. The extract was washed with NaCl solution, dried ($MgSO_4$), and evaporated to give **10** (1.41 g, 64.2%), thick oil, which was used for the next step without further purification. It crystallized upon standing, m.p. 68–70°; $\nu_{max}^{CHCl_3}$ 3600–2300, 1710, 1370, 1200, 1080, 1040, 960, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.02 (br. s, 2 H, H-2,3), 5.02 (br. s, 1 H, H-2), 4.47 (m, 1 H, H-5), 4.10 (d, 1 H, *J* 12.9 Hz, H-6*e*), 3.82 (dd, 1 H, *J* 12.9, 2.8 Hz, H-6*a*), 2.71 (dd, 1 H, *J* 16, 8.3 Hz, CH_2CO_2), and 2.63 (dd, 1 H, *J* 16, 5.7 Hz, CH_2CO_2).

(1S,6S)2,7-Dioxabicyclo[4,3,5]non-4-en-8-one[11] (**8**). — Acid **10** (980 mg, 4.89 mmol) resolidified after being kept for three days at 25°. Flash-column chromatography of the resulting black solid on silica gel with 1:1 ethyl acetate–hexane afforded **8** (200 mg, 43.9%), white crystalline solid; m.p. 88–90°; $\nu_{max}^{CHCl_3}$ 3020, 1770, 1340, 1260–1160, 1100, 1050, 990, and 720 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 6.28 (ddq, 1 H, *J* 11.5, 4.60, 1.1 Hz, H-5), 6.10 (m, 1 H, H-4), 4.56 (m, 1 H, H-3), 4.28 (dd, 1 H, *J* 4.6, 3.5 Hz, H-6*a*), 4.22 (ddd, 1 H, *J* 18.4, 4.6, 2.3 Hz, H-6*b*), 4.1 (ddd, 1 H, *J* 18.4, 4.6, 2.3 Hz, H-6*a*), 2.84 (dd, 1 H, *J* 18.4, 4.6 Hz, H-7*a*), and 2.64 (d, 1 H, *J* 18.4 Hz, H-7*b*); m.s. *m/z* 140 (M^+), 96, 84, and 70; lit.[11] (racemic) m.p. 71–72°.

Dimethyl (5R-cis)-5,6-dihydro-2H-pyran-5,6-bisacetate (**11**). — Compound **5** was heated at reflux in toluene (16 h), and then methylated as described for **9**. Purification by flash chromatography (1:4 ethyl acetate–hexane) gave **11**; $\nu_{max}^{CHCl_3}$ 3000, 2900, 1720, 1440, 1300–1160, 1080, and 990 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.92–5.83 (m, 1 H, H-5), 5.73 (br. d, 1 H, *J* 12 Hz, H-4), 4.25–4.11 (m, 3 H, H-2,6*e*,6*a*), 3.71 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3, and 2.62–2.31 (m, 5 H, 2 CH_2CO_2, H-2); m.s.: *m/z* 228 (M^+), 196, 169, 154, 108, and 98; m.s. calc. for $C_{11}H_{16}O_5$, 228.0998; found, 228.0990.

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 58.01; H, 7.02.

3,4-Di-O-acetyl-1,5-anhydro-2,6-dideoxy-L-ribo-1-enitol (**24**). — To a stirred solution of 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol[45] (**18**; 1.42 g, 10.9 mmol) in chloroform (25 mL) was added MnO_2 (10.9 g). After stirring for 36 h at 25°, the mixture was filtered and the filter cake washed with chloroform. Concentration of the organic layer, followed by flash-column chromatography (2:1 ethyl acetate–hexane) gave 1,5-anhydro-2,6-dideoxy-L-*erythro*-hex-1-en-3-ulose[45] (807 mg, 58%), white crystals, m.p. 92.5–93°, lit.[45] (for enantiomer) 87°; ^{1}H-n.m.r. ($CDCl_3$): δ 7.38 (d, 1 H, *J* 5.7 Hz), 5.45 (d, 1 H, *J* 5.7 Hz), 4.19 (m, 1 H), 3.96 (dd, 1 H, *J* 12.9, 1.8 Hz), 3.5 (d, 1 H, *J* 1.8 Hz), and 1.57 (d, 3 H, *J* 6.0 Hz).

To a warmed solution of lithium tri(*tert*-butoxy)aluminium hydride (45.4 mg, 0.18 mmol) in oxolane at 60° was added the aforementioned enone (17.6 mg, 0.14 mmol) in oxolane (1 mL). The mixture was heated for 2 h, cooled, and extracted with ether, followed by concentration of the ethereal solution to give 1,5-anhydro-2,6-dideoxy-L-*ribo*-1-enitol (13.6 mg) as a yellow liquid. Flash column chromatography of the residue (1:2 ethyl acetate–hexane) afforded the pure diol (6.2 mg, 34%), white solid, m.p. 116°, lit.[46] (for enantiomer) m.p. 115.3°, $[\alpha]_D^{25}$ −335° (*c* 0.185, methanol), lit.[46] (for enantiomer) +314° (*c* 1.03, methanol); ^{1}H-n.m.r. ($CDCl_3$): δ 6.43 (d, 1 H, *J* 5.9 Hz), 4.95 (t, 1 H, *J* 5.4 Hz), 4.09 (m, 1 H), 3.80 (m,

1 H), 3.48 (td, 1 H, *J* 9.3, 4.3 Hz), 2.53 (d, 1 H, *J* 9.3 Hz), 1.79 (d, 1 H, *J* 6.1 Hz), and 1.39 (d, 3 H, *J* 3.6 Hz).

Standard acetylation with acetic anhydride and pyridine of the just described compound (14.8 mg, 0.11 mmol) gave **24** (23.1 mg, 98%), white crystals, m.p. 52–53°, lit.[47] (for enantiomer) m.p. 51.5°; ^{1}H-n.m.r. ($CDCl_3$): δ 6.49 (d, 1 H, *J* 5.9 Hz), 5.40 (dd, 1 H, *J* 5.7, 4.0 Hz), 4.86 (m, 2 H), 4.17 (m, 1 H), 2.07 (s, 3 H), 2.05 (s, 3 H), and 1.29 (d, 3 H, *J* 6.3 Hz).

Standard preparation of ketenesilyl acetals from acetates. — trans-[*(3,4-Dihydro-2H-pyran-3,4-diyl)bis(oxyethenylideneoxy)]bis[(1,1-dimethylethyl)dimethylsilane*] (**13**). A solution of diisopropylamine (1.6 mL, 11.6 mmol) in oxolane (20 mL) was cooled to 0° and treated with butyllithium (6.9 mL, 11.1 mmol, 1.6M in hexane) over several min. After the mixture had been stirred for an additional 10 min, it was cooled to −78° and a mixture of 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol[47] (**12**) (1.06 g, 5.29 mmol) and *tert*-butylchlorodimethylsilane (1.75 g, 11.6 mmol) in HMPA (10 mL) was added. Completion of this experiment as described for **4** gave **13** (2.17 g, 95.7%), clear oil; ^{1}H-n.m.r. ($CDCl_3$): δ 6.33 (d, 1 H, *J* 7 Hz), 4.9–4.85 (m, 1 H), 4.52–4.46 (m, 1 H), 4.22 (m, 1 H), 4.03 (m, 1 H), 3.80 (m, 1 H), 3.56 (d, 1 H, *J* 2.5 Hz), 3.54 (d, 1 H, *J* 2.5 Hz), 3.40 (d, 1 H, *J* 4 Hz), 3.30 (d, 1 H, *J* 4 Hz), 0.97 (s, 9 H), 0.96 (s, 9 H), 0.17 (s, 6 H), and 0.15 (s, 6 H).

General Claisen rearrangement of ketenesilyl acetals (^{1}H-n.m.r. study). — Ketenesilyl acetal (~10 mg; 0.5 mL) in an appropriate solvent (C_6D_6 or $CDCl_3$) was placed in an n.m.r. tube under N_2 and then heated in an oil bath at the desired temperature. After an appropriate time-period, the solution was cooled to room temperature. The regions of peaks typical of ketenesilyl acetals and silyl esters (rearranged product) were scanned by ^{1}H-n.m.r. spectroscopy and integrated.

Methyl (2R,5S)-5-acetoxy-5,6-dihydro-2H-pyran-2-acetate (**15**). — Ketenesilyl acetal **13** was heated for 1 h at 65°, followed by standard methylation as described above, to give **15** (59%), clear oil, $[\alpha]_D^{25}$ +114° (*c* 1.22, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1750, 1430, 1360, 1200, 1160, 1090, 1040, 990, 950, 920, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.95 (m, 2 H, H-3,4), 5.21 (m, 1 H, H-5), 4.61 (m, 1 H, H-2), 4.07 (dd, 1 H, *J* 11.7, 4.9 Hz, H-6), 3.71 (s, 3 H, OCH_3), 3.58 (dd, 1 H, *J* 11.7, 6.2 Hz, H-6), 2.60 (dd, 1 H, *J* 15.4, 8.4 Hz, CH_2CO_2), 2.48 (dd, 1 H, *J* 15.4, 5.6 Hz, CH_2CO_2), and 2.06 (s, 3 H, $COCH_3$); m.s.: *m/z* 184, 154, and 141; m.s. calc. for $C_9H_{12}O_4$ (M − CH_2O), 184.0736; found, 184.0736.

Dimethyl (5S,6R)-5,6-dihydro-2H-pyran-5,6-bisacetate (**17**). — Prepared in benzene for 2 days at 65° (yield 20%), $[\alpha]_D^{25}$ −107° (*c* 0.275, chloroform); $\nu_{max}^{CHCl_3}$ 2950, 2840, 1730, 1440, 1360, 1280–1200, 1160, 1120, 1080, and 1020 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.78 (dq, 1 H, *J* 10.3, 2.2 Hz, H-4 or -5), 5.70 (dq, 1 H, *J* 10.3, 2.5 Hz, H-4 or -5), 4.14 (m, 2 H, H-6*a*,6*e*), 3.83 (q, 1 H, *J* 7 Hz, H-2), 3.71 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 2.58 (d, 2 H, *J* 6.5 Hz, CH_2CO_2), 2.56 (m, 1 H, H-3), 2.44 (dd, 1 H, *J* 15.5, 5.6 Hz, CH_2CO_2), and 2.27 (dd, 1 H, *J* 15.5, 8.3 Hz, CH_2CO_2); m.s. calc. for $C_{11}H_{16}O_5$, 228.0998; found, 228.0998.

Methyl (2S,5R,6S)-5-acetoxy-6-methyl-5,6-anhydro-2H-pyran-2-acetate (**21**). — Prepared in benzene for 1 h at 60° (yield 53%), $[\alpha]_D^{25}$ −136.5° (*c* 1.085, chloroform); $\nu_{max}^{CHCl_3}$ 2930, 2800, 1730, 1430, 1370, 1275, 1200, 1130, 1100, 1070, 1040, 1020, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.82 (dt, 1 H, *J* 10.3, 1.4 Hz, H-3), 5.72 (dt, 1 H, *J* 10.3, 1.8 Hz, H-4), 5.02 (m, 1 H, H-5), 4.57 (m, 1 H, H-2), 3.62 (s, 3 H, OCH_3), 3.62 (m, 1 H, H-6), 2.57 (dd, 1 H, *J* 15.5, 7.6 Hz, CH_2CO_2), 2.46 (dd, 1 H, *J* 15.6, 6.3 Hz, CH_2CO_2), 2.07 (s, 3 H, $OCOCH_3$), and 1.22 (d, 3 H, *J* 6.1 Hz, CH_3).

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.65; H, 7.13.

Dimethyl (2S,5R,6S)-2-methyl-5,6-dihydro-2H-pyran-5,6-bisacetate (**23**). — Prepared in benzene for 6 days at 60° (yield 29%), $[\alpha]_D^{25}$ +107.5° (*c* 0.73, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 2950, 1740, 1430, 1200, 1160, 1150, and 990 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.65 (m, 1 H, H-4 or -5), 5.62 (m, 1 H, H-4 or -5), 4.21 (m, 1 H, H-6), 3.75 (dd, 1 H, *J* 8.0, 3.5 Hz, H-2), 3.70 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 2.59 (dd, 1 H, *J* 15.5, 3.5 Hz, CH_2CO_2), 2.55 (m, 1 H, H-3), 2.50 (dd, 1 H, *J* 11.5, 8.7 Hz, CH_2CO_2), 2.36 (dd, 1 H, *J* 15.6, 4.7 Hz, CH_2CO_2), 2.16 (dd, 1 H, *J* 15.6, 9.1 Hz, CH_2CO_2), and 1.18 (d, 3 H, *J* 6.8 Hz, CH_3).

Anal. Calc. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.29; H, 7.29.

Methyl (2R,5R,6S)-5-acetoxy-6-methyl-5,6-dihydro-2H-pyran-2-acetate (**27**). — Prepared in benzene for 2 h at 60° (yield 40%), $[\alpha]_D^{25}$ −127.5° (*c* 0.765, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1740, 1650, 1380, 1240, 1110, 1080, 1020, 930, and 900 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.93 (br. d, 1 H, *J* 10.3 Hz, H-3 or -4), 5.81 (br. d, 1 H, *J* 10.3 Hz, H-3 or -4), 4.90 (s, 1 H, H-5), 4.64 (m, 1 H, H-2), 3.87 (m, 1 H, H-6), 3.72 (s, 3 H, OCH_3), 2.70 (dd, 1 H, *J* 15.3, 8.4 Hz, CH_2CO_2), 2.53 (dd, 1 H, *J* 15.3, 5.7 Hz, CH_2CO_2), 2.08 (s, 3 H, $OCOCH_3$), and 1.23 (d, 3 H, *J* 6.5 Hz, CH_3); m.s. calc. for $C_9H_{12}O_4$ (M − CH_3CHO), 184.0736; found, 184.0736.

Dimethyl (2R,5R,6S)-2-methyl-5,6-dihydro-2H-pyran-5,6-bisacetate (**29**). — Prepared in benzene for 48 h at 60° (yield 9%), $[\alpha]_D^{25}$ +220° (*c* 0.13, chloroform); $\nu_{max}^{CHCl_3}$ 2950, 1730, 1440, 1370, 1300–1160, 1050, and 1000 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.83 (ddd, 1 H, *J* 10.1, 5.2, 2.2 Hz, H-4 or -5), 5.69 (dd, 1 H, *J* 10.3, 2.5 Hz, H-5 or -4), 4.33–4.28 (m, 2 H, H-2,6), 3.70 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.56–2.45 (m, 2 H, H-3, CH_2CO_2), 2.43 (dd, 1 H, *J* 6.0, 3.6 Hz, CH_2CO_2), 2.40 (dd, 1 H, *J* 12.8, 2.0 Hz, CH_2CO_2), 2.30 (dd, 1 H, *J* 15.4, 8.3 Hz, CH_2CO_2), and 1.22 (d, 3 H, *J* 6.9 Hz, CH_3); m.s. calc. for $C_{12}H_{18}O_5$, 242.1154; found, 242.1155.

Methyl (2R,5S,6R)-5-acetoxy-6-(acetyloxymethyl)-5,6-dihydro-2H-pyran-2-acetate (**33**). — Prepared in benzene for 1.5 h at 60° (yield 55%), $[\alpha]_D^{25}$ +113° (*c* 0.75, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1740, 1470, 1390, 1230, 1150, and 1080 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.88 (d, 1 H, *J* 10.3 Hz, H-3 or -4), 5.76 (d, 1 H, *J* 10.3 Hz, H-3,4), 5.26 (dm, 1 H, *J* 7.8 Hz, H-5), 4.62 (m, 1 H, H-2), 4.18 (m, 2 H, CH_2OAc), 3.72 (m, 1 H, H-6), 3.70 (s, 3 H, OCH_3), 2.63 (dd, 1 H, *J* 15.5, 7.0 Hz, CH_2CO_2), 2.48 (dd, 1 H, *J* 15.57 Hz, CH_2CO_2), 2.08 (s, 3 H, $OCOCH_3$), and 2.07 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 226, 213, 184, and 142; m.s. calc. for $C_{11}H_{14}O_5$ (M − AcOH), 226.0841; found, 226,0841.

Anal. Calc. for $C_{13}H_{16}O_5$: C, 54.45; H, 6.34. Found: C, 54.26; H, 6.23.

Dimethyl (2S,5S,6R)-2-(acetoxymethyl)-5,6-dihydro-2H-pyran-5,6-bisacetate (**35**). — Prepared in benzene for 4 d at 60° (yield 13%), $[\alpha]_D^{25}$ −106.5° (*c* 0.555, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1760, 1430, 1370, 1200, and 980 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.77 (br. d, 1 H, *J* 10.4 Hz, H-4 or -5), 5.67 (br. d, 1 H, *J* 10.4 Hz, H-4 or -5), 4.33 (m, 1 H, H-6), 4.07 (m, 1 H, CH_2OAc), 3.77 (td, 1 H, *J* 8.5, 3.7 Hz, H-2), 3.69 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 2.63 (m, 2 H, CH_2CO_2, H-3), 2.53 (dd, 1 H, *J* 16.3, 9.1 Hz, CH_2CO_2), 2.37 (dd, 1 H, *J* 15.9, 4.8 Hz, CH_2CO_2), 2.18 (dd, 1 H, *J* 15.9, 4.8 Hz, CH_2CO_2), and 2.05 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 269, 240, 227, 167, and 153; m.s. calc. for $C_{13}H_{17}O_6$ (M − OCH_3), 269.1205; found, 269.1204.

Anal. Calc. for $C_{14}H_{20}O_7$: C, 56.00; H, 6.71; Found: C, 55.91; H, 6.86.

Methyl cis-*4-acetoxy-2-cyclohexene-1-acetate.* — Prepared in benzene for 18 h at 60° and purified by chromatography in 1:3 ethyl acetate–hexane. This monoester was isolated from a mixture of **38** and **39** by the methylation procedure described for **9** (yield 25%); $\nu_{max}^{CHCl_3}$ 3000, 2940, 1720, 1500, 1430, 1370, 1220, 1000, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.85 (dd, 1 H, *J* 10, 1 Hz), 5.78 (m, 1 H), 5.22 (m, 1 H), 3.71 (s, 3 H), 2.58 (m, 1 H), 2.41 (dd, 1 H, *J* 15, 6 Hz), 2.34 (dd, 1 H, *J* 15, 7 Hz), 2.34 (dd, 1 H, *J* 15, 7 Hz), 2.06 (s, 3 H), and 1.9–1.7 (m, 4 H); m.s.: *m/z* 170 (M^+), 153, 152, 139, and 96; m.s. calc. for $C_9H_{14}O_3$, 170.0943; found, 170.0943.

Dimethyl cis-*3-cyclohexene-1,2-diacetate.* — This diester was isolated from a mixture of **38** and **39** by the methylation procedure described for **9** (yield 10%): $\nu_{max}^{CHCl_3}$ 2925. 1730, 1435, 1300–1160, 1000, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$):δ 5.17 (m, 1 H), 5.56 (m, 1 H), 4.69 (s, 3 H), 4.68 (s, 3 H), 2.77 (m, 1 H), 2.4–2.14 (m, 6 H), 2.06 (m, 1 H), and 1.70–1.4 (m, 2 H); m.s.: *m/z* 226 (M^+), 195, 194, and 152; m.s. calc. for $C_{12}H_{18}O_4$, 226.1205; found, 226.1205.

Methyl 5,6-dihydro-2H-pyran-2-acetate. — Prepared in chloroform for 30 min at 60° (yield 60.3%), $\nu_{max}^{CHCl_3}$ 3000–2850, 1730, 1430, 1360, 1280–1160, 1080, 990, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.9 (m, 1 H), 5.66 (ddd, 1 H, *J* 10, 5, 2.5 Hz), 4.56 (m, 1 H), 3.96 (m, 1 H), 3.70 (s, 3 H), 3.71–3.65 (m, 1 H), 2.59 (dd, 1 H, *J* 15.8, 7.5 Hz), 2.48 (dd, 1 H, *J* 15, 5 Hz), 2.35–2.16 (m, 1 H), and 1.96 (d, 1 H, *J* 15 Hz); m.s.: *m/z* 156 (M^+), 124, 96, 83, 82, 58 and 43; m.s. calc. for $C_8H_{12}O_3$, 156.0786; found, 156.0784.

Anal. Calc. for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.29; H, 7.72.

Methyl (2R,5S)-5-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-2H-pyran-2-acetate (**48**). — Prepared from **9** (68 mg) by the procedure described for **56** and purified by l.c. (1:4 ethyl acetate–hexane) to give 133 mg (96%), clear oil, $[\alpha]_D^{25}$ −115° (*c* 0.480, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1440, 1380, 1300, 1180, 1100, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.86 (ddt, 1 H, *J* 10, 5, 1.5 Hz, H-4), 5.78 (dt, 1 H, *J* 10, 1 Hz, H-3), 4.53 (m, 1 H, H-2), 4.2 (m, 4 H, CO_2CH_2), 3.89 (dt, 1 H, *J* 12, 1.5 Hz, H-6*e*), 3.77 (dd, 1 H, *J* 12, 4 Hz, H-6*a*), 3.72 (s, 3 H, OCH_3), 3.55 [d, 1 H, *J* 10 Hz, $CH(CO_2Et)_2$], 2.78 (m, 1 H, H-5), 2.56 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 2.48 (dd,

1 H, *J* 15, 5 Hz, CH_2CO_2), and 1.3 (overlapping t, 6 H, 2 $CO_2CH_2CH_3$); m.s.: *m/z* 283, 251, and 154; m.s. calc. for $C_{13}H_{17}O_6$ (M − OEt), 269.1025; found, 269.1025.

Anal. Calc. for $C_{15}H_{22}O_7$: C, 57.35; H, 7.06. Found: C, 57.15; H, 7.01.

Methyl (2S,3R,4R,5S)-5-[bis(ethoxycarbonyl)methyl]-3,4-dihydroxytetrahydropyran-2-acetate (**49**). — This compound was prepared, by the procedure described for **57**, from **48** (60 mg, 0.19 mmol) to give 65.5 mg (99%), clear oil, $[\alpha]_D^{25}$ −15.8° (*c* 0.576, chloroform); $\nu_{max}^{CHCl_3}$ 3550, 3000, 1740, 1480, 1450, 1380, 1310, 1250, 1190, 1110, 1070, 1030, and 860 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.2 (m, 2 H), 4.0–3.85 (m, 2 H), 3.71 (s, 3 H), 3.60 (m, 2 H), 3.02 (m, 2 H), 2.81 (dd, 1 H, *J* 16, 4 Hz), 2.62 (d, 1 H, *J* 12 Hz), 2.54 (dd, 1 H, *J* 14, 8 Hz), and 1.27 (q, 6 H, *J* 8 Hz); m.s.: *m/z* 330, 317, and 161; m.s. calc. for $C_{15}H_{22}O_8$ (M − H_2O), 330.1315; found, 330.1315.

Methyl (2S,3R,4R,5S)-3,4-diacetoxy-5-[bis(ethoxycarbonyl)methyl]tetrahydropyran-2-acetate (**50**). — $[\alpha]_D^{25}$ −14.8° (*c* 0.426, chloroform); $\nu_{max}^{CHCl_3}$ 1735 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.31 (br. t, 1 H, *J* 3 Hz, H-4), 4.86 (dd, 1 H, *J* 10, 7 Hz, H-3), 4.4–4.2 (m, 4 H, CO_2CH_2), 3.98 (dd, 1 H, *J* 12.6, 3 Hz, H-6*e*), 3.77 [d, 1 H, *J* 11.1 Hz, $CH(CO_2Et)_2$], 3.75 (d, 1 H, *J* 12.6 Hz, H-6*a*), 3.72 (s, 3 H, OCH_3), 2.62 (br. d, 1 H, H-5), 2.55 (dd, 1 H, *J* 16, 9 Hz, CH_2CO_2), 2.47 (dd, 1 H, *J* 16, 3.7 Hz, CH_2CO_2), 2.12 (s, 3 H, $OCOCH_3$), 1.98 (s, 3 H, $OCOCH_3$), 1.34 (t, 3 H, $CO_2CH_2CH_3$), and 1.28 (t, 3 H, $CO_2CH_2CH_3$); m.s.: *m/z* 433 (M + H) and 387; m.s. calc. for $C_{18}H_{25}O_{10}$ (M − OCH_3), 401.1448; found, 401.1448.

Anal. Calc. for $C_{19}H_{28}O_{11}$: C, 52.78; H, 6.52. Found: C, 52.61; H, 6.33.

Methyl (2S,3R,4R,5S)-3,4-dibenzoyloxy-5-[bis(ethoxycarbonyl)methyl]tetrahydropyran-2-acetate (**51**). — $\nu_{max}^{CHCl_3}$ 1735 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 8.03 (dd, 2 H, *J* 8, 2 Hz), 7.85 (dd, 2 H), 7.6–7.2 (m, 6 H), 5.68 (br. t, 1 H, *J* 3.0 Hz), 5.22 (dd, 1 H, *J* 9.8, 3.1 Hz), 4.47 (ddd, 1 H, *J* 9.8, 8.1, 5.0 Hz), 4.35 (m, 2 H), 4.22 (m, 2 H), 4.19 (dd, 1 H, *J* 12, 3 Hz), 3.93 (d, 1 H, *J* 10.9 Hz), 3.88 (dt, 1 H, *J* 12, 1 Hz), 3.65 (s, 3 H), 2.87 (br. d, 1 H, *J* 10.9 Hz), 2.64 (dd, 1 H, *J* 15.3, 5 Hz), 2.61 (dd, *J* 15.3, 8.1 Hz), 2.37 (t, 3 H), and 1.29 (t, 3 H); m.s.: *m/z* 511, 319, and 274; m.s. calc. for $C_{28}H_{29}O_{10}$ (M − OCH_3), 525.1759; found, 525.1761.

Methyl (2R,4R)-5-[bis(ethoxycarbonyl)methyl]-5,6-dihydro-2H-pyran-2-acetate (**53**). — By the procedure described for **56**, **33** (9.4 mg) gave a 9:5 mixture of **53** and regioisomer **54** (5.7 mg, 42%). Flash-column chromatography of the mixture on silica gel with 1:2 ethyl acetate–hexane gave pure **53** (3.9 mg, 29%), clear oil; $\nu_{max}^{CHCl_3}$ 2980, 1720, 1440, 1370, 1330, 1300–1160, 1020, and 850 cm^{-1}; ^{1}H-n.m.r. (C_6D_6): δ 5.90 (dt, 1 H, *J* 12, 2.5 Hz, H-3 or -4), 5.50 (dt, 1 H, *J* 12, 2 Hz, H-3 or -4), 4.56 (m, 1 H, H-2), 4.0–3.8 (m, 5 H, CO_2CH_2, H-6), 3.57 (dd, 1 H, *J* 12, 7 Hz, H-6), 3.32 [d, 1 H, *J* 7.5 Hz, $CH(CO_2Et)_2$], 3.30 (s, 3 H, OCH_3), 3.14 (m, 1 H, H-5), 2.49 (dd, 1 H, *J* 18, 12 Hz, CH_2CO_2), 2.14 (dd, 1 H, *J* 18, 6 Hz, CH_2CO_2), and 0.94–0.97 (m, 6 H, 2 $CO_2CH_2CH_3$).

Isomer **54** could not be isolated in pure form. The following peaks were assigned from the ^{1}H-n.m.r. spectrum (C_6D_6) of the mixture: δ 5.85 (m, 1 H, H-4 or -5), 5.40 (dq, 1 H, *J* 10, 1 Hz, H-4 or -5), 4.4 (m, 1 H, H-2), 3.91 (m, 6 H, CO_2CH_2,

H-6*a*,6*e*), 3.69 [d, 1 H, *J* 7 Hz, $CH(CO_2Et)_2$], 3.33 (s, 3 H, OCH_3), 2.92 (m, 1 H, H-4), 2.60 (dd, 1 H, *J* 15, 10 Hz, CH_2CO_2), 2.39 (dd, 1 H, *J* 15, 5 Hz, CH_2CO_2), and 1.85 (m, 6 H, 2 $CO_2CH_2CH_3$).

*Methyl (2*R*,5*S*,6*S*)-5-[bis(ethoxycarbonyl)methyl]-6-methyl-5,6-dihydro-2*H*-pyran-2-acetate* (**52**). — Prepared by the procedure described for **56**; $\nu_{max}^{CHCl_3}$ 2980, 1725, 1440, and 1370 cm^{-1}; ^{1}H-n.m.r. (C_6D_6): δ 5.84 (dd, 1 H, *J* 10, 5 Hz, H-3), 5.55 (d, 1 H, *J* 10 Hz, H-4), 4.55 (m, 1 H, H-2), 4.15 (br. q, 1 H, H-6), 4.0–3.8 (m, 4 H, 2 CO_2CH_2), 3.69 [d, 1 H, *J* 8 Hz, $CH(CO_2Et)_2$], 3.31 (s, 3 H, OCH_3), 2.74 (m, 1 H, H-5), 2.49 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 2.25 (dd, 1 H, *J* 15, 8 Hz, CH_2CO_2), 1.17 (d, 3 H, *J* 7 Hz, CH_3), 0.91 (t, 3 H, $CO_2CH_2CH_3$), and 0.86 (t, 3 H, $CO_2CH_2CH_3$); m.s.: *m/z* 328 (M^+), 282, 255, and 168.

*(2*R*-cis)-1-(5-Acetoxy-5,6-dihydro-2*H*-pyran-2-yl)-2-propanone.* (**55**). — To a stirred solution of **10** (50.7 mg, 0.25 mmol) in oxolane (1 mL) containing triethylamine (35 μL, 0.25 mmol) at −10° was added a solution of *o*-anisoyl chloride (35 μL, 0.25 mmol) in oxolane (1 mL). The resulting mixture was stirred for 0.5 h at the same temperature and then cooled to −78°. To this was added dropwise methylmagnesium bromide (88 μL, 0.26 mmol, 2.8M in ether). After stirring for 0.5 h, the reaction was quenched with 10% NH_4Cl solution and extracted with ether (2 × 50 mL). The combined extracts were washed with sat. $NaHCO_3$ solution, water, and NaCl solution, and dried ($MgSO_4$). Concentration of the ether solution gave **55** (31.2 mg) clear oil unstable to storage. Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded pure **55** (12.9 mg, 41.2%), colorless oil, $[\alpha]_D^{25}$ −158° (*c* 1.21, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1715, 1400, 1380, 1200, 1090, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.97 (m, 2 H, H-3,-4), 5.11 (m, 1 H, H-5), 4.50 (m, 1 H, H-2), 4.06 (d, 1 H, *J* 12.3 Hz, H-6), 3.77 (dd, 1 H, *J* 12.3, 2.8 Hz, H-6), 2.82 (dd, 1 H, *J* 16.6, 7.6 Hz, CH_2CO), 2.59 (dd, 1 H, *J* 16.6, 5.5 Hz, CH_2CO), 2.21 (s, 3 H, $COCH_3$), and 2.09 (s, 3 H, $OCOCH_3$); m.s.: *m/z* 168 (M − HCHO), 138, 126, 96, 81, and 43; m.s.: calc. for $C_9H_{12}O_3$, 168.0786; found, 168.0782.

*Ethyl {3*S*-[3α-(*S**),6α]}-6-(2-oxopropyl)-α-(phenylsulfonyl)-3,6-dihydro-2*H*-pyran-2-acetate*[38,40] (**56**). — To oil-free NaH (108 mg, 4.5 mmol) in oxolane (5 mL) was added ethyl phenylsulfonylacetate (1.03 g, 4.4 mmol) in oxolane (5 mL), and the mixture was stirred for 30 min at 25°. To the resulting turbid solution, *N,N*-dimethylformamide (3 mL) was added and the mixture centrifuged under N_2. The clear solution (12.6 mL, 4.36 mmol) was added to a mixture of **55** (439 mg, 2.22 mmol) and $Pd(dppe)_2$ (308 mg) in oxolane (5 mL). The mixture was stirred for 4.5 h and poured into a mixture of ether (50 mL) and dilute $NaHSO_4$ solution (30 mL), and extracted with ether (2 × 100 mL). The combined ether solution was washed with water and NaCl solution, and dried ($MgSO_4$). Flash chromatography of the residue from the concentrated ether solution with 1:1 ethyl acetate–hexane gave a 1:1 mixture (690 mg, 85%) of two isomers as a clear, thick oil; $\nu_{max}^{CHCl_3}$ 3000, 1730, 1600, 1320, 1140, 1080, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 8.0–7.89 (m), 7.71–7.66 (m), 7.62–7.55 (m), 5.83–5.76 (m), 4.56 (m), 4.21 (d, *J* 5 Hz), 4.20 (d, *J* 5 Hz),

4.0–3.89 (m), 3.76 (dd, *J* 11.9, 3.2 Hz), 3.71 (m), 2.70 (dd, *J* 16.4, 7.9 Hz), 2.69 (dd, *J* 16.4, 7.9 Hz), 2.50 (ddd, *J* 16.4, 5.0, 2.5 Hz), 2.18 (s), 2.17 (s), 1.40 (t, *J* 5 Hz), and 1.20 (t, *J* 5 Hz).

*Ethyl (3*S-cis*)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran-2-acetate*[42] (**37**). — To a solution of **56** (197.3 mg, 0.54 mmol) and $NaH_2PO_4 \cdot H_2O$ (298 mg, 2.16 mmol) in methanol (6 mL), cooled to −20°, was added pulverized 6% Na–Hg (0.8 g). The resulting solution was stirred for 30 min at the same temperature and poured into water (10 mL). The aqueous solution was extracted with ether (2 × 100 mL), and the combined ether solution was washed with water and NaCl solution, and dried ($MgSO_4$). Flash-column chromatography of the residue with 1:1 ethyl acetate–hexane afforded pure **57** (99.5 mg, 81%), clear oil, $[\alpha]_D^{25}$ −73° (*c* 1.02, chloroform); $\nu_{max}^{CHCl_3}$ 3000, 1730, 1360, 1250, 1150, 1080, 1010, and 750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.86 (d, 1 H, *J* 10.1 Hz, H-4), 5.61 (d, 1 H, *J* 10.1 Hz, H-3), 4.54 (m, 1 H, H-2), 4.13 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 3.75 (m, 2 H, H-6*a*,6*e*), 2.71 (dd, 1 H, *J* 16.0, 8.1 Hz, CH_2CO_2), 2.55–2.39 (m, 4 H, 2 CH_2CO_2), 2.20 (s, 3 H, $COCH_3$), and 1.26 (t, 3 H, *J* 7.3 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 226 (M^+), 211, 138, and 81; m.s. calc. for $C_{12}H_{18}O_4$, 226.1205; found, 226.1195.

Anal. Calc. for $C_{12}H_{18}O_4$: C, 63.69; H, 8.02. Found: C, 63.56; H, 8.19.

(E)*-4,8-Anhydro-5,6-*O*-cyclohexylidene-1,3,7-trideoxy-7-*C*-(ethoxycarbonyl)methyl-*D-allo*-2-octulose* (**58**). — A mixture of **57** (164 mg, 0.73 mmol), *N*-methylmorpholine-*N*-oxide dihydrate (105.8 mg, 0.77 mmol), water (2 mL), acetone (800 μL), 1,1-dimethylpropanol (300 μL), and a catalytic amount of OsO_4 was stirred for 36 h at 25°. The resulting black mixture was stirred with $NaHSO_4$ (100 mg) for 1 h and diluted with ethyl acetate. The ethyl acetate solution was filtered through Florisil, washed with $Na_2S_2O_3$ solution and NaCl solution, and dried ($MgSO_4$). Concentration of the ethyl acetate solution gave 4,8-anhydro-1,3,7-trideoxy-7-*C*-(ethoxycarbonyl)methyl-D-*allo*-2-octulose[39] (139.1 mg, 73.2%) as a clear oil. Extraction of the aqueous layer (saturated with salt) with ethyl acetate gave additional diol (10.5 mg). This clear oil was used without further purification; $\nu_{max}^{CHCl_3}$ 3700–3150, 2930, 1720, 1360, 1320–1140, 1110, 1060, 940, and 740 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.13 (q, 2 H, *J* 7.1 Hz), 4.0–3.85 (m, 3 H), 3.52 (d, 1 H, *J* 11.7 Hz), 3.42 (d, 1 H, *J* 9.3 Hz), 2.82 (dd, 1 H, *J* 16.4, 5.0 Hz), 2.73 (dd, 1 H, *J* 16.4, 7.1 Hz), 2.55 (dd, 1 H, *J* 17.8, 10.1 Hz), 2.41–2.3 (m, 2 H), 2.22 (s, 3 H), and 1.25 (t, 3 H, *J* 7.1 Hz).

A mixture of the diol (134 mg, 0.52 mmol), cyclohexanone (647 μL, 6.24 mmol), anhydrous $CuSO_4$ (497.6 mg, 3.12 mmol), and 4-toluenesulfonic acid (1.5 mg) in benzene (12 mL) was stirred for 30 h at 25°. The mixture was filtered and the solid washed with ether. The residue from concentration of the combined benzene–ether solutions was chromatographed with 1:2 ethyl acetate–hexane to give **58** (146.3 mg, 83%), clear, thick oil, $[\alpha]_D^{25}$ +6.7° (*c* 0.975, chloroform); $\nu_{max}^{CHCl_3}$ 2930, 1720, 1360, 1260–1160, 1110, 1020, 920, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.14 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 4.07 (s, 1 H), 3.80 (dd, 1 H, *J* 7.1, 2.4 Hz), 3.73 (m, 2 H), 3.61 (d, 1 H, 11.9 Hz), 2.73–2.52 (m, 4 H, CH_2CO_2, CH_2CO),

2.4 (dd, 1 H, *J* 18.6, 9.5 Hz, H-5), 2.18 (s, 3 H, $COCH_3$), 1.8–1.3 (m, 10 H), and 1.25 (t, 3 H, *J* 7.1 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 340 (M^+), 297, 242, 207, 197, and 185; m.s. calc. for $C_{18}H_{28}O_6$, 340.1886; found, 340.1884.

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.50; H, 8.29. Found: C, 63.48; H, 8.49.

Ethyl (E)-*5,9-anhydro-6,7-O-cyclohexylidene-2,3,4,8-tetradeoxy-8-C-(ethoxycarbonyl)methyl-3-methyl*-D-allo-*non-2-enoate* (**59**). — To a stirred solution of excess sodium triethylphosphonoacetate in oxolane (5 mL of a 0.36M solution) at 25° was added a solution of **58** (60 mg, 0.18 mmol) in oxolane (1.5 mL). The mixture was stirred for 15 min at 25°, and then heated for 4 h at 60°. The cooled mixture was poured into ether, washed with NH_4Cl solution and NaCl solution, and dried ($MgSO_4$). Concentration of the ether solution gave a 3:1 mixture of *trans*-(**59**) and *cis*-isomer as a yellow oil. Medium-pressure l.c. on silica gel with 1:9 ethyl acetate–hexane afforded **59** (*E*) 31.8 mg, 43%, clear oil, $[\alpha]_D^{25}$ −8.8° (*c* 0.24, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 1730, 1700, 1640, 1450, 1370, 1340, 1270–1030, 930, and 710 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.73 (d, 1 H, *J* 1 Hz, =C–H), 4.14 (q, 2 H, *J* 6.8 Hz, CO_2CH_2), 4.13 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 3.77–3.61 (m, 2 H, H-6, -3 or -4), 3.43 (td, 1 H, *J* 9.5, 3.0 Hz, H-3 or -4), 2.61–2.38 (m, 4 H, 2 CH_2CO_2), 2.19 (d, 3 H, *J* 1.2 Hz, CH_3), 2.34–2.16 (m, 1 H, H-5), 1.72–1.26 (m, 10 H), 1.26 (t, 3 H, *J* 7.1 Hz, $CO_2CH_2CH_3$), and 1.26 (t, 3 H, *J* 6.8 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 410 (M^+), 381, 296, 283, and 267; m.s. calc. for $C_{22}H_{34}O_7$, 340.2305; found, 340.2320.

(E)-*5,9-Anhydro-6,7-O-cyclohexylidene-2,3,4-tetradeoxy-8-C-(ethoxycarbonyl)methyl-3-methyl*-D-allo-*non-2-enal*[8,13] (**61**). — To a solution of diisobutylaluminumhydride (2.0 mL of a M solution in hexane), cooled to −78°, was added a solution of butyllithium (1.18 mL, 1.7M in hexane). After stirring for 15 min at the same temperature, oxolane (1.6 mL) was added. This mixture (70 μL, 0.03 mmol) was added to a solution of **59** (10.2 mg, 0.03 mmol) in oxolane (0.5 mL), cooled to −78°. The mixture was stirred for 2 h, poured into a mixture of water (3 mL) and dichloromethane (10 mL), and extracted with dichloromethane (10 mL). The combined extracts were washed with NaCl solution, dried ($MgSO_4$), and concentrated to give a clear oil (15.1 mg). Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded **61** (3.5 mg, 38%), **60** (3.5 mg, 38%), and **59** (1.0 mg, 9.8%). Aldehyde[8,13] **61**, $[\alpha]_D^{25}$ −11.3° (*c* 0.32, chloroform); $\nu_{max}^{CHCl_3}$ 2920, 2700, 1720, 1700, 1640, 1440, 1360, 1340, 1210, 1145, 1105, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 9.81 (s, 1 H), 5.73 (m, 1 H), 4.15 (q, 1 H, *J* 5 Hz), 4.03 (m, 1 H), 3.80 (dd, 1 H, *J* 11, 3 Hz), 3.68 (dd, 1 H, *J* 9.0, 5.0 Hz), 3.58 (d, 1 H, *J* 12 Hz), 3.45 (td, 1 H, *J* 10, 3 Hz), 2.78 (ddd, 1 H, *J* 15, 6.1 Hz), 2.68 (m, 1 H), 2.60–2.47 (m, 2 H), 2.24–2.17 (m, 1 H), 2.20 (d, 3 H, *J* 1 Hz), 1.75–1.35 (m, 10 H), and 1.30 (t, 3 H, *J* 5 Hz).

(E)-*5,9-Anhydro-6,7-O-cyclohexylidene-2,3,4,8-tetradeoxy-8-C-(ethoxycarbonyl)methyl-3-methyl*-D-allo-*non-2-enitol*[8] (**60**). — $[\alpha]_D^{25}$ −9.7° (*c* 0.415, chloroform); $\nu_{max}^{CHCl_3}$ 3450, 2910, 1690, 1640, 1430, 1360, 1200, 1140, 1100, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.73 (m, 1 H), 4.14 (q, 2 H, *J* 7 Hz), 4.08 (m, 1 H), 3.76–3.70 (m, 4 H), 3.60 (dd, 1 H, *J* 11.3 Hz), 3.53 (td, 1 H, *J* 8.3 Hz), 2.51 (d, 1

H, *J* 14 Hz), 2.27–2.0 (m, 2 H), 2.20 (d, 3 H, *J* 1 Hz), 1.82–1.33 (m, 13 H), and 1.27 (t, 3 H, *J* 7 Hz).

7-O-Acetyl-4,8-anhydro-5,6-O-cyclohexylidene-1,3-dideoxy-L-talo-*2-octulose* (**62**). — By the procedure described for **58**, **55** (132.5 mg, 0.67 mmol) gave 7-*O*-acetyl-4,8-anhydro-1,3-dideoxy-L-*talo*-2-octulose (111.5 mg 72%), clear oil, $\nu_{max}^{CHCl_3}$ 3700–3150, 3000, 1720, 1370, 1200, 1120, and 1040 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 4.88–4.87 (m, 1 H), 4.01 (m, 1 H), 3.90 (d, 1 H, *J* 12.9 Hz), 3.74 (d, 1 H, *J* 12.9 Hz), 3.56 (d, 1 H, *J* 9.3 Hz), 3.10 (s, 1 H), 2.88 (dd, 1 H, *J* 16.4, 4.7 Hz), 2.74 (dd, 1 H, *J* 16.4, 7.1 Hz), 2.23 (s, 3 H), and 2.10 (s, 3 H).

By the procedure described for **58** and flash-column chromatography (1:1 ethyl acetate–hexane), the just described diol (192 mg, 0.83 mmol) gave pure **62** (222 mg, 80%), white crystals; m.p. 79–80°, $[\alpha]_D^{25}$ +1.3° (*c* 1.145, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 1730, 1370, 1240–1200, 1100, 1050, and 930 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.13 (m, 1 H, H-5), 4.14 (m, 1 H, H-4), 3.88–3.84 (m, 2 H), 3.76 (dd, 1 H, *J* 13.3, 1.8 Hz), 3.69 (td, 1 H, *J* 9.3, 3.4 Hz), 2.73 (dd, 1 H, *J* 16, 3.4 Hz, CH_2CO), 2.63 (dd, 1 H, *J* 16.8, 8.9 Hz, CH_2CO), 2.20 (s, 3 H, $COCH_3$), 2.11 (s, 3 H, $OCOCH_3$), and 1.74–1.25 (m, 10 H); m.s.: *m/z* 312 (M^+), 269, 252, 214, 171, and 155; m.s. calc. for $C_{16}H_{24}O_6$, 312.1573; found, 312.1582.

Anal. Calc. for $C_{16}H_{24}O_6$: C, 61.65; H, 7.74. Found: C, 61.63; H, 7.67.

4,8-Anhydro-5,6-O-cyclohexylidene-1,3-dideoxy-2-C-(ethoxycarbonyl)methyl-L-talo-*7-octulose* (**63**). — This compound was obtained by the procedure described for **59**, and flash-column chromatography (1:1 ethyl acetate–hexane) of **32** (10.1 mg, 0.03 mmol) gave a 4:1 mixture of *trans* and *cis* isomers (8.5 mg, 90%), clear oil, $[\alpha]_D^{25}$ −9.3° (*c* 1.24, chloroform); $\nu_{max}^{CHCl_3}$ 2940, 2850, 1740, 1700, 1640, 1440, 1370, 1240–1200, 1150, 1100, 1040, and 700 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$):δ 5.75 (d, *J* 0.8 Hz), 5.11 (m), 4.17–4.10 (m), 3.87–3.81 (m), 3.65 (dd, *J* 13.3, 2.1 Hz), 3.36 (td, *J* 9.8, 2.3 Hz), 2.55 (d, *J* 14.5 Hz), 2.30–2.19 (m), 2.19 (d, *J* 1.2 Hz), 2.11 (s), 1.95 (d, *J* 1.4 Hz), 1.71–1.31 (m), and 1.29–1.23 (t, *J* 7.1 Hz); m.s.: *m/z* 382 (M^+), 353, 339, 255, and 208; m.s. calc. for $C_{20}H_{30}O_7$, 382.1992; found, 382.1991.

Anal. Calc. for $C_{20}H_{30}O_7$: C, 62.91; H, 7.90. Found: C, 62.82; H, 7.98.

To a stirred solution of sodium ethoxide (catalytic amount) in absolute ethanol (0.8 mL) was added a solution of the just described acetate (25.8 mg, 0.07 mmol) in absolute ethanol (0.8 mL) at 0°. The mixture was stirred for 2 h at the same temperature and poured into sat. NH_4Cl solution, and extracted with ethyl acetate. The extract was washed with NaCl solution, dried ($MgSO_4$), and evaporated to give the alcohol (23.4 mg 100%), clear oil, $\nu_{max}^{CHCl_3}$ 3550, 2930, 1700, 1640, 1440, 1360, 1200, 1140, 1100, 1040, and 930 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.76 (s), 5.74 (s), 4.24–4.22 (m), 4.14 (q, *J* 7.1 Hz), 4.12 (q, *J* 7.12 Hz), 4.0–3.67 (m), 3.50–3.46 (m), 3.38 (td, *J* 9.5, 2.9 Hz), 2.98–2.96 (m), 2.54 (d, *J* 14.4 Hz), 2.27–2.11 (m), 2.19 (d, *J* 1.0 Hz), 1.94 (d, *J* 1.4 Hz), 1.71–1.32 (m), 1.27 (t, *J* 7.1 Hz), and 1.25 (t, *J* 7.1 Hz); m.s.: *m/z* 340 (M^+), 311, 295, 251, 224, and 213; m.s. calc. for $C_{18}H_{28}O_6$, 340.1886; found, 340.1878.

To a stirred solution of the just described alcohol (65.3 mg, 0.19 mmol) and

triethylamine (80 μL, 0.57 mmol) in 1:1 dichloromethane–dimethyl sulfoxide (1.3 mL), cooled to 0°, was added SO_3–pyridine complex (91.6 mg, 0.57 mmol) in 1:1 dichloromethane–dimethyl sulfoxide[48] (800 μL). The resulting solution was stirred for 5 h at the same temperature, poured into sat. NH_4Cl solution (10 mL), and extracted with ethyl acetate (60 mL). The combined ethyl acetate solution was washed with sat. NH_4Cl solution, water, and NaCl solution, dried ($MgSO_4$), and concentrated to give a clear oil (58.3 mg). Flash-column chromatography of the residue with 1:2 ethyl acetate–hexane afforded a 4:1 mixture of *trans* and *cis* isomers of **63** (31.7 mg, 63.6% based on recovered starting material), which were separable by chromatotron (1:4 ethyl acetate–hexane).

E-isomer. $[\alpha]_D^{25}$ +11.0° (*c* 0.345, chloroform); $\nu_{max}^{CHCl_3}$ 2925, 2858, 1740, 1640, 1440, 1360, 1200, 1150, 1100, 1040, and 920 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 5.77 (s, 1 H, =C–H), 4.60 (d, 1 H, *J* 7.9 Hz, H-4), 4.39 (t, 1 H, *J* 8.1 Hz, H-3), 4.31 (d, 1 H, *J* 18 Hz, H-6), 4.17 (q, 2 H, *J* 7.1 Hz, CO_2CH_2), 4.04 (dd, 1 H, *J* 18, 1.4 Hz, H-6), 3.49 (td, 1 H, *J* 8.9, 3.8 Hz, H-2), 2.63 (dd, 1 H, *J* 14.1, 4.2 Hz, CH_2CO_2), 2.47 (dd, 1 H, *J* 14.7, 8.9 Hz, CH_2C=), 2.22 (d, 3 H, *J* 1.2 Hz, CH_3), 2.22–1.30 (m, 10 H), and 1.28 (t, 3 H, *J* 7.0 Hz, $CO_2CH_2CH_3$); m.s.: *m/z* 338 (M^+), 309, 295, 240, and 211; m.s. calc. for $C_{18}H_{26}O_6$, 338.1729; found, 338.1731.

Z-isomer. ^{1}H-n.m.r. ($CDCl_3$): δ 5.81 (s, 1 H), 4.62 (d, 1 H, *J* 7.8 Hz), 4.51 (t, 1 H, *J* 7.9 Hz), 4.31 (d, 1 H, *J* 18 Hz), 4.15 (q, 2 H, *J* 7.1 Hz), 4.02 (dd, 1 H, *J* 7.8, 1.2 Hz), 3.65–3.58 (m, 1 H), 3.18–3.15 (m, 1 H), 1.96 (d, 3 H, *J* 1.4 Hz), 2.0–1.32 (m, 10 H), and 1.27 (t, 3 H, *J* 7.1 Hz).

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