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Stereoselective Functionalization of Dihydropyran-3-ols: Application to the Synthesis of Enantiopure Ethyl Deoxymonate B

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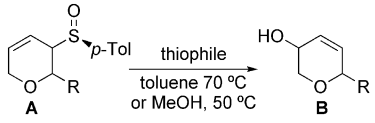
The behavior of readily available enantiopure *cis* and *trans* 3,6-disubstituted dihydropyran-3-ols and derivatives in epoxidation, osmium-catalyzed dihydroxylations, S_N2', and Claisen-related processes has been examined. The highly diastereoselective dihydroxylation of a suitably functionalized *cis* 3,6-disubstituted dihydropyran-3-ol has been used in the synthesis of ethyl deoxymonate B from a 3-sulfinyldihydropyran intermediate.

Introduction

Enantiomerically pure allylic alcohols are useful building blocks in organic synthesis,[1] widely used for the preparation of natural products and bioactive compounds.[2] We have recently studied the transformation of readily available *cis*- and *trans*-2,3-disubstituted 3-sulfinyldihydropyrans (**A**) into 3,6-disubstituted dihydropyran-3-ols (**B**) by an efficient [2,3]-sigmatropic rearrangement of allylic sulfoxides with complete stereoselectivity (Scheme 1).[3] Usually, (2*S*,3*S*) derivatives are easily transformed with $P(OMe)_3$ in MeOH, whereas (2*S*,3*R*) isomers require other thiophiles like DABCO or DBU in toluene at a higher temperature. The resulting products presented a dihydropyran core containing an allylic alcohol moiety with a defined stereochemistry that could be susceptible to further chemical transformations. In this paper we report some unoptimized model studies of the behavior of these substrates in selected processes such as epoxidation, dihydroxylation, S_N2', and Claisen-related processes, as well as the application of these methodologies to the synthesis of methyl and ethyl deoxymonates B.[4]

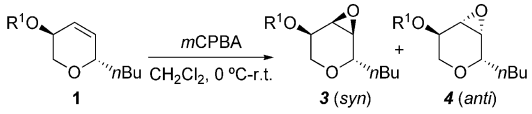


Scheme 1. [2,3]-Sigmatropic rearrangement of allylic sulfoxides.

Results and Discussion

Allylic alcohols obtained by the above route can be useful synthetic intermediates, hence we decided to study first the reactivity of the isomers 3,6-*trans*-**1** and 3,6-*cis*-**2** in simple epoxidation and dihydroxylation processes which would lead to more functionalized structures. The epoxidation of the free alcohol **1a** with *m*-CPBA[5] led to a mixture of diastereoisomers (Table 1, entry 1) with the *syn* epoxy alcohol as the major product as expected.[6] In an attempt to invert the selectivity by preventing coordination of the alcohol with the reagent and at the same time introducing steric hindrance, we prepared the silyl ether derivatives first by using a TBS group (Table 1, entry 2) and then by increasing the volume of the protecting group with a TIPS group. In both cases we obtained the opposite selectivity relative to the free alcohol, but only with moderate selectivity. There was no clear improvement in the selectivity as a result of increasing the steric hindrance by replacing the TBS group with TIPS (Table 1, entries 2 and 3).

Table 1. Epoxidation of 3,6-*trans*-dihydropyranols **1**.



Entry	Substrate	R^1	**3**/**4** Ratio	Yield [%]
1	**1a**	H	88:12	65
2	**1b**	TBS	23:77	81
3	**1c**	TIPS	20:80	76

The results for the epoxidation of the 3,6-*cis* alcohols are shown in Table 2. The free alcohol **2a** led to the *syn* isomer **5a** as the major product (Table 2, entry 1), and again protection of the hydroxy group inverted the selectivity but gave slightly lower ratios than the free alcohol. In this case, we prepared silyl ether **2b** (Table 2, entry 2) and acetate **2d** (Table 2, entry 3), which gave only poor selectivity.

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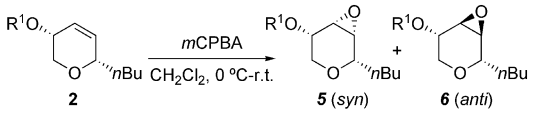
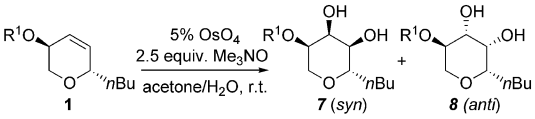
Table 2. Epoxidation of 3,6-*cis*-dihydropyranols **2**.



Entry	Substrate	R^1	**5/6** Ratio	Yield [%]
1	**2a**	H	77:23	62
2	**2b**	TBS	30:70	100
3	**2d**	CH_3CO	45:55	53

We next examined the OsO_4-catalyzed dihydroxylation of the *cis* and *trans* isomers of the free alcohols and silyl ethers.[7] Dihydroxylation of the 3,6-*trans* isomer **1** (Table 3) gave mixtures of *syn*-**7** and *anti*-**8** diastereoisomers with selectivities ranging from 60:40 for the free alcohol (Table 3, entry 1) to about 20:80 for the more hindered substrates (Table 3, entries 2 and 3), all with moderate-to-good yields.

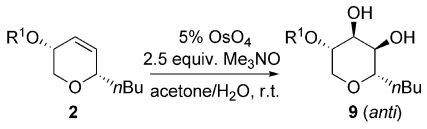
Table 3. Dihydroxylation of 3,6-*trans*-dihydropyranols **1**.



Entry	Substrate	R^1	**7/8** Ratio	Yield [%]
1	**1a**	H	60:40	67
2	**1b**	TBS	17:83	94
3	**1c**	TIPS	21:79	70

On the other hand, the 3,6-*cis* isomers **2** gave only the *anti* dihydroxylation products **9** with moderate-to-excellent yields (Table 4), showing parallel behavior to other structures with related substitution patterns described in the literature, which could also be accessible by this methodology, as will be described later.[8]

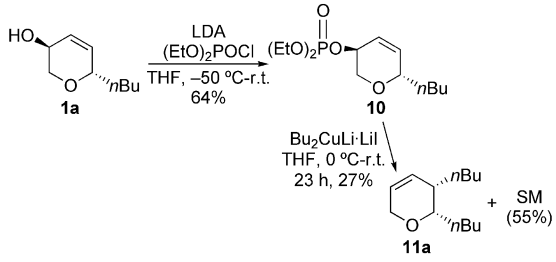
Table 4. Dihydroxylation of 3,6-*cis* dihydropyranols **2**.



Entry	Substrate	R^1	Yield [%]
1	**2a**	H	82
2	**2b**	TBS	100
3	**2d**	CH_3CO	43

Although it has been reported that directive effects in osmylation reactions are predominantly steric,[9] it has been suggested that at least in some allylic systems the stereochemistry of the process is relatively insensitive to steric factors and is governed by stereoelectronic effects.[10] An empirical rule states that usually osmium tetroxide preferentially approaches the alkene *anti* to the hydroxy group.[9a] This effect is more pronounced for substrates with a pseudoaxial hydroxy group, with more steric hindrance to the approach of the reagent. This would explain the result of the reaction of the free alcohol **2a** with a pseudoaxial hydroxy group,[3] as well as the reactions of the protected substrates **1b**,**c** and **2b**,**d**. On the other hand, the low *syn* selectivity found for **1a** with a pseudoequatorial hydroxy group is somewhat unexpected,[11] although there are examples in the literature that show similar behavior.[12]

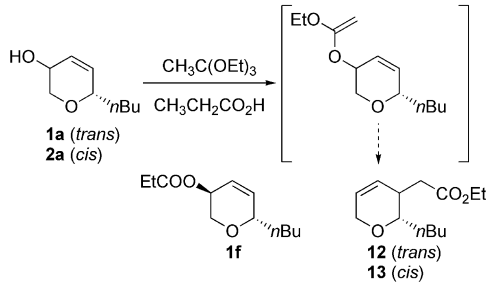
To broaden the scope of reactivity of 3-dihydropyranols, the transformation of alcohols **1a** and **2a** into suitable precursors for S_N2' displacement and sigmatropic rearrangement was also studied. In these processes the chirality of the oxygenated center is transferred to the allylic position, leading to 2,3-disubstituted dihydropyrans, an interesting core present in some natural products.[13] The S_N2' displacement of allylic phosphates with cyanocuprates in the presence of LiCl is a well-established protocol.[14] Thus, phosphate **10** was prepared from **1a** by using diethyl chlorophosphate and LDA because milder conditions with Et_3N were not effective in this case (Scheme 2). To our dismay, the reaction between **10** and MeCu(CN)MgBr in the presence of LiCl just gave recovered starting material whereas the use of MeCu(CN)MgBr afforded a low yield of the product of S_N2 displacement by bromide along with starting material (see the Supporting Information). The use of BuCu(CN)Li proved equally fruitless leading to recovery of the starting material. Finally, a low yield of the desired product **11a** was obtained upon reaction with $Bu_2CuLi{\cdot}LiI$. At this stage we explored briefly the preparation of the related mesylate, but the product was too unstable to be isolated and therefore we chose to abandon these studies.



Scheme 2. Synthesis of the allylic phosphate **10** and S_N2' reaction with alkyl cuprates.

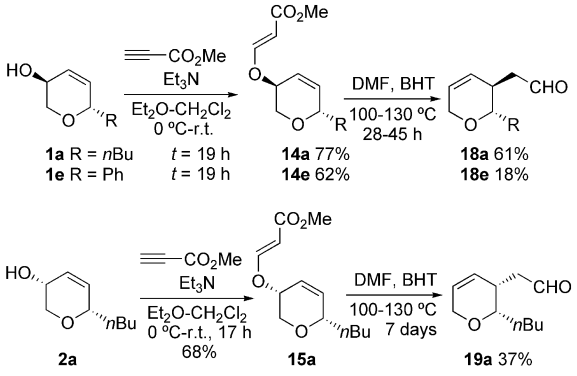
We next focused our attention on the Claisen–Johnson rearrangement with triethyl orthoacetate and propionic acid of both *cis*- and *trans*-dihydropyranols (Scheme 3) via a ketene acetal intermediate.[15] Assuming the process proceeded with retention of configuration, hence transferring the chirality of the oxygenated center to the allylic position, we expected functionalized 2,3-disubstituted dihydropyrans **12** and **13** to be formed. Unfortunately we were unable to obtain **12** or **13** under the conditions studied, obtaining complex reaction mixtures and in the case of **2a**, a low yield of the dihydropyranyl propionate derivative **1f**.

Because the substitution pattern and the functionalities of esters **12** and **13** were attractive from a synthetic point of view, we decided to explore the Claisen rearrangement[16] as an alternative approach to accessing similar targets. Encouraged by previous results in our group,[17] we chose to examine the rearrangements of the *trans*- and *cis*-acrylates



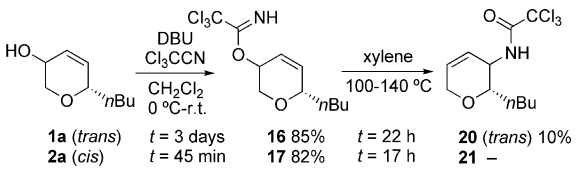
Scheme 3. Attempts at Claisen–Johnson rearrangement of **1a** and **2a**.

14a,**e** and **15a**, which were prepared uneventfully from alcohols **1a**,**e** and **2a**, respectively (Scheme 4). These acrylates were heated in DMF in the presence of a catalytic amount of butylated hydroxytoluene to yield products of a Claisen rearrangement and a concurrent decarboxylation with complete stereoselectivity but in variable yields (Scheme 4). Note that for acrylate **15a** with a *cis* relative stereochemistry, the reaction was much slower, and the yield was considerably lower than that of the *trans* isomer **14a**.



Scheme 4. Synthesis and Claisen rearrangement of acrylates **14** and **15**.

In a similar manner we also considered the possibility of carrying out the aza-Claisen process to obtain dihydropyranyl amides and therefore we also prepared trichloroacetimidates **16** and **17** in good yields (Scheme 5).[18] In this case, the substrates were heated in xylene between 100 and 140 °C to produce complex reaction mixtures from which a small amount of the expected trichloroacetamide **20** was isolated (Scheme 5). Acid-catalyzed decomposition of the allylic trichloroacetimidate could be a competing process, and usually the addition of sodium or potassium carbonate



Scheme 5. Synthesis and aza-Claisen rearrangement of trichloroacetimidates **16** and **17**.

could increase the yield of the rearrangement product.[19] Unfortunately, problems concerning the availability of the starting material prevented the study of the process under these modified conditions.

The results obtained show that the *trans* derivatives are more reactive in the sigmatropic processes. These findings may be tentatively rationalized on the basis of the conformational analysis of alcohol **1a**, which shows the hydroxy group to be pseudoequatorial, whereas the *cis* alcohol **2a** adopts a conformation in which the alcohol is in a pseudoaxial arrangement.[3b] For the sigmatropic process to occur, the oxygen of the acrylate or imidate must adopt a quasiaxial orientation to bring the reactive centers within bonding distance.[18f] Thus, the *trans* substrates (**14**, **16**) require the conversion from one chair conformer to another. In contrast, although the preferred chair-type conformer of the *cis* alcohol **2a** places the hydroxy group pseudoaxial, the acrylate **15a** and imidate **17** derivatives might suffer unfavorable steric interactions with the *cis* substituents and this could account for their lower reactivity in these processes (Figure 1).

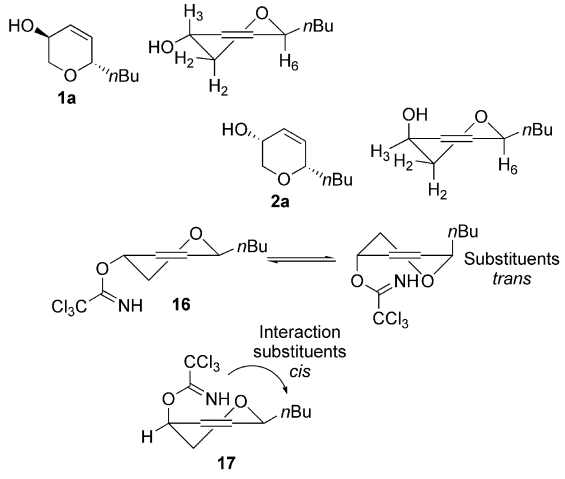
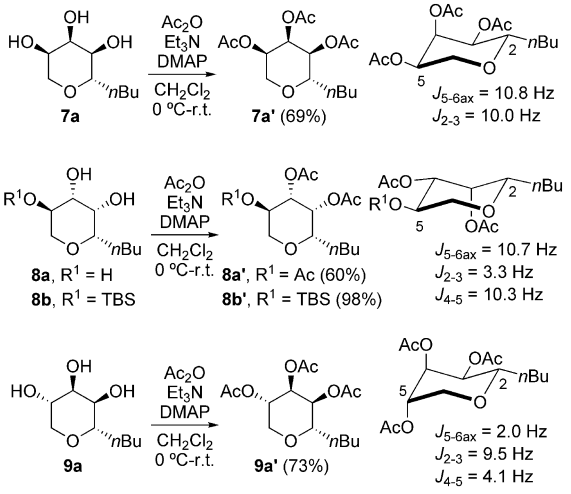


Figure 1. Possible conformations of the trichloroacetimidates **16** and **17**.

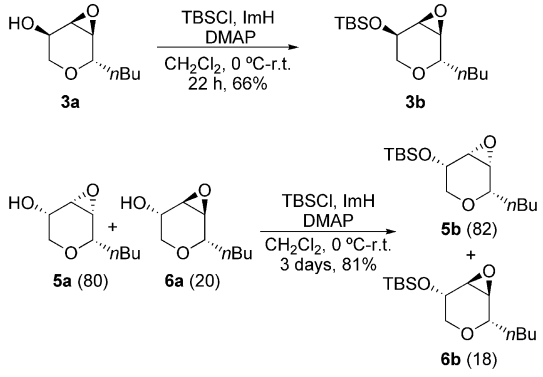
Stereochemical Assignments

To confirm the stereochemistries of the diols and triols, **7a**, **8a**,**b**, and **9a** were acetylated to give the triacetates **7a′**, **8a′**, and **9a′**, and the diacetate **8b′** (Scheme 6). The coupling constants measured for the acetylated derivatives confirmed the stereochemistry assigned to the precursors.

To correlate the oxirane structures obtained in the epoxidation of the free alcohols and silyl ethers, some epoxy alcohols were protected (Scheme 7). Silylation of epoxy alcohol **3a** afforded **3b**, which was the minor product obtained from the epoxidation of silyl ether **1b** (Table 1, entry 2). Similarly, silylation of an 80:20 mixture of **5a** and **6a** (Table 2, entry 1) gave an 82:18 mixture of protected oxiranes **5b** and **6b** with identical data but in an opposite ratio to the results of the epoxidation of **2b** (Table 2, entry 2).



Scheme 6. Acetylation of the diols and triols **7a**, **8a**,**b**, and **9a**.



Scheme 7. Silylation of epoxy alcohols.

The stereochemistries of the S_N2' and Claisen products were tentatively assigned on the basis of coupling constant values and in some cases were confirmed by NOE experiments (Figure 2).

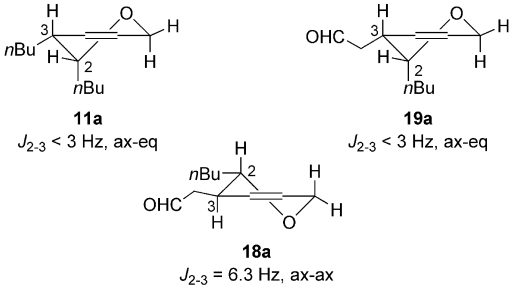
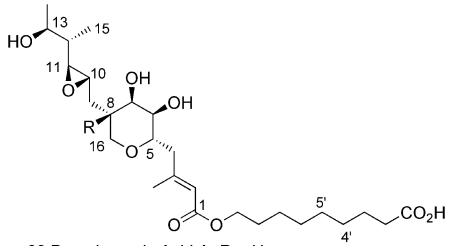


Figure 2. Stereochemical assignments for **11a**, **18a**, and **19a**.

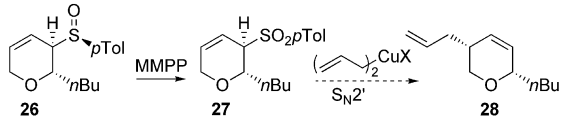
Synthetic Applications

The pseudomonic acids are *C*-glycopyranosides produced by a strain of *Pseudomonas fluorescens*, which present a potent antibiotic activity against Gram-positive aerobic bacteria;[20] pseudomonic acid A (**22**; Scheme 8) is used as a topical antibacterial agent (Bactroban). The pseudomonic acids present a tetrahydropyran ring α-*cis* disubstituted at C-5 and C-8 and β-*cis* hydroxy groups at C-6 and C-7. Pseudomonic acid B presents an additional hydroxy at C-8, and pseudomonic acids C and D present *E* alkenes in the side-chains (Scheme 8). Their challenging structural features, along with their potent biological activity, have attracted the attention of many groups and their efforts have led to several synthetic approaches.[21] The key tetrahydropyran core has been prepared from carbohydrates by Diels–Alder processes or from acyclic precursors. The stereocenters were installed by Claisen rearrangements, Pd-catalyzed alkylations, and free-radical processes. The side-chains were homologated by Wittig and Julia protocols and, recently, by cross-metathesis.



Scheme 8. Structure of the pseudomonic acids.

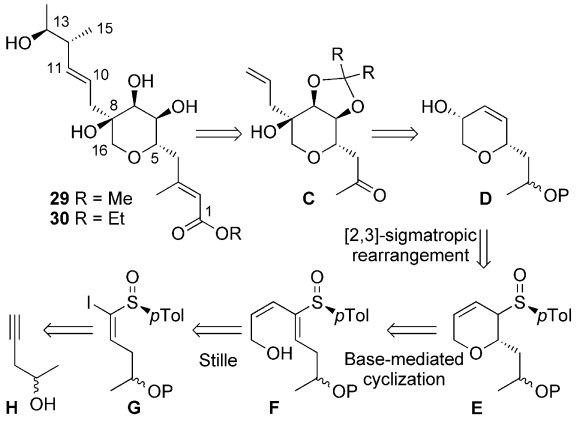
Our early approach to these products arose from our initial results of S_N2' displacements of allylic sulfones such as **27** (Scheme 9) and related sulfoximines with magnesium bromodialkylcuprates, which led to the expected γ-substitution products.[3] A model S_N2' product underwent a completely selective osmium-catalyzed dihydroxylation to afford a tetrahydropyranyl diol with the correct stereochemistry of the core of pseudomonic acid C. These promising results encouraged us to pursue the preparation of model compound **28**, which could allow us to test the viability of the cross-metathesis reaction between the allyl moiety and the C11–C15 fragment and also explore the selective dihydroxylation of the pyran double bond. This last process would be a challenge because the problem of regioselectivity has to be overcome, but if successful the core of pseudomonic acid C could be accessed expediently. Unfortunately, we were unable to introduce an allyl substituent cleanly, obtaining only traces of the desired product in complex reaction mixtures and thus we decided to abandon this approach and explore an alternative route.



Scheme 9. Model studies for the preparation of pseudomonic acid C.

Because the dihydroxylation of readily available *cis* 3,6-disubstituted dihydropyranyl-3-ols is highly stereoselective (see before), we considered an approach to pseudomonic

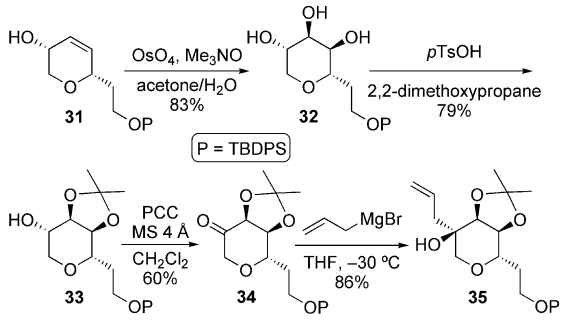
acid B, with an additional hydroxy group at C-8, from a sulfinyldihydropyran intermediate with the appropriate functionalization at C-2. Note that the preparation of pseudomonic acid B and related compounds with a hydroxy group at C-8 is comparatively less studied.[21g,22] Scheme 10 shows our retrosynthetic analysis for methyl and ethyl deoxymonates B (**29** and **30**), which should be available by homologation of the side-chain at C-8 of intermediate **C** by a cross-metathesis reaction in the presence of a free hydroxy group at C-8, inspired by the work of Markó and coworkers,[21h] followed by olefination to build the C-5 side-chain. Intermediate **C** would derive from allylic alcohol **D** by stereoselective dihydroxylation, protection, and an oxidation/allylation sequence. [2,3]-sigmatropic rearrangement of allylic sulfoxide **E** would lead to alcohol **D**. Sulfinyldihydropyran **E** would result from the base-mediated cyclization of dienyl sulfoxide **F**, in turn available from 4-pentyn-2-ol **H** through iodovinyl sulfoxide **G**. In this paper we report in full our efforts to synthesize methyl and ethyl deoxymonates B from a sulfinyldihydropyran intermediate by [2,3]-sigmatropic rearrangement of an allylic sulfoxide to install the hydroxy functionality at C-8, taking advantage of the directing effect of the allylic alcohol in the dihydroxylation reaction.



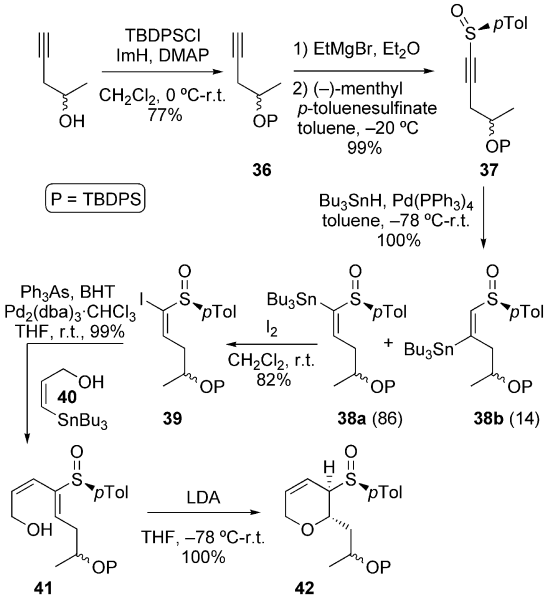
Scheme 10. Retrosynthetic analysis for methyl and ethyl deoxymonates B (**29** and **30**).

Because we had previously obtained similar intermediates in the development of a formal synthesis of *ent*-dysiherbaine,[23] a substrate similar to **D** was available to carry out a preliminary study of the viability of the sequence to transform **D** into **C** (Scheme 11). Stereoselective dihydroxylation of **31** and protection of the resulting diol as an isopropylidene ketal afforded **33**. Oxidation of the secondary alcohol to give ketone **34**, followed by stereoselective Grignard addition to the ketone afforded **35** as a single isomer. This result encouraged us to follow the same approach to access key intermediate **C** starting from the appropriate substrate.

Commercially available *rac*-4-pentyn-2-ol (Scheme 12) was protected as the TBDPS ether, and the resulting alkyne **36** was treated with EtMgBr and (–)-menthyl *p*-toluenesulfinate to produce alkynyl sulfoxide **37**. Pd-catalyzed hydrostannylation of **37** afforded an 86:14 mixture of the regioisomeric stannanes **38a** and **38b**. Treatment of **38a** with iodine led to vinyl iodide **39**, which readily underwent Stille coupling with stannane **40** to give the sulfinyl diene **41** in excellent yield. The key cyclization of **41** with LDA produced 2,3-*trans*-sulfinyldihydropyran **42**, with the pyran core of the target suitably substituted at C-5,[24] as a single isomer in excellent yield.

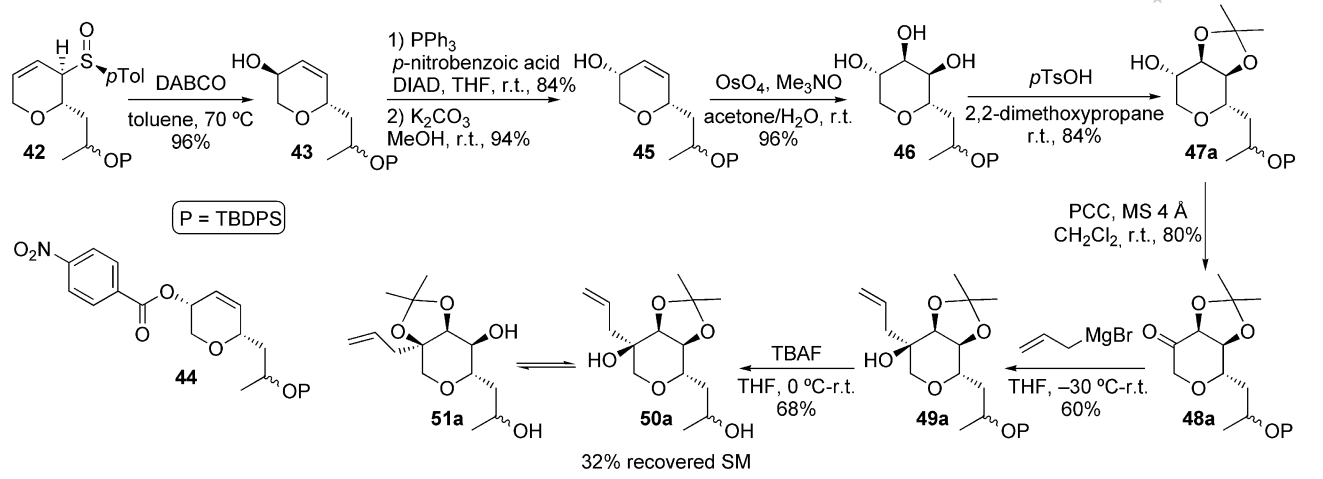


Scheme 11. Model study for the conversion of **D** into **C**.



Scheme 12. Synthesis of sulfinyldihydropyran **42**.

Allylic sulfoxide **42** readily underwent a [2,3]-sigmatropic rearrangement to afford *trans*-allylic alcohol **43** as a single isomer (Scheme 13), which was inverted by a Mitsunobu protocol via *p*-nitrobenzoate **44** to produce *cis*-alcohol **45**. The osmium-catalyzed dihydroxylation of **45** afforded triol **46**, which was protected as an isopropylidene ketal under standard conditions to give **47a**. Oxidation of **47a** with PCC gave ketone **48a** and addition of allylmagnesium bromide afforded exclusively the tertiary alcohol **49a** (Scheme 13).[22b] Deprotection of the secondary alcohol on the side-chain at C-5 led to diol **50a**. The process was quite slow and to our surprise after the first test reactions, we observed that the isolated product slowly isomerized to **51a** in which the isopropylidene ketal had migrated from the secondary to the tertiary hydroxy group. Our approach to deoxymonates B implies the oxidation of the hydroxy group



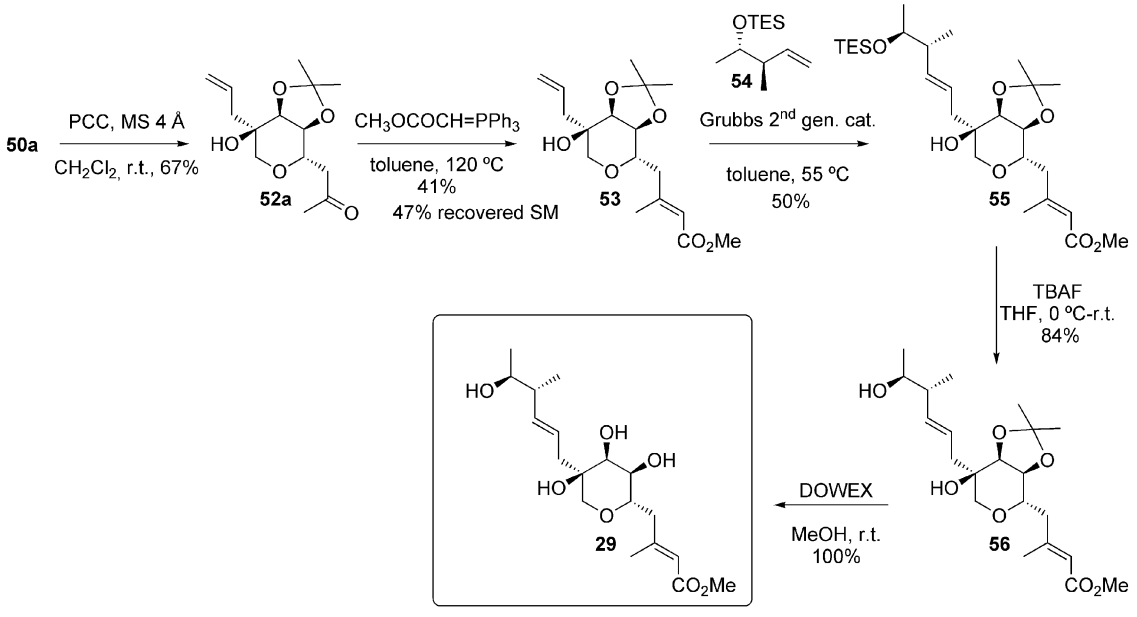
Scheme 13. Synthesis of diol **50a**.

on the side-chain without affecting the tertiary alcohol in the process. Because **51a** has another secondary alcohol that could compete in oxidation reactions, this substrate could not be used further in the synthesis of deoxymonates B.

Nonetheless, once alcohol **50a** was isolated, it could be rapidly used before **51a** was formed. Thus, **51a** was converted into ketone **52a** as a single product that appeared to be stable (Scheme 14). Wittig reaction of **52a** with methyl (triphenylphosphoranylidene)acetate afforded **53** as an 86:14 mixture of *E*/*Z* isomers. Because this step was performed on a small scale, the two isomers could not be separated and the product was used as a mixture in the next step. Homologation of the C-8 side-chain was carried out using the conditions described by Markó and co-workers for a related system lacking the extra hydroxy group at the homoallylic position.[21h]

The cross-metathesis of **53** and **54**, available in four steps from ethyl (*S*)-3-hydroxybutyrate,[25] afforded **55** predominantly as the *E* isomer at C-2/C-3 and with just the *E* geometry at the newly formed C-10/C-11 bond. Practically pure (*E*)-**55**, contaminated with traces of the *Z* isomer at C-2, was obtained by careful chromatographic purification. Treatment of **55** with TBAF led to cleavage of the silyl ether to give alcohol **56**, which was fully deprotected with DOWEX resin to give methyl deoxymonate B (**29**) with traces of the *Z* isomer (1.4%) in an 18-linear-step sequence (22 steps in total) from commercially available 4-pentyn-2-ol.

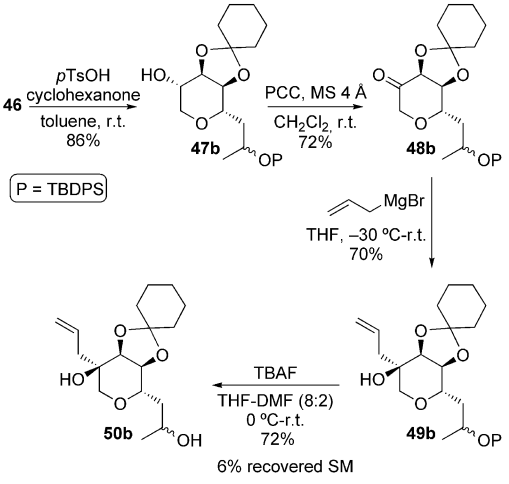
Although we had completed the synthesis of **29**, we had found major drawbacks in the sequence that affected the efficiency of the route. The first one was the isomerization of the isopropylidene ketal in alcohol **50a** leading to **51a**, which could not be further transformed into the next inter-



Scheme 14. Synthesis of methyl deoxymonate B, **29**.

mediate, and the second one was the Wittig reaction, which led to the desired unsaturated ester but in a low yield. We tried to improve these results by changing the protecting group on the *cis* diol from an isopropylidene to a cyclohexylidene ketal with the expectation that ketal migration would be more difficult, and also by trying different conditions for the Wittig step. Therefore we protected *cis*-diol **46** as the cyclohexylidene ketal to obtain **47b**, which was transformed into ketone **48b** (Scheme 15). Grignard addition to the ketone afforded alcohol **49b**, which was deprotected with TBAF in a mixture of THF/DMF, accelerating the reaction to form diol **50b**, which proved stable to ketal migration upon standing neat or in solution.

Next we focused our attention on the low-yielding Wittig step. The required ketone **52b** was obtained by oxidation of alcohol **50b** (Scheme 16) and then we explored the use of

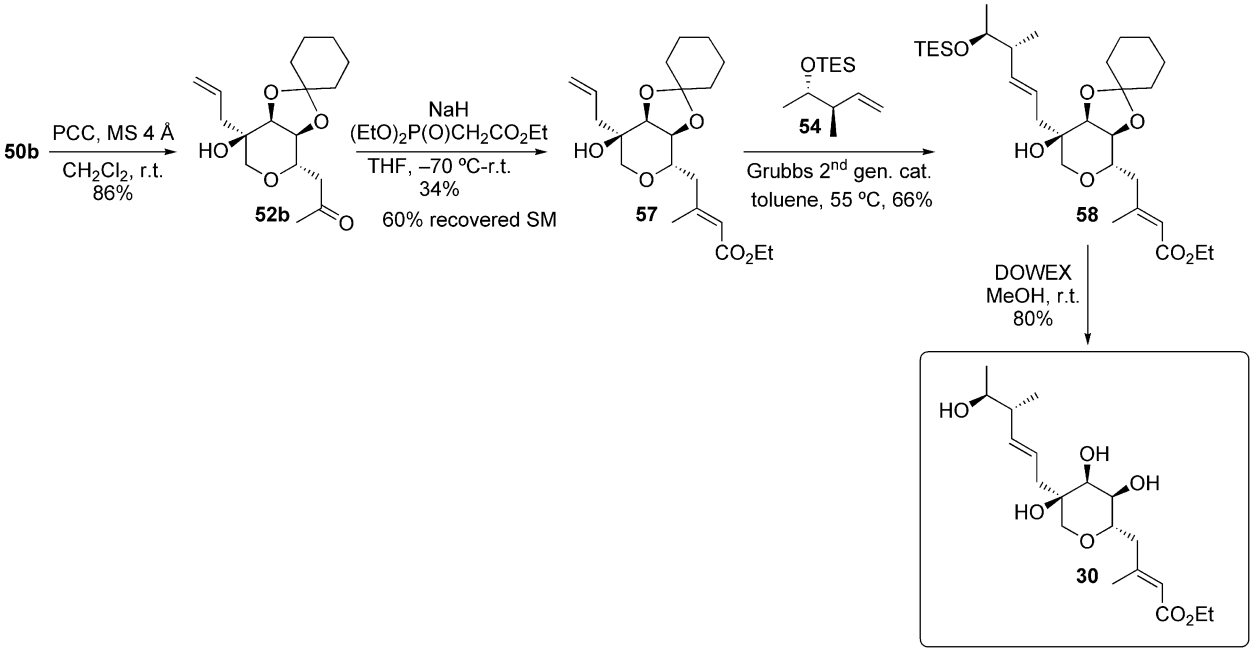


Scheme 15. Synthesis of intermediate **50b**.

Horner–Wadsworth–Emmons conditions, previously used for related substrates. Unfortunately we were unable to improve on the results obtained for the isopropylidene series, and the reaction of **52b** with the sodium anion of triethyl phosphonoacetate afforded **57** in low yield as an 80:20 mixture of *E*/*Z* isomers,[8] which was used as a mixture in the next step. Although it is likely that these results could be improved through a thorough study of this step, at this point, the lack of time and material prevented us from achieving this goal and we decided to continue the sequence. Homologation of the C-8 side-chain again was carried out as before by cross-metathesis of **57** and fragment **54** to afford **58** as an *E*/*Z* mixture at C-2 with the *E* isomer as the major product and again the *E* geometry at the C-10/C-11 alkene. Subsequent purification afforded (*E*)-**58** contaminated with traces of the *Z* isomer at C-2. The spectroscopic data for **58** (^{1}H NMR) was almost identical to that of a similar product described in the literature.[22b] The synthetic sequence was completed by cleavage of the silyl ether and cyclohexylidene ketal in one step by treatment of **58** with DOWEX resin to afford ethyl deoxymonate B (**30**; 2.2%) in 17 linear steps (21 steps in total) from the commercially available 4-pentyn-2-ol. A previous synthesis gave the related methyl deoxypseudomonate B in 21 linear steps (29 steps in total) from L-lyxose.[22b]

Conclusions

The behavior of the readily available enantiopure *cis*- and *trans*-3,6-disubstituted dihydropyran-3-ols and their derivatives in epoxidation, osmium-catalyzed dihydroxylations, S_N2', and Claisen-related processes has been examined. As a result, a variety of potentially useful pyran building blocks have been prepared. The highly diastereoselective di-



Scheme 16. Final steps for the synthesis of ethyl deoxymonate B (**30**).

hydroxylation of a suitably functionalized *cis*-3,6-disubstituted dihydropyran-3-ol, obtained by [2,3]-sigmatropic rearrangement of a 3-sulfinyldihydropyran, has been used in the synthesis of ethyl deoxymonate B, which also features the homologation of the C-8 side-chain by the cross-metathesis of a homoallylic free alcohol fragment.

Experimental Section

General: Reagents and solvents were handled using standard syringe techniques. All reactions were carried out under argon. Hexane, toluene, CH_3CN, and CH_2Cl_2 were distilled from CaH_2, and THF and Et_2O from sodium. Crude products were purified by flash chromatography on 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on silica gel plates with detection by UV light, iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol, and 0.3% ninhydrin solution with 3% AcOH. All reagents were commercial products. Throughout this section, the volume of solvents is reported in mL/mmol of the starting material. ^1H and ^{13}C NMR spectra were recorded at 25 °C at 200, 300, 400, or 500 MHz (^1H) using $CDCl_3$ as solvent and with the residual solvent signal as the internal reference ($CDCl_3$, 7.24 and 77.0 ppm) unless otherwise noted. The following abbreviations are used to describe multiplicities when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), qui (quintet), m (multiplet), br. (broad). Melting points are uncorrected. Optical rotations were measured in $CHCl_3$ solution at 20 °C by using a sodium lamp. Low-resolution mass spectra were recorded by using the electronic impact technique with an ionization energy of 70 eV or by using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in the positive or negative mode.

(+)-(1*S*,2*S*,5*R*,6*R*)-2-Butyl-3,7-dioxabicyclo[4.1.0]heptan-5-ol (3a) and (1*R*,2*S*,5*R*,6*S*)-2-Butyl-3,7-dioxabicyclo[4.1.0]heptan-5-ol (4a): From alcohol **1a** (19 mg, 0.122 mmol) and *m*-CPBA (30 mg, 0.122 mmol, 1 equiv.), according to the general procedure described in the Supporting Information (23 h), an 88:12 mixture of epoxides **3a** and **4a** was obtained. Purification by chromatography (0–20% EtOAc/CH_2Cl_2) afforded **3a** (11 mg, 0.064 mmol, 52%) and a 73:27 mixture of **3a** and **4a** (3 mg, 0.017 mmol, 13%) as colorless oils.

Data for 3a: R_f = 0.26 (20% EtOAc/CH_2Cl_2). $[a]_D^{20}$ = +28.6 (*c* = 1.03, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, COSY): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.29–1.43 (m, 4 H, 2 CH_2), 1.55–1.62 (m, 2 H, CH_2), 1.79 (br. s, 1 H, OH), 3.10 (dd, *J* = 11.2, 9.5 Hz, 1 H, 4-H), 3.23 (dd, *J* = 4.4, 0.5 Hz, 1 H, 1-H), 3.44 (m, 1 H, 6-H), 3.65 (app. dd, *J* = 5.9, 0.7 Hz, 1 H, 4-H), 3.67 (app. dd, *J* = 7.2, 6.1 Hz, 1 H, 2-H), 4.04 (m, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.6, 27.4, 32.7, 53.7, 59.0, 64.4, 65.2, 73.4 ppm. IR (film): $\tilde{\nu}$ = 3401, 2961, 2926, 2862, 1644, 1460, 1412, 1379, 1260, 1099, 1068, 1035, 893, 868, 805 cm^{-1}. MS (ES): *m*/*z* (%) = 195 (100) [M + Na]$^+$, 173 [M + 1]$^+$.

Partial Data for 4a (from the Mixture): R_f = 0.24 (20% EtOAc/CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.18 (dd, *J* = 4.2, 2.0 Hz, 1 H), 3.18 (dd, *J* = 11.7, 5.6 Hz, 1 H), 3.31 (dd, *J* = 4.1, 1.3 Hz, 1 H), 3.83 (dd, *J* = 11.5, 3.8 Hz, 1 H) ppm.

(+)-*tert*-Butyl[(1*S*,2*S*,5*R*,6*S*)-2-butyl-3,7-dioxabicyclo[4.1.0]heptan-5-yloxy]dimethylsilane (3b): From epoxy alcohol **3a** (10 mg, 0.058 mmol), TBDMSCl (11 mg, 0.070 mmol, 1.2 equiv.), imidazole (5 mg, 0.070 mmol, 1.2 equiv.), and DMAP (1 crystal, 0.05 equiv.), according to the general procedure described in the Supporting Information (22 h), **3b** was obtained. Purification by chromatography (10–50% CH_2Cl_2/hexane) afforded **3b** (11 mg, 0.038 mmol, 66%) as a colorless oil.

From protected alcohol **1b** (18 mg, 0.067 mmol) and *m*-CPBA (17 mg, 0.067 mmol, 1 equiv.), according to the general procedure described in the Supporting Information (20 h), a 77:23 mixture of epoxides **4b** and **3b** was obtained. Purification by chromatography (15–50% CH_2Cl_2/hexane) afforded an inseparable 77:23 mixture of **4b** and **3b** (16 mg, 0.054 mmol, 81%), along with recovered starting material (4 mg, 0.013 mmol, 19%) as colorless oils.

Data for 3b: R_f = 0.21 (50% CH_2Cl_2/hexane). $[a]_D^{20}$ = +45.1 (*c* = 1.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, COSY): δ = 0.08 (s, 3 H, CH_3 TBS), 0.11 (s, 3 H, CH_3 TBS), 0.89 (br. s, 12 H, *t*Bu, CH_3), 1.26–1.44 (m, 4 H, 2 CH_2), 1.54–1.62 (m, 2 H, CH_2), 3.14 (d, *J* = 4.2 Hz, 1 H, 6-H), 3.20 (d, *J* = 10.3 Hz, 1 H, 4-H), 3.29 (d, *J* = 3.9 Hz, 1 H, 1-H), 3.49 (ddd, *J* = 11.0, 6.1, 0.7 Hz, 1 H, 4-H), 3.66 (t, *J* = 6.6 Hz, 1 H, 2-H), 4.09 (ddd, *J* = 10.0, 6.0, 1.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6 (2 C), 14.0, 18.2, 22.6, 25.8 (3 C), 27.4, 33.3, 54.2, 58.3, 64.3, 66.6, 73.6 ppm. IR (film): $\tilde{\nu}$ = 2956, 2931, 2860, 1471, 1464, 1388, 1361, 1259, 1114, 1032, 875, 838, 777 cm^{-1}. MS (ES): *m*/*z* (%) = 309 [M + Na]$^+$, 280 (100) [M + 1 – 2Me]$^+$.

Partial Data for 4b (from the Mixture): R_f = (50% CH_2Cl_2/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3 H), 0.10 (s, 3 H), 0.88 (br. s, 12 H), 1.26–1.50 (m, 4 H), 1.54–1.68 (m, 2 H), 2.95 (dd, *J* = 11.0, 9.0 Hz, 1 H), 3.06 (dd, *J* = 3.9, 0.7 Hz, 1 H), 3.20 (dd, *J* = 3.9, 1.0 Hz, 1 H), 3.69 (td, *J* = 6.7, 1.0 Hz, 1 H), 3.80 (ddd, *J* = 10.9, 6.1, 1.0 Hz, 1 H), 3.90 (dd, *J* = 9.0, 6.1 Hz, 1 H) ppm.

(–)-(2*S*,3*R*,4*R*,5*S*)-2-Butyltetrahydro-2*H*-pyran-3,4,5-triol (9a): From alcohol **2a** (15 mg, 0.096 mmol, 1 equiv.), $Me_3NO{\cdot}2H_2O$ (27 mg, 0.240 mmol, 2.5 equiv.), and OsO_4 [63 μL (2.5%), 0.005 mmol, 0.05 equiv.], according to the general procedure described in the Supporting Information (22 h), triol **9a** was obtained as a single isomer. Purification by chromatography (0–10% MeOH/CH_2Cl_2) afforded **9a** (15 mg, 0.079 mmol, 82%) as a colorless oil. R_f = (10% MeOH/CH_2Cl_2). $[a]_D^{20}$ = –11.1 (*c* = 1.06, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, COSY): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.20–1.70 (m, 5 H), 1.75 (m, 1 H), 2.03 (br. s, 2 H, 2 OH), 2.32 (br. s, 1 H, OH), 3.42 (td, *J* = 8.8, 2.8 Hz, 1 H, 2-H), 3.62 (dd, *J* = 6.9, 3.5 Hz, 1 H, 6-H), 3.65 (dd, *J* = 9.4, 2.9 Hz, 1 H, 3-H), 3.81 (m, 1 H, 6-H), 3.85 (dd, *J* = 11.9, 1.8 Hz, 1 H, 4-H), 3.97 (td, *J* = 3.5, 0.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.7, 27.6, 30.9, 66.4, 69.5, 69.9, 70.4, 76.6 ppm. IR (film): $\tilde{\nu}$ = 3369, 2956, 2926, 2861, 1650, 1453, 1259, 1109, 1070, 1032 . MS (ES): *m*/*z* (%) = 213 (100) [M + Na]$^+$.

(–)-(2*S*,3*R*,4*R*,5*S*)-2-[2-(*tert*-Butyldiphenylsilyloxy)propyl]tetrahydro-2*H*-pyran-3,4,5-triol (46): From alcohol **45** (205 mg, 0.517 mmol, 1 equiv.), $Me_3NO{\cdot}2H_2O$ (144 mg, 1.293 mmol, 2.5 equiv.), and OsO_4 [0.33 mL (2.5%), 0.026 mmol, 0.05 equiv.], according to the general procedure described in the Supporting Information (15 h), triol **46** was obtained. Purification by chromatography (0–5% MeOH/CH_2Cl_2) afforded **46** (213 mg, 0.495 mmol, 96%) as a colorless oil. R_f = 0.15 (5% MeOH/CH_2Cl_2). $[a]_D^{20}$ = –3.9 (*c* = 0.89, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, COSY): δ = 1.03 (s, 9 H, *t*Bu 1 isom.), 1.03 (d, *J* = 6.5 Hz, 3 H, CH_3 1 isom.), 1.06 (s, 9 H, *t*Bu 1 isom.), 1.10 (d, *J* = 6.3 Hz, 3 H, CH_3 1 isom.), 1.47 [ddd, *J* = 14.3, 8.8, 2.9 Hz, 1 H, CH_2CH(CH_3)OTBDPS], 1.64 (br. s, 1 H, OH), 1.77 [dt, *J* = 14.4, 4.2 Hz, 1 H, CH_2CH(CH_3)-OTBDPS], 1.86–2.10 [m, 2 H, CH_2CH(CH_3)OTBDPS], 2.15 (br. s, 1 H, OH), 2.38 (br. s, 1 H, OH), 2.75 (br. s, 1 H, OH), 3.48 (dd, *J* = 13.7, 1.5 Hz, 2 H, 2-H 2 isom.), 3.55 (m, 1 H, OH), 3.61 (d, *J* = 12.2 Hz, 2 H, 6-H 2 isom.), 3.57–3.69 (m, 3 H, 3-H 1 isom, 4-H 2 isom.), 3.75 (t, *J* = 1.7 Hz, 1 H, 3-H 1 isom.), 3.82 (app. d, *J* =

9.5 Hz, 1 H, 6-H 1 isom.), 3.83 (d, J = 11.0 Hz, 1 H, 6-H 1 isom.), 3.92 (app. s, 1 H, 5-H 1 isom.), 4.02 (app. d, J = 2.7 Hz, 1 H, 5-H 1 isom.), 4.07–4.17 [m, 2 H, $CH_2CH(CH_3)$OTBDPS], 4.71 (br. s, 1 H, OH), 7.33–7.47 (m, 12 H, Ar-H), 7.62–7.72 (m, 8 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 19.3, 21.7, 24.5, 26.9 (3 C), 27.0 (3 C), 42.6, 42.7, 66.6, 66.8, 67.0, 67.8, 69.4, 69.5, 69.8 (2 C), 70.0, 72.4, 73.1, 127.4 (2 C), 127.5 (2 C), 127.7 (2 C), 127.8 (2 C), 129.5, 129.6, 129.9, 130.0, 132.9, 133.2, 134.1, 134.6, 135.9 (8 C) ppm. IR (film): $\tilde{\nu}$ = 3401, 3068, 2962, 2930, 2855, 1665, 1588, 1471, 1428, 1376, 1111, 1065, 821, 702 cm^{-1}. MS (ES): m/z (%) = 453 (100) [M + Na]$^+$. $C_{24}H_{34}O_5Si$ (430.61): calcd. C 66.94, H 7.96; found C 67.15, H 8.21.

(–)-(3a*S*,4*S*,7*S*,7a*R*)-4-[2-(*tert*-Butyldiphenylsilyloxy)propyl]tetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-7-ol (47b): Cyclohexanone (0.19 mL, 1.86 mmol, 8 equiv.) and *p*-toluenesulfonic acid (2 mg, 0.012 mmol, 0.05 equiv.) were added to a solution of triol **46** (100 mg, 0.232 mmol, 1 equiv.) in toluene (2.3 mL, 0.1 M) under argon at room temp. and the reaction was stirred until disappearance of the starting material was observed (TLC, 18 h.) The reaction was quenched by the addition of solid $NaHCO_3$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (5–20% EtOAc/hexane) to afford **47b** (102 mg, 0.20 mmol, 86%) as a colorless oil. R_f = 0.18 and 0.12 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –21.1 (c = 0.96, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, COSY): δ = 0.99 (d, J = 6.1 Hz, 3 H, CH_3 isom. A), 1.03 (s, 18 H, *t*Bu 2 isom.), 1.07 (d, J = 6.1 Hz, 3 H, CH_3 isom. B), 1.28–1.43 [m, 7 H, $CH_2CH(CH_3)$OTBDPS isom. A, 3 CH_2 cyclohexane], 1.56–1.70 [m, 15 H, $CH_2CH(CH_3)$OTBDPS isom. B, 7 CH_2 cyclohexane], 1.84 [m, 1 H, $CH_2CH(CH_3)$OTBDPS isom. B], 1.94 [m, 2 H, $CH_2CH(CH_3)$OTBDPS isom. A, OH], 3.26 (t, J = 8.6 Hz, 1 H, 4-H isom. B), 3.45 (td, J = 8.6, 2.2 Hz, 1 H, 4-H isom. A), 3.50 (d, J = 12.5 Hz, 1 H, 6-H 1 isom.), 3.58 (d, J = 12.2 Hz, 1 H, 6-H 1 isom.), 3.64 (app. dd, J = 12.2, 7.3 Hz, 2 H, 6-H 2 isom.), 3.73 (dd, J = 9.6, 5.0 Hz, 1 H, 3a-H isom. A), 3.75 (dd, J = 10.3, 4.9 Hz, 1 H, 3a-H isom. B), 3.90 (d, J = 8.8 Hz, 2 H, 7-H 2 isom.), 4.06 [m, 1 H, $CH_2CH(CH_3)$OTBDPS isom. B], 4.12–4.22 [m, 3 H, 7a-H 2 isom., $CH_2CH(CH_3)$OTBDPS isom. A], 7.32–7.40 (m, 12 H, Ar-H), 7.67 (m, 8 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.4, 22.9, 23.7 (2 C), 24.0 (2 C), 24.4, 25.0 (2 C), 27.0 (9 C), 29.7, 35.6 (2 C), 38.0, 38.1, 42.4, 43.8, 65.6, 66.6, 66.8, 68.2 (2 C), 74.3 (2 C), 74.9, 75.3, 76.2, 110.1 (2 C), 127.3 (2 C), 127.4, 129.4, 134.2, 134.5, 134.7, 135.0, 135.8 (4 C), 135.9 (10 C) ppm. IR (film): $\tilde{\nu}$ = 3401, 2932, 2857, 1652, 1449, 1428, 1112, 1046, 822, 702 cm^{-1}. MS (ES): m/z (%) = 533 [M + Na]$^+$, 527 (100), 511 [M + 1]$^+$, 433 [M – Ph]$^+$. $C_{30}H_{42}O_5Si$ (510.74): calcd. C 70.55, H 8.29; found C 70.82, H 7.94.

(+)-(3a*S*,4*S*,7a*S*)-4-[2-(*tert*-Butyldiphenylsilyloxy)propyl]dihydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-7(4*H*)-one (48b): From alcohol **47b** (102 mg, 0.20 mmol), PCC (88 mg, 0.40 mmol, 2 equiv.), and 4 Å molecular sieves (600 mg, 3 g/mmol), according to the general procedure described in the Supporting Information (22 h), ketone **48b** was obtained. Purification by chromatography (5–20% EtOAc/hexane) afforded **48b** (73 mg, 0.144 mmol, 72%) as a colorless oil. R_f = 0.22 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +5.6 (c = 1.53, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 18 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.11 (d, J = 6.1 Hz, 3 H), 1.37 (m, 4 H), 1.54–1.66 (m, 18 H), 1.88 (m, 1 H), 2.00 (ddd, J = 14.3, 8.6, 2.7 Hz, 1 H), 3.42 (dd, J = 9.2, 3.0 Hz, 1 H), 3.50 (m, 1 H), 3.51 (dd, J = 18.1, 1.5 Hz, 1 H), 3.91 (dd, J = 17.8, 1.2 Hz, 1 H), 4.03 (dd, J = 17.8, 0.7 Hz, 1 H), 4.10 (m, 2 H), 4.14 (d, J = 17.3 Hz, 1 H), 4.21 (t, J = 8.5 Hz, 1 H), 4.34 (t, J = 8.1 Hz, 1 H), 4.48 (d, J = 8.1 Hz, 1 H), 4.53 (d, J = 8.1 Hz, 1 H), 7.31–7.44 (m, 12 H), 7.62–7.68 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (2 C), 23.2, 23.7 (2 C), 23.8 (2 C), 24.3, 24.9 (2 C), 27.0 (12 C), 34.8 (2 C), 36.8, 36.9, 43.0, 44.3, 65.9, 66.4, 73.0, 77.2, 78.0, 78.3, 112.2 (2 C), 127.4 (3 C), 127.5 (3 C), 127.5 (2 C), 127.6 (2 C), 129.5, 129.6, 129.7, 134.1, 134.2, 134.5, 134.6, 135.9 (3 C), 135.9 (2 C), 207.1 (2 C) ppm. IR (film): $\tilde{\nu}$ = 3049, 3072, 2935, 2858, 1739, 1428, 1372, 1217, 1111, 998, 940, 822, 758, 703 cm^{-1}. MS (ES): m/z (%) = 563 (100) [M + Na + MeOH]$^+$.

(–)-(3a*S*,4*S*,7*R*,7a*S*)-7-Allyl-4-[2-(*tert*-butyldiphenylsilyloxy)propyl]-tetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-7-ol (49b): From ketone **48b** (70 mg, 0.138 mmol) and allylmagnesium bromide (1.7 mL, 0.33 M, 0.552 mmol, 4 equiv.), according to the general procedure described in the Supporting Information (1 h 40 min), alcohol **49b** was obtained. Purification by chromatography (5–20% EtOAc/hexane) afforded **49b** (53 mg, 0.096 mmol, 70%) as a colorless oil along with recovered starting material (3 mg, 0.006 mmol, 4%). R_f = 0.37 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –18.9 (c = 0.19, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, COSY): δ = 0.97 (d, J = 6.1 Hz, 3 H, CH_3 isom. A), 1.02 (s, 9 H, *t*Bu 1 isom.), 1.03 (s, 9 H, *t*Bu 1 isom.), 1.06 (d, J = 6.1 Hz, 3 H, CH_3 isom. B), 1.29–1.41 [m, 5 H, CH_2 cyclohexyl, 1 H $CH_2CH(CH_3)$OTBDPS isom. A], 1.43–1.70 [m, 17 H, CH_2 cyclohexyl, 1 H $CH_2CH(CH_3)$-OTBDPS isom. B], 1.79 [ddd, J = 13.9, 8.5, 2.2 Hz, 1 H, $CH_2CH(CH_3)$OTBDPS isom. B], 1.89 [ddd, J = 14.0, 9.3, 2.5 Hz, 1 H, $CH_2CH(CH_3)$OTBDPS isom. A], 2.30 (m, 5 H, CH_2=CHCH_2 2 isom., OH), 3.17 (d, J = 11.2 Hz, 1 H, 6-H 1 isom.), 3.22 (d, J = 11.2 Hz, 1 H, 6-H 1 isom.), 3.24 (td, J = 9.0, 2.4 Hz, 1 H, 4-H isom. B), 3.42 (d, J = 10.7 Hz, 1 H, 6-H 1 isom.), 3.44 (d, J = 10.5 Hz, 1 H, 6-H 1 isom.), 3.48 (dd, J = 9.8, 2.2 Hz, 1 H, 4-H isom. A), 3.59 (dd, J = 9.0, 6.6 Hz, 1 H, 3a-H isom. A), 3.61 (dd, J = 9.2, 6.3 Hz, 1 H, 3a-H isom. B), 4.05 [app. dd, J = 10.9, 5.0 Hz, 3 H, 7a-H 2 isom., $CH_2CH(CH_3)$OTBDPS isom. B], 4.18 [ddd, J = 9.3, 6.3, 3.2 Hz, 1 H, $CH_2CH(CH_3)$OTBDPS isom. A], 5.07–5.16 (m, 4 H, CH_2=$CHCH_2$ 2 isom.), 5.91 (m, 2 H, CH_2=$CHCH_2$ 2 isom.), 7.30–7.42 (m, 12 H, Ar-H), 7.64–7.69 (m, 8 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 19.4, 22.8, 23.6 (2 C), 24.0 (2 C), 24.4, 25.0 (3 C), 27.0 (8 C), 29.7, 35.7 (2 C), 38.0 (2 C), 41.1 (3 C), 42.5, 43.7, 65.8, 66.8, 69.7 (2 C), 70.1 (2 C), 74.6, 75.5, 76.2, 110.4 (2 C), 119.0 (2 C), 127.3 (2 C), 127.4 (4 C), 127.5 (3 C), 129.4 (3 C), 132.4 (2 C), 135.9 (10 C) ppm. IR (film): $\tilde{\nu}$ = 3445, 3068, 2933, 2857, 1471, 1462, 1447, 1428, 1365, 1269, 1159, 1111, 1085, 1047, 997, 936, 822, 759, 702 cm^{-1}. MS (ES): m/z (%) = 573 (100) [M + Na]$^+$. $C_{33}H_{46}O_5Si$ (550.80): calcd. C 71.96, H 8.42; found C 72.21, H 8.77.

(–)-(3a*S*,4*S*,7*R*,7a*S*)-7-Allyl-4-(2-hydroxypropyl)tetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-7-ol (50b): From alcohol **49b** (52 mg, 0.094 mmol) and TBAF (0.28 mL, 1 M, 0.282 mmol, 3 equiv.) in a THF/DMF (8:2) mixture, according to the general procedure A described in the Supporting Information [5 d, with an addition of 1 equiv. of TBAF (0.1 mL) after 4 d] diol **50b** was obtained. Purification by chromatography (0–40% EtOAc/CH_2Cl_2) afforded **50b** (21 mg, 0.067 mmol, 72%) as a colorless oil along with recovered starting material (3 mg, 0.006 mmol, 6%). A second purification of a smaller fraction (0–40% EtOAc/CH_2Cl_2) afforded both isomers of **50b** separately.

Data for Isomer 50b-A: R_f = 0.38 (40% EtOAc/CH_2Cl_2). $[\alpha]_D^{20}$ = –16.2 (c = 0.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, COSY): δ = 1.17 (d, J = 6.1 Hz, 3 H, CH_3), 1.38 (m, 3 H, CH_2 cyclohexyl, OH), 1.52–1.73 [m, 9 H, 4 CH_2 cyclohexyl, $CH_2CH(CH_3)$OH], 1.81 [app. dt, J = 14.2, 3.0 Hz, 1 H, $CH_2CH(CH_3)$OH], 2.27 (m, 3 H, CH_2=CHCH_2, OH), 3.41 (d, J = 11.2 Hz, 1 H, 6-H), 3.43 (td, J = 9.3, 3.6 Hz, 1 H, 4-H), 3.61 (d, J = 11.0 Hz, 1 H, 6-H), 3.75 (dd, J

= 9.0, 5.1 Hz, 1 H, 3a-H), 4.00 [ddd, *J* = 9.2, 6.3, 2.7 Hz, 1 H, $CH_2CH(CH_3)OH$], 4.11 (d, *J* = 4.9 Hz, 1 H, 7a-H), 5.10–5.18 (m, 2 H, CH_2=$CHCH_2$), 5.92 (ddt, *J* = 17.4, 10.0, 7.2 Hz, 1 H, CH_2=$CHCH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 23.6, 24.1, 24.9, 35.5, 38.0, 41.0, 41.8, 67.5, 69.5, 70.0, 76.0, 77.8, 78.9, 110.7, 119.3, 132.1 ppm. IR (film): ṽ = 3435, 2926, 2854, 1642, 1452, 1367, 1263, 1161, 1110, 1037, 927 cm^{-1}. MS (ES): *m*/*z* (%) = 335 (100) [M + Na]$^+$.

Data for Isomer 50b-B: R_f = 0.30 (40% EtOAc/CH_2Cl_2). $[\alpha]_D^{20}$ = –20.3 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.1 Hz, 3 H), 1.22–1.38 (m, 2 H), 1.53–1.86 (m, 10 H), 2.36 (m, 2 H), 3.39 (d, *J* = 11.2 Hz, 1 H), 3.46 (app. dt, *J* = 8.3, 6.0 Hz, 1 H), 3.59 (d, *J* = 11.0 Hz, 1 H), 3.86 (dd, *J* = 9.0, 4.9 Hz, 1 H), 3.98 (m, 1 H), 4.13 (d, *J* = 4.6 Hz, 1 H), 5.11–5.18 (m, 2 H), 5.93 (ddt, *J* = 17.5, 10.2, 7.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 23.6, 24.0, 35.5, 37.9, 41.1, 41.9, 64.9, 69.6, 70.3, 75.5, 76.3, 77.3, 110.7, 119.2, 132.1 ppm. IR (film): ṽ = 3429, 2934, 2860, 1641, 1451, 1368, 1276, 1161, 1110, 1037, 726 cm^{-1}. MS (ES): *m*/*z* (%) = 335 (100) [M + Na]$^+$.

(–)-1-[(3a*S*,4*S*,7*R*,7a*S*)-7-Allyl-7-hydroxytetrahydro-3a*H*-spiro-[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-4-yl]propan-2-one (52b): From alcohol **50b** (21 mg, 0.067 mmol), PCC (29 mg, 0.134 mmol, 2 equiv.), and 4 Å molecular sieves (201 mg, 3 g/mmol), according to the general procedure described in the Supporting Information (2 h 30 min), ketone **52b** was obtained. Purification by chromatography (0–20% EtOAc/CH_2Cl_2) afforded **52b** (18 mg, 0.058 mmol, 86%) as a colorless oil. R_f = 0.33 (20% EtOAc/CH_2Cl_2). $[\alpha]_D^{20}$ = –1.8 (*c* = 1.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31–1.44 (m, 2 H), 1.52–1.78 (m, 8 H), 2.17 (s, 3 H), 2.36 (m, 3 H), 2.54 (dd, *J* = 15.9, 8.5 Hz, 1 H), 2.67 (dd, *J* = 15.8, 3.0 Hz, 1 H), 3.40 (d, *J* = 11.2 Hz, 1 H), 3.56 (d, *J* = 11.2 Hz, 1 H), 3.69 (td, *J* = 9.0, 3.2 Hz, 1 H), 3.77 (dd, *J* = 9.3, 4.6 Hz, 1 H), 4.11 (d, *J* = 4.4 Hz, 1 H), 5.09–5.17 (m, 2 H), 5.92 (ddt, *J* = 17.5, 10.4, 7.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 24.0, 24.9, 30.8, 35.5, 37.9, 41.0, 46.6, 69.6, 70.4, 74.6, 74.9, 77.3, 110.8, 119.1, 132.2, 206.3 ppm. IR (film): ṽ = 3456, 2936, 2862, 1718, 1641, 1450, 1432, 1366, 1275, 1231, 1164, 1110, 1051, 927, 851, 757 cm^{-1}. MS (ES): *m*/*z* (%) = 643 [2M + Na]$^+$, 333 (100) [M + Na]$^+$, 311 [M + 1]$^+$. $C_{17}H_{26}O_5$ (310.39): calcd. C 65.78, H 8.44; found C 65.53, H 8.19.

Ethyl (–)-(*E*)-4-[(3a*S*,4*S*,7*R*,7a*S*)-7-Allyl-7-hydroxytetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-4-yl]-3-methylbut-2-enoate (57): A solution of triethyl phosphonoacetate (42 μL, 0.211 mmol, 6.6 equiv.) in THF (0.1 mL) was added dropwise to a cold suspension (0 °C) of NaH (5 mg, 0.192 mmol, 6 equiv.) in THF (0.2 mL) and the mixture was stirred at room temp. for 30 min. The reaction was cooled to –70 °C, a solution of ketone **52b** (10 mg, 0.032 mmol, 1 equiv.) in THF (0.1 mL) was added, and the reaction was stirred from –70 °C to room temp. until no change was observed (TLC, 3 d). The reaction was quenched by the addition of H_2O and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL/mmol) and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5–20% EtOAc/hexane) to afford an 80:20 mixture of (*E*/*Z*)-**57** (4 mg, 0.011 mmol, 34%) as a colorless oil along with impure recovered starting material (6 mg, 0.019 mmol, 60%).

Data for (*E*)-57 (from the Mixture): R_f = 0.23 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –13.0 (*c* = 0.71, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.29–1.40 (m, 2 H), 1.54–1.74 (m, 8 H), 2.17 (s, 3 H), 2.19 (dd, *J* = 14.7, 9.3 Hz, 1 H), 2.32–2.41 (m, 3 H), 2.47 (dd, *J* = 14.7, 2.0 Hz, 1 H), 3.35 (d, *J* = 11.2 Hz, 1 H), 3.40 (td, *J* = 9.3, 2.9 Hz, 1 H), 3.57 (d, *J* = 11.2 Hz, 1 H), 3.72 (dd, *J* = 9.0, 4.9 Hz, 1 H), 4.11 (d, *J* = 4.2 Hz, 1 H), 4.12 (q, *J* = 7.3 Hz, 2 H), 5.11–5.17 (m, 2 H), 5.72 (s, 1 H), 5.92 (ddt, *J* = 17.4, 10.0, 7.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 19.1, 23.6, 24.0, 24.9, 35.6, 38.1, 41.1, 43.9, 59.5, 69.6, 70.5, 75.5, 77.0, 77.2, 110.6, 117.7, 119.1, 132.2, 156.0, 166.9 ppm. IR (film): ṽ = 3480, 3077, 2936, 2860, 1716, 1650, 1450, 1367, 1347, 1276, 1225, 1151, 1109, 1043, 927, 758 cm^{-1}. MS (ES): *m*/*z* (%) = 403 (100) [M + Na]$^+$, 381 [M + 1]$^+$.

Partial Data for (*Z*)-57 (from the Mixture): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (s, 3 H), 2.87 (dd, *J* = 13.5, 8.9 Hz, 1 H), 2.99 (dd, *J* = 13.5, 4.0 Hz, 1 H), 3.34 (d, *J* = 11.0 Hz, 1 H), 3.48 (td, *J* = 8.8, 4.4 Hz, 1 H), 3.55 (d, *J* = 11.2 Hz, 1 H), 3.82 (dd, *J* = 8.8, 4.9 Hz, 1 H), 5.73 (s, 1 H) ppm.

Ethyl (–)-(*E*)-4-{(3a*S*,4*S*,7*R*,7a*S*)-7-Hydroxy-7-[(4*R*,5*S*,*E*)-4-methyl-5-(triethylsilyloxy)hex-2-enyl]tetrahydro-3a*H*-spiro[[1,3]dioxolo[4,5-*c*]pyran-2,1′-cyclohexan]-4-yl}-3-methylbut-2-enoate (58): From **57** (3 mg, 0.008 mmol, 1 equiv.), **54** (3 mg, 0.016 mmol), and Grubbs catalyst (0.3 mg, 0.0004 mmol, 0.05 equiv.), according to the general procedure described in the Supporting Information, **58** was obtained. Purification by chromatography (5–30% EtOAc/hexane) afforded **58** (3 mg, 0.005 mmol, 66%) as a colorless oil. (The spectral data was assigned following the pseudomonic acid numbering.) R_f = 0.33 (20% EtOAc/hexane.) $[\alpha]_D^{20}$ = –9.7 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.56 (q, *J* = 8.0 Hz, 6 H), 0.93 (t, *J* = 7.8 Hz, 9 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 1.03 (d, *J* = 6.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.35 (m, 2 H), 1.54–1.73 (m, 8 H), 2.17 (d, *J* = 1.0 Hz, 3 H), 2.14–2.24 (m, 2 H), 2.29 (m, 2 H), 2.47 (d, *J* = 14.4 Hz, 1 H), 3.35 (d, *J* = 11.3 Hz, 1 H), 3.41 (td, *J* = 9.3, 2.9 Hz, 1 H), 3.55 (d, *J* = 11.3 Hz, 1 H), 3.70 (dd, *J* = 9.3, 4.7 Hz, 1 H), 3.71 (app. d, *J* = 4.3 Hz, 1 H), 4.09 (d, *J* = 3.9 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 5.50 (m, 2 H, 10-H), 5.71 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.0 (3 C), 6.9 (3 C), 14.3, 15.5, 19.1, 20.5, 23.6, 24.0, 24.9, 31.9, 35.5, 38.1, 40.1, 44.2, 59.5, 69.7, 70.6, 71.6, 75.5, 76.1, 76.4, 110.5, 117.7, 123.2, 137.7, 156.1, 166.6 (C-1) ppm. IR (film): ṽ = 3446, 2927, 2855, 1713, 1650, 1451, 1368, 1263, 1217, 1150, 1108, 1039, 928, 759, 667 cm^{-1}. MS (ES): *m*/*z* (%) = 589 (100) [M + Na]$^+$, 567 [M + 1]$^+$.

Ethyl (+)-(*E*)-3-Methyl-4-{(2*S*,3*R*,4*S*,5*R*)-3,4,5-trihydroxy-5-[(4*R*,5*S*,*E*)-5-hydroxy-4-methylhex-2-enyl]tetrahydro-2*H*-pyran-2-yl}but-2-enoate (30): From **58** (3 mg, 0.005 mmol) and DOWEX resin (3 mg, 0.5 g/mmol), according to the general procedure B described in the Supporting Information (5 d), alcohol **30** was obtained. Purification by chromatography (80–100% EtOAc/CH_2Cl_2) afforded **30** (2 mg, 0.004 mmol, 80%) as a colorless oil. (The spectral data was assigned following the pseudomonic acid numbering.) R_f = 0.18 (EtOAc). $[\alpha]_D^{20}$ = +7.2 (*c* = 0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, COSY): δ = 1.00 (d, *J* = 6.8 Hz, 3 H, 15-H), 1.17 (d, *J* = 6.2 Hz, 3 H, 14-H), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2O), 1.53–1.65 (m, 3 H, 3 OH), 2.12 (q, *J* = 6.8 Hz, 1 H, 12-H), 2.19 (s, 3 H, 17-H), 2.26 (dd, *J* = 15.0, 9.3 Hz, 1 H, 4-H), 2.35 (app. d, *J* = 6.9 Hz, 2 H, 9-H), 2.62 (d, *J* = 15.0 Hz, 1 H, 4-H), 3.38 (d, *J* = 11.2 Hz, 1 H, 16-H), 3.39 (m, 1 H, 6-H), 3.46 (d, *J* = 10.8 Hz, 1 H, 16-H), 3.53 (qui, *J* = 6.3 Hz, 1 H, 13-H), 3.62 (app. t, *J* = 6.7 Hz, 2 H, 5-H, OH), 3.81 (br. s, 1 H, 7-H), 4.12 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2O), 5.49 (dd, *J* = 15.5, 7.0 Hz, 1 H), 5.55 (dd, *J* = 15.5, 6.3 Hz, 1 H), 5.74 (s, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 16.7, 20.7, 24.3, 31.9, 38.3, 44.9, 59.6, 68.8, 70.0, 71.2, 71.4, 72.5, 74.4, 117.7, 124.6, 138.4, 156.5, 166.6 (C-1) ppm. IR (film): ṽ = 3405, 2925, 2854, 1713, 1647, 1463, 1378, 1262, 1217, 1151, 1099, 1045, 759 cm^{-1}. MS (ES): *m*/*z* (%) = 395 (100) [M + Na]$^+$.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and spectroscopic data for all new compounds.

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[25] The scale of the preparation of fragment **54** proved to be critical. No methylation of ethyl (*S*)-3-hydroxybutyrate was observed on a small scale or in the absence of DMPU.

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