An Efficient and General Method for the Synthesis of α,ω-Difunctional Reduced Polypropionates by Zr-Catalyzed Asymmetric Carboalumination: Synthesis of the Scyphostatin Side Chain**

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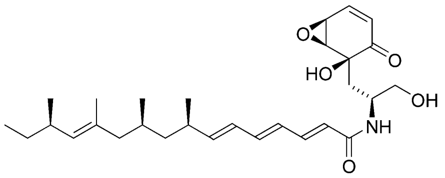
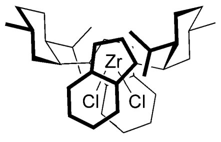
We recently reported an efficient and general method for the synthesis of reduced polypropionates with a single heterofunction[1] through the application of Zr-catalyzed asymmetric carboalumination.[2,3] In view of the large number of complex natural products that are of medicinal and biological interest, such as scyphostatin (**1**),[4] ionomycin,[5] doliculide,[6] and borrelidin,[7] we thought it worthwhile to search for a related method for the synthesis of terminally differentiated α,ω-difunctional reduced polypropionates through the use of Zr-catalyzed asymmetric carboalumination.[1–3] We report herein one such method involving 1) just one relatively inexpensive and enantiomerically pure (≥ 99 % *ee*) methyl (*R*)- or (*S*)-3-hydroxy-2-methylpropionate and 2) a catalytic and reagent-controlled asymmetric carbometalation[1–3] with Me_3Al and either enantiomer of $[ZrCl_2(nmi)_2]$ (nmi = 1-neomenthylindenyl; see **2**).[8] We also report the application of this method to the synthesis of the scyphostatin side chain.



scyphostatin (**1**)



(−)-$[ZrCl_2(nmi)_2]$ (**2**)

Preparation of **3** (Scheme 1) started with protection of methyl (*S*)-3-hydroxy-2-methylpropionate (≥ 99 % *ee*; TCI,

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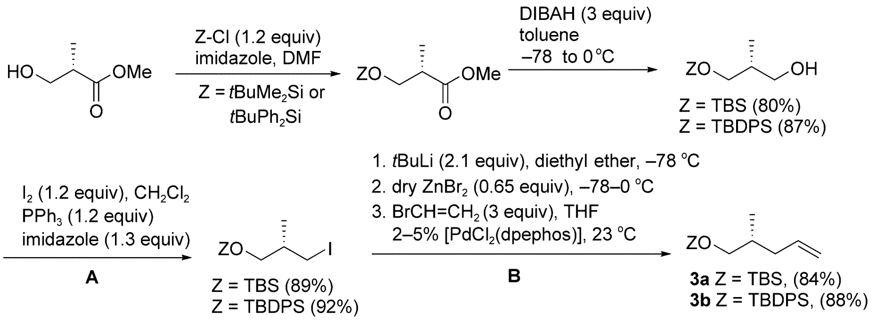


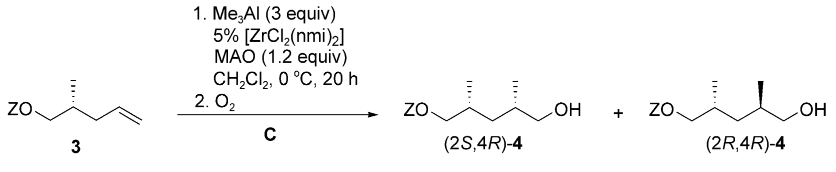
Scheme 1. Synthesis of TBS- or TBDPS-protected (*R*)-2-methyl-4-penten-1-ol (**3**) from methyl (*S*)-3-hydroxy-2-methylpropionate. TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, DMF = dimethylformamide, DIBAH = diisobutylaluminium hydride, THF = tetrahydrofuran, dpephos = bis[2-(diphenylphosphanyl)phenyl] ether.

Tokyo, Kasei Kogyo Co., Ltd) by treatment with either TBSCl or TBDPSCl in the presence of imidazole and DMF (ca. 95% yield). Reduction by treatment with DIBAH, followed by iodination led to the TBS- or TBDPS-protected (*S*)-3-iodo-2-methyl-1-propanol. This compound was converted into the corresponding zinc reagent in situ by treatment with *t*BuLi (2.1 equiv) in diethyl ether at −78 °C[9a] and then with dry $ZnBr_2$ (0.65 molar equiv) at −78–0 °C. The organozinc intermediate was vinylated with $BrCH{=}CH_2$ (3 equiv) in THF/diethyl ether[9b–d] in the presence of $[PdCl_2(dpephos)]$[10] (2–5 mol%) at 23 °C to give either **3a** (Z = TBS) or **3b** (Z = TBDPS) in a yield of 84 or 88%, respectively. The overall yields of **3a** and **3b** from methyl (*S*)-3-hydroxy-2-methylpropionate over four steps were 57% and 67%, respectively.

Treatment of **3a** with Me_3Al (3 equiv), methylaluminoxane (MAO; 1.2 equiv), and (+)-$[ZrCl_2(nmi)_2]$ (5 mol%) in CH_2Cl_2 at 0 °C for 20 h produced, after oxidation with O_2, a 13:1 mixture of (2*S*,4*R*)- and (2*R*,4*R*)-**4** in 75% combined yield (Table 1). The observed diastereomeric ratio (d.r.) of 13:1 suggests that the enantioselectivity at C2 would be 93%, were it not for the pre-existing asymmetric carbon center at C4. This value, which is somewhat higher than the 85–90% enantioselectivity range observed with achiral alkenes, suggests a modest level of favorable internal asymmetric induction. The corresponding reaction in the presence of (−)-$[ZrCl_2(nmi)_2]$ led to the formation of a 1:8 mixture of the same two isomers, with a combined yield of 72%. This d.r. value of 1:8 corresponds to 89% stereoselectivity at C2. The observed modest preference for the formation of *syn*-2,4-dimethyl-1-alkanols over that of *anti*-2,4-dimethyl-1-alkanols appears to be a general trend in Zr-catalyzed asymmetric carboalumination, although the corresponding reaction of the TBDPS-protected **3b** did not show any clear sign of internal asymmetric induction (Table 1). To probe the extent of internal asymmetric induction, we treated **3a** and **3b** with Me_3Al in the presence of $[ZrCl_2(ind)_2]$ (ind = indenyl). Yields of 73% and 78% were obtained from **3a** and **3b** after oxidation, and the products exhibited 2*S*,4*R*/2*R*,4*R* ratios of 1.12:1 and 1.1:1, respectively, which suggests that there is indeed a minor preference for the formation of the *syn* isomer. Chromatographic separation of the minor isomer (2*R*,4*R*)-**4** from (2*S*,4*R*)-**4** was readily achieved in one operation on silica gel (EtOAc/hexanes, 1:50). (2*S*,4*R*)-**4a** (Z = TBS; d.r. ≥ 40:1) and (2*S*,4*R*)-**4b** (Z = TBDPS; d.r. ≥ 37:1) were obtained in yields of 55 and 61%, respectively, based on the starting alkene **3**. These yields correspond to 73% and 77% recovery in the chromatographic separation. Since d.r. values of 13:1 and 10:1 indicate maximum possible recovery rates of 93% and 91%, respectively, there seems to be room for further improvement in the recovery in view of the ease of diastereomeric separation in these cases.

The high enantiomeric purity of **3** (≥ 98% *ee*) guarantees an overall *ee* value at least this high, regardless of the extent of stereoselection in the conversion of **3** into **4**. Statistical enantiomeric amplification, which is nothing more than a manifestation of the kinetic mass action law, would further elevate the overall *ee* value after each additional asymmetric stereogenic step. For example, the overall *ee* values established on the basis of the mass action law for asymmetric reaction of compounds of 98.0% *ee* in the absence of internal asymmetric induction may reliably be predicted as shown in Table 2. The overall *ee* value of the products **4a** and **4b** may be estimated from Table 2 to be 99.6% or more. HPLC analysis of the urethanes derived from **4a** and (+)- and (−)-1-

Table 1: Conversion of **3** into 5-siloxy-2,4-dimethyl-1-pentanols (**4**).



3	Z	$[ZrCl_2(nmi)_2]$	Combined yield [%][a]	2*S*,4*R*/2*R*,4*R* before chromatography[b]	Yield of **4** after chromatography [%]	2*S*,4*R*/2*R*,4*R* after chromatography[b]
3a	TBS	(+)	75	13/1	55 (31 over 5 steps)	≥ 40/1
3a	TBS	(−)	72	1/8	[c]	[c]
3b	TBDPS	(+)	82	10/1	61 (41 over 5 steps)	≥ 37/1
3b	TBDPS	(−)	81	1/10	[c]	[c]

[a] Combined yield of **4** before chromatography. [b] Determined by ^{13}C NMR spectroscopy. [c] Not purified by chromatography.

Table 2: Estimation of overall *ee* values and maximum attainable yields for asymmetric reactions of chiral compounds of 98.0% *ee*.

Asymmetric induction *R*/*S* or *S*/*R*[a]	*de* [%] (d.r.)	Max. possible yield [%]	Overall *ee* [%][b]
50/50	00.0 (1:1)	50.0	98.0
80/20	58.8 (3.9:1)	79.4	99.5
85/15	68.6 (5.4:1)	84.3	99.6
90/10	78.4 (8.3:1)	89.2	99.8
95/05	88.2 (9.4:1)	94.1	99.9
100/0	100.0 (∞)	100.0	100.0

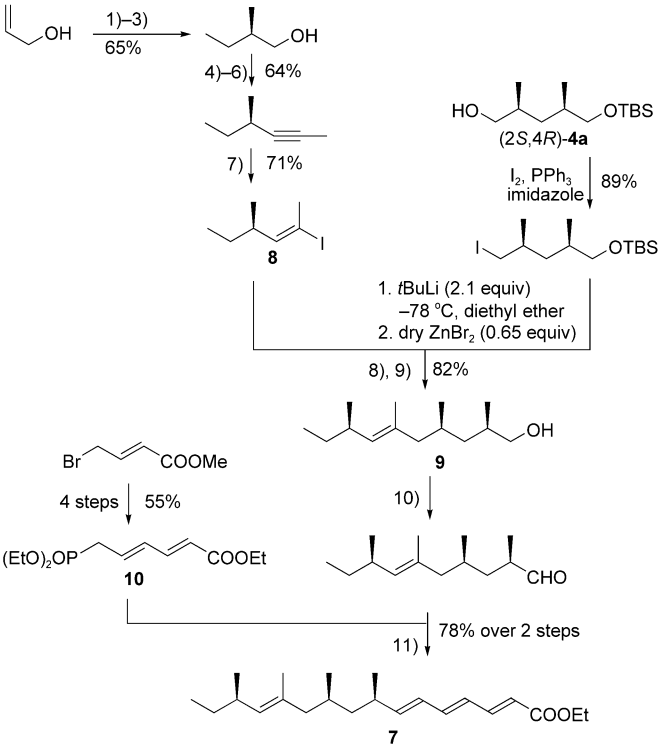
[a] The *R*/*S* or *S*/*R* ratio at the stereogenic center. [b] Statistically estimated.

(α-naphthyl)ethyl isocyanates provides experimental evidence of *ee* values of more than 99%. In these cases, however, the maximum possible product yields are in practice much more important. If yields of at least 80% are assumed to be desirable for practical purposes, asymmetric reactions with stereoselectivities at the second stereogenic center of 80% or higher would suffice to attain this practical goal. Such a stereoselectivity corresponds to over 4:1 d.r. and the generation of chiral compounds of over 99% *ee*. In short, we have developed an efficient, selective, and practical five-step protocol for the synthesis of 2,4-dimethyl-1-alkanols that is catalytic in chiral auxiliaries (Table 1). Synthesis of (2*S*,4*R*)-**4a** and (2*R*,4*R*)-**4b** from methyl (*S*)-3-hydroxy-2-methylpropionate was achieved with total yields over five steps of 31% and 41%, respectively, 97–98% diastereomeric purity, and at least 99.6% *ee* (estimated).

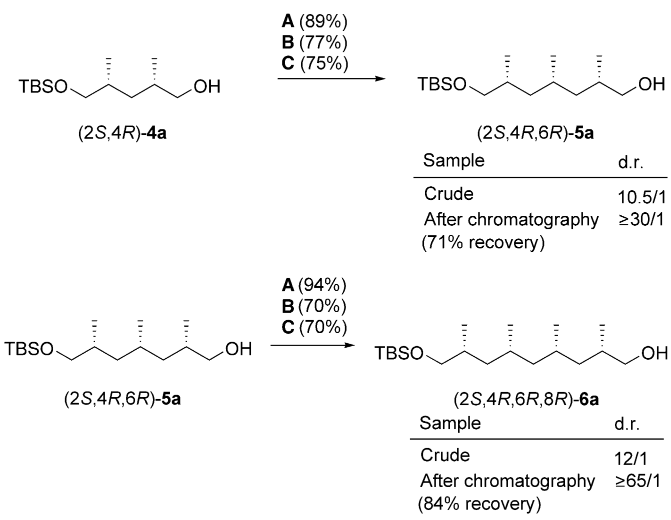
Conversion of 2,4-dimethyl-1-alkanols into 2,4,6-trimethyl-1-alkanols and higher reduced polypropionates can be achieved by application of an iterative three-step protocol[1] consisting of 1) iodination (**A**), 2) Pd-catalyzed vinylation (**B**), and 3) Zr-catalyzed methylalumination (**C**, Scheme 2). (2*S*,4*R*)-**4a** was converted into (2*S*,4*R*,6*R*)-**5a** (d.r. > 30:1) in 36% combined yield over three steps, and iteration of the same three-step protocol converted (2*S*,4*R*,6*R*)-**5a** into (2*S*,4*R*,6*R*,8*R*)-**6a** (d.r. > 65:1) in 40% combined yield over three steps. The diastereomeric ratios observed for the products of the Zr-catalyzed asymmetric carboalumination itself (step **C**) were 10.5:1 and 12:1 (Scheme 2).

Scyphostatin (**1**), a potent inhibitor of neutral sphingomyelinase,[4a] was first reported in 1997 but its total synthesis does not appear to have been reported.[11] The structure of this compound consists of a C_{20} carboxylic acid side chain and a bicyclic amine core fragment. The side chain has been synthesized once before in the form of ethyl ester **7** in nine steps (six isolation steps) from (2*S*,4*R*)-**4b** and in 15% yield.[4b] However, the preparation of (2*S*,4*R*)-**4b** from diethyl 2-methylmalonate and ethyl α-bromoisobutyrate by enzyme-catalyzed monoacetylation of *meso*-2,4-dimethyl-1,5-pentanediol required seven additional steps and was achieved in a mere 4% yield. Thus, the linear 16-step synthesis of **7** proceeded in 0.6% total yield. Use of the 5-step synthesis of (2*S*,4*R*)-**4b** (d.r. ≥ 37:1) in 41% total yield (Table 1) would alone amount to a tenfold increase in the yield of **7**.

We sought a convergent synthetic scheme to make the synthesis of **7** even more efficient. We developed a synthesis whose longest linear sequence is 11 steps (Scheme 3). In



Scheme 3. Convergent synthesis of the scyphostatin side chain (**7**) by Zr-catalyzed asymmetric carboalumination. 1) TBDPSCl (1.2 equiv), imidazole, DMF; 2) a) 5 mol% (−)-[ZrCl$_2$(nmi)$_2$], MAO (1.2 equiv), Et$_3$Al (3 equiv), 0°C; b) aq HCl; 3) TBAF (1.5 equiv), THF; 4) Swern oxidation; 5) PPh$_3$ (2 equiv), CBr$_4$ (2 equiv), Zn dust (2 equiv), CH$_2$Cl$_2$, 0°C; 6) a) *n*HexLi (2.05 equiv), −78–0°C; b) MeI (3 equiv); 7) a) [HZrCp$_2$Cl] (1.5 equiv), THF, 60°C; b) I$_2$ (1.5 equiv), 0°C; 8) 5 mol% [PdCl$_2$(dpephos)], vinyl bromide (3 equiv), 23°C; 9) TBAF (1.5 equiv); 10) cat. TPAP, NMO, CH$_2$Cl$_2$; 11) LDA, 0°C. TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, LDA = lithium diisopropylamide.



Scheme 2. Synthesis of trimethyl- and tetramethyl-1-alkanols from (2*S*,4*R*)-**4a** through application of a three-step protocol. **A**, **B**, and **C** are defined in Scheme 1 and Table 1.

addition to (2*S*,4*R*)-**4a**, (2*E*,4*R*)-2-iodo-4-methyl-2-hexene (**8**) and the previously employed 6-P-substituted (2*E*,4*E*)-hexa-2,4-dienoic acid ethyl ester[4b] (**10**) were used as key intermediates. The preparation of **8** started with protection of allyl alcohol with TBDPSCl. Asymmetric ethylalumination of the TBDPS-protected allyl alcohol with Et$_3$Al (3 equiv), MAO (1 equiv), and 5 mol% (−)-[ZrCl$_2$(nmi)$_2$], followed by protonolysis and desilylation by treatment with TBAF gave (*R*)-2-methyl-1-butanol in 92% *ee* and 65% combined yield over three steps. No enantiomeric separation was carried out. The crude (*R*)-2-methyl-1-butanol was 1) oxidized under Swern conditions,[12] 2) subjected to the Corey–Fuchs reaction[13] to give (*R*)-1,1-dibromo-3-methyl-1-pentene, and 3) converted into (*R*)-4-methyl-2-hexyne. Hydrozirconation/iodinolysis of this compound provided (2*E*,4*R*)-2-iodo-4-methyl-2-hexene (**8**) in more than 98% isomeric purity and 71% yield. The total yield of **8** from allyl alcohol over seven steps (six isolation steps) was 30%.

Iodination of (2*S*,4*R*)-**4a** produced the desired iodide in 89% yield. This iodide was treated first with *t*BuLi (2.1 equiv) in diethyl ether at −78°C and then with dry ZnBr$_2$ (0.65 molar equiv). The alkyl zinc derivative thus generated was cross-coupled with **8** in the presence of [PdCl$_2$(dpephos)] (5 mol%).[10] The coupling proceeded in 94% yield based on the amount of iodide used. After desilylation with TBAF, column chromatography on silica gel (ethyl acetate/hexanes, 1:25) provided the desired compound **9** in more than 98% isomeric purity and 87% yield. Compound **9** was thus synthesized in 25% overall yield and the longest linear synthetic sequence consisted of nine steps starting with allyl alcohol. An additional six steps were needed for the synthesis of the TBS-protected 5-iodo-2,4-dimethyl-1-pentanol in 37% overall yield. Since the previously reported synthesis of **7** employed **9** as a key intermediate, a formal synthesis of **7** was complete at this point. For a variety of reasons, we nevertheless decided to complete the synthesis of **7** by following the reported procedure involving 1) oxidation of **9** with TPAP and NMO and 2) olefination of the resultant aldehyde with **10**, which was prepared from methyl (*E*)-4-bromocrotonate in 55% yield over four steps.[4b] These two processes were completed in 78% combined yield. Our convergent and efficient synthesis of **7** therefore occurred in 19% yield. The longest linear sequence of the synthesis involved 11 steps. The ^{1}H and ^{13}C NMR spectra of the product were not only consistent with the assigned structure but also agreed well with those reported by Hoye and Tennakoon.[4b]

In conclusion, 1) an efficient and potentially general method for the synthesis of α,ω-difunctional reduced polypropionates through the use of Zr-catalyzed asymmetric carboalumination has been developed, 2) catalysis with respect to a chiral auxiliary for asymmetric C–C bond formation, coupled with high overall efficiency makes the method reported herein unique among the known methods for the synthesis of α,ω-difunctional reduced polypropionates, 3) the use of commercially available and relatively inexpensive methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates with *ee* values of at least 98% makes enantiomeric separation unnecessary for the synthesis of reduced polypropionates of more than 98% *ee*, and 4) a convergent and efficient synthesis of the scyphostatin side chain in the form of its ethyl ester **7** was achieved in 11 linear steps (nine isolation steps) with 19% overall yield. These results should prove to be useful for exploitation of **7** in the total synthesis of scyphostatin.

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Keywords: carboalumination · enantioselectivity · homogeneous catalysis · synthesis design · zirconium

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[11] Note added in proof: After submission of this paper, we were informed of an oral report of a total synthesis of scyphostatin. We thank Prof. Katoh for providing us with this information (M. Inoue, W. Yokota, M. G. Murugesh, T. Izuhara, T. Katoh, 45th Symposium on the Chemistry of National Products, October 6–8, **2003**, Kyoto, Japan).

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