# Synthesis of Both Top and Bottom Fragments of (-)-Talaromycin A through Enantiospecific and Diastereoselective Elaboration of Asymmetrized Tris(hydroxymethyl)methane

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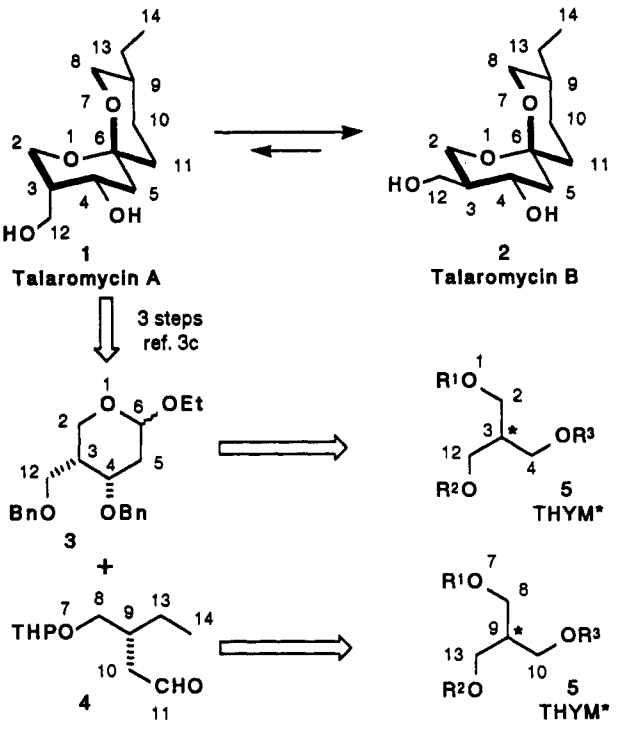
Asymmetrized tris(hydroxymethyl)methane equivalents of general formula **5** have been employed as chiral building blocks for the enantiospecific and diastereoselective synthesis of both fragments **3** and **4**, whose conversion into Talaromycin A was already reported. Preparation of bottom half fragment **3** was achieved through a "protecting group-controlled" stereoselective allylation of an asymmetrized bis(hydroxymethyl)acetaldehyde with allyltributyltin, while the top half fragment **4** was obtained in high overall yield by sequential elongation of two of the three synthetically equivalent masked hydroxymethyl group of **5**, via nucleophilic substitution reactions.

Talaromycins A and B[1] are two toxic metabolites produced by *Talaromyces stipitatus*, a fungus that grows on animal feed produced from chicken litter and which renders the feed toxic to mammals. The toxicity of these compounds is probably due to their ability to block outward potassium fluxes, thus leading to muscle dysfunction. Much synthetic interest has been also stimulated by the fact that they are the first spiroacetals of fungal origin, a structural feature which occurs also in other biologically active substances of great pharmacological interest, such as the milbemycin-avermectin family of macrolide antibiotics.[2] It is important to stress that the less stable talaromycin A (**1**), which possesses an axially disposed hydroxymethyl group, can be quantitatively converted into talaromcyin B (**2**), by acid catalysis. In the last years these molecules have attracted the attention of many synthetic investigators. Efforts on the nonracemic front have culminated in six enantioselective total syntheses.[3] In particular a highly convergent synthesis of (-)-Talaromycin A (**1**) has been realized by Mori et al.[3c] by assembling the two fragments **3** and **4** corresponding, respectively, to the bottom half and to the top half of **1** (Scheme I).

Examination of the structure of these two fragments suggested that they could both be retrosynthetically disconnected to a common chiral precursor of general formula **5** [asymmetrized tris(hydroxymethyl)methane (THYM*)]. Equivalents of this new chiral building block have recently been obtained by us through a chemoenzymatic methodology,[4a,b,e] and some synthetic applications, demonstrating their peculiar stereochemical properties, have been reported.[4c,d] In particular, the latent $C_{3v}$ symmetry of **5** allows us to prepare in enantiodivergent or diastereodivergent manner all possible stereoisomers of simple derivatives of **5** possessing one or two asymmetric centers. We report here the successful exploitation of **5** in the formal total synthesis of (-)-Talaromycin A via fragments **3** and **4**.

**Scheme I**




**Synthesis of the Bottom Half Fragment 3.** Our plan for the preparation of **3** required the addition of a suitable acetaldehyde equivalent to an "asymmetrized bis(hydroxymethyl)acetaldehyde", BHYMA* (**7**) (Scheme II).

(1) (a) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennell, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319-7322. (b) Hutton, W. C.; Philips, N. J.; Graden, D. W.; Lynn, D. G. *J. Chem. Soc., Chem. Commun.* **1983**, 864.

(2) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(3) Talaromycin A: (a) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143-1144. (b) Crimmins, M. T.; O'Mahony, R. *J. Org. Chem.* **1989**, *54*, 1157-1161. (c) Mori, K.; Ikunaka, M. *Tetrahedron* **1987**, *43*, 45-58. Talaromycin B: (d) Iwata, C.; Fujita, M.; Moritani, Y.; Sugiyama, K.; Hattori, K.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 3131-3134. (e) Tietze, L. F.; Schneider, C. *J. Org. Chem.* **1991**, *56*, 2476-2481. Talaromycins A and B: (f) Smith, A. B. III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469-1471. Racemic syntheses: (g) Schreiber, S. L.; Sommer, T. J. *Tetrahedron Lett.* **1983**, *24*, 4781-4784. (h) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035-2038. (i) Kozikowski, A. P.; Scripko, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 353-355. (j) Kocienski, P.; Yeates, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1879-1883. (k) Whitby, R.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1987**, 906-907. (l) Schreiber, S. L.; Sommer, T. J.; Satake, K. *Tetrahedron Lett.* **1985**, *26*, 17-20. (m) Baker, R.; Boyes, A. L.; Swain, C. J. *Tetrahedron Lett.* **1989**, *30*, 985-988.

(4) (a) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 2697-2698. (b) *Tetrahedron: Asymmetry* **1990**, *1*, 721-724. (c) *Tetrahedron Lett.* **1990**, *31*, 6421-6424. (d) Guanti, G.; Banfi, L.; Ghiron, C.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 267-270. (e) Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *57*, 1540-1554.

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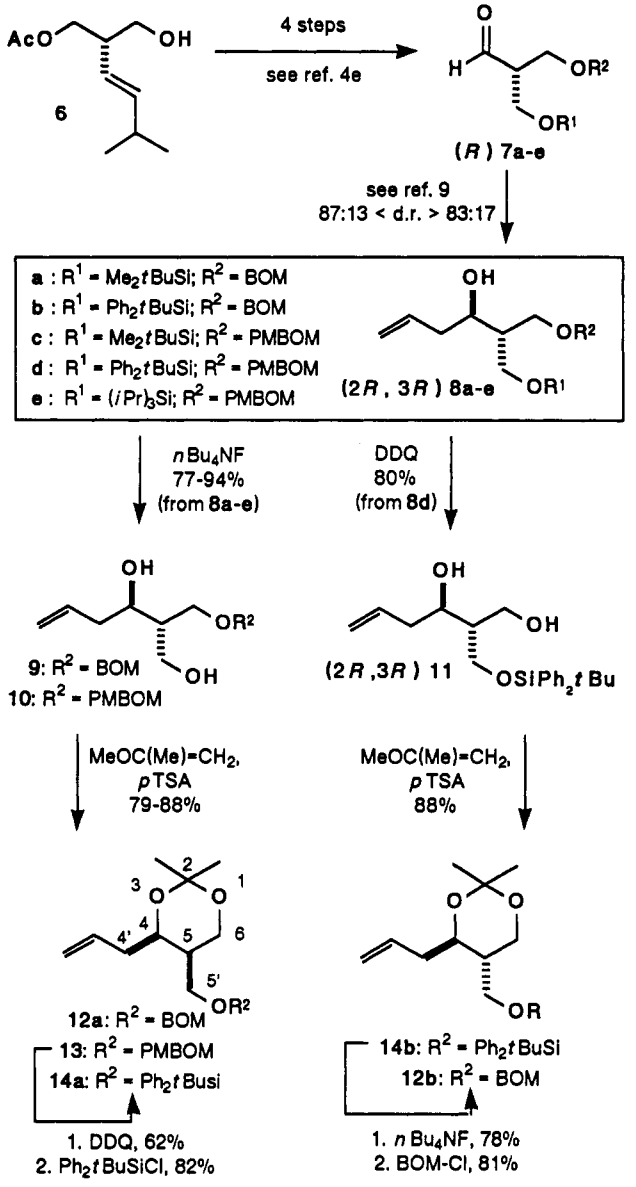
**Scheme II**




A series of aldehydes with this general structure was previously prepared by us[4e] in both enantiomeric forms[5] starting from monoacetate **6**, which was in turn prepared in excellent ee's through pig pancreatic lipase catalyzed monohydrolysis of the corresponding diacetate.[4e] Since in **7** the two synthetically equivalent $CH_2OR$ branches are distinguished only by the protecting groups $R^1$ and $R^2$, the achievement of good diastereoselectivity in additions to it requires a "protecting group-controlled asymmetric synthesis". This goal was previously achieved by us through "chelation-controlled" additions, employing two protecting groups that can be classified as "chelating"[6] like the (benzyloxy)methyl (BOM) or the ((*p*-methoxybenzyl)oxy)methyl (PMBOM)[7] groups or "nonchelating"[6] like the silyl ethers.[8] By this approach we have obtained good to excellent results in the addition to aldehydes **7** of dialkyllithium cuprates[4c,d] and in the $MgBr_2$-catalyzed addition of allyltributyltin.[9] The latter condensation, affording homoallylic alcohols **8a–e** in diastereoselectivities ranging from 83:17 to 87:13[10] (Scheme II), seemed particularly suited for the synthesis of fragment **3**, thanks to the synthetic equivalence of allylmetal compounds with acetaldehyde in aldol-type reactions.[11]

The relative configurations of major adducts **8a–e** were unambiguously established through conversion into cis isopropylidene derivatives **12a** and **13** and **14a** (for all compounds) or (only for **8d**) into trans derivatives **14b** and **12b** (Scheme II). These acetonides were recognized as such through $^1H$ and $^{13}C$ NMR analysis. For example in cis compounds $J_{4-5}$ ranged from 2.4 to 2.6 Hz, while $J_{5-6}$ were 1.6–1.7 and 2.6–2.7 Hz. These values suggest an equatorial disposition for the allyl group and an axial disposition for the $CH_2OR^2$ group. On the other hand, in trans compounds, $J_{4-5}$ were $\approx$ 10.0 Hz in both compounds, while $J_{5-6}$ were 5.0 and 10.2–10.5 Hz, suggesting an equatorial disposition for the $CH_2OR^2$ and the allyl groups. The $^{13}C$ NMR data ruled out the intervention of twist-like conformations, since the values for C-2 and for the two methyl groups bonded to it are well in agreement with chair-like conformations.[12,13] Moreover we have recently had the opportunity to compare the $^1H$ and $^{13}C$ NMR of several 4-substituted 5-(alkoxymethyl)-2,2-dimethyl-1,3-dioxanes bearing various protecting groups and found regular trends along the two diastereomeric series.[14] The values obtained for all acetonides shown in Scheme II are well in agreement with those trends.

Having now in hand a strategy for controlling the relative and absolute stereochemistry of allylation adducts, we applied this methodology for the synthesis of the bottom half fragment **3** of Talaromycin (Scheme III).

In this case we needed an (*S*)-BHYMA* **7d**, which was easily obtained from monoacetate **6** in 66% overall yield by the already reported procedure.[4e] This aldehyde was then allylated with allyltributyltin under the catalysis of $MgBr_2$ to give homoallylic alcohol (2*S*,3*S*)-**8d** as the main product in 87:13 diastereomeric ratio and in 84% overall yield. The absence of racemization during the allylation reaction was checked through Mosher's ester analysis of

(5) Although for the sake of brevity Scheme II shows only the *R* aldehydes **7a–e**, we have also prepared the enantiomeric *S* aldehydes **7a–e**.

(6) With the term "chelating protecting group" we mean a group which increases (or at least does not decrease) the Lewis basicity of oxygen, thus allowing, when other conditions are met, the establishment of a cyclic chelated transition state; on the contrary, with "nonchelating protecting group" we denote a group which sensibly decreases (or completely suppresses) the ability of oxygen to coordinate a Lewis acid. For a review on "chelation control" in addition to chiral aldehydes or ketones, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(7) (a) Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1987**, *28*, 5125. (b) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.

(8) The low tendency of silyl ethers to coordinate metal ions, both for electronic and steric reasons, is well-known. See: Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130 and references therein. Shambayati, S.; Blake, J. F.; Wiersche, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697, and references therein.

(9) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1991**, *32*, 6939–6942.

(10) Details on the results of additions of allyltributyltin as well as other allylmetal compounds to aldehydes **7a–e** have been already reported in ref 9. The characterizing data of compounds **8a–c** and **8e** can be found in the supplementary material.

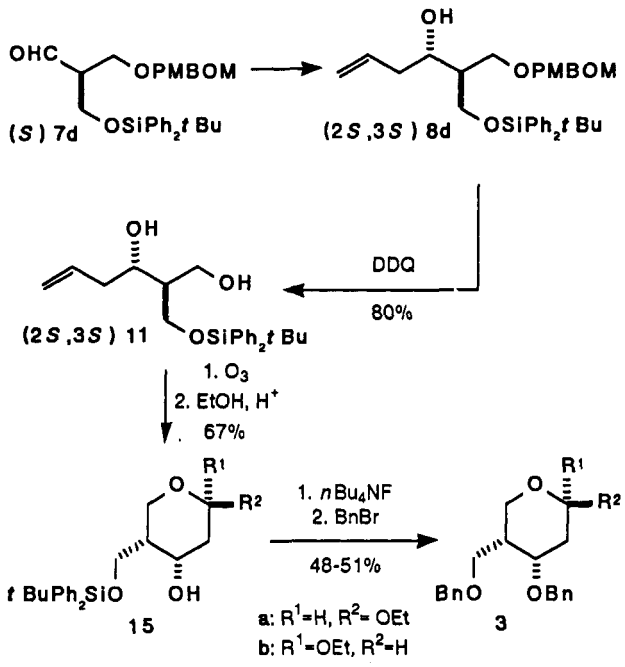
(11) Roush, W. R. Allyl Organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1–53.

(12) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(13) In **12a**, **13**, **14a**, **14b**, and **12a**, C-2 resonates at 98.76, 98.74, 98.76, 98.13, and 98.37 ppm, while the methyl groups resonate at 19.14 and 29.81, 19.13 and 29.80, 19.09 and 29.68, 19.41 and 29.32, 19.83 and 29.02 ppm. Twist conformations are expected to display resonances of 100.6 ± 0.25 ppm for C-2 and 24.6 ± 0.76 for both methyl groups (ref 12).

(14) Guanti, G.; Banfi, L.; Merlo, V.; Narisano, E.; Zannetti, M. T. To be published.

**Scheme III**




this adduct[15] which showed an ee > 95%. Oxidative deblocking of the ((*p*-methoxybenzyl)oxy)methyl group with buffered DDQ[7] furnished diol (2*S*,3*S*)-**11** in good yield. Ozonolysis of the double bond gave a 3,5-dihydroxy aldehyde which was directly transformed, under acidic conditions, into the two epimeric cyclic acetals **15a** and **15b** in a 55:45 ratio. Assignment of the relative configuration was based on the vicinal coupling constants at $^1$H NMR of **15a,b** and **3a,b**. The low stereoselection in acetal formation has no practical consequence on the synthesis, since the anomeric asymmetric center is lost in a later step.

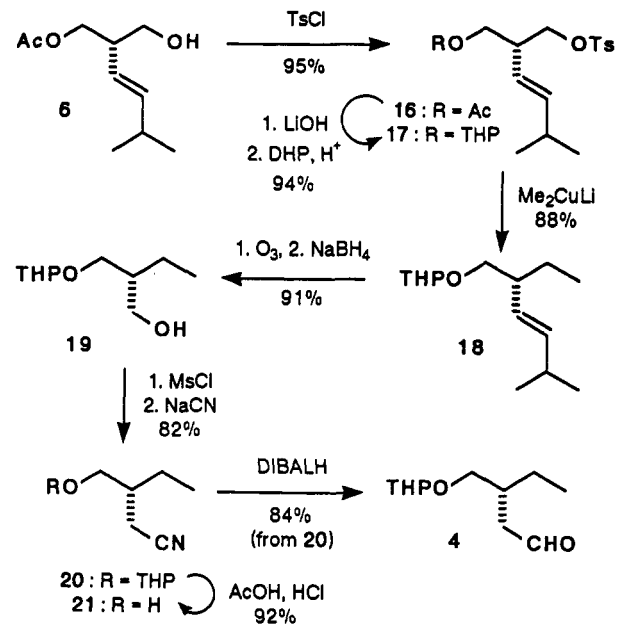
These two anomers were easily separated and independently converted into the corresponding dibenzyl derivatives **3a** and **3b**, which are known intermediates for the synthesis of Talaromycin A.[3c] Mori[3c] reported an $[\alpha]_D$ = −16.3° for a 37:63 mixture of **3a** (optically pure) and **3b** (43% ee). We measured −62.4° for **3a** and +11.8° for **3b** and estimated an ee of 97% by Mosher's ester analysis of **8d**.[15] From these values we calculated a theoretical $[\alpha]_D$ = −20.5° for Mori's mixture, which is in fair agreement with the reported value. It is worth noting that the completion of the synthesis of Talaromycin A by using Mori's methodology[3c] can probably be achieved without need to convert **15a,b** into **3a,b** by simply protecting the secondary hydroxyl with any suitable group. However we have not explored these possible alternatives.

The synthesis here reported appears to be superior to the previous one, since it requires a comparable number of steps, but proceeds in better overall yield (13% from monoacetate **6**, 10 steps) and, most of all, furnishes products with higher ee (Mori obtained **3a,b** in 64% overall ee).

It should be stressed that, thanks to the fact that in **8d** the two protected hydroxymethyl groups are synthetically equivalent, it is in principle possible, following a similar strategy, but reversing the order of protecting group removal,[4c] to obtain also the C-5 epimers of **3a,b**, which are potential intermediates for the synthesis of Talaromycin B. This fact descends from a peculiar property of BHYMA* and THYM* (*diastereodivergency*),[4c] which is further demonstrated by the synthesis of both **12a** and **12b** as well as **14a** and **14b** starting from a common precursor (**8d**) (Scheme II). Since starting BHYMA* aldehydes **7a–e** can also be prepared in both enantiomeric forms with the same number of steps from monoacetate **6**,[4e] all four stereoisomers of **12** or **14**, as well as of the anomeric mixture **3a,b**, can be stereoselectivity produced. Thus we can conclude that **6**, like other THYM* equivalents, is a *doubly stereodivergent chiral building block*.[4c]

(15) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. All Mosher's ester analyses were carried out synthesizing the two diastereomeric compounds using (*R*)- and (*S*)-MTPA-Cl ((methoxyphenyl)(trifluoromethyl)acetyl chlorides).

**Scheme IV**




**Synthesis of the Top Half Fragment 4.** Scheme IV shows the synthesis of the top fragment **4**. In this case we needed to homologate two of the three synthetically equivalent side arms. There are in principle at least 12 different ways to transform **6** into (*S*)- or (*R*)-**4**, 6 of which will lead to the desired *R* enantiomer.[16] Among these possibilities we chose the one which appeared to require the lower number of steps. For this purpose we converted monoacetate **6** into tosylate **16**. Attempts to carry out a cross-coupling condensation with dimethyllithium cuprate at this stage failed, due to side reactions involving the acetyl group. Thus we transformed **16**, in excellent yield, into the tetrahydropyranyl ether **17**,[17] whose condensation with $Me_2CuLi$[18] proceeded smoothly to give the homologated alkene **18**. Ozonolysis–reduction afforded **19**, which was ready for the second homologation.

This was realized, after activation of the OH group by conversion into a mesylate, via substitution with sodium cyanide. Our attempts to carry out a cross-coupling

(16) **6** has three synthetically equivalent side arms, in any of which the OH can be substituted by the methyl group. Then each of the remaining 2 OH groups can be substituted by a formylanion equivalent, giving a total of six possibilities. Reversing the order of introduction of formyl and methyl group, six more chances can be devised.

(17) **17** was obtained as a 1:1 mixture of epimers at the THP asymmetric center.

(18) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777–7782, 7783–7788. Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 3999–4000. Johnson, C. R.; Senanayake, C. H. *J. Org. Chem.* **1989**, *54*, 735–736. Mori, K.; Ebata, T.; Takechi, S. *Tetrahedron* **1984**, *40*, 1761–1766. Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831–5833.

between the tosylate derived from **19** (TsCl, $CH_2Cl_2$, $Et_3N$, rt 75%) and lithium divinyl cuprate gave only poor yields (20–25%) of the desired vinyl derivative. The main byproduct turned out to be alcohol **19**, probably arising from attack of the cuprate on the sulfur atom rather than on carbon. This result is in contrast with the known tendency of lithium *dialkyl* cuprates to attack cleanly at carbon in reaction with alkanesulfonates.[18] A similar behavior was detected by complexing the cuprate with $Me_2S$, while using the higher order cuprate $(CH_2{=}CH)$-(thienyl)$CuCNLi_2$[19] or $(CH_2{=}CH)MgBr$ in the presence of catalytic CuI no reaction took place.

Finally, DIBALH reduction of nitrile **20** furnished aldehyde **4**, whose $[\alpha]_D$ (+24.1°), by comparison with the value previously reported by Mori (+25.2°),[3c] indicated an optical purity of 96%. In order to gain further evidence that the overall procedure was nonracemizing, we also prepared alcohol **21** and determined its ee by Mosher's ester analysis, measuring a value of 95%. The overall yield of **4** from **6** (8 steps) was an excellent 49%.

In conclusion we have further demonstrated that "asymmetrized tris(hydroxymethyl)methane" equivalents represent highly versatile chiral building blocks, thanks to the many possible elaborations of the three synthetically equivalent protected hydroxymethyl groups. In this context we employed a stereoselective organometallic addition to its oxidized form (BHYMA* aldehyde **7**) and two homologations via substitution of the OH group with carbon nucleophiles, in order to realize an efficient and convergent synthesis of (−)-Talaromycin A. Studies aimed to further applications of **5** (THYM*) to the synthesis of other biologically active substances are in progress in our laboratories.

## Experimental Section

In NMR spectra, an asterisk (*) means that the value was obtained through double resonance experiments. All NMR were measured in $CDCl_3$ at 200 MHz (H) or 50 MHz (C) in ppm ($\delta$ scale). Attribution of $^{13}C$ signals was made also with the aid of DEPT and HETCOR experiments. All reactions employing dry solvents were carried out under a nitrogen atmosphere.

TLC analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in $H_2SO_4$ (31 cm$^3$) and $H_2O$ (469 cm$^3$) and warming. $R_f$ were measured after an elution of 7–9 cm. Chromatographies were carried out on 70–230-mesh silica gel using the "flash" methodology.[20] Petroleum ether (40–60 °C) is abbreviated as PE. In extractive workup aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were dried over $Na_2SO_4$ and filtered before evaporation of the solvent under reduced pressure. Preparation of aldehydes **7** and of monoacetate **6** is described in ref 4e.

**(2*S*,3*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-((((*p*-methoxybenzyl)oxy)methoxy)methyl)hex-5-en-3-ol (8d).** A solution of crude aldehyde (*S*)-**7d** [538 mg, just obtained from ozonolysis of 1.09 mmol of the corresponding alkene (see ref 4e)] in dry $CH_2Cl_2$ (4 mL) was treated with powdered 4-Å molecular sieves (100 mg) and stirred at rt for 15 min. The resulting suspension was then added via syringe (washing the flask twice with 2 mL of $CH_2Cl_2$) to a suspension of $MgBr_2{\cdot}Et_2O$ (564 mg, 2.18 mmol) in dry $CH_2Cl_2$ (6 mL), precooled to −78 °C. After 5 min, a 1 M solution of allyltributyltin in $CH_2Cl_2$ (2.18 mmol, 2.18 mL) was added. After the mixture was stirred for 3 h at −78 °C, the temperature was allowed to rise slowly (during 1 h) to −40 °C, and the mixture was stirred overnight. After further stirring for 3 h at −20 °C, the reaction was quenched with 0.5 N pH 7 $KH_2PO_4/K_2HPO_4$ buffer (10 mL), stirred at rt for 15 min, and extracted with $Et_2O$, to give, after chromatography (PE/$Et_2O$ (7:3)), pure (2*S*,3*S*)-**8d** as an oil (426 mg, 73%). Anal. Found: C, 71.70; H, 8.05. $C_{32}H_{42}O_5Si$ requires C, 71.87; H, 7.92. $[\alpha]_D$ = −4.75° (*c* 2.21, $CHCl_3$). $R_f$ = 0.21 (PE/$Et_2O$ (7:3); $R_f$ of (2*S*,3*R*) epimer = 0.27). $^1H$ NMR: $\delta$ 1.06 (9 H, s, $(CH_3)_3CSi$), 1.89 (1 H, sextuplet, $CHCH_2O$, $J$ = 5.1 Hz), 2.31 (2 H, bt, $C{=}CHCH_2$, $J$ = 6.8 Hz), 3.06 (1 H, d, OH, $J$ = 4.6 Hz), 3.80 (3 H, s, $OCH_3$), 3.77–4.00 (5 H, m, $CHCH_2O$ and $CHOH$), 4.48 (2 H, s, $OCH_2Ar$), 4.67 (2 H, s, $OCH_2O$), 5.00–5.16 (2 H, m, $CH_2{=}CHCH_2$), 5.84 (1 H, ddt, $CH_2{=}CH$, $J$ = 7.0 (t), 9.6 (d), 17.6 (d) Hz), 6.86 (2 H, d, H ortho to $OCH_3$, $J$ = 8.7 Hz), 7.23 (2 H, d, H meta to $OCH_3$, $J$ = 8.7 Hz), 7.30–7.70 (10 H, m, other aromatics). The diastereomeric ratio was determined by $^1H$ NMR of crude product, by integration of the OH signals (which falls at higher fields in the major diastereoisomer). This measurement was further corroborated by $^1H$ NMR in the presence of $Yb(FOD)_3$, by integrating the signals of $CH_3OAr$ protons.

**(2*S*,3*R*)-2-(((Benzyloxy)methoxy)methyl)hex-5-ene-1,3-diol (9).** A solution of (2*R*,3*R*)-**8b** (110 mg, 0.218 mmol) in dry THF (5 mL) was treated with a 1 M solution of $n$-$Bu_4NF{\cdot}3H_2O$ in THF (0.654 mL) and stirred at rt for 3 h. The solution was diluted with saturated aqueous NaCl and extracted with $Et_2O$ to give, after chromatography (PE/$Et_2O$ (1:9)), diol **9** as an oil (46.1 mg, 79%). By the same procedure **9** was also prepared from **8a** in 77% yield. $R_f$ = 0.29 (PE/$Et_2O$ (1:9)). $^1H$ NMR: $\delta$ 1.89 (1 H, sextuplet, $CHCH_2O$, $J$ = 5.2 Hz), 2.20–2.42 (3 H, m, $CHCH_2OH$ and $C{=}CCH_2$), 2.48 (1 H, d, $CHOH$, $J$ = 4.7 Hz), 3.75–4.00 (5 H, m, $CHOH$, $CH_2O$, and $CH_2OH$), 4.62 (2 H, s, $OCH_2Ph$), 4.78 (2 H, s, $OCH_2O$), 5.10–5.20 (2 H, m, $CH_2{=}CCH_2$, $\nu_a$ and $\nu_b$ 5.14* and 5.15*), 5.84 (1 H, ddt, $CH_2{=}CH$, $J$ = 7.0 (t), 9.7 (d), and 17.6 (d) Hz), 7.35 (5 H, s, aromatics).

**(2*S*,3*R*)-2-((((4-Methoxybenzyl)oxy)methoxy)methyl)-hex-5-ene-1,3-diol (10).** It was prepared in 94%, 92%, 83% yield from **8c–e** by the same procedure employed for **9**. $R_f$ = 0.25 (PE/$Et_2O$ (1:9)).

**(2*S*,3*S*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hex-5-ene-1,3-diol (11).** A solution of (2*S*,3*S*)-**8d** (514 mg, 0.962 mmol) in $CH_2Cl_2$ (14 mL) was treated with a 0.2 M pH 7 buffer solution ($KH_2PO_4$–$K_2HPO_4$) (1.4 mL), with *t*-BuOH (1.4 mL) and with DDQ (436 mg, 1.924 mmol). The mixture was stirred for 3 h at rt, quenched with saturated aqueous $NaHCO_3$, filtered through a Celite cake, and extracted with $Et_2O$ to give, after chromatography, pure (2*S*,3*S*)-**11** (296 mg, 80%), $R_f$ = 0.22 (PE/$Et_2O$ (1:1)). $^1H$ NMR: $\delta$ 1.06 (9 H, s, $(CH_3)_3C$), 1.74 (1 H, sextuplet, $CHCH_2OH$, $J$ = 5.2 Hz), 2.10–2.40 (2 H, m, $CH_2CH{=}CH_2$), 2.50–2.75 (2 H, m, OH), 3.82 and 3.85 (2 H, AB part of an ABX syst, $CH_2OSi$, $J_{AB}$ = 10.4, $J_{AX}$ and $J_{BX}$ = 4.8 and 5.8 Hz), 3.89–4.02 (3 H, broad m, $CHOH$ and $CH_2OH$), 5.02–5.18 (2 H, m, $CH_2{=}CH$), 5.66–5.92 (1 H, m, $CH_2{=}CH$ mc 5.79 ppm), 7.30–7.50 (6 H, m, aromatics), 7.60–7.80 (4 H, m, aromatics). This reaction was also carried out on 2*R*,3*R* compound. These products were not further characterized, but directly converted respectively into **15a,b** or into (4*R*,5*R*)-**14b** (vide infra).

**(4*R*,5*R*)-*cis*-4-Allyl-5-(((benzyloxy)methoxy)methyl)-2,2-dimethyl-1,3-dioxane (12a).** A solution of (2*S*,3*R*)-**9** (53 mg, 0.199 mmol) in dry $CH_2Cl_2$ (5 mL), cooled to 0 °C, was treated with 2-methoxypropene (0.057 mL, 0.60 mmol) and with *p*-toluenesulfonic acid hydrate (0.040 mL of a 0.1 M solution in THF). The solution was warmed to rt and stirred for 10 min. After addition of $Et_3N$ (0.5 mL) and evaporation, the residue was directly chromatographed via preparative TLC (PE/$Et_2O$ (8:2)) to give **12a** as an oil (48 mg, 79%). Anal. Found: C, 70.75; H, 8.70. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55. $[\alpha]_D$ = −7.8° (*c* 1.74, $CHCl_3$). $R_f$ = 0.42 (PE/$Et_2O$ (8:2)). $^1H$ NMR: $\delta$ 1.39 and 1.46 (2 × 3 H, $H_3CCCH_3$), 1.65 (1 H, ddq (apparent decuplet), $CHCH_2$-OBOM, $J \approx$ 2.4 (q), 4.8 (d), and 9.6 (d) Hz), 2.06–2.39 (2 H, m, $CH_2CH{=}CH_2$), 3.78 and 3.92 (2 H, AB part of an ABX syst, $CH_2OBOM$, $J_{ab}$ = 9.5, $J_{ax}$ and $J_{bx}$ = 9.6 and 4.9 Hz), 3.98 and 4.03 (2 H, AB part of an ABX syst, $CH_2OC(Me)_2$, $J_{ab}$ = 11.8, $J_{ax}$ and $J_{bx}$ = 1.7 and 2.8 Hz), 4.07 (1 H, dt, CHO, $J_{4\text{-}5}$ = 2.6, $J_{4\text{-}4'}$ = 7.2 Hz), 4.59 and 4.62 (2 H, AB syst, $CH_2Ph$, $J$ = 11.7 Hz), 4.79 (2 H, s, $OCH_2O$), 5.02–5.20 (2 H, m, $CH_2{=}CHCH_2$, $\nu_a$ and $\nu_b$ = 5.07* and 5.18*, $J_{ab}$ = 2.0*, $J_{ax}$ and $J_{bx}$ = 10.0* and 17.3* Hz), 5.79 (1 H, dddd, $CH_2{=}CH$, $J$ = 6.2, 7.5, 10.0, 17.3 Hz), 7.25–7.40 (5 H, m, aromatics). $^{13}C$ NMR: $\delta$ 19.14 and 29.81 ($CH_3$), 37.05 ($CHCH_2$-

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OBOM), 37.25 ($CH_2CH=CH_2$), 61.87 (C-6 or C-5'), 63.37 (C-5' or C-6), 69.40 ($OCH_2Ph$), 70.57 (C-4), 94.84 ($OCH_2O$), 98.76 (C-2), 117.02 ($CH_2=C$), 127.53, 127.84, and 128.25 (aromatic CH), 134.07 ($CH_2=CH$), 137.79 (aromatic C).

**(4*R*,5*R*)-*cis*-4-Allyl-5-((((4-methoxybenzyl)oxy)methoxy)methyl)-2,2-dimethyl-1,3-dioxane (13).** It was prepared from (2*S*,3*R*)-**10** in 88% yield, using the same procedure employed for **12a**. Anal. Found: C, 67.80; H, 8.45. $C_{19}H_{28}O_5$ requires C 67.83; H, 8.39. $[\alpha]_D = -8.5°$ (*c* 2.5, $CHCl_3$). $R_f = 0.22$ (PE/$Et_2O$ (8:2)). $^1H$ NMR: δ 1.39 and 1.46 (2 × 3 H, $H_3CCCH_3$), 1.66 (1 H, ddq (apparent decuplet), $CHCH_2OPMBOM$, $J \approx 2.4$ (q), 4.8 (d), and 9.6 (d) Hz), 2.05–2.35 (2 H, m, $CH_2CH=CH_2$), 3.80 (3 H, s, $CH_3O$), 3.76 and 3.91 (2 H, AB part of an ABX syst, $CH_2OPMBOM$, $J_{ab}$ = 9.5, $J_{ax}$ and $J_{bx}$ = 9.6 and 4.7 Hz), 3.98 and 4.03 (2 H, AB part of an ABX syst, $CH_2OC(Me)_2$, $J_{ab}$ = 11.4, $J_{ax}$ and $J_{bx}$ = 1.6 and 2.7 Hz), 4.07 (1 H, dt, CHO, $J_{4-5}$ = 2.4 Hz*), 4.51 and 4.55 (2 H, AB syst, $CH_2Ar$, $J$ = 11.3 Hz), 4.76 (2 H, s, $OCH_2O$), 4.96–5.20 (2 H, m, $CH_2=CHCH_2$, $\nu_a$ and $\nu_b$ = 5.08* and 5.13*, $J_{ab}$ = 2.0*, $J_{ax}$ and $J_{bx}$ = 10.0* and 17.3* Hz), 5.80 (1 H, dddd, $CH_2=CH$, $J$ = 6.2, 7.4, 10.0, and 17.3 Hz), 6.88 (2 H, d, H ortho to OMe, $J$ = 8.7 Hz), 7.29 (2 H, d, H meta to OMe, $J$ = 8.7 Hz). $^{13}C$ NMR: δ 19.13 and 29.80 ($CH_3$), 37.05 ($CHCH_2OPMBOM$), 37.24 ($CH_2CH=CH_2$), 55.31 ($OCH_3$), 61.85 (C-5'), 63.28 (C-6), 69.00 ($OCH_2Ar$), 70.57 (C-4), 94.54 ($OCH_2O$), 98.74 (C-2), 116.99 ($CH_2=C$), 113.72 and 129.46 (aromatic CH), 129.88 (aromatic C), 134.08 ($CH_2=CH$), 159.06 (aromatic C).

**(4*R*,5*S*)-*cis*-4-Allyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxane (14a).** A solution of **13** (50.6 mg, 0.150 mmol) in $CH_2Cl_2$ (2 mL) was treated with a 0.2 M pH 7 buffer solution ($KH_2PO_4$–$K_2HPO_4$) (0.2 mL), with *t*-BuOH (0.02 mL), and with DDQ (68.3 mg, 0.301 mmol). The mixture was stirred for 4 h at rt, quenched with saturated aqueous $NaHCO_3$, filtered through a Celite cake, and extracted with $Et_2O$ to give, after chromatography, pure (4*R*,5*R*)-4-allyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane as an oil (17.4 mg, 62%). $R_f$ = 0.22 (PE/$Et_2O$ (2:8)). It was taken up in dry DMF (1 mL) and treated at 0 °C with imidazole (14.4 mg, 0.211 mmol), and $Ph_2t$-BuSiCl (0.027 mL, 0.106 mmol). After stirring for 3 h at rt, the mixture was treated with $H_2O$ and extracted with $Et_2O$/PE to give, after preparative TLC (PE/$Et_2O$ (95:5)), pure **14a** as an oil (32.5 mg, 82%). Anal. Found: C, 73.35; H, 8.60. $C_{26}H_{36}O_3Si$ requires C, 73.54; H, 8.54. $R_f$ = 0.50 (PE/$Et_2O$ (9:1)). $^1H$ NMR: δ 1.04 (9 H, s, $(CH_3)_3C$), 1.35 and 1.45 (2 × 3 H, 2 s, $(CH_3)_2C$), 1.50–1.68 (1 H, m, $CHCH_2O$, mc 1.58), 1.87–2.23 (2 H, m, $CH_2CH=CH_2$), 3.79 and 4.04 (2 H, AB part of an ABX syst, $CH_2OSi$, $J_{ab}$ = 10.0 Hz, $J_{5-5'}$ = 5.1 and 10.0 Hz), 3.96 and 4.24 (2 H, AB part of an ABX syst, $CH_2OC(Me)_2$, $J_{ab}$ = 11.6 Hz, $J_{5-6}$ = 1.6 and 2.6 Hz), 4.02 (1 H, dt, *CH*O, $J$ = 2.6 (d) and 7.2 (t) Hz), 4.88–5.04 (2 H, m, $C=CH_2$), 5.50–5.74 (1 H, m, $CH=CH_2$), 7.30–7.50 (6 H, m, aromatics), 7.60–7.80 (4 H, m, aromatics). $^{13}C$ NMR: δ 19.27 ($C(CH_3)_3$), 19.09 and 29.68 ($(CH_3)_2C$), 26.94 ($(CH_3)_3C$), 37.01 ($CH_2CH=CH_2$), 39.19 (C-5), 59.08 and 61.32 (C-6 and C-5'), 70.68 (C-4), 98.76 (C-2), 116.88 ($CH_2=CH$), 127.66 (aromatic CH ortho to Si), 129.59 (aromatic CH para to Si), 133.77 and 134.06 (aromatic C), 134.32 ($CH=CH_2$), 135.64 and 135.72 (aromatic CH meta to Si).

**(4*R*,5*R*)-*trans*-4-Allyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxane (14b).** It was prepared from (2*R*,3*R*)-**11** by the same procedure utilized for the synthesis of **12a**. Anal. Found: C, 73.45; H, 8.55. $C_{26}H_{36}O_3Si$ requires C, 73.54; H, 8.54. $[\alpha]_D = +7.0°$ (*c* = 2.6, $CHCl_3$). $R_f$ = 0.37 (PE/$Et_2O$ (9:1)). $^1H$ NMR: δ 1.06 (9 H, s, $(CH_3)_3C$), 1.40 and 1.45 (2 × 3 H, 2 s, $(CH_3)_2C$), 1.83 (1 H, tq (apparent octuplet), $CHCH_2O$, $J \approx 5.0$ (q) and $\approx 10.0$ Hz (t)), 2.00–2.40 (2 H, m, $CH_2CH=CH_2$, $\nu_a$ and $\nu_b$ = 2.11* and 2.30*, $J_{ab}$ = 14.8*, $J_{4-4'}$ = 3.3* and 7.3* Hz), 3.57 (2 H, d, $CH_2OSi$, $J$ = 4.9 Hz), 3.89 and 3.93 (2 H, AB part of an ABX syst, $CH_2OC(Me)_2$, $J_{ab}$ = 11.8 Hz, $J_{5-6}$ = 5.0 and 10.5 Hz), 3.75–3.95 (1 H, m, CHO), 4.91–5.07 (2 H, m, $CH=CH_2$, $\nu_a$ and $\nu_b$ = 4.97* and 5.01*, $J_{ab}$ = 2.1*, $J_{ax}$ and $J_{bx}$ = 10.5* and 17.0* Hz), 5.86 (1 H, ddt, $CH_2=CH$, $J$ = 6.9 (t), 10.7 (d), and 16.8 (d) Hz), 7.35–7.50 (6 H, m, aromatics), 7.60–7.70 (4 H, m, aromatics). $^{13}C$ NMR: δ 19.79 ($C(CH_3)_3$), 19.41 and 29.32 ($(CH_3)_2C$), 26.96 ($(CH_3)_3C$), 37.92 ($CH_2CH=CH_2$), 41.16 (C-5), 62.09 (C-6 and C-5'), 69.87 (C-4), 98.13 (C-2), 116.39 ($CH_2=CH$), 127.62 (aromatic CH ortho to Si), 129.66 (aromatic CH para to Si), 133.07 and 133.14 (aromatic C), 134.57 ($CH=CH_2$), 135.43 (aromatic CH meta to Si).

**(4*R*,5*S*)-*trans*-4-Allyl-5-(((benzyloxy)methoxy)methyl)-2,2-dimethyl-1,3-dioxane (12b).** A solution of (4*R*,5*R*)-**14b** (54 mg, 0.127 mmol) in dry THF (3 mL) was treated with a 1 M solution of *n*-$Bu_4NF{\cdot}3H_2O$ in THF (0.381 mL, 0.381 mmol) and stirred at rt for 3 h. After dilution with $H_2O$/saturated aqueous NaCl, 1:1, the mixture was extracted with $Et_2O$ to give, after chromatography (PE/$Et_2O$ (1:9)) (4*R*,5*S*)-4-allyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane as an oil (18.5 mg, 78%). $R_f$ = 0.49 (PE/$Et_2O$ (1:9)). This compound was taken up in dry $CH_2Cl_2$, cooled to 0 °C, and treated with $EtN(i\text{-}Pr)_2$ (0.027 mL, 0.155 mmol) and with BOM-Cl (0.019 mL, 0.137 mmol). The solution was warmed to rt and stirred for 24 h. It was treated with $Et_2NH$ (0.007 mL), stirred for 20 min, diluted with saturated aqueous NaCl, extracted with $Et_2O$ to give, after preparative TLC, **12b** as an oil (25 mg, 81%). Anal. Found: C, 70.45; H, 8.60. $C_{18}H_{26}O_4$ requires C, 70.56; H, 8.55. $R_f$ = 0.42 (PE/$Et_2O$ (8:2)). $^1H$ NMR: δ 1.39 and 1.43 (2 × 3 H, $H_3CCCH_3$), 1.91 (1 H, tq (apparent octuplet), $CHCH_2OBOM$, $J \approx 5.0$ (q) and $\approx 10.0$ (t) Hz), 2.12–2.49 (2 H, m, $CH_2CH=CH_2$), 3.48 (2 H, d, $CH_2OBOM$, $J$ = 5.8 Hz), 3.77 and 3.84 (2 H, AB part of an ABX syst, $CH_2OC(Me)_2$, $J_{ab}$ = 11.4, $J_{ax}$ and $J_{bx}$ = 5.0 and 10.2 Hz), 3.69–3.92 (1 H, m, CHO), 4.58 (2 H, s, $CH_2Ph$), 4.70 (2 H, s, $OCH_2O$), 4.91–5.17 (2 H, m, $CH=CHCH_2$), 5.89 (1 H, ddt, $CH_2=CH$, $J$ = 7.0 (t), 10.7 (d), and 16.8 (d) Hz), 7.34 (5 H, s, aromatics). $^{13}C$ NMR: δ 19.83 and 29.02 ($CH_3$), 38.02 ($CH_2CH=CH_2$), 39.42 ($CHCH_2OBOM$), 62.06 (C-6), 66.31 (C-5'), 69.67 ($OCH_2Ph$), 70.21 (C-4), 94.94 ($OCH_2O$), 98.37 (C-2), 116.58 ($CH_2=C$), 127.77, 127.83, and 128.47 (aromatic CH), 134.72 ($CH_2=CH$), 137.86 (aromatic C).

**(2*R*,4*S*,5*S*)- and (2*S*,4*S*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-ethoxy-4-hydroxytetrahydropyrans (15a and 15b).** A solution of (2*S*,3*S*)-**11** (296 mg, 0.770 mmol) in dry $CH_2Cl_2$ (4 mL) and dry MeOH (7 mL) was ozonolyzed at −78 °C until the blue-gray coloration persisted. After addition of dimethyl sulfide (0.4 mL), the solution was stirred at rt for 2 h, evaporated to dryness, and stripped for 2 h at $10^{-2}$ mbar. The oily residue was taken up in dry EtOH (10 mL), treated with powdered 4-Å molecular sieves (100 mg) and with a 1 M solution of *p*-toluenesulfonic acid hydrate in absolute EtOH (0.4 mL), and stirred at rt for 3 h. The reaction was quenched with solid $NaHCO_3$ (100 mg) and filtered. After evaporation of the solvent, chromatography (PE/$Et_2O$ (8:2 → 7:3)) gave pure **15a** (118 mg, 37%) and **15b** (96 mg, 30%).

**15a.** Anal. Found: C, 69.50; H, 8.30. $C_{24}H_{34}O_4Si$ requires: C, 69.53; H, 8.27. $[\alpha]_D = -37.6°$ (*c* 2.88, $CHCl_3$). $R_f$ = 0.42 (PE/$Et_2O$ (1:1)). $^1H$ NMR: δ 1.06 (9 H, s, $SiC(CH_3)_3$), 1.22 (3 H, t, $CH_3CH_2O$, $J$ = 7.1 Hz), 1.73 (1 H, ddd, $HOCHCHCHOEt$, $J$ = 3.4, 6.8, and 13.3 Hz), 1.95 (1 H, ddd, $HOCHCHCHOEt$, $J$ = 2.8, 6.3, and 13.4 Hz), 1.91–2.06 (1 H, m, $SiOCH_2CHCHOH$), 3.50 (1 H, dq, $OCHHCH_3$, $J$ = 7.1 (q) and 10.1 (d) Hz), 3.81 (1 H, dq, $OCHHCH_3$, $J$ = 7.1 (q) and 10.1 (d) Hz), 3.80 and 3.74 (2 H, AB part of an ABX syst, $CHCH_2OC$, $J_{ab}$ = 10.0, $J_{ax}$ and $J_{bx}$ = 6.6 and 2.6 Hz), 3.86 (2 H, d, $CH_2OSi$, $J$ = 5.14 Hz), 4.37 (1 H, dt, *CH*OH, $J$ = 3.3 (t) and 6.3 (d) Hz), 4.85 (1 H, dd, *CH*OEt, $J$ = 2.8 and 6.8 Hz), 7.35–7.50 (6 H, m, aromatics), 7.60–7.70 (4 H, m, aromatics). $^{13}C$ NMR: δ 15.38 ($CH_3CH_2O$), 19.21 ($Me_3C$), 26.92 ($(CH_3)_3C$), 37.85 ($CH_2CHOH$), 41.37 ($CHCH_2OSi$), 61.84 ($OCH_2CH_3$), 63.78 and 63.88 ($CH_2OSi$ and $CH_2OCH(OEt)$), 67.44 (*C*HOH), 97.86 (O*C*H(OEt)), 127.73 (Ar*C*H ortho to Si), 129.86 (Ar*C*H para to Si), 132.39 (Ar*C*), 135.38 (Ar*C*H meta to Si).

**15b.** Anal. Found: C, 69.40; H, 8.35. $C_{24}H_{34}O_4Si$ requires: C, 69.53; H, 8.27. $[\alpha]_D = +56.15°$ (*c* 2.88, $CHCl_3$). $R_f$ = 0.64 (PE/$Et_2O$ (1:1)). $^1H$ NMR: δ 1.05 (9 H, s, $SiC(CH_3)_3$), 1.22 (3 H, t, $CH_3CH_2O$, $J$ = 7.1 Hz), 1.84 (1 H, dt, $HOCHCHCHOEt$, $J$ = 3.4 (t) and 14.2 (d) Hz), 1.98 (1 H, ddd, $HOCHCHCHOEt$, $J$ = 1.7, 3.4 and 14.4 Hz), 2.05 (1 H, ddq, $SiOCH_2CHCHOH$, $J$ = 2.7 (d), 7.0 (d), and 8.3 (q) Hz), 3.43 (1 H, dq, $OCHHCH_3$, $J$ = 7.05 (q) and 9.7 (d) Hz), 3.78 (1 H, dq, $OCHHCH_3$, $J$ = 7.0 (q) and 9.0 (d) Hz), 3.77 and 3.61 (2 H, AB part of an ABX syst, $CHCH_2OC$, $J_{ab}$ = 10.2, $J_{ax}$ and $J_{bx}$ = 6.3 and 7.9 Hz), 3.69 (2 H, d, $CH_2OSi$, $J$ = 8.1 Hz), 3.90–4.00 (1 H, m, *CH*OH), 4.87–4.94 (1 H, m, *CH*OEt), 7.35–7.50 (6 H, m, aromatics), 7.60–7.70 (4 H, m, aromatics). $^{13}C$ NMR: δ 15.29 ($CH_3CH_2O$), 19.38 ($(Me)_3C$), 26.98

((*C*H$_3$)$_3$C), 36.06 (*C*H$_2$CHOH), 42.85 (CHCH$_2$OSi), 57.51 (O*C*H$_2$CH$_3$), 63.26 (*C*H$_2$OSi and *C*H$_2$OCH(OEt)), 64.70 (*C*HOH), 97.43 (O*C*H(OEt)), 127.51 (Ar*C*H ortho to Si), 129.47 (Ar*C*H para to Si), 133.46 (Ar*C*), 135.41 (Ar*C*H meta to Si).

**(2*R*,4*S*,5*R*)-4-(Benzyloxy)-5-((benzyloxy)methyl)-2-ethoxytetrahydropyran (3a).** A solution of **15a** (98 mg, 0.236 mmol) in dry THF (5 mL) was treated with a 1 M solution of *n*-Bu$_4$NF·3H$_2$O in THF (0.709 mL) and stirred at rt for 3 h. The mixture was diluted with saturated aqueous NaCl/H$_2$O, 1:1, and extracted with Et$_2$O to give, after chromatography (PE/AcOEt/MeOH (19:76:5)) pure 2-ethoxy-5-(hydroxymethyl)tetrahydropyran-4-ol (35.4 mg) ($R_f$ = 0.35, PE/AcOEt/MeOH (19:76:5)) as an oil. It was taken up in dry DMF (1 mL), cooled to 0 °C, and treated sequentially with benzyl bromide (0.071 mL, 0.60 mmol) and NaH (50% suspension in mineral oil, 29 mg, 0.6 mmol). The mixture was stirred overnight at rt, quenched with saturated aqueous NH$_4$Cl/H$_2$O, 1:1, and extracted with Et$_2$O to give, after chromatography (PE/Et$_2$O (7:3)), pure **3a** as an oil (43 mg, 51% from **15a**). Anal. Found: C, 74.00; H, 8.00. $C_{22}H_{28}O_4$ requires C, 74.14; H, 7.92. $[\alpha]_D$ = −62.4° (*c* 0.95, CHCl$_3$). $R_f$ = 0.50 (PE/Et$_2$O (7:3)). $^1$H NMR: $\delta$ 1.22 (3 H, t, C*H*$_3$CH$_2$O, *J* = 7.1 Hz), 1.73 (1 H, dt, BzlOCHC*H*CHOEt, *J* = 4.7 (t) and 13.3 (d) Hz), 1.92 (1 H, ddd, BzlOCHC*H*CHOEt, *J* = 3.1, 7.8, and 13.3 Hz), 2.15–2.33 (1 H, m, BzlOCH$_2$C*H*CHOBzl), 3.46 (1 H, dq, OC*H*HCH$_3$, *J* = 7.1 (q) and 9.7 (d) Hz), 3.62 and 3.58 (2 H, AB part of an ABX syst, CHC*H*$_2$OC or C*H*$_2$OBzl, $J_{ab}$ = 9.1, $J_{ax}$ and $J_{bx}$ = 5.4 and 8.6 Hz), 3.79 and 3.80 (2 H, AB part of an ABX syst, CHC*H*$_2$OC or C*H*$_2$OBzl, $J_{ab}$ = 9.1, $J_{ax}$ + $J_{bx}$ = 9.8 Hz), 3.81 (1 H, dq, OC*H*CH$_3$, *J* = 7.1 (q) and 9.7 (d) Hz), 4.01 (1 H, dt, C*H*OBzl, *J* = 3.9 (t) and 7.7 (d) Hz), 4.50 and 4.55 (2 H, AB syst, OC*H*$_2$Ph, *J* = 11.6 Hz), 4.51 (2 H, s, OC*H*$_2$Ph), 4.83 (1 H, dd, C*H*OEt, *J* = 3.1 and 5.3 Hz), 7.25–7.40 (10 H, m, aromatics). $^{13}$C NMR: $\delta$ 15.19 (*C*H$_3$CH$_2$O), 33.96 (*C*H$_2$CHOBzl), 39.62 (*C*HCH$_2$OBzl), 61.14 (*C*H$_2$OBzl or *C*H$_2$OCH(OEt)), 63.43 (*C*H$_2$CH$_3$), 66.61 (*C*H$_2$OBzl or *C*H$_2$OCH(OEt)), 70.45 (*C*H$_2$Ph), 72.22 (*C*HOBzl), 73.32 (*C*H$_2$Ph), 97.92 (O*C*H(OEt)), 128.363, 127.629, and 127.524 (aromatic CH), 138.55 and 138.46 (aromatic C).

**(2*S*,4*S*,5*R*)-4-(Benzyloxy)-5-((benzyloxy)methyl)-2-ethoxytetrahydropyran (3b).** It was prepared from **15b** in 48% yield by the same procedure employed for **3a**. Found: C, 74.05; H, 8.00. $C_{22}H_{28}O_4$ requires C, 74.14; H, 7.92. $[\alpha]_D$ = +11.8° (*c* 0.55, CHCl$_3$). $R_f$ = 0.47 (PE/Et$_2$O (7:3)). $^1$H NMR: $\delta$ 1.23 (3 H, t, C*H*$_3$CH$_2$O, *J* = 7.1 Hz), 1.72 (1 H, ddd, BzlOCHC*H*CHOEt, *J* = 7.1, 9.4, and 13.2 Hz), 1.94 (1 H, dt, BzlOCHC*H*CHOEt, *J* = 3.6 (t) and 13.2 (d) Hz), 2.15–2.30 (1 H, m, BzlOCH$_2$C*H*CHOBzl), 3.38 (1 H, dd, CHC*H*$_2$OC or C*H*$_2$OBzl, *J* = 7.0 Hz), 3.48 (1 H, dq, OC*H*CH$_3$, *J* = 7.1 (q) and 9.7 (d) Hz), 3.68 (2 H, d, CHC*H*$_2$OC or C*H*$_2$OBzl, *J* = 7.0 Hz), 3.73 (1 H, dt, C*H*OBzl, *J* = 4.6 (t) and 9.4 (d) Hz), 3.89 (1 H, dq, OC*H*CH$_3$, *J* = 7.1 (q) and 9.7 (d) Hz), 4.18 (1 H, dd, C*H*$_2$CHOEt, *J* = 4.5 and 11.8 Hz), 4.47 (1 H, dq, C*H*OEt, *J* = 3.0 and 7.1 Hz), 4.56 and 4.49 (2 H, AB syst, OC*H*$_2$Ph, $J_{ab}$ = 11.3 Hz), 4.55 and 4.52 (2 H, AB syst, OC*H*$_2$Ph, $J_{ab}$ = 12.0 Hz), 7.25–7.40 (10 H, m, aromatics). $^{13}$C NMR: $\delta$ 15.37 (*C*H$_3$CH$_2$O), 34.05 (*C*H$_2$CHOBzl), 39.01 (*C*HCH$_2$OBzl), 61.82 and 64.17 (*C*H$_2$OBzl or *C*H$_2$OCH(OEt) and *C*H$_2$CH$_3$), 66.58 (*C*H$_2$OBzl or *C*H$_2$OCH(OEt)), 69.82 (*C*H$_2$Ph), 73.10 (*C*HOBzl), 73.37 (*C*H$_2$Ph), 99.43 (O*C*H(OEt)), 127.53, 127.46, 127.40, and 128.22 (aromatic CH), 138.40 and 138.32 (aromatic C).

**(*R*)-(*E*)-2-(Acetoxymethyl)-5-methyl-1-((*p*-toluenesulfonyl)oxy)hex-3-ene (16).** A solution of **6**[4e] (2.017 g, 10.83 mmol) in dry CH$_2$Cl$_2$ (20 mL), cooled to 0 °C, was treated with Et$_3$N (6.0 mL, 43.32 mmol) and *p*-toluenesulfonyl chloride (4.13 g, 21.66 mmol). The temperature was allowed to rise to rt, and the mixture was stirred at this temperature overnight. Quenching with saturated aqueous NH$_4$Cl and extraction with Et$_2$O gave, after chromatography (PE/Et$_2$O (7:3)), pure **16** as colorless liquid (3.51 g, 95%). Anal. Found: C, 60.00; H, 7.10. $C_{17}H_{24}O_5S$ requires C, 59.98; H, 7.11. $[\alpha]_D$ = +10.0° (*c* 2.31, CHCl$_3$). $R_f$ = 0.30 (PE/Et$_2$O (7:3)). $^1$H NMR: $\delta$ 0.93 (6 H, d, (C*H*$_3$)$_2$CH, *J* = 6.7 Hz), 1.96 (3 H, s, C*H*$_3$C=O), 2.21 (1 H, d of octuplet, (CH$_3$)$_2$C*H*, *J* = 1.1 (d) and 6.7 Hz (oct)), 2.45 (3 H, s, C*H*$_3$Ar), 2.66 (1 H, d of sextuplet, C*H*CH$_2$O, *J* = 0.6 (d) and 6.7 Hz (sext)), 3.96 and 4.04 (2 H, AB part of an ABX syst, C*H*$_2$O, $J_{ab}$ = 11.1, $J_{ax}$ and $J_{bx}$ = 6.9 and 5.7 Hz), 4.02 (2 H, d, C*H*$_2$O, *J* = 6.2 Hz), 5.12 (1 H, ddd, C*H*=CHCH(CH$_3$)$_2$, *J* = 1.2, 8.0, and 15.7 Hz), 5.52 (1 H, ddd, CH=C*H*CH(CH$_3$)$_2$, *J* = 0.6, 6.7, and 15.6 Hz), 7.35 (2 H, d, aromatics, *J* = 8.1 Hz), 7.80 (2 H, d, aromatics, *J* = 8.1 Hz).

**(2*R*,2′*R*)- and (2*R*,2′*S*)-(*E*)-5-Methyl-2-(((tetrahydropyran-2-yl)oxy)methyl)-1-((*p*-toluenesulfonyl)oxy)hex-3-enes (17).** A solution of **16** (3.51 g, 10.31 mmol) in THF (33 mL) was treated with a solution of LiOH (479 mg, 20.0 mmol) in H$_2$O (17 mL). The resulting solution was stirred overnight at rt, quenched with saturated aqueous NH$_4$Cl, and extracted with Et$_2$O to give, after chromatography, pure (*R*)-(*E*)-5-methyl-2-(((*p*-toluenesulfonyl)oxy)methyl)-3-hexen-1-ol (2.948 g, 96%). $[\alpha]_D$ = +18.9° (*c* 2.0, CHCl$_3$). $R_f$ = 0.23 (PE/Et$_2$O (6:4)). $^1$H NMR: $\delta$ 0.94 (6 H, d, (C*H*$_3$)$_2$CH, *J* = 6.7 Hz), 2.23 (1 H, d of octuplet, C*H*(CH$_3$)$_2$, *J* = 1.1 (d) and 6.7 Hz (oct)), 2.45 (3 H, s, C*H*$_3$Ar), 2.40–2.60 (1 H, m, C*H*CH$_2$O), 3.60 (2 H, d, C*H*$_2$OH, *J* = 6.3 Hz), 4.04 and 4.08 (2 H, AB part of an ABX syst, $J_{ab}$ = 9.7, $J_{ax}$ and $J_{bx}$ = 6.8 and 5.3 Hz), 5.17 (1 H, ddd, C*H*=CHCH(CH$_3$)$_2$, *J* = 1.1, 8.1, and 15.7 Hz), 5.55 (1 H, dd, CH=C*H*CH(CH$_3$)$_2$, *J* = 6.8 and 15.9 Hz), 7.35 (2 H, d, aromatics, *J* = 8.1 Hz), 7.80 (2 H, d, aromatics, *J* = 8.1 Hz). This alcohol was taken up in dry CH$_2$Cl$_2$ (25 mL), cooled to 0 °C, and treated with dihydropyran (2.70 mL, 29.64 mmol) and with a 0.1 M solution of *p*-toluenesulfonic acid hydrate in THF (1 mL). The solution was stirred at rt for 1 h and then quenched with saturated aqueous NaHCO$_3$ (2.5 mL), diluted with H$_2$O (50 mL), and extracted with Et$_2$O to give, after chromatography (PE/Et$_2$O (8:2)) pure **17** (1:1 diastereomeric mixture, as judged by NMR) as a colorless liquid (3.712 g, 98%). Anal. Found: C, 62.70; H, 7.95. $C_{20}H_{30}O_5S$ requires C, 62.80; H, 7.90. $[\alpha]_D$ = +0.45° (*c* 1.88, CHCl$_3$). $R_f$ = 0.28 (PE/Et$_2$O (8:2)). $^1$H NMR: $\delta$ 0.92 (6 H, d, (C*H*$_3$)$_2$CH, *J* = 6.8 Hz), 1.35–1.85 (6 H, m, OCH$_2$(C*H*$_2$)$_3$), 2.20 (1 H, octuplet, (CH$_3$)C*H*, *J* = 6.7 Hz), 2.45 (3 H, s, ArC*H*$_3$), 2.50–2.65 (1 H, m, C*H*CH$_2$O), 3.27 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 7.7 and 9.7 Hz), 3.34 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 4.7 and 9.8 Hz), 3.40–3.54 and 3.65–3.82 (2 × 1 H, 2 m, OC*H*$_2$CH$_2$), 3.64 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 6.9 and 9.7 Hz), 3.68 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 5.2 and 9.8 Hz), 4.03 and 4.13 (1 H, AB part of an ABX syst, C*H*$_2$OTs of one diast, $J_{ab}$ = 9.2, $J_{ax}$ and $J_{bx}$ = 6.1 Hz), 4.08 (1 H, d, C*H*$_2$OTs of one diast, *J* = 5.1 Hz), 4.43–4.53 (1 H, m, OCHO), 5.18 ($^1$/$_2$ H, ddd, C*H*=CHCH(CH$_3$)$_2$ of one diast, *J* = 1.1, 7.9, and 15.6 Hz), 5.19 ($^1$/$_2$ H, ddd, C*H*=CHCH(CH$_3$)$_2$ of one diast, *J* = 1.1, 7.9, and 15.6 Hz), 5.50 (1 H, dd, CH=C*H*CH(CH$_3$)$_2$, *J* = 6.6 and 15.6 Hz), 7.35 (2 H, d, aromatics, *J* = 8.1 Hz), 7.80 (2 H, d, aromatics, *J* = 8.1 Hz).

**(2*R*,2′*R*)- and (2*R*,2′*S*)-(*E*)-2-((2-Ethyl-5-methylhex-3-enyl)oxy)tetrahydropyrans (18).** A suspension of CuI (4.7 g, 24.7 mmol) in dry Et$_2$O (40 mL), kept under an He atmosphere and cooled to −10 °C, was treated with a 1.6 M solution of MeLi in Et$_2$O (30.875 mL, 49.4 mmol). During this addition a yellow precipitate formed first, which, upon completion of the addition, dissolved completely forming a brown solution. After stirring for 10 min at −10 °C, this solution was added through a syringe to a solution of **17** (1.82 g, 4.94 mmol) in Et$_2$O (20 mL), cooled to −40 °C. The temperature was allowed to rise slowly to rt, and the mixture was stirred overnight. After dilution with saturated aqueous NH$_4$Cl (50 mL), 10% NH$_4$OH (50 mL), and Et$_2$O, the mixture was transferred into a beaker and stirred in the air for 1 h to give two homogeneous phases, which were separated. The organic layer was washed with saturated aqueous NaCl to give, after chromatography (PE/Et$_2$O (100:0 → 97:3)) pure **18** as a colorless liquid (979 mg, 88%). Anal. Found: C, 74.20; H, 11.55. $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58. $[\alpha]_D$ = +2.1° (*c* 2.35, CHCl$_3$). $R_f$ = 0.67 (PE/MeO*t*-Bu (9:1)). $^1$H NMR: $\delta$ 0.86 (3 H, t, CH$_2$C*H*$_3$, *J* = 7.4 Hz), 0.97 (6 H, d, (C*H*$_3$)$_2$CH, *J* = 6.7 Hz), 1.10–1.35 (2 H, m, C*H*$_2$CH$_3$), 1.40–1.90 (6 H, m, OCH(C*H*$_2$)$_3$CH$_2$O), 2.05–2.20 (1 H, m, C*H*CH$_2$O), 2.25 (1 H, octuplet, (CH$_3$)$_2$C*H*, *J* = 6.7 Hz), 3.26 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 6.0 and 9.6 Hz), 3.29 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 6.0 and 9.6 Hz), 3.42–3.55 and 3.80–3.92 (2 H, 2 m, OC*H*$_2$CH$_2$), 3.59 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 4.2 and 9.6 Hz), 3.62 ($^1$/$_2$ H, dd, C*H*HOTHP of one diast, *J* = 3.6 and 9.6 Hz), 4.55–4.62 (1 H, m, OCHO), 5.14 ($^1$/$_2$ H, ddd, C*H*=CHCH(CH$_3$)$_2$ of one diast, *J* = 1.1, 8.3, and 15.4 Hz), 5.15 ($^1$/$_2$ H, ddd, C*H*=CHCH(CH$_3$)$_2$ of one diast, *J* = 1.1, 8.3, and 15.4 Hz), 5.43 (1 H, dd, CH=C*H*CH(CH$_3$)$_2$, *J* = 6.6 and 15.4 Hz).

**(2*R*,2′*R*)- and (2*R*,2′*S*)-2-((Tetrahydropyran-2-yloxy)-methyl)-1-butanols (19).** A solution of **18** (951 mg, 4.20 mmol) in dry MeOH (23 mL) and dry $CH_2Cl_2$ (15 mL) was ozonolyzed at −78 °C until the solution became blue-gray. Then dimethyl sulfide (2 mL) was added. After 5 min solid $NaBH_4$ (795 mg, 21.00 mmol) was added, and the temperature was allowed to rise to rt. Quenching with saturated aqueous $NH_4Cl$ (40 mL) followed by evaporation of most MeOH and extraction with $Et_2O$ afforded, after chromatography (PE/$Et_2O$ (4:6 → 3:7)), pure **19** as a colorless liquid (723 mg, 91%). Anal. Found: C, 63.65; H, 10.60. $C_{10}H_{20}O_3$ requires C, 63.80; H, 10.71. $[\alpha]_D$ = +12.2° (*c* 2.06, $CHCl_3$). $R_f$ = 0.27 (PE/$Et_2O$ (4:6)). $^1H$ NMR: δ 0.95 (3 H, t, $CH_3CH_2$, *J* = 7.3 Hz), 1.20–1.50 (2 H, m, $CH_2CH_3$), 1.45–1.90 (7 H, m, $OCH(CH_2)_3CH_2O$ and $CHCH_2OH$), 3.40 (½ H, dd, *CH*HOTHP of one diast, *J* = 7.1 and 9.6 Hz), 3.45–3.94 (5 H, m, $CH_2OH$, $OCH_2CH_2$, *CH*HOTHP), 3.95 (½ H, dd, *CH*HOTHP of one diast, *J* = 4.1 and 9.6 Hz), 4.54–4.63 (1 H, m, OCHO).

**(3*R*,2′*R*)- and (3*R*,2′*S*)-3-((Tetrahydropyran-2-yloxy)-methyl)pentanonitriles (20).** A solution of **19** (603 mg, 3.20 mmol) in dry $CH_2Cl_2$ (15 mL), cooled to −30 °C, was treated with $Et_3N$ (1.338 mL, 9.60 mmol) and methanesulfonyl chloride (0.496 mL, 6.40 mmol). After 1 h, the reaction was quenched with $H_2O$ and extracted with AcOEt. The organic layer was washed with saturated aqueous NaCl, dried ($Na_2SO_4$), and evaporated to dryness. The residue was taken up in dry DMSO (6 mL) and treated at rt with *n*-$Bu_4NI$ (236 mg, 0.64 mmol) and NaCN (470 mg, 9.60 mmol). The solution was warmed to 70 °C, stirred for 4 h, cooled to rt, diluted with saturated aqueous $NH_4Cl$, and extracted with $Et_2O$ to give, after chromatography (PE/$Et_2O$ (7:3)) pure **20** (518 mg, 82%). Anal. Found: C, 67.10; H, 9.60; N, 7.00. $C_{11}H_{19}NO_2$ requires C, 66.97; H, 9.71; N, 7.1 $[\alpha]_D$ = +21.1° (*c* 1.57, $CHCl_3$). $R_f$ = 0.46 (PE/AcOEt (8:2)). IR ($CHCl_3$): $\nu_{max}$ 2931, 2871, 2248, 1454, 1353, 1189, 1121, 1063, 1023 $cm^{-1}$. $^1H$ NMR: δ 0.95 (3 H, t, $CH_3CH_2$), 1.40–2.00 (9 H, m, $OCH_2(CH_2)_3CHO$, $CH_2CH_3$, $CHCH_2CH_3$), 2.47 and 2.52 (1 H, AB part of an ABX syst, $CH_2CN$ of one diast, $J_{ab}$ = 16.6, $J_{ax}$ and $J_{bx}$ = 6.0 and 6.1 Hz), 2.50 (1 H, d, $CH_2CN$ of one diast, *J* = 6.0 Hz), 3.24 (½ H, dd, *CH*HOTHP of one diast, *J* = 8.0 and 9.9 Hz), 3.42 (½ H, dd, *CH*HOTHP of one diast, *J* = 4.4 and 10.0 Hz), 3.42–3.60 and 3.74–3.90 (2 H, m, $OCH_2CH_2$), 3.65 (½ H, dd, *CH*HOTHP of one diast, *J* = 7.6 and 10.0 Hz), 3.83 (½ H, dd, *CH*HOTHP of one diast, *J* = 4.5 and 9.9 Hz), 4.52–4.64 (1 H, m, OCHO). $^{13}C$ NMR: δ 11.20 and 11.24 ($CH_3$), 19.26, 19.30, 19.34, 19.54, 23.41, 23.62, 25.38 (×2), 30.48, 30.54 ($CH_2C$), 37.49 and 37.52 ($CHCH_2OTHP$), 62.09, 62.47, 68.18, 68.67 ($CH_2O$), 98.63 and 99.44 (OCHO), 118.67 and 118.79 (C≡N).

**(3*R*,2′*R*)- and (3*R*,2′*S*)-3-((Tetrahydropyran-2-yloxy)-methyl)pentanals (4).** A solution of **20** (407 mg, 2.06 mmol) in dry $Et_2O$ (15 mL) was cooled to −35 °C and treated with 1 M DIBALH in toluene (4.12 mL). The temperature was allowed to rise slowly to −20 °C during 1 h. The reaction was quenched with AcOEt (12 mL), diluted with saturated aqueous Na,K tartrate, and stirred at rt for 1 h. Extraction with $Et_2O$ gave, after chromatography (PE/$Et_2O$ (7:3)), pure **4** as a colorless liquid (347 mg, 84%). Anal. Found: C, 65.65; H, 10.25. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.06. $[\alpha]_D$ = +24.1° (*c* 2.185, $CHCl_3$). $R_f$ = 0.50 (PE/AcOEt (8:2)). IR ($CHCl_3$): $\nu_{max}$ 2998, 2939, 2875, 2730, 1721 $cm^{-1}$. $^1H$ NMR: δ 0.94 (3 H, t, $CH_3CH_2$), 1.20–1.90 (8 H, m, $OCH_2(CH_2)_3$ and $CH_2CH_3$), 2.15–2.35 (1 H, m, $CHCH_2CHO$), 2.30–2.60 (2 H, m, $CH_2CHO$), 3.16 (½ H, dd, *CH*HOTHP of one diast, *J* = 7.9 and 9.5 Hz), 3.40 (½ H, dd, *CH*HOTHP of one diast, *J* = 4.6 and 9.6 Hz), 3.38–3.59 and 3.70–3.90 (2 H, m, $OCH_2CH_2$), 3.58 (½ H, dd, *CH*HOTHP of one diast, *J* = 8.0 and 9.6 Hz), 3.83 (½ H, dd, *CH*HOTHP of one diast, *J* = 4.7 and 9.5 Hz), 4.46–4.62 (1 H, m, OCHO), 9.76 (½ H, t, CH=O of one diast, *J* = 2.5 Hz), 9.79 (½ H, t, CH=O of one diast, *J* = 2.5 Hz).

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**Supplementary Material Available:** Characterizing data of compounds **8a–c,e** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.