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Stereoselective synthesis of functionalised triol units by $SnCl_4$ promoted allylation of α-benzyloxyaldehydes: crucial role of the stoichiometry of the Lewis acid

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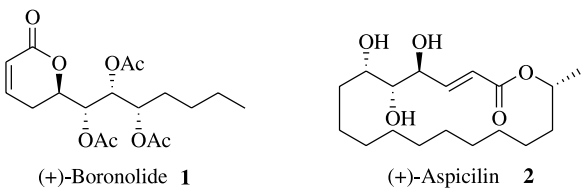
Dedicated with deep respect to Professor Dieter Seebach

Abstract—Enantiomerically pure *syn–anti* and *syn–syn* configured triol units are efficiently synthesized by the $SnCl_4$ mediated allylation of chiral α-benzyloxyaldehydes with the uniquely functionalised allylstannane **9**. Remarkably, the stereochemistry of the adducts is solely governed by the amount of Lewis acid employed.

1. Introduction

Numerous natural products, exhibiting interesting biological activities, contain a polyhydroxylated subunit in their structures. These fragments are present, for example, in molecules such as (+)-boronolide[1] **1** or (+)-aspicilin[2] **2**, which possess a *syn–syn* and *syn–anti* triol sequence, respectively (Fig. 1).



(+)-Boronolide **1** (+)-Aspicilin **2**

Figure 1.

In views of the ubiquitousness of these polyol entities, it is not surprising that numerous synthetic methods have been developed to assemble these structures with excellent levels of relative and absolute stereocontrol.[3] Among others, the reaction of allylic organometallic species with aldehydes has emerged as one of the most synthetically useful procedures for acyclic stereoselection. Over the past few years, the allylation of chiral alkoxyaldehydes has been extensively studied and has become a particularly valuable tool for the construction of homoallylic alcohols. Numerous allylic derivatives such as allylborons,[4] allylchromiums,[5] allyltins,[6] etc. were found to be efficient reagent in this transformation, leading to the desired adducts with high stereoselectivity for this process (Fig. 2).

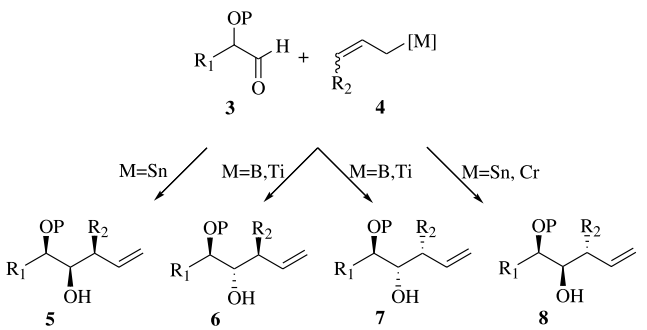


Figure 2. R_1=Me, Et, *n*Bu; R_2=OR, Me, SR P=Bn, TBDMS, MOM.

All four possible diastereoisomers of the triol subunit can be obtained by varying the nature of the allylic metal, the

Keywords: Allylation; Allylstannane; Chelation; Triols; Stereocontrol; Lewis acid.
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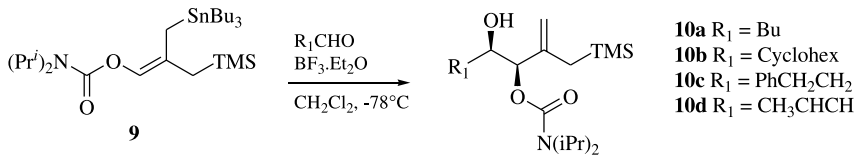


Figure 3.

conditions of the reaction (Lewis acid catalysed, high pressure or thermal), or the geometry of the double bond[7] present in the allylating agent. Roush et al.[4a–c] showed that β-substituted allylborons provided access to **5**, **6** and **7** but each isomer corresponds to a specific combination of the double bond geometry of **4** and the nature of the ligand on the boron. Chromium[5] derivatives were found to be less flexible, giving access only to isomer **8**. In sharp contrast, allyltin species afford isomers **5** and **8**, depending upon the type of transition states involved in the condensation.[8] Thus Lewis acids such as $BF_3{\cdot}Et_2O$ give rise to isomer **8** through a non chelating Felkin–Anh process whilst $MgBr_2$ a chelating Lewis acid provides access to isomer **5** as described by Keck.[8a–d] Furthermore, Marshall[8f–g] has reported complementary examples of this transformation by using enantioenriched (γ-alkoxyallyl) stannanes, which provide well defined (E) configured alkenes. Therefore, the use of β-alkoxyallylstannanes has become an efficient method for the assembly of stereodefined triols by modulating the experimental parameters.

Recently, we became interested in the reactivity of the uniquely functionalised allylstannane **9** and studied its condensation with various aldehydes. In the presence of $BF_3{\cdot}Et_2O$, the *syn* diols[9] **10a–d** were stereoselectively produced (Fig. 3).

Extension of this methodology to α-alkoxyaldehydes should increase its scope by giving access to stereodefined, protected, triols. In this article, we wish to report in full our results on the successful implementation of this approach.

Allylic alcohol **12** was prepared in good yield according to the procedure described by Trost[10] and starting from methallylalcohol **11** (Fig. 4). Allylsilane **12** was then condensed with isopropylcarbamoylchloride to afford allylcarbamate **13** in 93% yield. The use of NaH as the base and of Et_2O as the solvent proved essential to obtain high yields of the desired products. Deprotonation of **13** with *sec*BuLi,[11] followed by transmetallation with $Ti(O^iPr)_4$, generated the allyltitanium species **14a**, which subsequently reacted with tributyl tin chloride to give the allylating agent **9** in high yields.

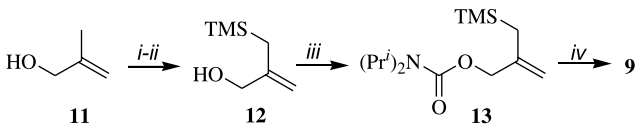


Figure 4. (i) *n*BuLi, TMEDA, TMSCl, Et_2O/THF, −78 °C; (ii) H_2SO_4, THF rt (47% 2 steps); (iii) $(^iPr)_2NCOCl$, NaH, Et_2O, 0 °C to rt (93%); (iv) *sec*BuLi, TMEDA, $Ti(O^iPr)_4$, Bu_3SnCl, Et_2O, −78 °C (80%).

This reaction proceeded efficiently at −78 °C and gave only the (*Z*)-isomer of allylstannane **9**. The observed stereoselectivity can be explained by the preferential pseudo-axial configuration adopted by the carbamate substitutent in the chair-like transition state **14b** leading to a better chelation of the titanium (Fig. 5). This preferred configuration is in agreement with previous observations reported by Yamamoto.[12]

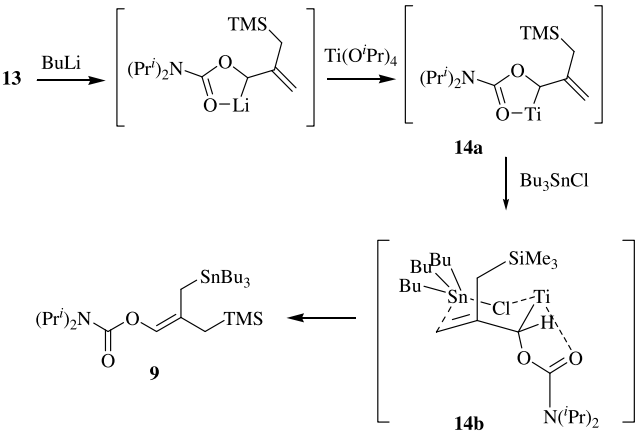
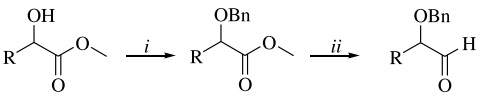


Figure 5. Synthesis of allystannane **9**.

Having access to large quantities of **9**, we next turned our attention to its condensation with various aldehydes. In the presence of $BF_3{\cdot}Et_2O$ simple aldehydes reacted smoothly with **9** to afford selectively the *syn* diol[9] products **10a–d** (Fig. 3). In order to extend the scope of this allylation protocol, we decided to study the Lewis acid catalysed addition of **9** to various α-alkoxyaldehydes.

The desired aldehydes were prepared from the corresponding racemic or enantiomerically pure α-hydroxy esters **15(b–d)**, by protection of the alcohol function with a benzyl substitutent followed by reduction of the ester group (Fig. 6). The benzyl protection was introduced using benzyltrichloroacetimidate under acidic catalysis.[13] This protocol suppressed some undesired transesterification problems we have encountered with the classical procedure using benzylbromide.[14] The α-benzyloxyesters **16(b–d)** were then submitted to controlled reduction with DIBAL-H to afford the expected aldehydes **17(b–d)** in good yields.



15b R= *rac*-Me
15c R=(*S*)-Me
15d R=(*R*)-Cyclohex

16b R=R= *rac*-Me (99%)
16c R=(*S*)-Me (99%)
16d R=(*R*)-Cyclohex (47%)

17a R=H
17b R= *rac*-Me (82%)
17c R=(*S*)-Me (82%)
17d R=(*R*)-Cyclohex (80%)

Figure 6. (i) Benzyl-2,2,2-trichloroacetimidate, TfOH cat., Hex/CH_2Cl_2, rt; (ii) DIBALH, CH_2Cl_2, −78 °C.

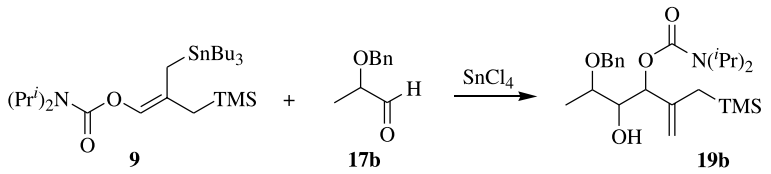


Figure 7.

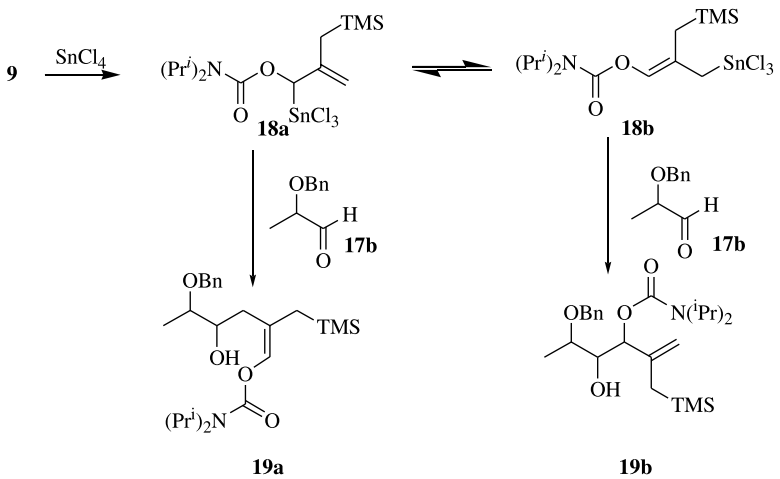


Figure 8. proposed allylation mechanism.

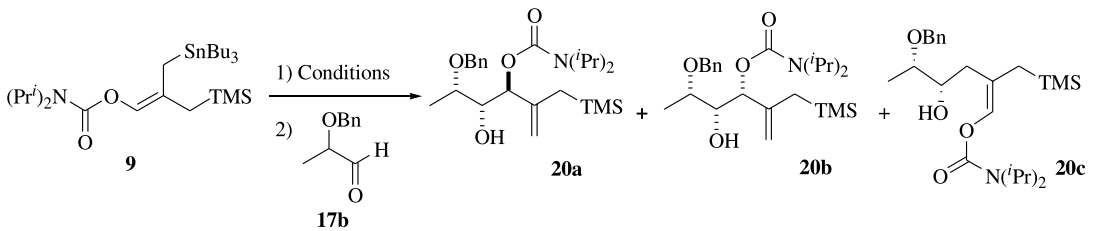
The enantiomeric purity of the optically active aldehydes was controlled by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as resolving agent or by HPLC whenever possible. In all cases, the freshly prepared aldehydes exhibited an enantiomeric purity greater than 95%.

Surprisingly, under these conditions that proved successful with simple aldehydes, α-alkoxyaldehydes such as **17b** did not give rise to the desired products.

Several Lewis acids were then screened and tin tetrachloride was found to be the reagent of choice for this transformation (Fig. 7).

This methodology takes advantage of the rapid transmetallation[15] that occurs between an allyltrialkylstannane and tin tetrachloride, producing an allylic trichlorometal species **18a** that exhibits a higher reactivity and a stronger coordinating power as compared to the parent allylic trialkyltin reagent. The α-isomer **18a** is in dynamic equilibrium with its γ-form **18b** either through an intramolecular transposition of tin or by reaction of **18a** with tin tetrachloride still available in the reaction medium. The condensation of intermediate **18a** with an aldehyde then leads to the α-adducts **19a**, whilst reaction with **18b** produces the δ-addition product **19b** (Fig. 8).

Table 1. Conditions optimisation[a]



Entry	Eq. of $SnCl_4$	T (°C)	Solvent	Equilibration time	Ratio **20a/20b/20c**[b]
1	1	−60	CH_2Cl_2	1 h 30 min	85/15/0
2	1	−76	CH_2Cl_2	2 h 30 min	97/3/0
3	1	−76	CH_2Cl_2	1 h	96/4/0
4	1	−96	CH_2Cl_2	1 h	97/3/0
5	2	−60	CH_2Cl_2	1 h 30 min	16/31/53
6	2	−76	CH_2Cl_2	1 h 30 min	7/57/36
7	2	−96	CH_2Cl_2	1 h	1/83/16
8	2	−102	1,2 dichloropropane	1 h	20/80/0
9	2	(±)-120	$CClF_3/CH_2Cl_2$ 9/1	1 h	7/45/48

[a] The isolated yields were equal to the NMR yields.
[b] Determined by integration of the ^{1}H NMR signal belonging to the vinylic protons.

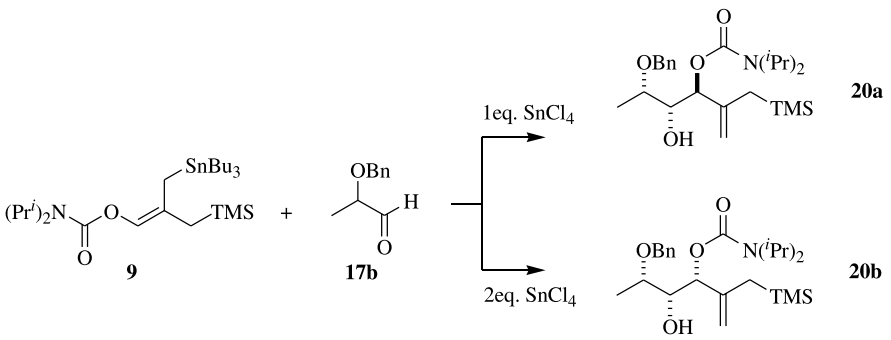


Figure 9.

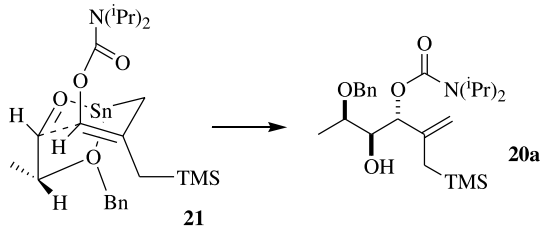


Figure 10. Cyclic transition state.

Such a transmetallation also occurs with allylsilanes, though it has been shown to proceed more slowly.[16]

Since a mixture of α- and δ-adducts are produced under these initial conditions, and taking into account the proposed transmetallation mechanism, we reasoned that by changing the temperature of the reaction, it might be possible to alter the position of the equilibrium and hence produce either **19a** or **19b** at will. Our first attempts were carried out by mixing **9** and $SnCl_4$ at low temperature followed, after a period of equilibration of one hour, by the addition of **17b**. We were delighted to observe that under these conditions the γ-adduct **19b** largely predominated (Table 1). Lowering the temperature even further resulted in a significant improvement of the diastereoselectivity and, at −96 °C, a d.r. of 97:3 in favour of the *syn–anti* isomer **20a** was observed. In order to further improve this procedure, two equivalents of $SnCl_4$ were added instead of one. Much to our surprise, an inversion of diastereoselectivity occurred, leading to the preferential formation of the previously minor *syn–syn* diastereoisomer **20b**.

Again, lowering the temperature resulted in the overwhelming generation of **20b** (d.r.=83:1). Thus, in the presence of one equivalent of $SnCl_4$, allylstannane **9** reacts quantitatively with **17b** to afford the *syn–anti* diastereoisomer **20a** whilst the use of two equivalents of the same Lewis acid resulted in a complete inversion of selectivity, leading to the *syn–syn* isomer **20b** (Fig. 9).

To the best of our knowledge, such inversions related to the stoichiometry of the Lewis acid employed have never been reported in the literature and this parameter seems, in most of the cases, to have been largely underestimated. Examples of allylation by similar γ-substituted allyltin compounds, mediated by magnesium dibromide or titanium tetrachloride and affording *syn–syn* alcohols with high stereoselectivity have already been described.[8d–g] However, in these cases, the amount of Lewis acid has never been considered as a key parameter to influence the stereochemical outcome of the reaction.

To rationalise these results, we propose the involvement of two different transition states. When one equivalent of $SnCl_4$ is used, the transmetallated species **18b** would react with the aldehyde through a bicyclic transition state **21** as depicted in Figure 10. This transition state has been postulated for thermal and high pressure reactions of allyltrialkyltin reagents. In these cases, the tin plays the role of a weak Lewis acid.[17] In contrast the trichlorotin generated under our conditions, possesses a greater chelating ability. The carbamate would thus adopt a pseudo-axial orientation in order to interact with the tin which is already chelated to the benzyl ether and to the carbonyl of the aldehyde. Allyl transfer through this rigid, hydrindane-like, transition state then leads to the observed *syn–anti* selectivity.

In contrast, when 2 equiv. of $SnCl_4$ are used, one equivalent reacts with the aldehyde to form the chelate **22** whilst the second equivalent of Lewis acid transmetallates the allylating agent **9**.[18,19] The allyl transfer now takes place through an open transition state such as **23**, leading to the *syn–syn* diastereoisomer **20b** (Fig. 11). Such a reaction pathway has been proposed by Keck et al.[8a–d] to rationalize the selectivities observed during the allylation of aldehydes with crotyl tin derivatives. In this case, the carbamate will occupy the less hindered quadrant.

The choice of the protecting group present on the

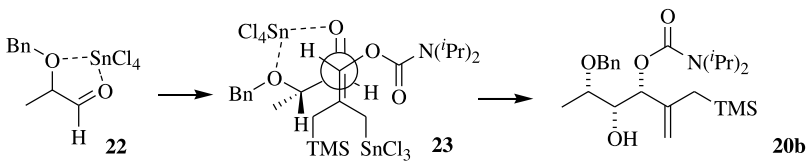
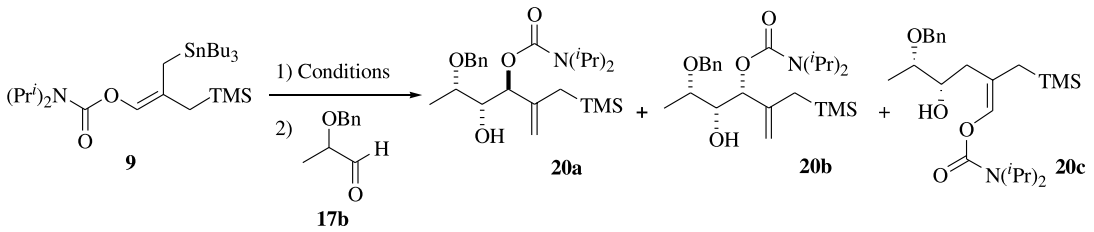


Figure 11. Open transition state.

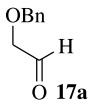
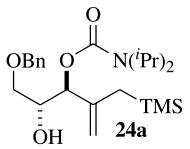
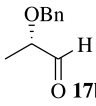
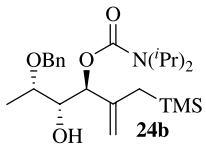
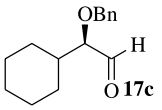
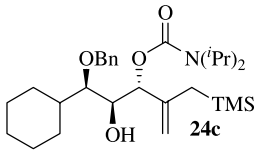
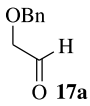
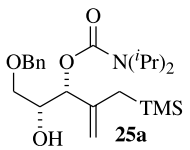
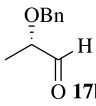
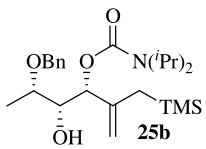
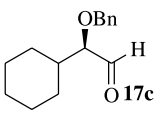
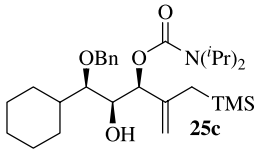
Table 2. Effect of the order of addition[a]



Entry	Eq. of $SnCl_4$	T (°C)	Solvent	Equilibration time (h)	Ratio **20a/20b/20c**[b]
1	2	−96	CH_2Cl_2	1	1/78/21
2	2	−102	1,2 dichloropropane	1	15/75/5

[a] The isolated yields were equal to the NMR yields.
[b] Determined by integration of the ^1H NMR signal belonging to the vinylic protons.

Table 3. Allylation of chiral aldehydes

Entry	Aldehyde	Product	Yield[a] (%)	de[b] (%)	ee[c]
1[d]	 **17a**	 **24a**	84	90	n.a[e]
2[d]	 **17b**	 **24b**	96	94	>95%
3[d]	 **17c**	 **24c**	81	94	>95%
4[f]	 **17a**	 **25a**	70	91	n.a[e]
5[f]	 **17b**	 **25b**	83	97	>95%
6[f]	 **17c**	 **25c**	81	90	>95%

[a] Isolated yields.
[b] Determined by integration of the ^1H NMR signal belonging to the vinylic protons.
[c] Determined by chiral HPLC.
[d] Using 1 equiv. of $SnCl_4$.
[e] Diol obtained as a racemic mixture.
[f] Using 2 equiv. of $SnCl_4$.

alkoxyaldehyde is of paramount importance for the success of this reaction. The use of benzyl ether, exhibiting a high Lewis basicity on the oxygen, enables the formation of a strong chelate. In sharp contrast, the use of a silicon-based protecting group such as a TBDMS which prevents efficient coordination by the Lewis acid leads to poor selectivities.

In order to lend further support to the postulated open-transition state pathway, it was decided to effect the transmetallation first and then to add to the in situ generated allyltrichlorotin species **18b**, one equivalent of the pre-complexed aldehyde. As can be seen from Table 2, the same ratios are obtained, at two different temperatures, either using this 'inverse' protocol or the 'normal' addition procedure described previously. (Vide supra). This observation lends further credit to our proposed transition states.

Having demonstrated that the addition of the allylating agent **9** onto a variety of racemic α-benzyloxyaldehydes proceeded with excellent levels of diastereocontrol, we turned our attention to the use of optically pure substrates with a view to generate enantioenriched triols. Our results are summarised in Table 3.

In all cases, the triols were formed in good to excellent yields (70–96%) and with high diastereoselectivities. (90–97%). Gratifyingly, no erosion of the enantiopurity of the starting α-benzyloxyaldehydes was observed and the final adducts were isolated in essentially optically pure form (Table 3, entries 2, 3, 5 and 6). It thus transpires that racemisation is a slower process than addition of the allylating agent.

At this stage, it is important to note that each oxygen function of the triol unit present in adducts **24a–c** and **25a–c** is differently substituted. Such orthogonal protection allows subsequent chemoselective transformations to be readily effected on adducts **20a–b** as shown in Figure 12.

The stereochemistry of both *syn–anti* and *syn–syn* triol units was determined by synthesizing the acetonides derived from each pair of vicinal diols, themselves obtained by chemoselective deprotection of either the carbamate or the benzylether function. Analysis of the ^{1}H NMR coupling constants between the adjacent protons at C2, C3 and C3, C4 is a reliable method to determine the stereochemistry of these two stereogenics centres.[20]

Initially, treatment of **20a** and **20b** by $BF_3{\cdot}Et_2O$ removed the allylic silane which proved to be troublesome at times. Substrates **26(a–b)** were then hydrogenated in order to cleave the benzyl ether. This reaction occurred with concomitant reduction of the C–C double bond. Alternatively, reduction of the carbamate moiety with $LiAlH_4$ afforded diols **27b** and **27d**. Finally, the reaction of the resulting diols **27(a–d)** with acetone under acidic conditions produces the desired acetonides **28(a–d)** (Fig. 12).

The ^{1}H NMR data clearly revealed that in all cases, the vicinal diols were *syn* configured (^3J>8 Hz) except in the case of **28b** where an *anti* configuration (^3J<7 Hz) was

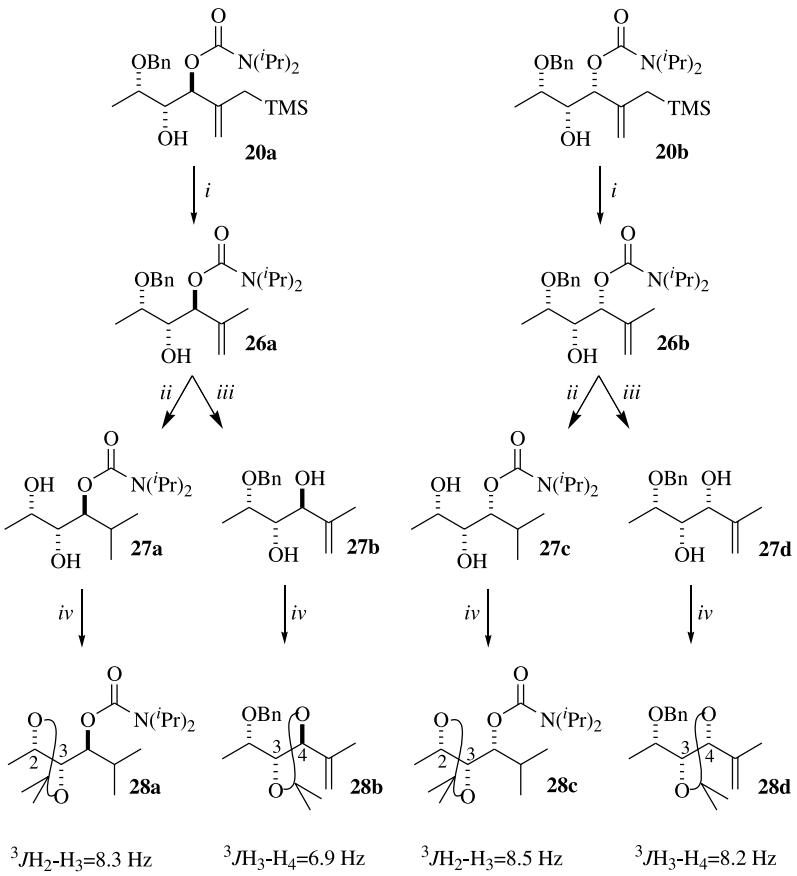


Figure 12. (i) $BF_3{\cdot}Et_2O$, DCM, −15 °C; (ii) H_2, Pd/C cat., AcOEt, 40 °C; (iii) $LialH_4$, THF, reflux; (iv) Acetone, APTS, reflux.

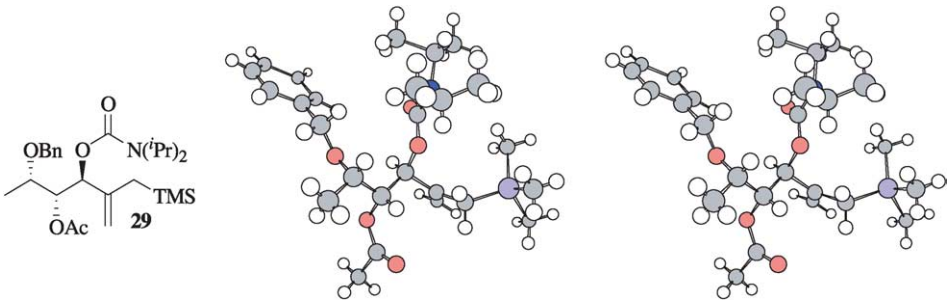


Figure 13. Cross-eyed stereo view of X-ray analysis of acetate derivative **29**.

observed. Finally, having access to the enantiomerically pure, chemoselectively protected compounds **24b** and **25b**, we attempted to derivatize the free alcohol function in order to obtain suitable crystals for an X-ray diffraction analysis. Gratifyingly, the acetate **29**, derived from the *syn–anti* triol **24b** eventually crystallised upon standing. A three-dimensional view of compound **29** clearly reveals the *syn–anti* relationship between the three oxygenated functions, thus fully corroborating our previous assignments (Fig. 13).

In summary, we have developed an efficient methodology for the rapid assembly of consecutive triols arrays in good yields (70–96%) and high diastereoselectivities (de. 90–97%). A remarkable and complete inversion of stereochemistry is observed when the amount of Lewis acid is varied. Thus, 1 equiv. of $SnCl_4$ leads to the *syn–anti* triol whilst two equivalents give access to the *syn–syn* triol. This stereodivergent behaviour has been rationalized by invoking the participation of two different transition states. This convenient procedure allows a ready access to stereocomplementary, orthogonally protected triol subunits present in a variety of interesting natural products. The scope and limitations of this protocol and its application to the preparation of highly oxygenated natural products are currently under active investigation. The results of these studies will be reported in due course.

2. Experimental

2.1. Generalities

Unless otherwise stated all the reactions were carried out using anhydrous conditions and in an atmosphere of argon. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200, 300 and 2000 instruments. Chemical shifts are expressed as parts per million (ppm) down-field from tetramethylsilane or calibrated from $CDCl_3$. Mass spectra were obtained using Varian MAT-44 and Finnigan MAT-TSQ 70 spectrometers with electron impact (70 eV) and chemical ionisation (100 eV, ionisation gas, isobutane). IR spectra were taken with a BIO-RAD FTS 135 spectrometer. Microanalysis were performed in Professor V. Jäger's analytical laboratory (Institut für Organishe Chemie, Universität Stuttgart, Germany). High resolution mass spectra were recorded in Professor R. Flamant's laboratory (Université de Mons, Belgium).

(*S*)-Methyl 2-hydroxypropanoate **15b** is commercially available from Sigma-Aldrich and was used as received.

2-(Benzyloxy)acetaldehyde **17a** is commercially available from Acros and was used as received.

2.2. Synthesis of allylstannane 9

2.2.1. 2-((Trimethylsilyl)methyl)prop-2-en-1-ol 12. In a 2 l round bottom flask equipped with a mechanical stirrer were added TMEDA (140 ml, 107.73 g, 0.92 mol, 2.6 equiv.) and freshly distilled Et_2O (440 ml). At 0 °C, a solution of *n*BuLi (10 M in hexane, 100 ml, 1 mol, 2.8 equiv.) is added via a large diameter canula. Then, methallylic alcohol **7** (30 ml, 25.71 g, 0.35 mol, 1 equiv.) was added dropwise to the solution, at 0 °C. (300 ml) Dry THF was added and the resulting orange solution was allowed to reach room temperature and was stirred for 24 h to afford a red gum. The mixture was cooled to −30 °C and TMSCl (204 ml, 1.60 mol, 4.5 equiv.) was added slowly. The cooling bath was removed and the white suspension was stirred 15 min at room temperature to give a brown suspension. After dilution with Et_2O (1.2 l), the mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (1.2 l). The organic phase was separated and washed with a saturated aqueous solution of $CuSO_4$ (1.2 l), water (1.2 l) and dried with $MgSO_4$. The solvent was then removed under reduced pressure and the resulting viscous oil is distilled (90–120 °C at 20 mbar) to give 36.51 g (47%) of allylsilane **12**. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.90 (1H, bs), 4.62 (1H, bs), 3.94 (2H, s), 1.48 (2H, s), 0.13 (9H, s), 0.01 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 145.92, 106.62, 66.49, 22.77, −0.47, −1.37; IR (neat, NaCl) 2957, 1647, 1636, 1251, 1085 cm^{-1}; MS (CI) *m/z*: 216.0 ($M^{\cdot+}$).

2.2.2. 2-((Trimethylsilyl)methyl)allyl diisopropylcarbamate 13. Allylsilane **12** (3 g, 13.85 mmol, 1 equiv.) was dissolved in 50 ml of THF and a 1 N aqueous solution of sulfuric acid (6 ml, 3 mmol, 0.21 equiv.) was added. The mixture was stirred for 1 h 30 min and then neutralised with solid K_2CO_3 until pH 7 was reached. After dilution with water (50 ml) and extraction with Et_2O, the organics were combined and dried over $MgSO_4$. Removing of the solvent under reduced pressure afforded a viscous oil. This oil, diluted in 12 ml of Et_2O, was poured dropwise over a suspension of NaH (60% in mineral oil, prewashed with Et_2O (833 mg, 20.83 mmol, 1.5 equiv.) in Et_2O (12 ml) at 0 °C. A solution of diisopropylcarbamoyl chloride (4.54 g, 27.77 mmol, 2 equiv.) in Et_2O (12 ml) was added slowly.

The mixture was then allowed to reach room temperature and to stir for 18 h. The reaction was quenched by adding slowly a saturated aqueous solution of NH_4Cl (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (2×30 ml). The organics were combined, dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography (PE/EA=30/1, Et_3N 5%) to give pure allylcarbamate **13** (3.48 g, 93%) as a colourless oil; ^1H NMR (200 MHz, $CDCl_3$) δ: 4.85 (1H, q, J=1.6 Hz), 4.66 (1H, bs), 4.43 (2H, s), 3.61–4.19 (2H, m), 1.52 (2H, s), 1.18 (12H, d, J=6.2 Hz), 0.02 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 155.93, 143.45, 109.21, 68.64, 46.56, 24.35, 21.70, −0.75; IR (neat, NaCl) 3084, 2998, 2967, 2894, 1699, 1645, 1439, 1368, 1314, 1296, 1249, 1219, 1158, 1134, 1067, 843, 770 cm^{-1}; MS (CI) m/z: 271.2 ($M^{\cdot+}$); Anal. calcd for $C_{14}H_{29}NO_2Si$ C, 61.94; H, 10.77 N, 5.16; found C, 61.97; H, 10.88; N, 5.10.

2.2.3. (*Z*)-3-(Tributylstannyl)-2-((trimethylsilyl)methyl)-prop-1-enyl diisopropylcarbamate 9. In a 100 ml round bottom flask were introduced TMEDA (1.11 ml, 858 mg, 7.38 mmol, 2 equiv.) and Et_2O (15 ml). At −78 °C a solution of *sec*BuLi (1.3 M in hexanes, 5.67 ml, 7.38 mmol, 2 equiv.) was added dropwise and the mixture allowed to stir 30 min at −78 °C. A solution of allylcarbamate **13** in Et_2O (15 ml) was added quickly and the orange-brown media was stirred 30 min at −78 °C. A solution of tributyltin chloride (3.00 ml, 3.60 g, 11.07 mmol, 3 equiv.) in Et_2O (15 ml) was added quickly at −78 °C and the dry ice/acetone cooling bath was replaced immediately with an Ice/Water cooling bath. The yellow solution was stirred for 15 min at 0 °C, poured over an aqueous solution of HCl (50 ml, 1 N) and diluted with Et_2O (20 ml). The layers were separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated. The crude oil was purified by column chromatography (PE/EA=30/1) to give pure allylstannane **9** (1.61 g, 80%) as a colourless oil; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.53 (1H, s), 3.91–3.95 (2H, m), 1.73 (2H, s), 1.17–1.63 (14H, m), 1.24 (12H, d, J=6.8 Hz), 0.88 (9H, t, J=7.2 Hz), 0.74–0.96 (6H, m), 0.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.05, 126.19, 120.34, 45.91, 29.15, 27.38, 22.94, 21.43, 13.95, 13.69, 9.68, −1.08; IR (neat, NaCl) 3084, 2956, 2928, 2875, 2857, 1696, 1594, 1461, 1428, 1338, 1302, 1285, 1247, 1152, 1079, 1046, 857, 761 cm^{-1}; MS (EI) m/z: 561.4 ($M^{\cdot+}$); Anal. calcd for $C_{26}H_{55}NO_2SiSn$: C, 55.72; H, 9.89 N, 2.50; found C, 55.98; H, 9.95; N, 2.45.

2.2.4. (*R*)-Methyl 2-cyclohexyl-2-hydroxyacetate 15d. (*R*)-hexahydromandelic acid (900 mg, 5.68 mmol, 1 equiv.) was dissolved in methanol (50 ml) and $SOCl_2$ (4.14 ml, 6.75 g, 56.8 mmol, 10 equiv.) was added dropwise at room temperature. After 30 min the mixture was evaporated to dryness and dissolved in CH_2Cl_2, washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was obtained in 99% yield was essentially pure ester **15c**. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.03 (1H, d, J=3.3 Hz), 3.79 (3H, s), 2.70 (1H, bs), 1.9–1 (11H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.17, 74.84,52.38, 41.94, 29.10, 26.37, 26.262, 26.02, 25.97; IR (neat, NaCl) 3495, 2998, 2927, 2854, 2665, 1736, 1450, 1261, 1220, 1117, 986 cm^{-1}; MS (CI) m/z: 172.9 ($M+H^+$).

2.3. General procedure for the preparation of the α-benzyloxy esters

The corresponding α-hydroxyester was dissolved in CH_2Cl_2 (0.5 ml/mmol of ester). At room temperature, were added sequentially a solution of 2,2,2-trichlorobenzylacetimidate (2 equiv.) in hexane (1.5 ml/mmol) and triflic acid (5% mol). The white suspension that formed was stirred for 16 h at room temperature. The white solid was filtered off and rinsed with hexane. The filtrate was then washed with a saturated aqueous solution of $NaHCO_3$, the layers separated and the aqueous phase extracted with hexane. The combined organics were dried over $MgSO_4$ and concentrated. The resulting oil was purified by column chromatography to give pure α-benzyloxyesters.

2.3.1. (*S*)-Methyl 2-(benzyloxy)propanoate 16c. The title compound obtained as a colourless oil in 99% yield following the general procedure; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.23 (5H, m), 4.69 (1H, d, J=11.7 Hz), 4.44 (1H, d, J=11.7 Hz), 4.21 (2H, q, J=7.1 Hz), 4.04 (2H, q, J=6.9 Hz), 1.43 (3H, d, J=6.9 Hz), 1.29 (3H, t, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.15, 137.49, 128.31, 127.87, 127.73, 79.96, 71.88, 60.75, 18.64, 14.17; IR (neat, NaCl) 3058, 2984, 2937, 2902, 2872, 1751, 1449, 1264, 1133, 1065, 1026, 737 cm^{-1}; MS (EI) m/z: 209.0 ($M+H^+$).

2.3.2. (*R*)-Methyl 2-(benzyloxy)-2-cyclohexylacetate 16d. The title compound as a colourless oil in 49% yield following the general procedure; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.30 (5H, m), 4.68 (1H, d, J=11.7 Hz), 4.35 (1H, d, J=11.7 Hz), 3.74 (H, s), 3.72 (1H, d, J=6 Hz), 1.85–1.60 (5H, m), 1.35–1.05 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.85, 137.52, 128.22, 127.88, 127.66, 82.93, 72.49, 51.65, 41.14, 29.11, 28.30, 26.19, 26.07, 25.97; IR (neat, NaCl) 3031, 2927, 2854, 2669, 1735, 1452, 1268, 1120, 1012, 737 cm^{-1}.

2.4. General procedure for the preparation of the α-benzyloxy aldehydes

A solution of the corresponding ester in dry CH_2Cl_2 (5 ml/mmol of ester) was cooled to −78 °C. Cold DIBAL-H (1.5 M in Tol, 1 equiv.) was added dropwise and the mixture was allowed to stir at −78 °C for an hour. Then, small portions of DIBAL-H were added every 15 min until all the starting material disappeared by TLC (~1 more equiv.). After completion of the reaction, a saturated aqueous solution of NH_4Cl was poured directly in the cold reaction mixture and vigorous stirring was maintained until the mixture reached rt. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was either purified by column chromatography, to give pure α-alkoxyaldehydes required for analysis, or used directly in the subsequent step to avoid degradation.

2.4.1. (*S*)-2-(Benzyloxy)propanal 17c. The title compound obtained as a colourless oil in 75% yield following the

general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.67 (1H, d, J=1.7 Hz), 7.38–7.26 (5H, m), 4.66 (1H, d, J=11.7 Hz), 4.60 (1H, d, J=11.7 Hz), 3.90 (1H, qd, J=7.0, 1.7 Hz), 1.34 (3H, d, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.4, 137.23, 128.51, 128.02, 127.97, 79.35, 71.95, 15.26; IR (neat, NaCl) 3031, 2981, 2869, 1735, 1496, 1454, 1374, 1094, 1047, 737 cm^{-1}; MS (EI) m/z: 165.1 (M+H$^+$).

2.4.2. (*S*)-2-(Benzyloxy)-2-cyclohexylacetaldehyde 17d. The tile compound obtained as a colourless oil in 80% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.66 (1H, d, J=2.7 Hz), 7.35–7.32 (5H, m), 4.67 (1H, d, J=11.7 Hz), 4.47 (1H, d, J=11.7 Hz), 3.49 (1H, dd, J=5.7, 2.7 Hz), 1.85–1.6 (5H, m), 1.35–1.05 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.43, 137.38, 128.36, 127.83, 87.67, 72.80, 39.57, 28.774, 28.03, 26.17, 26.04, 25.96; IR (neat, NaCl) 3031, 2928, 2854, 1729, 1497, 1452, 734 cm^{-1}; MS (CI) m/z: 231.2 (M−H$^+$).

2.5. General procedure for the allylation of α-benzyloxyaldehydes with 1 equiv. of $SnCl_4$

Allylstannane **9** was dissolved in freshly distilled CH_2Cl_2 (30 ml/mmol of stannane) and cooled to −78 °C with a dry ice–acetone bath. $SnCl_4$ (1 M in CH_2Cl_2, 1 equiv.) was added and the mixture allowed to stir at −78 °C for 1 h. A solution of aldehyde in CH_2Cl_2 (10 ml/mmol of aldehyde), cooled to −78 °C, was added dropwise with a canula over 5 min. The resulting mixture was stirred at −78 °C for 1 h. The reaction bulk was then diluted with CH_2Cl_2 (2×volume) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase extracted 3× with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to give pure triols.

2.5.1. 1-(Benzyloxy)-2-hydroxy-4-((trimethylsilyl)-methyl)pent-4-en-3-yl diisopropylcarbamate 24a. The tile compound obtained as a colourless oil in 84% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24–7.35 (5H, m), 5.16 (1H, d, J=4.8 Hz), 4.96 (1H, s), 4.82 (1H, s), 4.57 (1H, d, J=12.0 Hz), 4.53 (1H, d, J=12.0 Hz), 3.76–4.08 (3H, m), 3.62 (1H, dd J=10.0, 2.9 Hz), 3.50 (1H, dd, J=9.9, 7.7 Hz), 2.99 (1H, d, J=5.3 Hz), 1.61 (1H, d, J=14.4 Hz), 1.50 (1H, d, J=14.4 Hz), 1.17 (12H, d, J=6.7 Hz), 0.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl^3$) δ: 154.39, 143.04, 137.76, 128.12, 127.57, 127.41, 110.25, 78.28, 73.23, 70.69, 70.68, 45.54, 23.31, 20.52–20.94, −1.30; IR (neat, NaCl) 3447, 3029, 2965, 2931, 2875, 1700, 1636, 1435, 1368, 1317, 1248, 1133, 1048, 850 cm^{-1}; MS (CI+) m/z: 422.3 (M+H$^+$); HRMS (CI+, M+H$^+$) calcd for $C_{23}H_{40}NO_4Si$, 422.2734; found 422.2726.

2.5.2. (3*S*,4*R*,5*S*)-5-(Benzyloxy)-4-hydroxy-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 24b. The tile compound obtained as a colourless oil in 97% yield following the general procedure; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.38–7.27 (5H, m), 5.24 (1H, d, J=7.0 Hz), 5.04 (1H, s), 4.88 (1H, d, J=1.2 Hz), 4.61 (1H, d, J=11.1 Hz), 4.46 (1H, d, J=11.1 Hz), 3.90 (2H, hept, J=6.9 Hz), 3.67 (1H, qd, J=6.3, 3.0 Hz), 3.56 (1H, td, J=7.4, 3.1 Hz), 2.44 (1H, d, J=7.4 Hz), 1.58 (2H, bs), 1.28 (3H, d, J=6.3 Hz), 1.19 (12H, m), 0.05 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 153.98, 144.33, 138.34, 128.33, 128.01, 127.61, 111.99, 77.7, 75.06, 73.62, 71.40, 45.92, 22.56, 20.94, 16.76, −1.05; IR (neat, NaCl) 3488, 3067, 3032, 2966, 2928, 2876, 1699, 1636, 1432, 1367, 1298, 1133, 1071, 1048, 848 cm^{-1}; MS (EI) m/z: 435.3 (M−H$^+$). $[\alpha]_{20}^{D}$=2.7 (c 1.0, CH_2Cl_2); Anal. calcd for $C_{24}H_{41}NO_4Si$: C, 66.17; H, 9.49; N, 3.21; found: C, 65.48; H, 9.46; N, 3.09.

2.5.3. (1*R*,2*S*,3*R*)-1-(Benzyloxy)-1-cyclohexyl-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-3-yl diisopropylcarbamate 24c. The tile compound obtained as a colourless oil in 81% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.26 (5H, m), 5.15 (1H, d, J=8.7 Hz), 5.04 (1H, s), 4.89 (1H, d, J=1 Hz), 4.64 (1H, d, J=11 Hz), 4.59 (1H, d, J=11 Hz), 3.90 (2H, bs), 3.75 (1H, bd, J=8.7 Hz), 3.28 (1H, d, J=7 Hz), 2.52 (1H, bs),1.92–0.8 (25H, m), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.69, 144.37, 138.22, 128.25, 127.95, 127.58, 112.26, 81.39, 78.01, 74.374, 70.435, 45.92, 40.53, 29.61, 29.35, 26.60, 26.34, 26.30, 22.30, 21.41, 17.58, 13.703, −0.92; IR (neat, NaCl) 3489, 3031, 2959, 2928, 2854, 1700, 1636, 1436, 1305, 1048, 851 cm^{-1}; MS (CI) m/z: 504.5 (M−H$^+$); HRMS (CI+, M+H$^+$) calcd for $C_{29}H_{50}NO_4Si$, 504.3509; found 504.3519. $[\alpha]_{20}^{D}$=8.7 (c 1.0, CH_2Cl_2).

2.6. General procedure for the allylation of α-benzyloxyaldehydes with 2 equiv. of $SnCl_4$

Allylstannane **9** was dissolved in freshly distilled CH_2Cl_2 (30 ml/mmol of stannane) and cooled to −78 °C with a dry ice–acetone bath. $SnCl_4$ (1 M in CH_2Cl_2, 2 equiv.) was added and the mixture allowed to stir at −78 °C for 1 h. The solution was cooled to −97 °C with a MeOH/N_2 bath and a solution of aldehyde in CH_2Cl_2 (10 ml/mmol of aldehyde), cooled to −97 °C, was added dropwise with a canula over 5 min. The resulting mixture was stirred at −97 °C for 1 h. The reaction bulk was then diluted with CH_2Cl_2 (2×volume) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase extracted 3× with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography to give pure triols.

2.6.1. 1-(Benzyloxy)-2-hydroxy-4-((trimethylsilyl)-methyl)pent-4-en-3-yl diisopropylcarbamate 25a. The tile compound obtained as a colourless oil in 70% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19–7.31 (5H, m), 5.13 (1H, d, J=4.3 Hz), 4.89 (1H, s), 4.76 (1H, s), 4.49 (2H, s), 3.91 (1H, dt J=5.7, 4.3 Hz), 3.76–3.95 (2H, m), 3.50 (1H, dd J=9.6, 4.8 Hz), 3.45 (1H, dd, J=9.6, 6.2 Hz), 2.30–2.52 (1H, m), 1.54 (1H, d, J=14.4 Hz), 1.43 (1H, d, J=13.9 Hz), 1.15 (6H, d, J=7.2 Hz), 1.14 (6H, d, J=7.2 Hz), 0.01 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.47, 143.60, 137.87, 128.28, 127.72, 127.58, 110.08, 76.99, 73.49, 71.36, 70.93, 45.97, 23.71, 20.70–21.58, −1.18; IR (neat, NaCl): 3457, 3065, 3032, 2965, 2930, 2866, 1699, 1630, 1437, 1368, 1300, 1248, 1126, 1050, 850 cm^{-1}; MS (EI) m/z: 421.5 (M$^{\cdot+}$); HRMS (EI+, M$^+$) calcd for $C_{29}H_{39}NO_4Si$, 421.2650; found 421.2648.

2.6.2. (3*R*,4*R*,5*S*)-5-(Benzyloxy)-4-hydroxy-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 25b. The tile compound obtained as a colourless oil in 83% yield following the general procedure; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.37–7.30 (5H, m), 5.29 (1H, d, J=3.3 Hz), 4.98 (1H, s), 4.85 (1H, s), 4.71 (1H, d, J=11.4 Hz), 4.48 (1H, d, J=11.4 Hz), 4.03–3.87 (2H, m), 3.68–3.60 (2H, m), 2.71 (1H, d, J=3.9 Hz), 1.63 (1H, d, J=14.1 Hz), 1.51 (1H, d, J=14.1 Hz), 1.29 (3H, d, J=5.8 Hz), 1.24 (12H, d, J=6.3 Hz), 0.09 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.54, 143.64, 138.17, 128.27, 127.61, 127.49, 110.03, 76.36, 75.51, 75.12, 70.72, 45.58, 23.35, 20.44, 15.52, −1.39; IR (neat, NaCl) 3457, 2967, 2931, 1694, 1635, 1431, 1300, 1248, 1135, 1048, 851 cm^{-1}; MS (EI) m/z: 435.3 ($M-H^+$). $[\alpha]_{20}^{D}$=42.3 (c 1.0, CH_2Cl_2); Anal. calcd for $C_{24}H_{41}NO_4Si$: C, 66.17; H, 9.49; N, 3.21; found: C, 65.62; H, 9.51; N, 3.09.

2.6.3. (1*R*,2*S*,3*S*)-1-(Benzyloxy)-1-cyclohexyl-2-hydroxy-4-((trimethylsilyl)methyl)pent-4-en-3-yl diisopropylcarbamate 25c. The tile compound obtained as a colourless oil in 81% yield following the general procedure; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41–7.26 (5H, m), 5.20 (1H, d, J=4.8 Hz), 4.96 (1H, s), 4.84 (1H, s), 4.66 (2H, s), 3.95 (2H, bs), 3.90 (H, q, J=4.8 Hz), 3.30 (1H, t, J=4.8 Hz), 2.55 (1H, d, J=4.8 Hz),1.92–0.8 (25H, m), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.42, 143.83, 138.57, 128.28, 127.52, 127.45, 110.82, 83.23, 77.69, 74.18, 71.77, 45.97, 40.00, 30.21, 28.01, 27.90, 26.919, 26.576, 26.34, 23.40, 21.52, 20.71, 17.59, 13.688, −1.08; IR (neat, NaCl) 3547, 3032, 2926, 2853, 1698, 1451, 1432, 1311, 1157, 1048, 849 cm^{-1}; MS (CI) m/z: 504.4 ($M-H^+$); HRMS (CI+, $M+H^+$) calcd for $C_{29}H_{50}NO_4Si$, 504.3509; found 504.3494. $[\alpha]_{20}^{D}$=32.9 (c 1.0, CH_2Cl_2).

2.7. Determination of stereochemistry

2.7.1. *Syn–anti* 5-(benzyloxy)-4-hydroxy-2-methylhex-1-en-3-yl diisopropylcarbamate 26a. Allylsilane **20a** (822 mg, 1.89 mmol, 1 equiv.) was dissolved in 25 ml of CH_2Cl_2. At −15 °C, $BF_3.Et_2O$ (233 μl, 269 mg, 1.89 mmol, 1 equiv.) was added and the mixture allowed to stir 18 h at −15 °C. The mixture was diluted with CH_2Cl_2 (20 ml) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=6/1) to give pure alcohol **26a** as a colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26–7.37 (5H, m), 5.27 (1H, d, J=7.7 Hz), 5.08 (1H, s), 5.05 (1H, t, J=1.8 Hz), 4.62 (1H, d, J=11.3 Hz), 4.48 (1H, d, J=11.3 Hz), 3.72–4.08 (2H, m), 3.65 (1H, qd J=6.0, 3.0 Hz), 3.57 (1H, bd, J=7.8 Hz), 2.35 (1H, m), 1.82 (3H, s), 1.29 (3H, d, J=6.3 Hz), 1.13–1.25 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.95, 142.14, 137.90, 128.16, 127.82, 127.46, 115.20, 77.02, 74.31, 73.06, 71.06, 46.08, 20.49, 18.62, 16.23; IR (neat, NaCl) 3472, 2971, 2934, 2879, 1695, 1437, 1298, 1136, 1088, 1049, 851, 738 cm^{-1}; MS (EI) m/z: 363.3 ($M^{\cdot+}$); HRMS for $C_{21}H_{33}NO_4$ (CI+, $M+H^+$): Calcd 364.2488; found 364.2492.

2.7.2. *Syn–syn* 5-(benzyloxy)-4-hydroxy-2-methylhex-1-en-3-yl diisopropylcarbamate 26b. Allylsilane **20b** (277 mg, 0.63 mmol, 1 equiv.) was dissolved in 10 ml of CH_2Cl_2. At −15 °C, $BF_3.Et_2O$ (79 μl, 91 mg, 0.63 mmol, 1 equiv.) was added and the mixture allowed to stir 18 h at −15 °C. The mixture was diluted with CH_2Cl_2 (20 ml) and quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 ml). The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=7/1) to give pure alcohol **26b** as colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27–7.36 (5H, m), 5.30 (1H, d, J=5.2 Hz), 4.98 (2H, s), 4.66 (1H, d, J=11.5 Hz), 4.42 (1H, d, J=11.5 Hz), 3.74–4.12 (2H, m), 3.55–3.65 (2H, m), 1.79 (3H, s), 1.28 (3H, d, J=6.0 Hz), 1.21 (12H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.14, 141.79, 138.17, 128.43, 127.76, 127.67, 114.04, 77.61, 75.57, 74.54, 70.81, 46.34, 21.44, 19.32, 15.73; IR (neat, NaCl) 3474, 2970, 2932, 2872, 1686, 1438, 1297, 1132, 1053, 903, 737 cm^{-1}; MS (EI) m/z: 363.3 ($M^{\cdot+}$); HRMS for $C_{21}H_{33}NO_4$ (CI+, $M+H^+$): Calcd 364.2488; found 364.2492.

2.7.3. *Syn–anti* 4,5-dihydroxy-2-methylhexan-3-yl diisopropylcarbamate 27a. Carbamate **26a** (17 mg, 0.046 mmol, 1 equiv.) was mixed with Pd/C (10 mol%) in AcOEt (5 ml). The flask was purged 4 times with nitrogen and 5 times with hydrogen. The mixture was heated to 40 °C under hydrogen pressure (1 atm) for 48 h. The crude mixture was filtered through celite, rinsed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=3/1) to give pure diol **27a** as a colourless oil (10 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.56 (1H, dd, J=9.6, 2.4 Hz), 4.03–3.82 (2H, m), 3.66 (1H, qd, J=6.6, 1.2 Hz), 3.30 (1H, bd, J=9.9 Hz), 2.30 (1H, hept d, J=7.2, 2.4 Hz), 1.32–1.22 (15H, m), 1.00 (3H, d, J=6.9 Hz), 0.98 (3H, d, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.64, 77.90, 73.22, 65.01, 46.60–45.78, 27.84, 21.28–20.01, 20.65, 18.39, 15.76; IR (neat, NaCl) 3421, 2969, 2937, 2877, 1674, 1443, 1295, 1051, 936, 770 cm^{-1}; MS (CI+) m/z: 276.1 ($M+H^+$); HRMS (CI+, $M+H^+$) calcd for $C_{14}H_{29}NO_4$, 276.2175; found 276.2178.

2.7.4. *Syn–syn* 4,5-dihydroxy-2-methylhexan-3-yl diisopropylcarbamate 27c. Carbamate **26c** (45 mg, 0.12 mmol, 1 equiv.) was mixed with Pd/C (10 mol%) in AcOEt (5 ml). The flask was purged 4 times with nitrogen and 5 times with hydrogen. The mixture was heated to 40 °C under hydrogen pressure (1 atm) for 48 h. The crude mixture was filtered through celite, rinsed with CH_2Cl_2 and the solvent evaporated under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=2/3) to give pure diol **27c** as a colourless oil (17 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.56 (1H, dd, J=7.1, 4.1 Hz), 4.03–3.81 (2H, m), 3.71 (1H, qd, J=6.3, 5.2 Hz), 3.47 (1H, dd, J=5.2, 4.1 Hz), 2.20 (1H, oct, J=6.8 Hz), 1.26–1.21 (15H, m), 0.99 (3H, d, J=6.6 Hz), 0.95 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.21, 80.49, 75.54, 68.56, 46.43–45.82, 29.12, 21.41, 20.38, 19.35, 18.04; IR (neat, NaCl) 3414, 2968, 2931, 1688, 1440, 1298, 1136, 1050, 768 cm^{-1}; MS (EI) m/z: 275.1 ($M^{\cdot+}$).

2.7.5. *Syn–anti* 5-(benzyloxy)-2-methylhex-1-ene-3,4-diol 27b. To a solution of carbamate **26b** (178 mg,

0.49 mmol, 1 equiv.) in THF (20 ml) was added dropwise a solution of $LiAlH_4$ (1 M in Et_2O, 1.96 ml, 1.96 mmol, 4 equiv.). After completion the mixture was heated at reflux for 3 h. After cooling to room temperature, the solution was diluted with 20 ml of Et_2O and 30 ml of water. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE 3/EA 1) to give pure diol **21b** as a colourless oil (75 mg, 65%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.28 (5H, m), 5.03 (1H, bs), 4.98 (1H, bs), 4.64 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 4.17 (1H, d, J=5.8 Hz), 3.83 (1H, qd, J=6.1, 3.1 Hz), 3.53 (1H, dd, J=5.8, 3.1 Hz), 1.75 (3H, s), 1.31 (3H, d, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.72, 137.70, 128.48, 127.93, 112.72, 77.00, 74.64, 73.46, 70.85, 18.48, 15.69; IR (neat, NaCl) 3439, 3069, 3028, 2975, 2924, 1451, 1131, 1067, 1022, 995, 901, 737 cm^{-1}; MS (EI) m/z: 236.3 (M$^{\cdot+}$); Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; found: C, 71.13; H, 8.71.

2.7.6. *Syn–syn* 5-(benzyloxy)-2-methylhex-1-ene-3,4-diol 27d. To a solution of carbamate **26d** (84 mg, 0.231 mmol, 1 equiv.) in THF (17 ml) was added dropwise a solution of $LiAlH_4$ (1 M in Et_2O, 0.926 ml, 0.926 mmol, 4 equiv.). After completion the mixture was heated at reflux for 5 h. After cooling to room temperature, the solution was diluted with 20 ml of Et_2O and 30 ml of water. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated to give pure diol **27d** as a colourless oil (55 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.27 (5H, m), 5.00 (1H, bs), 4.96–4.93 (1H, m), 4.68 (1H, d, J=11.5 Hz), 4.41 (1H, d, J=11.5 Hz), 4.08 (1H, d, J=3.8 Hz), 3.70 (1H, qd, J=6.3, 4.1 Hz), 3.46 (1H, bt, J=4.1 Hz), 3.11–2.99 (1H, m), 2.69–2.60 (1H, m), 1.74 (3H, s), 1.31 (3H, d, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.31, 137.75, 128.52, 127.91, 112.73, 75.60, 74.58, 74.84, 70.84, 18.59, 15.79; IR (neat, NaCl) 3428, 3063, 3024, 2975, 2922, 1452, 1137, 1069, 1020, 901, 733 cm^{-1}; MS (CI−) m/z: 235.2 (M−H$^-$).

2.7.7. *Syn–anti 2*-methyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl diisopropylcarbamate 28a. Diol **27a** (54 mg, 0.19 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 10 ml of acetone. The mixture was heated at reflux for 5 h. After cooling, 20 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=5/1, Et_3N 5%) to give pure acetonide **28a** as a colourless oil (55 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.91 (1H, dd, J=8.5, 3.6 Hz), 4.13 (1H, dq, J=7.7, 6.0 Hz), 4.02–3.80 (2H, m), 3.61 (1H, t, J=8.3 Hz), 2.08 (1H, hept d, J=6.9, 3.6 Hz),1.40 (3H, s), 1.37 (3H, s), 1.32–1.19 (15H, m), 0.98 (3H, d, J=6.9 Hz), 0.94 (3H, d, J=6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 154.60, 108.03, 26.86, 21.48–20.57, 19.28, 18.86, 16.43; IR (neat, NaCl) 2968, 2936, 2882, 1701, 1430, 1369, 1293, 1215, 1154, 1090, 1048, 985, 858, 766 cm^{-1}; MS (CI+) m/z: 316.2 (M−H$^+$); Anal. calcd for $C_{17}H_{33}NO_4$: C, 64.73; H, 10.54; N, 4.44; found: C, 64.94; H, 10.51; N, 4.37.

2.7.8. *Syn–syn* 2-methyl-1-(2,2,5-trimethyl-1,3-dioxolan-4-yl)propyl diisopropylcarbamate 28c. Diol **27c** (29 mg, 0.10 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 15 ml of acetone. The mixture was heated at reflux for 3 h. After cooling, 15 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated to give pure acetonide **28c** as a colourless oil (30 mg, 91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.65 (1H, dd, J=8.5, 1.9 Hz), 4.02–3.88 (2H, m), 3.77 (1H, dq, J=8.5, 5.8 Hz), 3.68 (1H, dd, J=8.5, 1.9 Hz), 2.08 (1H, hept d, J=8.4, 6.6 Hz), 1.39 (3H, s), 1.37 (3H, s), 1.22 (3H, d, J=5.8 Hz), 1.22 (12H, m), 0.99 (3H, d, J=6.9 Hz), 0.95 (3H, d, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.27, 107.69, 81.83, 74.75, 72.93, 46.12–45.55, 30.40, 27.21, 26.91, 29.67–20.56 −19.29, 19.16, 17.25; IR (neat, NaCl) 2969, 2933, 2876, 1695, 1435, 1370, 1310, 1221, 1097, 1048, 935, 874, 767 cm^{-1}; MS (EI) m/z: 316.3 (M+H$^+$).

2.7.9. *Syn–anti* 4-(1-(benzyloxy)ethyl)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane 28b. Diol **27b** (16 mg, 0.066 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 5 ml of acetone. The mixture was heated at reflux for 18 h. After cooling, 20 ml of Et_2O were added followed by a saturated aqueous solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=8/1, Et_3N 5%) to give pure acetonide **28b** as a colourless oil (7 mg, 39%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.23 (5H, m), 4.97 (1H, t, J=0.8 Hz), 4.94 (1H, t, J=1.6 Hz), 4.67 (1H, d, J=12.1 Hz), 4.62 (1H, d, J=12.1 Hz), 4.52 (1H, d, J=6.9 Hz), 4.20 (1H, dd, J=8.0, 6.9 Hz), 3.51 (1H, dq, J=8.0, 6.0 Hz), 1.73 (3H, s), 1.58 (3H, s), 1.57 (3 h, s), 1.14 (3H, d, J=6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 141.94, 139.01, 128.20, 127.67, 127.31, 115.12, 108.63, 82.41, 81.12, 72.99, 71.43, 26.57, 25.12, 19.66, 17.27; IR (neat, NaCl) 2983, 2930, 1451, 1374, 1260, 1212, 1159, 1088, 1045, 874, 735 cm^{-1}; MS (EI) m/z: 276.3 (M$^{\cdot+}$).

2.7.10. *Syn–syn* 4-(1-(benzyloxy)ethyl)-2,2-dimethyl-5-(prop-1-en-2-yl)-1,3-dioxolane 28d. Diol **27d** (54 mg, 0.23 mmol, 1 equiv.) was mixed with a few crystals of PTSA in 20 ml of acetone. The mixture was heated to reflux for 3 h. After cooling, 10 ml of Et_2O were added followed by a saturated solution of $NaHCO_3$. The phases were separated and the aqueous layer extracted twice with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (PE/EA=15/1) to give pure acetonide **28d** as a colourless oil (52 mg, 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.24 (5H, m), 4.93–4.91 (2H, m), 4.70 (1H, d, J=12.1 Hz), 4.55 (1H, d, J=12.1 Hz), 4.35 (1H, d, J=8.1 Hz), 3.80 (1H, dd, J=8.3, 4.4 Hz), 3.55 (1H, qd, J=6.4, 4.5 Hz), 1.75 (3H, s), 1.45 (3H, s), 1.44 (3 h, s), 1.23 (3H, d, J=6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.97, 139.57, 128.31, 127.85, 127.52, 115.22, 108.91, 82.07, 81.07, 73.33, 71.08, 27.09, 27.03, 17.07, 16.25; IR (neat, NaCl) 3068, 3033, 2986, 2935, 2871, 1652, 1454, 1372, 1244, 1214, 1154, 1091, 1070, 883, 737 cm^{-1}; MS (EI) m/z: 276.2 (M$^{\cdot+}$).

2.7.11. (3*R*,4*R*,5*S*)-4-Acetoxy-5-(benzyloxy)-2-((trimethylsilyl)methyl)hex-1-en-3-yl diisopropylcarbamate 29. Alcohol **24b** (1.1 g, 2.52 mmol, 1 equiv.) was dissolved in 25 ml of pyridine and cooled to 0 °C. Acetic anhydride (700 μl, 743 mg, 7.58 mmol, 3 equiv.) was added slowly. Then the mixture was allowed to reach room temperature within 1 h and was stirred another 12 h. The solution was poured over a saturated solution of $NaHCO_3$ (50 ml) and diluted with Et_2O (50 ml). The organic phase was washed with a saturated solution of $CuSO_4$ (50 ml), water (50 ml) and a saturated solution of NaCl (50 ml). After drying over $MgSO_4$, the solution was filtered and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography (PE/EA=10/1) to give pure acetate **29** as a colourless oil (1.02 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.22 (5H, m), 5.30 (1H, d, J=3.6 Hz), 5.21 (1H, t, J=3.6 Hz), 4.89 (1H, s), 4.73 (1H, s), 4.61 (1H, d, J=12 Hz), 4.41 (1H, d, J=12 Hz), 3.99 (2H, bs), 3.70 (1H, m), 2.03 (3H, s), 1.58 (1H, d, J=14.4 Hz), 1.47 (1H, d, J=14.4 Hz), 1.18 (15H, m), 0.06 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.25, 153.77, 142.92, 138.34, 128.16, 127.41, 127.32, 110.38, 75.259, 73.96, 71.00, 45.43, 23.05, 21.56, 20.95, 15.98, −1.14; IR (neat, NaCl) 2966, 2875, 1744, 1701, 1434, 1370, 1306, 1234, 1046, 848 cm^{-1}; MS (CI) m/z: 478.4 ($M+H^+$); Anal. calcd for $C_{26}H_{43}NO_5Si$: C, 65.43; H, 9.08; N, 2.93; found: C, 65.43; H, 9.09; N, 2.90. $[\alpha]_{20}^{D}$=57.1 (c 1.0, CH_2Cl_2).

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