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Highly Diastereoselective Chelation-Controlled 1,3-*anti*-Allylation of (*S*)-3-(Methoxymethyl)hexanal Enabled by Hydrate of Scandium Triflate

Uladzimir S. Masiuk [1,2], Iryna V. Mineyeva [1,*] and Dzmitry G. Kananovich [2,*]

[1] Department of Organic Chemistry, Belarusian State University, Leningradskaya 14, 220050 Minsk, Belarus; masiukvs@yandex.ru
[2] Department of Chemistry and Biotechnology, School of Science, Tallinn University of Technology, Akadeemia Tee 15, 12618 Tallinn, Estonia
* Correspondence: i.mineyeva@yandex.ru (I.V.M.); dzmitry.kananovich@taltech.ee (D.G.K.)

Abstract: En route to the total synthesis of (+)-Neopeltolide, we explored Lewis acid-assisted diastereoselective allylation of MOM-protected 3-hydroxylhexanal with β-(2,2-diethoxyethyl)-substituted (allyl)tributylstannane. The hydrated form of scandium triflate was found to be essential for attaining high 1,3-*anti*-diastereoselectivity (d.r. 94:6), while the use of anhydrous catalyst resulted in a modest diastereocontrol (d.r. 76:24). The preferred 1,3-*anti*-selectivity in this transformation can be rationalized in the framework of the Reetz chelate model of asymmetric induction. The 1,3-*anti*-configuration of the product was confirmed by its conversion into the known C^7-C^{16} building block of (+)-Neopeltolide. We also report an improved protocol for the synthesis of β-(2,2-diethoxyethyl)-substituted (allyl)tributylstannane, which can be utilized as a cost-efficient bipolar isoprenoid-type C_5-building block in the synthesis of natural compounds.

Keywords: Reetz–Keck-type allylation; stannylation; Lewis acids; organotin compounds; β-oxyaldehydes; scandium triflate; chelation control; asymmetric synthesis; asymmetric induction

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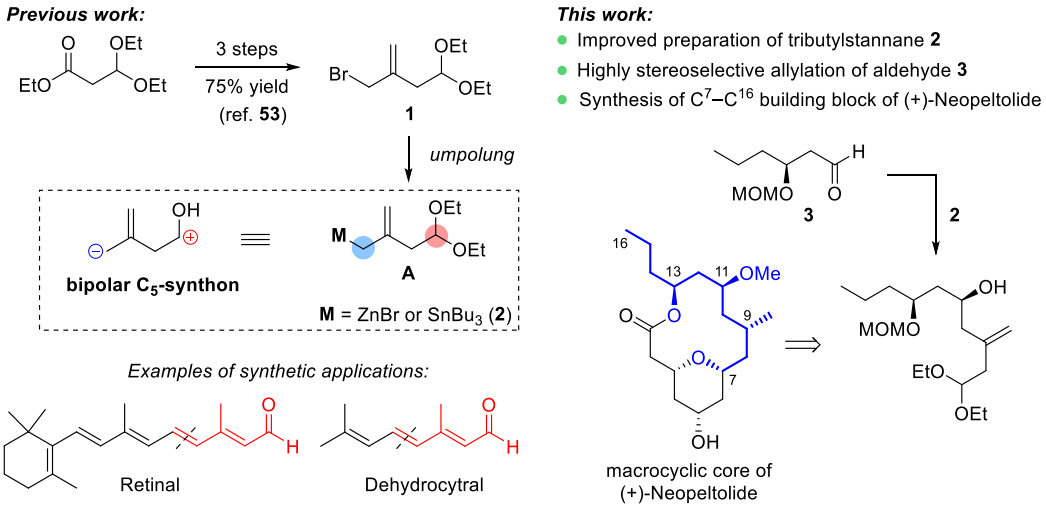
1. Introduction

Stereoselective allylation of carbonyl compounds allows to assemble a carbon–carbon bond along with installation of a new stereocenter [1–4]. The produced homoallylic alcohols provide multiple opportunities for the subsequent modifications and therefore are widely used in the target-oriented synthesis of natural and bioactive compounds [2–5].

In the event of asymmetric induction, the transfer of chirality to the newly formed stereocenters is typically enabled either by a chiral catalyst/reagent or a chiral substrate itself. The latter case commonly occurs in the multistep synthesis of natural products and could require fine tuning of the reaction parameters to attain a high level of stereocontrol. In that sense, diastereoselective allylation of chiral α- and β-oxysubstituted aldehydes is advantageous [4,6–14] since its stereochemical outcome can be usually [15] predicted in the framework of Felkin-Ahn [16–21], Cornforth-Evans [16,17,22–24], or Cram [16,17,25–27] and Reetz chelation [16,17,28–30] models. The Reetz model is valid in the case of stereoselective addition of allylstannanes to β-oxysubstituted aldehydes, where the high 1,3-*anti*-selectivity is commonly achieved due to the formation of a chelate complex between a Lewis acid catalyst and the aldehyde substrate [31,32]. On the other hand, the successful chelation control takes place only for a limited set of known β-hydroxy-protecting groups and Lewis acids [7–14,31–35]. Moreover, rather ordinary unsubstituted allylic organotin reagents are commonly employed in these transformations, with only rare examples of β-functionalized analogues [8,14,36–39]. The development of more complex allyl-transfer reagents is appealing in view of their evidently high synthetic value [40–48].

During the implementation of our research programs devoted to the synthesis of natural and bioactive compounds from cyclopropanols [49–52] and cyclopropanol-derived build-

ing blocks [53–56], we expected to develop a bifunctional allylation reagent **A** (Scheme 1) based on metalation of easily available allyl bromide **1** [53]. The reagent **A** can act as a synthetic equivalent of a bipolar isopentane synthon, as it was previously demonstrated by the synthesis of retinoid compounds via the Barbier-type chemistry [53,56]. We envisioned that besides the assembly of polyene scaffolds, organometallic derivatives of **1**, especially its organotin derivative **2**, could also be suitable for the stereoselective allylation of carbonyl compounds and therefore applied in the asymmetric synthesis of natural products. Our preliminary tests revealed that organotin compound **2** [57], along with its carboxymethyl analogue [54,55], are suitable for highly enantioselective Keck allylations. However, the substrate-controlled stereoselective coupling of **2** with oxy-functionalized aldehydes has not been examined. Moreover, we required to develop an expedient synthetic protocol for the preparation of **2** in multigram amount. As a result of our endeavors, here we report a convenient and cost-efficient procedure for multigram preparation of **2**, and its application in the Lewis acid-mediated diastereoselective 1,3-*anti*-allylation of (*S*)-3-(methoxymethyl)hexanal **3**. The stereochemical outcome of the reaction was further validated by the synthesis of known C^7-C^{16} bulding block of (+)-Neopeltolide [55], containing three stereocenters.



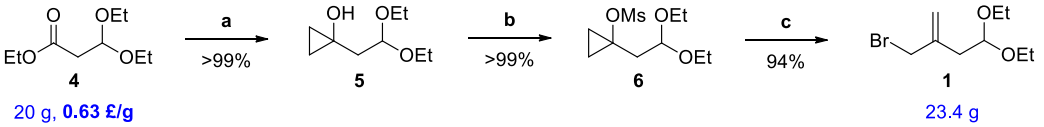
Scheme 1. Preparation of a bifunctional allylation reagent **A** and outline of the current work.

2. Results and Discussion

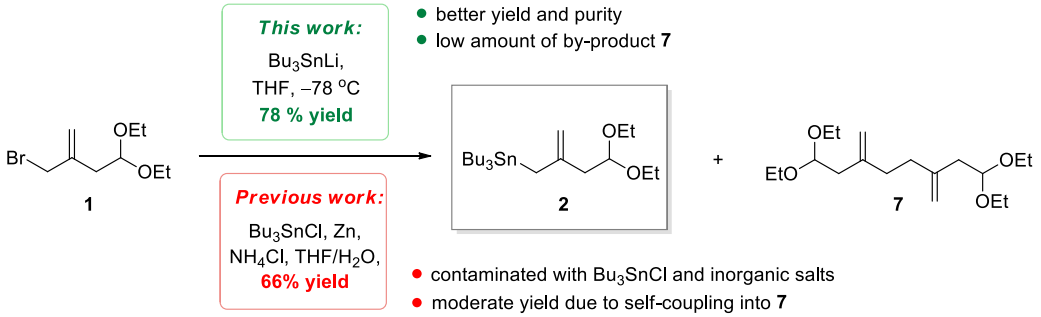
2.1. Improved Protocol for the Preparation of Functionalized (Allyl)Tributylstannane **2**

Multistep synthesis commonly requires substantial quantity of starting materials at the initial stages. Therefore, a facile and cost-efficient access to large quantities of **2** was of primary importance. Using the advantages of cyclopropanol chemistry [58,59], allyl bromide **1** was readily prepared in multigram amounts and 94% overall yield from cheap and easily available ethyl 3,3-diethoxypropionate (**4**) via the consequent Kulinkovich cyclopropanation [60], mesylation, and $MgBr_2$-mediated cyclopropyl-allyl rearrangement steps (Scheme 2) [53,61–63]. The reaction sequence was flawlessly performed in a single run starting from 20 g of ester **4** (see the experimental part). No purification was required for the cyclopropane intermediates **5** and **6**, which were obtained in nearly quantitative yields.

The previously reported method [57] for the preparation of organotin compound **2** via Barbier-type coupling of **1** and Bu_3SnCl was found impractical for multigram preparation. Following the previously reported approach, organotin compound **2** was obtained in a moderate 66% yield due to accompanying homo-coupling of **1** leading to **7**. The purity of **2** was also unsatisfactory because of the contaminant inorganic salts. Incompatibility of acid-sensitive **2** with silica gel made its chromatographic purification impossible [57].



Reagents and conditions: (**a**) EtMgBr, Ti(O*i*-Pr)$_4$ (20 mol%), THF, r.t.; (**b**) MsCl, DIPEA, Et$_2$O, 0 °C; (**c**) MgBr$_2$, Et$_2$O, r.t.

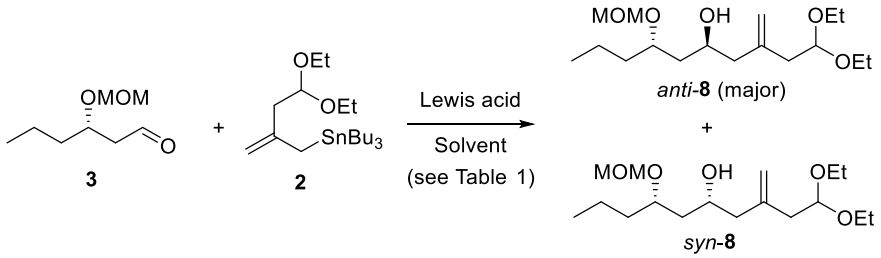


Scheme 2. Synthesis of allyl bromide **1** and its conversion into organotin derivative **2**.

Therefore, we tested an alternative procedure of halogen substitution in **1** with Bu_3SnLi (Scheme 2) [14]. To our delight, the new approach delivered the target organotin compound **2** in affordable 78% yield and noticeably better purity. According to ^{1}H NMR analysis, the content of homo-coupled product **7** was reduced to 8 mol.%, along with the presence of 15 mol.% of $(Bu_3Sn)_2$ dimer. These impurities do not interfere the reactivity of **2** and can be removed after the performing the allylation reaction. The same transformation was also convenient for multigram preparation (up to 7 g in a single run, see the experimental part). Hence, high yields and utilization of cheap chemicals have provided a convenient, scalable, and cost-effective access to **1** and **2** in the sufficient amounts.

2.2. Diastereoselective Allylation of Aldehyde **3** *with (Allyl)Tributylstannane* **2**

While examining the potential routes towards the synthesis of (+)-Neopeltolide and its analogues [64–66], we attempted to perform the stereoselective allylation of MOM-protected 3-hydroxylhexanal **3** with (allyl)tributylstannane **2**. The aldehyde **3** (ee > 99%) was prepared by following the known procedure [55] (see the Supplementary Materials). Initially, we planned to apply the venerable Keck asymmetric allylation, by using a catalytic system based on titanium tetraisopropoxide and a chiral BINOL ligand [57,67–69]. Although being a well-developed approach, the Keck reaction has several restrictions, such as allylation of unsaturated or sterically hindered aldehydes [46,67–70]. Moreover, the presence of multiple oxygen-containing functionalities in both **2** and **3** could interfere the reaction outcome due to the highly oxophilic nature of the titanium catalyst. In our hands, allylation of **3** with **2** by following the Keck reaction protocol has led to only trace amounts of the desired homoallylic alcohol **8** (Scheme 3) after an exhausting search for the optimal reaction conditions and even in the presence of trifluoroacetic acid [67,69] or B(OMe)$_3$ [71] as activating additives (Table 1, entry 1).



Scheme 3. Diastereoslective allylation aldehyde **3** with (allyl)tributylstannane **2**.

Table 1. Allylation of aldehyde **3** with allylstannane **2** promoted by Lewis acids. [a]

Entry	Lewis Acid	Solvent	Time, h	T, °C	Conv. % [b]	d.r. *anti*/*syn* [b]
1	Ti((*S*)-BINOL)$_2$	CH_2Cl_2	120	−20	trace	–
2	$TiCl_4$	CH_2Cl_2	1	−78	– [c]	–
3	$SnCl_4$	CH_2Cl_2	1	−78	– [c]	–
4	TiCl(O*i*-Pr)$_3$	CH_2Cl_2	15	−20	no reaction	
5	Cp_2TiCl_2	CH_2Cl_2	15	−20	no reaction	
6	$MgBr_2 \cdot Et_2O$ [d]	CH_2Cl_2	5	−78	72	76:24
7	$ZnCl_2 \cdot Et_2O$ [d]	CH_2Cl_2	15	−20	100	60:40
8	$ZrCl_4$ [d]	CH_2Cl_2	1	−60	78	73:27
9	Sc(OTf)$_3$, old batch	CH_2Cl_2	4	−25	65	84:16
10	Sc(OTf)$_3$, old batch	toluene	4	−25	86	88:12
11	In(OTf)$_3$	toluene	5	−70	48	75:25
12	Y(OTf)$_3$	toluene	2	−20	45	55:45
13	Hf(OTf)$_4$	toluene	4	+20	28	65:35
14	Sc(OTf)$_3$, fresh batch	toluene	5	−70	60	76:24 [e]
15	Sc(OTf)$_3$ + H_2O	toluene	2	−25	65	83:14
16	Sc(OTf)$_3$ + 2H_2O	toluene	4	−25	72	88:12
17	Sc(OTf)$_3$ + 2H_2O	toluene/Et_2O	4	−70	78	91:9
18	Sc(OTf)$_3$ + 2H_2O	toluene/Et_2O	12	−70	92 (72) [f]	94:6

[a] Unless indicated otherwise, the optimization reactions (entries 1–17) were performed on 0.1–0.3 mmol scale with 1.5 equiv. of Lewis Acid and 2.5 equiv. of allyl stannane **2**. [b] Conversion of aldehyde **3** into alcohol **8** and d.r. ratios were determined by ^{1}H NMR. [c] Complex mixture of products. [d] The reaction was performed with 3 equiv. of a Lewis acid. [e] The use of Sc(OTf)$_3$ pre-dried in vacuum at heating afforded the same d.r. [f] The reaction was performed with 11.5 mmol of aldehyde **3** and 1.7 equiv. of **2** in the presence of 1.1 equiv. of the hydrated Sc(OTf)$_3$. Isolated yield of *anti*-**8** is given in parentheses.

On the other hand, the presence of a β-hydroxy-substituted stereocenter in aldehyde **3** ensured an alternative opportunity to carry out the diastereoselective chelation-controlled 1,3-*anti*-allylation [16,17,28–32]. However, in this case, the ratio of diastereoisomers substantially depends on the choice of protective group as well as Lewis acid [32]. Typically, benzyl or *p*-methoxybenzyl ethers are used [7–13,31,32]. However, these protecting groups were unsuitable according to our planned synthetic route towards (+)-Neopeltolide. Therefore, while keeping the MOM-protection in **3** intact, we began to investigate the effect of various Lewis acids, available at our laboratory (Table 1).

First, we tried to carry out the reaction with $TiCl_4$, which is known as an effective catalyst for the chelation-controlled Reetz-Keck-type allylation [28–32]. Unfortunately, a complex mixture of products was formed (Table 1, entry 2). Tin(IV) chloride behaved similarly (entry 3), while the less reactive titanium catalysts failed to furnish any products at all (entries 4 and 5). Magnesium bromide as another prominent catalyst [31,32] delivered the desired homoallylic alcohol **8**, albeit with moderate diastereoselectivity (entry 6). The ratio of diastereomers was determined by ^{1}H NMR analysis of the crude reaction mixture, by integration of signals at δ 2.98 (d, J = 2.9 Hz) and 3.09 (d, J = 2.1 Hz) ppm, which correspond to hydroxyl protons of *anti*- and *syn*-**8**, respectively. Analogously to $MgBr_2$, zinc and zirconium(IV) chlorides also produced **8** with unsatisfactory diasteroisomeric ratios (entries 7 and 8).

While testing different metal triflates (entries 9–13), we found that allylation of **3** occurred with promising yield and diastereoslectivity in the presence of scandium(III) triflate [72–75]. The reaction mediated by Sc(OTf)$_3$ was especially successful in toluene as solvent (entry 10), while triflates of indium, ytterbium, and hafnium were noticeably less efficient (entries 11–13). During these preliminary tests we also noticed that the stereochemical outcome of the reaction with Sc(OTf)$_3$ and the reactivity of the catalyst were strongly depended on the catalyst batch. While the allylation with an old reagent did not occur at −70 °C and required higher temperature (−25 °C), a fresh sample of commercial Sc(OTf)$_3$, as well as the catalyst dried in vacuum at heating, were much more reactive and

delivered the target alcohol **8** already at −70 °C but with noticeably lower 76:24 d.r. (entry 10 vs. 14).

We surmised that the difference in reactivity between the batches can be explained by hydration of the old reagent with atmospheric moisture since $Sc(OTf)_3$ is hygroscopic and eventually forms octahydrate upon storage. Indeed, powder X-ray diffraction (PXRD) analysis of the old and new reagent confirmed our hypothesis and showed that the old reagent contained $Sc(OTf)_3 \cdot 8H_2O$ as the main phase (Figure 1).

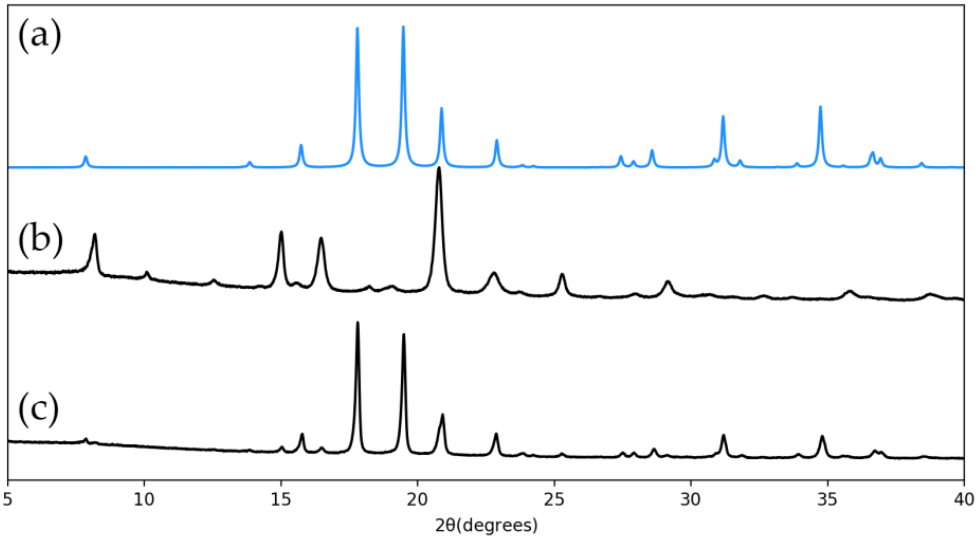
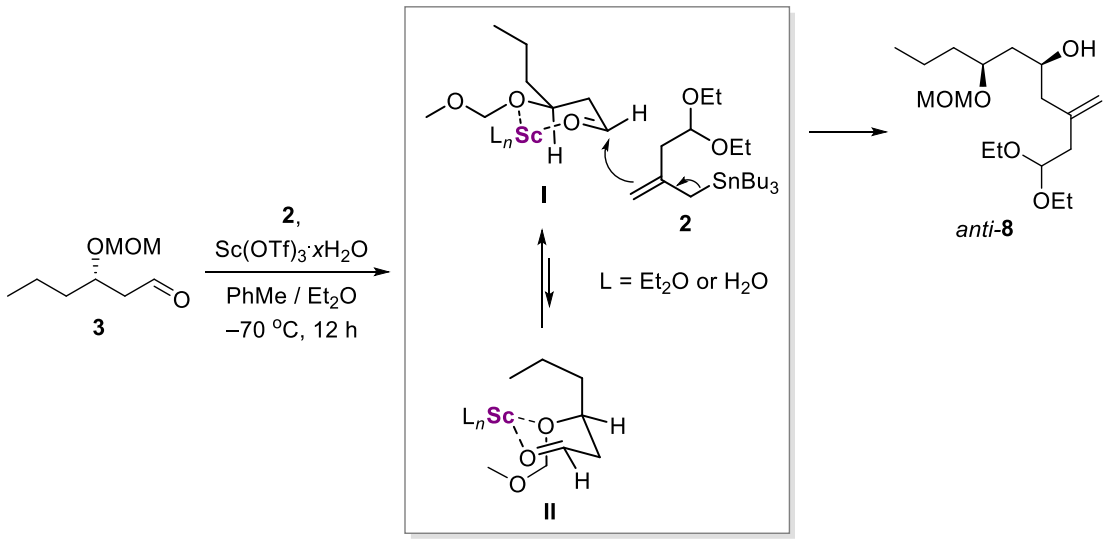


Figure 1. (**a**) Powder X-ray diffraction (PXRD) patterns calculated for $Sc(OTf)_3 \cdot 8H_2O$ from the corresponding single-crystal X-ray diffraction data. Crystallographic data are available from the Cambridge Structural Database (CSD 415177). (**b**) PXRD pattern of commercially available anhydrous $Sc(OTf)_3$. The main phase corresponds to $Sc(OTf)_3 \cdot xH_2O$ ($x < 8$) [76]. Slight hydration occurred since the sample was exposed to atmospheric moisture during the measurement. (**c**) PXRD patterns of the hydrated reagent, which contains $Sc(OTf)_3 \cdot 8H_2O$ as the main phase and trace amount of $Sc(OTf)_3 \cdot xH_2O$ phase.

To our delight, controlled addition of water to the anhydrous $Sc(OTf)_3$ allowed to prepare a catalyst with reproducible performance (see the experimental part), similar to those of the old batches (entries 15 and 16). The best outcome and the highest diastereoselectivity was observed when 2 equiv. of water was added. Moreover, we found that addition of diethyl ether as a co-solvent to toluene (ca. 20% *v/v*) allows to decrease the reaction temperature to −70 °C and therefore further improve the diastereoselectivity (up to 91:9, entry 17). Finally, *anti*-alcohol **8** was prepared in 72% isolated yield and with excellent 94:6 diastereomeric purity in a preparative reaction run starting from 11.5 mmol of aldehyde **3** (entry 18). It is important to note that at least 1.1 equiv. of hydrated $Sc(OTf)_3$ must be used to attain high yields, probably due to the presence of several oxygen-containing functionalities in **8** and formation of a stable chelate complex with scandium.

Our results indicate that controlled hydration of $Sc(OTf)_3$ can be considered as a tool to attenuate the reactivity of $Sc(OTf)_3$ in allylation of carbonyl compounds, and perhaps in other transformations mediated by the same Lewis acid. Scandium(III) triflate has multiple catalytic uses in organic synthesis and can operate even in aqueous media [72–75]. However, the influence of small amounts of water on the catalytic performance of $Sc(OTf)_3$, especially in stereoselective transformations, has been only scarcely reported, to the best of our knowledge [77–79].

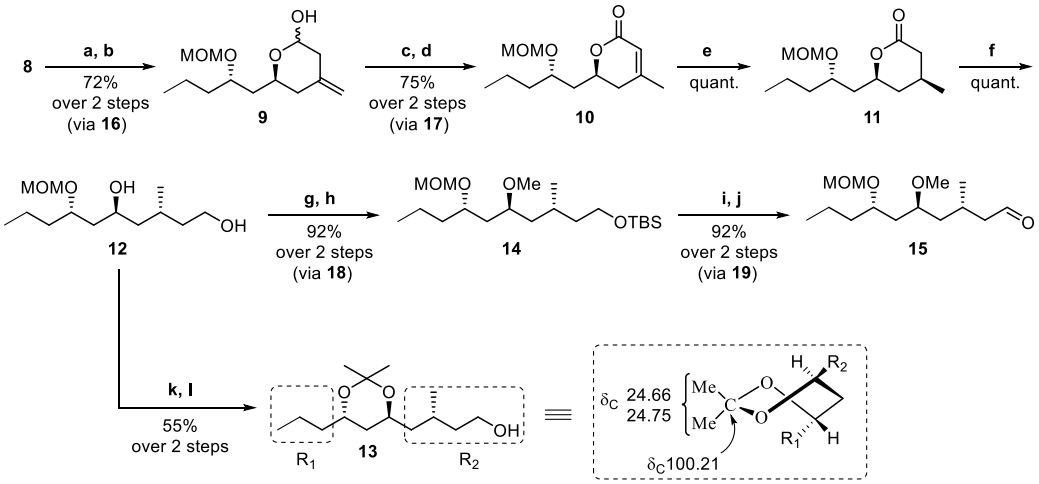
The preferred 1,3-*anti*-selectivity in this transformation can be rationalized in the framework of the Reetz chelate model [16,17,28–32]. We assume that the reaction could proceed through the formation of six-membered chelate intermediates **I** and **II** (Scheme 4) [9].



Scheme 4. The proposed stereochemical model explaining the preferred 1,3-*anti*-selectivity.

Intermediate **II** is less preferred than **I**, since *n*-propyl substituent and MOM-protecting group are both occupy axial positions in the former. Moreover, the reaction of **I** with allylstannane **2** leading to *anti*-alcohol **8** should proceed faster since the reagent **2** approaches from the least hindered side of the carbonyl group, as shown on Scheme 4. On the contrary, in complex **II**, both sides of the carbonyl group are sterically shielded with axial *n*-propyl and MOM substituents, which should result in higher activation barrier for the reaction of **II** with **2** in comparison with those of **I**. Although a mechanistic rationale for the improved d.r. in the case of hydrated catalyst is not fully clear, aqua ligands coordinated to scandium should introduce additional steric hindrances thus further enhancing the difference in reactivity between **I** and **II** and shifting the equilibrium towards the less sterically hindered intermediate **I**.

Having alcohol *anti*-**8** in hand, we confirmed its stereochemical configuration by conversion into the known C^7–C^{16} building block of (+)-Neopeltolide (Scheme 5) [55]. Thus, cyclization of **8** in the presence of catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) and subsequent mild hydrolysis led to the formation of lactol **9**. Oxidation of **9** with pyridinium chlorochromate (PCC) followed by base-catalyzed isomerization of the double bond yielded unsaturated lactone **10**. Hydrogenation of **10** resulted in the formation of saturated lactone **11** as a single diastereoisomer and in a quantitative yield. Reduction of **11** with $LiAlH_4$ afforded diol **12**. To confirm 1,3-*anti* configuration of the stereocenters, diol **12** was transformed into the corresponding acetonide **13**. The values of chemical shifts in ^{13}C NMR spectrum of **13** indicated the 1,3-*anti*-configuration of hydroxyl groups (Scheme 5), according to a known configuration assignment method [80,81]. The selective TBS-protection of the primary hydroxyl group in compound **12** and the subsequent methylation of the secondary hydroxyl produced ether **14** in 92% yield over two steps. Treatment of **14** with catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in methanol and subsequent Swern oxidation furnished aldehyde **15** in 92% yield as a final C^7–C^{16} building block of (+)-Neopeltolide.



Scheme 5. Assignment of 1,3-*anti*-configuration for **8** by its chemical conversion into acetonide **13**. Preparation of C^7–C^{16} building block **15** of (+)-Neopeltolide [55]. Reagents and conditions: (**a**) *p*-TsOH·H_2O, CH_2Cl_2, rt, 40 min (90%); (**b**) PPTS, acetone/H_2O (3:1), reflux, 12 h (80%); (**c**) PCC, CH_2Cl_2, r.t., 8 h (87%); (**d**) Et_3N, THF, reflux, 5 h (86%); (**e**) 10% Pd/C, H_2 in *i*-PrOH, H-Cube (25 °C, 5 bar) (100%); (**f**) $LiAlH_4$, Et_2O, r.t., 25 min (100%); (**g**) TBSCl, imidazole, CH_2Cl_2, r.t., 1.5 h (96%); (**h**) NaH, MeI, Bu_4NI, THF, r.t., 14 h (96%); (**i**) PPTS, MeOH, r.t.,15 h (98%); (**j**) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C to 0 °C (94%); (**k**) pTsOH·H_2O, MeOH, reflux, 2 h; (**l**) pTsOH·H_2O, 2,2-dimethoxypropane, r.t., 24 h (55% for 2 steps). Preparation of intermediate compounds **16**–**19** (structures not shown here for the reasons of space) is described in the Section 3.

3. Experimental Section

3.1. General Experimental Methods

Solvents were used as obtained from commercial sources without any further purification or dried if required over 4 Å molecular sieves. Chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA), Fluorochem (London, UK) and Alfa Aesar (Ward Hill, MA, USA) and used as received unless other indicated. (*S*)-3-(Methoxymethoxy)hexanal (**3**) (ee > 99%) was prepared as described before [55] (see also the Supplementary Materials). Silica gel 40–100 µm was used for column chromatography; silica gel $60F_{254}$ plates were used for TLC. ^{1}H-NMR (400 MHz), ^{13}C-NMR (100.6 MHz) spectra were recorded on Avance III spectrometer (Bruker, Billerica, MA, USA). Chemical shifts are given in δ value with $CHCl_3$ (δ = 7.26 ppm) and $CDCl_3$ (δ = 77.0 ppm) as internal standards for ^{1}H-NMR and ^{13}C-NMR spectra, respectively. FT-IR spectra were recorded on a Bruker Tensor 27 FT spectrometer. Only selected characteristic IR absorption bands are given. Specific rotations were measured by using an Anton Paar MCP 500 polarimeter. HRMS data were obtained on a HPLC/Q-TOF G6540A Mass Spectrometer (Agilent, Santa Clara, CA, USA) using AJS ESI method in positive ion detection modes or a LTQ Orbitrap Discovery spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) using electrospray ionization (ESI). Powder X-ray diffraction (PXRD) patterns for the samples of $Sc(OTf)_3$ were recorded with an EMPYREAN diffractometer (PANalytical, Netherlands) using Cu-Kα radiation (Ni-filter) at 296 K with area detector 2θ range of ca. 0°–40°. Samples of $Sc(OTf)_3$ were not protected from atmospheric moisture during the measurements. Crystallographic data for $Sc(OTf)_3{\cdot}8H_2O$ are available from the Cambridge Structural Database (CSD 415177) [82].

*3.2. Preparation of 4,4-Diethoxy-2-methylenebutyl Bromide (**1**)*

3.2.1. 1-(2,2-Diethoxyethyl)cyclopropan-1-ol (**5**)

A solution of EtMgBr (1.6 M in THF, 200 mL, 320 mmol) was added dropwise over a period of 7 h to a solution of ethyl 3,3-diethoxypropionate (**4**) (20.0 g, 105 mmol) and titanium(IV) isopropoxide (6.0 mL, 20 mmol, 20 mol%) in THF (90 mL) under stirring and external cooling (water bath, 20 °C). The reaction mixture was additionally stirred at r.t. for 12 h, at which time the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (300 mL). The flask was placed in an ice-water bath and a saturated

aqueous solution of NH_4Cl (38 mL) was added by small portions at vigorous stirring. The mixture was additionally stirred at r.t. for 20 min and filtered. The precipitate was washed with CH_2Cl_2 (3 × 150 mL), and the combined organic phases were washed with a saturated aqueous solution of NaCl (150 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford cyclopropanol **5** (18.3 g, 100%) as a yellowish oil. The obtained compound was used directly in the next step; additional purification was not required. R_f = 0.55 (PE:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (t, *J* = 5.8 Hz, 1H), 3.77–3.68 (m, 2H), 3.59 (br.s, 1H), 3.62–3.51 (m, 2H), 1.89 (d, *J* = 5.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 6H), 0.78–0.73 (m, 2H), 0.47–0.42 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 102.97, 61.74 (2C), 53.13, 40.91, 15.30 (2C), 12.40 (2C). Spectral data are in agreement with previously reported [83].

3.2.2. 1-(2,2-Diethoxyethyl)cyclopropyl Methanesulfonate (**6**)

A solution of methanesulfonyl chloride (16.0 mL, 205 mmol) in anhydrous diethyl ether (100 mL) was added dropwise over a period of 10 min to a cooled (ice bath, 0 °C) solution of cyclopropanol **5** (18.3 g, 105 mmol) and *N*,*N*-diisopropylethylamine (48.0 mL, 275 mmol) in anhydrous diethyl ether (200 mL). The reaction mixture was stirred for 2 h and during this time gradually warmed to room temperature. A saturated solution of $NaHCO_3$ (200 mL) was added, and the mixture was stirred for 1 h. The organic layer was separated, the aqueous layer was extracted with diethyl ether (3 × 150 mL), and the combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude mesylate **6** (26.5 g, 100%) as a pale-orange oil, which was used in the next step without purification. R_f = 0.55 (PE:EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (t, *J* = 5.4 Hz, 1H), 3.72–3.62 (m, 2H), 3.59–3.49 (m, 2H), 3.00 (s, 3H), 2.14 (d, *J* = 5.4 Hz, 2H), 1.27–1.22 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 6H), 0.84–0.78 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 100.90, 63.79, 62.06 (2C), 40.34, 39.84, 15.26 (2C), 11.57 (2C). Spectral data are in agreement with previously reported [84].

3.2.3. 4,4-Diethoxy-2-methylenebutyl Bromide (**1**)

A solution of 1,2-dibromoethane (19.0 mL, 220 mmol) in anhydrous diethyl ether (50 mL) was added slowly in a dropwise manner to magnesium turnings (4.8 g, 200 mmol) in anhydrous diethyl ether (100 mL). The reaction mixture was additionally stirred until the complete dissolution of magnesium occurred. Then, a solution of the crude mesylate **6** (26.5 g, 105 mmol) in anhydrous diethyl ether (120 mL) was added dropwise over 15 min at room temperature to the obtained solution of $MgBr_2$ and the resulting mixture was vigorously stirred for 2 h. Afterwards, water (200 mL) was cautiously added by small portions at external cooling (ice-water bath, 0 °C). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (150 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and allyl bromide **1** was purified by using a short chromatographic column (SiO_2, eluent PE:EtOAc, 50:1). Yellowish oil (23.4 g, 94%). R_f = 0.63 (PE:EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (br.s, 1H), 5.06 (br.s, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.04 (br.s, 2H), 3.70–3.61 (m, 2H), 3.55–3.45 (m, 2H), 2.53 (d, *J* = 5.6 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 141.38, 117.82, 101.84, 61.32 (2C), 37.50, 37.37, 15.21 (2C). Spectral data are in agreement with previously reported [53].

*3.3. Preparation of Tributyl(4,4-diethoxy-2-methylenebutyl)stannane (**2**)*

A solution of naphthalene (0.16 g, 1.25 mmol) in THF (2 mL) was added to lithium chipping (0.60 g, 86 mmol) in THF (48 mL) under inert atmosphere (argon). The mixture turned green and was stirred at room temperature for 1 h. Then, tributyltin chloride (6.50 mL, 24.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 12 h. The resulting dark-green solution of Bu_3SnLi was transferred into another reaction vessel and cooled to −78 °C (acetone-dry ice bath). A solution of allylbromide **1** (4.74 g,

20.0 mmol) in THF (40 mL) was added dropwise and the resulting reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl (150 mL) and stirred while warming to room temperature for 1h. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic phases were washed with saturated $NaHCO_3$ solution (50 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude stannane **2** (9.3 g). According to ^{1}H NMR analysis, the crude product contains 7 g (77 mol.%, 78% yield) of **2**, contaminated with self-coupling products **7** (0.5 g, 8 mol.%) and $Bu_3SnSnBu_3$ (1.8 g, 15 mol.%). However, the crude stannane **2** can be used for the allylation of aldehydes without any further purification.

Tributyl(4,4-diethoxy-2-methylenebutyl)stannane (**2**): R_f = 0.68 (PE:EtOAc, 20:1). IR (neat): ν = 1627, 1215, 1119, 1060 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62 (t, *J* = 5.7 Hz, 1H), 4.63–4.57 (m, 1H), 4.57–4.51 (m, 1H), 3.70–3.61 (m, 2H), 3.56–3.46 (m, 2H), 2.29–2.23 (m, 2H), 1.93–1.75 (m, 2H), 1.56–1.38 (m, 6H), 1.37–1.24 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 6H), 0.89 (t, *J* = 7.3 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 145.61, 107.34, 102.31, 61.13 (2C), 42.41, 29.08 (3C), 27.36 (3C), 19.51, 15.30 (2C), 13.68 (3C), 9.44 (3C).

1,1,8,8-Tetraethoxy-3,6-dimethyleneoctane (**7**): R_f = 0.5 (PE:EtOAc, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.83 (br.s, 4H), 4.60 (t, J = 5.7 Hz, 2H), 3.70–3.59 (m, 4H), 3.54–3.43 (m, 4H), 2.35 (d, J = 5.7 Hz, 4H), 2.20 (br.s, 4H), 1.19 (t, J = 7.1 Hz, 12H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.93 (2C), 111.78 (2C), 102.09 (2C), 61.05 (4C), 40.31 (2C), 34.66 (2C), 15.25 (4C). HRMS (ESI) calcd. for $C_{18}H_{34}O_4Na^+$ $[M+Na]^+$ 337.2349, found *m/z* 337.2347.

3.4. Preparation of Hydrated Scandium Triflate Catalyst

Water (0.76 mL, 42 mmol) was added to a stirred suspension of anhydrous scandium triflate (10.3 g, 21 mmol) in anhydrous diethyl ether (240 mL). The resulting mixture was stirred until almost complete dissolution of solid occurred. The solvent was removed under reduced pressure. The solid residue was thoroughly grinded with mortar and pestle under air and not protected from atmospheric moisture. The obtained powder was dried on a rotary evaporator at 70 °C and reduced pressure (5 mm Hg) for 3 h.

*3.5. (5S,7S)-1,1-Diethoxy-7-(methoxymethoxy)-3-methylenedecan-5-ol (anti-**8**)*

A solution of (*S*)-3-(methoxymethoxy)hexanal (**3**) (1.84 g, 11.5 mmol) in anhydrous toluene (25 mL), and a solution of tributyl(4,4-diethoxy-2-methylenebutyl)stannane (**2**) (9.20 g, 20.6 mmol) in anhydrous toluene (30 mL) were sequentially added to a turbid solution of freshly prepared hydrated scandium triflate catalyst (8.04 g, 12.6 mmol) in a mixture of anhydrous toluene (55 mL) and diethyl ether (27 mL) at −70 °C under inert atmosphere (argon). The reaction mixture was stirred at −70 °C for 12 h. (TLC monitoring clearly revealed the product only after aqueous work up of the samples taken). The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (150 mL) and vigorously stirred until it warmed to room temperature (ca. 1 h). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the title compound was isolated by column chromatography (SiO_2, eluent PE:EtOAc, gradient 10:1 to 4:1). Colorless oil (2.63 g, 72%). R_f = 0.36 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$ = +24.7 (*c* 0.69, CH_2Cl_2). IR (neat): ν = 3474, 1644, 1444, 1374, 1130, 1042, 916 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (s, 1H), 4.94 (s, 1H), 4.67 (s, 2H), 4.63 (t, *J* = 5.8 Hz, 1H), 4.06–3.95 (m, 1H), 3.86–3.77 (m, 1H), 3.70–3.59 (m, 2H), 3.54–3.44 (m, 2H), 3.39 (s, 3H), 2.98 (d, *J* = 2.9 Hz, 1H), 2.47–2.32 (m, 2H), 2.27–2.14 (m, 2H), 1.64–1.26 (m, 6H), 1.18 (t, *J* = 7.0 Hz, 6H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.33, 115.07, 102.28, 96.25, 75.53, 65.66, 61.30, 61.14, 55.69, 45.35, 41.55, 39.82, 37.26, 18.51, 15.21, 15.18, 14.19. HRMS (ESI) calcd. for $C_{17}H_{34}O_5Na^+$ $[M+Na]^+$ 341.2298, found *m/z* 341.2296.

3.6. Preparation of C^7–C^{16} Building Block 15 for the Synthesis of (+)-Neopeltolide

3.6.1. (6*S*)-2-Ethoxy-6-((*S*)-2-(methoxymethoxy)pentyl)-4-methylenetetrahydro-2*H*-pyran (**16**)

p-Toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 0.06g, 0.32 mmol) was added to a solution of alcohol **8** (5.20 g, 16.4 mmol) in CH_2Cl_2 (125 mL) and the reaction mixture was stirred at room temperature for 30 min, at which time Et_3N (0.20 mL, 1.45 mmol) was added. The solvent was removed under reduced pressure and acetal **18** (mixture of epimers ~50:50 according to ^{1}H NMR) was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 20:1). Colorless oil (4.01 g, 90%). R_f = 0.60 (PE:EtOAc, 4:1). IR (neat): ν = 1655, 1443, 1374, 1350, 1215, 1145, 1042, 918, 890 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (d, *J* = 3.4 Hz, 1H), 4.80–4.74 (m, 4H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.65 (s, 2H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.32 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.02–3.93 (m, 1H), 3.93–3.81 (m, 2H), 3.76–3.64 (m, 2H), 3.57– 3.41 (m, 3H), 3.36 (s, 6H), 2.45–2.08 (m, 6H), 2.05–1.89 (m, 2H), 1.77–1.30 (m, 12H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.61, 140.67, 110.52, 110.39, 101.70, 97.07, 96.12, 96.00, 75.27, 74.20, 71.64, 66.63, 64.34, 62.46, 55.62, 55.56, 41.53, 41.30, 40.97, 40.64, 40.51, 39.04, 37.61, 37.47, 18.12, 18.11, 15.20, 14.89, 14.26, 14.24. HRMS (ESI) calcd. for $C_{15}H_{28}O_4Na^+$ $[M+Na]^+$ 295.1880, found *m*/*z* 295.1879.

3.6.2. (6*S*)-6-((*S*)-2-(Methoxymethoxy)pentyl)-4-methylenetetrahydro-2*H*-pyran-2-ol (**9**)

Pyridinium *p*-toluenesulfonate (PPTS, 4.56 g, 18.2 mmol) was added to a solution of cyclic acetal **16** (3.80 g, 14.0 mmol) in a mixture of acetone (600 mL) and H_2O (200 mL) and the reaction mixture was stirred under gentle reflux for 12 h. After cooling to room temperature acetone was evaporated under reduced pressure and the reaction product was extracted from the water phase with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the title compound was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 10:1). Obtained as ~50:50 mixture of epimers according to ^{1}H NMR. Colorless oil (2.73 g, 80%). R_f = 0.45 (PE:EtOAc, 2:1). IR (neat): ν = 3417, 1655, 1441, 1378, 1334, 1214, 1140, 1101, 1039, 895 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.38–5.33 (m, 1H), 4.86–4.83 (m, 1H), 4.83–4.80 (m, 1H), 4.79–4.76 (m, 2H), 4.67–4.58 (m, 5H), 4.23 (d, *J* = 5.3 Hz, 1H), 4.14–4.05 (m, 1H), 3.87–3.78 (m, 1H), 3.78–3.69 (m, 1H), 3.55 (dd, *J* = 3.9, 1.4 Hz, 1H), 3.51 (ddt, *J* = 11.9, 9.6, 2.7 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.53–1.87 (m, 8H), 1.75–1.28 (m, 12H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.36, 140.39, 111.35, 110.61, 96.70, 96.05, 95.75, 92.04, 75.26, 74.03, 71.84, 66.19, 55.65, 55.58, 42.07, 41.39, 41.26, 40.67, 40.22, 39.62, 37.90, 37.47, 18.38, 18.17, 14.22, 14.18. HRMS (ESI) calcd. for $C_{13}H_{24}O_4Na^+$ $[M+Na]^+$ 267.1567, found *m*/*z* 267.1567.

3.6.3. ((*S*)-6-((*S*)-2-(Methoxymethoxy)pentyl)-4-methylenetetrahydro-2*H*-pyran-2-one (**17**)

Pyridinium chlorochromate (PCC, 15.9 g, 73.8 mmol) was added to a solution of lactole **9** (3.60 g, 14.8 mmol) in anhydrous CH_2Cl_2 (170 mL) and the reaction mixture was vigorously stirred at room temperature for 8 h. Diethyl ether (200 mL) was added, and the mixture was filtrated through a layer of silica gel. Precipitate of chromium salts was washed with diethyl ether (2 × 100 mL) and the collected ether solution was filtrated through a layer of silica gel again. The organic extracts were combined; the solvent was removed under reduced pressure. Chromatography purification (SiO_2, eluent PE:EtOAc, 10:1) afforded lactone **17** as colorless oil (3.10 g, 87% yield). R_f = 0.45 (PE:EtOAc, 2:1). $[\alpha]_D^{20}$ = +44.1 (*c* 1.30, CH_2Cl_2). IR (neat): ν = 1750, 1655, 1376, 1290, 1237, 1151, 1096, 1041 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (br.s, 2H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.61–4.51 (m, 1H), 3.91–3.78 (m, 1H), 3.35 (s, 3H), 3.37–3.19 (m, 2H), 2.75–2.55 (m, 1H), 2.33 (ddd, *J* = 15.7, 10.8, 1.6 Hz, 1H), 1.84–1.62 (m, 2H), 1.62–1.28 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.36, 135.81, 112.17, 96.18, 75.45, 74.02, 55.60, 40.71, 38.32, 37.21, 36.65, 18.01, 14.18. HRMS (ESI) calcd. for $C_{13}H_{22}O_4Na^+$ $[M+Na]^+$ 265.1410, found *m*/*z* 265.1410.

3.6.4. (*S*)-6-((*S*)-2-(Methoxymethoxy)pentyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (**10**)

Triethylamine (1.86 mL, 1.36 g, 13.5 mmol) was added to a solution of lactone **17** (2.90 g, 12.0 mmol) in THF (50 mL) and the reaction mixture was stirred under gentle reflux for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography (SiO_2, eluent PE:EtOAc, 5:1). Colorless oil (2.50 g, 86%). R_f = 0.41 (PE:EtOAc, 2:1). $[\alpha]_D^{20}$ = −20.6 (*c* 0.75, CH_2Cl_2). IR (neat): ν = 1722, 1437, 1386, 1247, 1149, 1096, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.79 (br.s, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.66–4.55 (m, 1H), 3.94–3.82 (m, 1H), 3.35 (s, 3H), 2.38–2.24 (m, 1H), 2.18 (dd, *J* = 17.8, 4.0 Hz, 1H), 1.96 (br.s, 3H), 1.90 (ddd, *J* = 14.5, 9.6, 2.8 Hz, 1H), 1.68 (ddd, *J* = 14.5, 9.8, 2.9 Hz, 1H), 1.63–1.27 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 165.07, 157.16, 116.48, 96.16, 74.05, 73.75, 55.64, 40.43, 37.22, 35.25, 22.92, 18.01, 14.21. HRMS (ESI) calcd. for $C_{13}H_{22}O_4Na^+$ $[M+Na]^+$ 265.1410, found *m*/*z* 265.1405.

3.6.5. (4*S*,6*S*)-6-((*S*)-2-(Methoxymethoxy)pentyl)-4-methyltetrahydro-2*H*-pyran-2-one (**11**)

A solution of lactone **10** (2.4 g, 10 mmol) in 2-propanol (0.05 M, 200 mL) was subjected to flow hydrogenation with the aid of Thales Nano H-Cube™ flow reactor. The solution of starting material was passed through an H-Cube reactor with a flow rate of 1 mL/min at 25 °C and at 5 bar hydrogen pressure, using a 10% Pd/C 30 mm-length cartridge. The solvent was evaporated, yielding compound **11** as colorless oil (2.42 g, quantitative yield). R_f = 0.53 (PE:EtOAc, 2:1). $[\alpha]_D^{20}$ = +70.0 (*c* 0.78, CH_2Cl_2). IR (neat): ν = 1737, 1458, 1379, 1236, 1153, 1097, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.65 (s, 2H), 4.47 (ddt, *J* = 12.1, 9.3, 3.0 Hz, 1H), 3.90–3.81 (m, 1H), 3.34 (s, 3H), 2.71–2.59 (m, 1H), 2.12–1.96 (m, 2H), 1.92–1.82 (m, 1H), 1.74 (ddd, *J* = 14.6, 9.3, 3.2 Hz, 1H), 1.65 (ddd, *J* = 14.6, 9.5, 3.1 Hz, 1H), 1.60–1.26 (m, 4H), 1.25–1.13 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.27, 96.22, 77.13, 73.96, 55.58, 41.70, 37.95, 37.59, 37.27, 26.68, 21.65, 17.98, 14.19. HRMS (ESI) calcd. for $C_{13}H_{24}O_4Na^+$ $[M+Na]^+$ 267.1567, found *m*/*z* 267.1568.

3.6.6. (3*R*,5*S*,7*S*)-7-(Methoxymethoxy)-3-methyldecane-1,5-diol (**12**)

A solution of lactone **11** (1.42 g, 5.8 mmol) in anhydrous diethyl ether (12 mL) was added dropwise to a suspension of $LiAlH_4$ (0.22 g, 5.8 mmol) in anhydrous diethyl ether (12 mL) and the reaction mixture was stirred at room temperature under inert atmosphere (argon) for 25 min. The reaction mixture was diluted with diethyl ether (50 mL) followed by slow dropwise addition of water (ca. 2 mL) upon external cooling with an ice-bath. White precipitate was filtered off, washed with diethyl ether (3 × 20 mL), and combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding compound **12** as colorless oil (1.44 g, quantitative yield), which was used in the next step without further purification. R_f = 0.34 (EtOAc). $[\alpha]_D^{20}$ = +40.2 (*c* 0.90, CH_2Cl_2). IR (neat): ν = 3385, 1463, 1378, 1147, 1098, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.67 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.00–3.91 (m, 1H), 3.82–3.75 (m, 1H), 3.74–3.59 (m, 2H), 3.40 (s, 3H), 3.35 (d, *J* = 3.0 Hz, 1H), 2.43 (t, *J* = 5.6 Hz, 1H), 1.93–1.81 (m, 1H), 1.62–1.41 (m, 7H), 1.40–1.27 (m, 2H), 1.14–1.05 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 96.42, 76.04, 65.73, 60.45, 55.83, 44.15, 42.28, 40.37, 37.21, 26.06, 20.05, 18.65, 14.16. HRMS (ESI) calcd. for $C_{13}H_{28}O_4Na^+$ $[M+Na]^+$ 271.1880, found *m*/*z* 271.1877.

3.6.7. (*R*)-4-((4*S*,6*S*)-2,2-Dimethyl-6-propyl-1,3-dioxan-4-yl)-3-methylbutan-1-ol (**13**)

Two small crystals of *p*-TsOH·H_2O were added to a solution of diol **12** (15 mg, 0.06 mmol) in methanol (1 mL) and the reaction mixture was stirred under gentle reflux for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, the residue was dissolved in 2,2-dimethoxypropane (1 mL) and two small crystals of pTsOH·H_2O were added again. The reaction mixture was stirred at room temperature for 24 h. One drop of triethylamine was added, the solvent was evaporated under reduced

pressure, and the title compound was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 7:1). Colorless oil (8 mg, 55%). R_f = 0.45 (PE:EtOAc, 2:1). $[\alpha]_D^{20}$ = +27.3 (*c* 0.17, CH_2Cl_2). IR (neat): ν = 3406, 1460, 1379, 1225, 1172, 1134, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.87 (dtd, *J* = 11.2, 7.8, 3.4 Hz, 1H), 3.81–3.59 (m, 3H), 1.85–1.62 (m, 2H), 1.62–1.23 (m, 8H), 1.34 (s, 3H), 1.33 (s, 3H),1.19 (ddd, *J* = 14.0, 8.6, 3.4 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 100.21, 66.41, 64.83, 60.76, 42.89, 40.13, 39.44, 38.03, 26.18, 24.75, 24.66, 19.83, 18.58, 13.94. HRMS (ESI) calcd. for $C_{14}H_{28}O_3Na^+$ $[M+Na]^+$ 267.1931, found *m*/*z* 267.1929.

3.6.8. (5*S*,7*S*,9*R*)-9,13,13,14,14-Pentamethyl-5-propyl-2,4,12-trioxa-13-silapentadecan-7-ol (**18**)

tert-Butyldimethylsilyl chloride (1.51 g, 10.0 mmol) was added to a solution of diol **12** (2.34 g, 9.4 mmol) and imidazole (0.90 g, 13.2 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C and the reaction mixture was stirred for 1.5 h while gradually warming to room temperature. Then water (30 mL) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure, and the reaction product was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 15:1). Colorless oil (3.25 g, 96%). R_f = 0.43 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$ = +30.5 (*c* 1.18, CH_2Cl_2). IR (neat): ν = 3474, 1464, 1380, 1255, 1147, 1096, 1040, 837, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.02–3.92 (m, 1H), 3.85–3.76 (m, 1H), 3.72–3.59 (m, 2H), 3.41 (s, 3H), 2.93 (d, *J* = 3.6 Hz, 1H), 1.88–1.75 (m, 1H), 1.64–1.27 (m, 9H), 1.19–1.09 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 96.40, 76.01, 65.45, 61.45, 55.85, 44.99, 42.13, 40.54, 37.22, 26.32, 25.96 (3C), 19.58, 18.68, 18.31, 14.20, –5.28 (2C). HRMS (ESI) calcd. for $C_{19}H_{42}O_4SiNa^+$ $[M+Na]^+$ 385.2745, found *m*/*z* 385.2744.

3.6.9. (5*S*,7*S*,9*R*)-7-Methoxy-9,13,13,14,14-pentamethyl-5-propyl-2,4,12-trioxa-13-silapentadecane (**14**)

A solution of **18** (0.71 g, 1.96 mmol) in anhydrous THF (6 mL) was added dropwise with stirring to a suspension of NaH (60% dispersion in mineral oil, 0.43 g, 10.8 mmol) in anhydrous THF (10 mL). After 10 min, a solution of Bu_4NI (0.02 g, 0.05 mmol) in THF (1 mL) was added followed by a solution of iodomethane (0.50 mL, 1.14 g, 8.0 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature under inert atmosphere (argon) for 14 h, and then diethyl ether (20 mL) was added. The reaction mixture was cooled to 0 °C and quenched by slow dropwise addition of water, until the evolution of hydrogen stopped. The mixture was diluted with water (20 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and title compound was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 40:1). Colorless oil (0.71 g, 96%). R_f = 0.45 (PE:EtOAc, 10:1). $[\alpha]_D^{20}$ = +14.5 (*c* 0.84, CH_2Cl_2). IR (neat): ν = 1464, 1380, 1255, 1147, 1096, 1043, 836, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 3.75–3.58 (m, 3H), 3.49– 3.41 (m, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 1.79–1.66 (m, 1H), 1.65–1.27 (m, 9H), 1.16 (ddd, *J* = 13.8, 8.2, 5.3 Hz, 1H), 0.97–0.83 (m, 15H), 0.04 (s, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 95.94, 75.53, 75.05, 61.27, 55.89, 55.60, 42.01, 40.40, 40.36, 37.54, 26.29, 25.95 (3C), 20.03, 18.30, 18.25, 14.28, –5.28, –5.32. HRMS (ESI) calcd. for $C_{20}H_{44}O_4SiNa^+$ $[M+Na]^+$ 399.2901, found *m*/*z* 399.2902.

3.6.10. (3*R*,5*S*,7*S*)-5-Methoxy-7-(methoxymethoxy)-3-methyldecan-1-ol (**19**)

PPTS (0.021 g, 0.08 mmol) was added to a solution of silyl ether **14** (3.080 g, 8.20 mmol) in methanol (50 mL) and the reaction mixture was kept at room temperature for 15 h. Triethylamine (0.060 mL, 0.044 g, 0.44 mmol) was added, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2,

PE:EtOAc, 7:1). Colorless oil (2.10 g, 98%). R_f = 0.46 (PE:EtOAc, 2:1). $[\alpha]_D^{20}$ = +15.5 (*c* 0.84, CH_2Cl_2). IR (neat): ν = 3442, 1463, 1379, 1144, 1094, 1042 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.68 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 3.75–3.61 (m, 3H), 3.47–3.39 (m, 1H), 3.39 (s, 3H), 3.33 (s, 3H), 1.84–1.29 (m, 11H), 1.19(ddd, *J* = 13.5, 8.1, 5.1 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 95.81, 75.90, 75.05, 60.80, 56.13, 55.63, 41.78, 40.20, 40.14, 37.41, 26.20, 20.26, 18.23, 14.24. HRMS (ESI) calcd. for $C_{14}H_{30}O_4Na^+$ $[M+Na]^+$ 285.2036, found *m*/*z* 285.2039.

3.6.11. (3*S*,5*S*,7*S*)-5-Methoxy-7-(methoxymethoxy)-3-methyldecanal (**15**) [55]

A solution of DMSO (0.58 g, 7.4 mmol) in anhydrous CH_2Cl_2 (8 mL) was added to a solution of $(COCl)_2$ (0.32 mL, 0.47 g, 3.7 mmol) in anhydrous CH_2Cl_2 (7 mL) at −78 °C and the reaction mixture was stirred at the same temperature under inert atmosphere (argon) for 25 min. A solution of alcohol **19** (0.76 g, 2.9 mmol) in anhydrous CH_2Cl_2 (8 mL) was added and the reaction mixture was stirred at −78 °C for 1 h. Then triethylamine (2.30 mL, 1.68 g, 16.6 mmol) was added and the mixture was stirred while gradually warming to 0 °C for 1 h. The reaction mixture was quenched with water (25 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the title compound was isolated by column chromatography (SiO_2, eluent PE:EtOAc, 15:1). Colorless oil (0.71 g, 94%). R_f = 0.48 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$ = +9.4 (*c* 0.85, CH_2Cl_2). IR (neat): ν = 1725, 1463, 1380, 1143, 1091, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.74 (t, *J* = 2.1 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 3.74–3.63 (m, 1H), 3.48–3.39 (m, 1H), 3.38 (s, 3H), 3.32 (s, 3H), 2.47–2.36 (m, 1H), 2.30–2.20 (m, 2H), 1.69–1.19 (m, 8H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 202.56, 95.85, 75.46, 74.96, 55.92, 55.62, 51.32, 41.54, 40.02, 37.38, 24.99, 20.27, 18.21, 14.23. HRMS (ESI) calcd. for $C_{14}H_{28}O_4Na^+$ $[M+Na]^+$ 283.1880, found *m*/*z* 283.1884.

4. Conclusions

We have developed an improved and cost-efficient protocol for multigram preparation of (allyl)tributylstannane **2**, which can be used as a synthetic equivalent of a C_5-bipolar synthon in the synthesis of natural compounds. The use of **2** in stereoselective transformations was exemplified by highly diastereoselective 1,3-*anti*-allylation of aldehyde **3**, designed en route to the total synthesis of (+)-Neopeltolide. Scandium triflate was revealed as an effective Lewis acid catalyst in this transformation. Addition of water was found to be crucial for adjusting the catalytic activity of scandium triflate and led to greatly improved stereoselectivity. Although stoichiometric amounts of scandium triflate are required to attain high yield of **8**, this work represent a rare example of the use of functionalized allylstannanes in stereocontrolled allylation of oxysubstituted aldehydes.

Supplementary Materials: The following are available online at https://www.mdpi.com/2073-8994/13/3/470/s1, copies of ^1H, ^{13}C-NMR and HRMS spectra, synthesis of aldehyde **3**.

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