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# Enantioselective Synthesis of a Key Intermediate in a New Process for Orlistat Using Asymmetric Hydrogenation and a Grignard Reagent Promoted Lactone Cyclization

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## Abstract:

**A new enantioselective synthesis of Orlistat suitable for large-scale preparation is described. Therein, the first isolated key intermediate (*R*)-3-hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2*H*-pyran-2-one (12) is prepared via (a) the asymmetric hydrogenation of methyl 3-oxotetradecanoate to (*S*)-3-hydroxytetradecanoate (9); (b) the acylation of 9 with 2-bromooctanoyl halide (bromide/chloride) to (*R*)-3-[(2-bromo-1-oxooctyl)oxy]-tetradecanoic acid methyl ester (11) and finally (c) the *tert*-butyl magnesium chloride promoted cyclization of 11 to the single enantiomer 12. The single enantiomer intermediate 12, previously published as a mixture of enantiomers 2, has been carried on through several steps to Orlistat (1) without any process changes.**

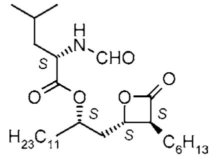

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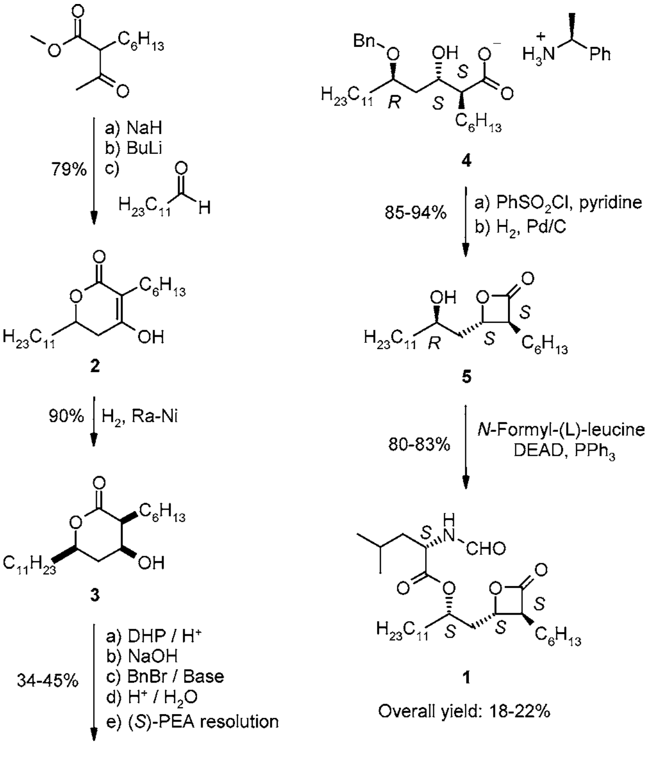
***Figure 1.*** **Orlistat (1).**

***Scheme 1.*** **First-generation, optical resolution based synthesis of Orlistat (1)**



## Introduction

Orlistat (**1**), the active pharmaceutical ingredient of Xenical, is a novel antiobesity agent that selectively inhibits gastrointestinal lipases, reducing the absorption of dietary fat by about 30% (Figure 1).[1] Also known as (−)-tetrahydrolipstatin or *N*-formyl-(*S*)-leucine (*S*)-1-[(2*S*,3*S*)-3-hexyl-4-oxo-2-oxetanyl]methyldodecyl ester, **1** is the hydrogenated derivative of lipstatin, a naturally occurring lipase inhibitor isolated from *Streptomyces toxytricini*.[2] (−)-Tetrahydrolipstatin has been the research target of numerous synthetic groups.[3]

A diagram of the first-generation Orlistat synthesis based on the optical resolution of the racemic key intermediate **4** is shown in Scheme 1.[3u] The isolated intermediates are the racemic dihydropyranone **2**, racemic all-*cis* δ-lactone **3**, the enantiomerically pure 1:1 PEA-salt **4**, and the (*S*,*S*,*R*)-oxetanone **5**.

The required relative configuration of the three stereocenters in **3** was established during the diastereoselective, heterogeneous hydrogenation of **2**, which afforded selectively **3** as a 1:1 mixture of the two all-*cis* enantiomers. Subsequently, the required absolute configuration for each of these centers was selected by the optical resolution of **4**. Finally, the fourth chiral center of Orlistat was introduced during the Mitsunobu coupling reaction of **5** with *N*-formyl-L-leucine.

The objective to elaborate a new, enantioselective, second-generation synthesis of **1** was to develop and demonstrate a more efficient process with an increased throughput. The strategy therefore was to retain the final reaction sequence **4** to **1** but to avoid the first-generation's late-stage resolution

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(1) (a) Hauptman, J. B. *8th International Congress on Obesity, Paris, France*, August 1998. (b) Prous, J.; Mealy, N.; Castaner, J. *Drugs of the Future* **1994**, *19*, 1003.

(2) (a) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081. (b) Hochuli, E.; Kupfer, E.; Mauer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086.

10.1021/op060208q CCC: $37.00

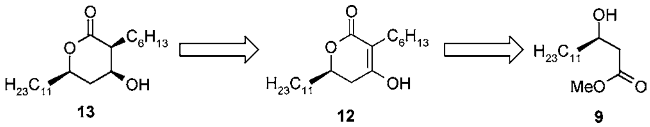


***Figure 2.*** **New retrosynthetic strategy: (*S*)-hydroxyester 9, (*R*)-dihydropyrone 12 and (3*S*,4*S*,6*R*)-lactone 13.**

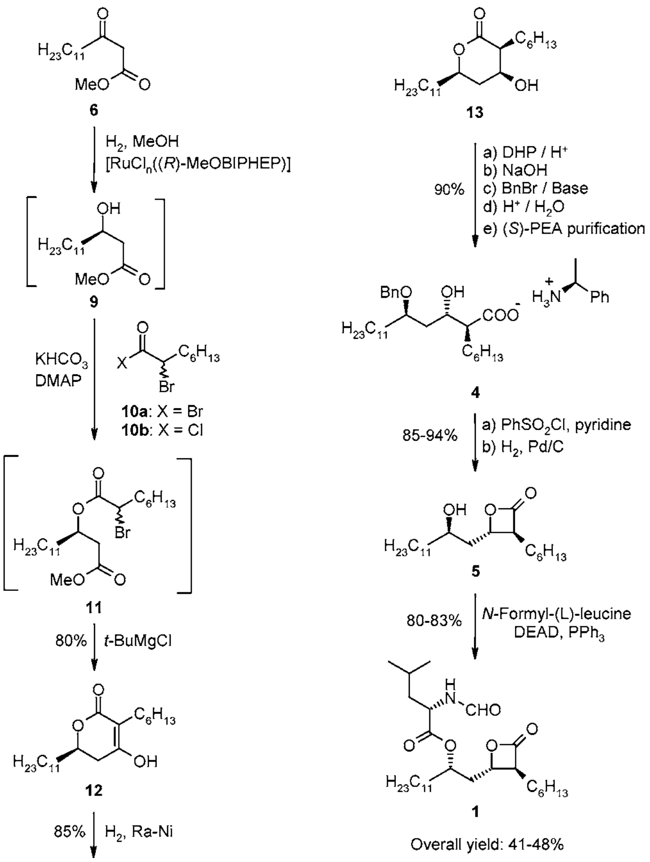
of **4** by the use of enantiomerically pure intermediate **12** (Figure 2) rather than its racemate analogue **2**.

A few of the envisioned advantages of this second-generation strategy were the following: (a) the only asymmetric center to be created by asymmetric synthesis would involve a well-precedented asymmetric reduction of a $\beta$-ketoester;[3e,4,5] (b) the throughput from **12** to **5** would be greatly increased due to avoidance of the undesired enantiomer of **2**; (c) the process development from **12** to **1** was to be expedited by utilization of much of the first-generation process technology; and (d) the critical last step and crystallization were to be left unchanged.

Several synthetic routes[6] to **12** were evaluated preliminarily. Scheme 2 illustrates the final optimized magnesium-mediated route.[7]

The magnesium-mediated route was a basic extension of an earlier approach reported by Ramig and co-workers from Roche Nutley, who described the acylation of **9** to the diester **11** and the subsequent zinc-mediated Reformatsky cyclization of **11** to **12** in about a 60% yield.[3f,8]

***Scheme 2.*** **Second-generation, new enantioselective synthesis of Orlistat (1)**



Overall yield: 41-48%

In their publication, Ramig and co-workers did not mention the use of magnesium for the cyclization step but mentioned two papers which described magnesium-metal based cyclizations to $\gamma$-lactones in moderate yields.[9,10] A number of researchers have found ways to utilize Grignard reagents in the preparation of ketones from carboxylic acid derivatives by various methods.[11] The large-scale use of magnesium rather than zinc is advantageous due to fewer disposal issues with magnesium salt wastes. Also, the use of magnesium would allow utilization of the higher-boiling and less-flammable tetrahydrofuran rather than diethyl ether. However, the use of magnesium under Ramig's conditions failed to afford **12** in an acceptable yield. The following discussion describes the development of a novel enantioselective synthesis of (*R*)-3-hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2*H*-pyran-2-one **12** as a key intermediate in a new synthesis of Orlistat from the conception of the idea to the demonstration of a potential second generation large-scale process.

## Results and Discussion

**Synthesis of (*R*)-Dihydropyrone 12.** The first reaction sequence in the new, enantioselective synthesis of **1** consists of three distinct chemical reactions: (a) the asymmetric

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(4) Heiser, B.; Broger, E.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.

(5) A preliminary report on this topic has been given in: (a) Schmid R.; Scalone M. *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; 1999; p 1446. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, *131*.

(6) Harrington, P. J.; Hodges, L. M.; Püntener, K.; Scalone, M. Eur. Pat. Appl. EP 1127886 A1, 2001; U.S. Patent 6552204 B1, 2000.

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(8) (a) Ramig, K. M.; Landi, J. J., Jr. U.S. Patent 5274143, 1993. (b) Ramig, K. M.; Landi, J. J., Jr. U.S. Patent 5420305, 1995.

(9) Kelly, T. R.; Chandrakumar, N. S.; Cutting, J. D.; Goehring, R. R.; Weibel, F. R. *Tetrahedron Lett.* **1985**, *26*, 2173.

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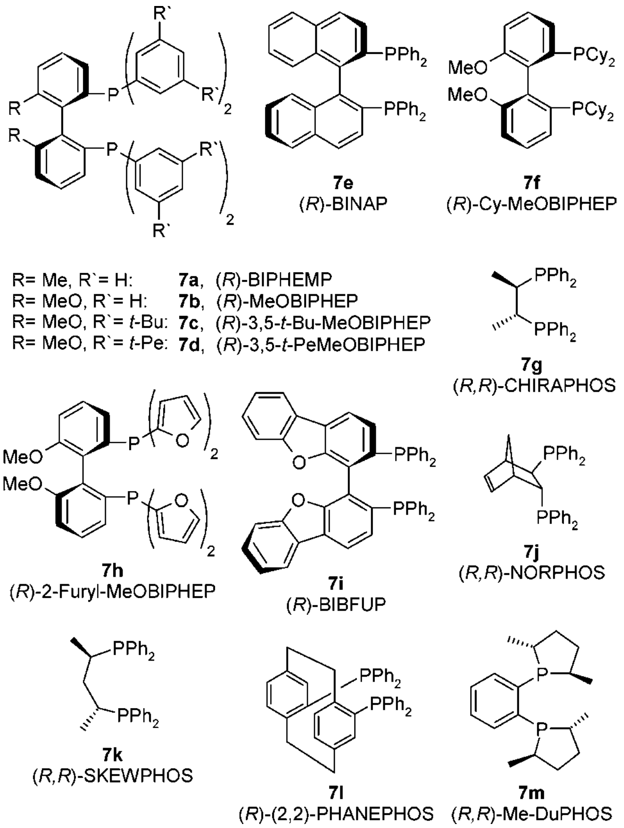
(11) O'Neill, B. T. Nucleophilic Addition to Carboxylic Acid Derivatives. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; 1991; p 398.

hydrogenation of **6** to (*R*)-hydroxyester **9**; (b) the acylation of **9** to the (*R*)-bromodiester **11**; and (c) the cyclization of **11** to (*R)*-dihydropyranone **12** with only **12** being isolated as a solid intermediate.

**a. Asymmetric Hydrogenation of 6:** The substrate for the asymmetric hydrogenation, the $\beta$-ketoester **6**, became commercially available during the course of our investigations but was first prepared in-house on a multi-100 kg scale by condensation of lauroyl chloride with the magnesium salt of methyl acetoacetate in up to 87% yield.[7a,12] Originally the starting material (*S*)-hydroxyester **9** was prepared by a Raney-Nickel/tartaric acid catalyzed asymmetric hydrogenation of **6**. This heterogeneous hydrogenation process was successfully used in the first in-house production of **9** on a multi-100 kg scale (84−91% ee).[5] However, a single use of the catalyst was economically not feasible, and a reuse proved to be on a large scale not practicable because after each run a laborious remodification with tartaric acid was required to maintain its activity and selectivity. Furthermore, one crystallization step was necessary to enhance the ee of **9** to >99%. Therefore this process was not further developed. The promising results obtained with the ruthenium catalyzed asymmetric hydrogenation of **6** using (*S*)-BINAP[3e] or a (*S*)-BIPHEMP[4] based catalysts (97% ee) resulted in a focus on this approach with the goal to elaborate a technically feasible, highly enantioselective (>99% ee) hydrogenation process which affords enantiomerically pure **9** and avoids an ee-enhancing crystallization step.

The pre-catalysts **8a−m** for asymmetric hydrogenation of **6** were prepared by reaction of the chiral diphosphines (structures cf. Scheme 3) with commercially available $[RuCl_2(COD)]_n$ (exemplified with **8b**, Scheme 4).[4,13] As expected, the diacetoxy complex **8b** was catalytically inactive (Table 1, entry 1), but addition of hydrogen chloride generated a catalytically active species.[5,14] Although only 2 molar equiv of hydrogen chloride are formally required to exchange the two coordinated acetates in **8b** and form the proposed dichloro catalyst (Scheme 4),[15] the addition of up to a 20-fold excess was extremely advantageous leading to highly increased reaction rates and higher enantioselectivities. The exact role of the excess of chloride remains unknown; we assume it drives the pre-catalyst to the active catalyst, which we suggest to write as $[RuCl_n((R)\text{-MeOBIPHEP})]$, not excluding the presence of dimeric species.[16] Suitable chloride sources were both aqueous and anhydrous hydrogen chloride. Interestingly, lithium chloride led to a very active catalyst, whereas other additives such as HBr, $Bu_4NI$, $HBF_4$, or *p*-toluenesulfonic acid were much less effective.

***Scheme 3.*** **Structure of various chiral diphosphine ligands**



***Scheme 4.*** **Synthesis of the hydrogenation catalyst**

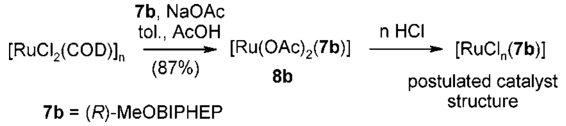


***Table 1.*** **Influence of additive and additive/Ru molar ratio**[a]

| entry | additive | equiv of additive | conversion (%) 1 h | conversion (%) 4 h | **9**, % ee |
|---|---|---|---|---|---|
| 1 | | | <1 | <1 | n.d. |
| 2 | HCl[b] | 2 | 4 | 13 | 36[c] |
| 3 | HCl[b] | 4 | 12 | 35 | 26 |
| 4 | HCl[b] | 10 | 72 | 99.9 | 96 |
| 5 | HCl[b] | 20 | 90 | >99.9 | 99 |
| 6 | $HCl_{aq}$ | 20 | 90 | >99.9 | 99 |
| 7 | LiCl | 20 | 87 | 99.9 | 97 |
| 8 | $HBr_{aq}$ | 20 | 31 | 78 | 46 |
| 9 | $HBF_4$ | 20 | 1 | 15 | 33[c] |
| 10 | *p*-TsOH | 20 | 50 | 96 | 62 |
| 11 | $Bu_4NI$ | 20 | <1 | <1 | n.d. |

[a] **8b**/additive, S/C 50 000, 70 bar of $H_2$, 80 °C, MeOH (30 wt %, argon distilled); 15 g scale. [b] Anhydrous methanolic HCl (prepared by addition of AcCl to MeOH). [c] (*S*)-**9** was formed.

The influence of a variety of chiral diphosphines on the hydrogenation rate and enantioselectivity in the catalysts of type $[Ru(OAc)_2(\text{diphosphine})]/20\ HCl_{aq}$ was investigated (Table 2). Very high enantioselectivities of >99% were achieved only by applying atropisomeric diphosphines such as (*R*)-BIPHEMP **7a**, (*R*)-MeOBIPHEP **7b**, (*R*)-3,5-*t*-Bu-MeOBIPHEP **7c**, and (*R*)-2-Furyl-MeOBIPHEP **7h**.[17] The most active catalyst (98% conversion within 1 h at S/C

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[13] Chan, A. S. C.; Laneman, S. *Inorg. Chim. Acta* **1994**, *223*, 165.

[14] King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689.

[15] (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Noyori, R. *Acta Chem. Scand.* **1996**, *50*, *380.*

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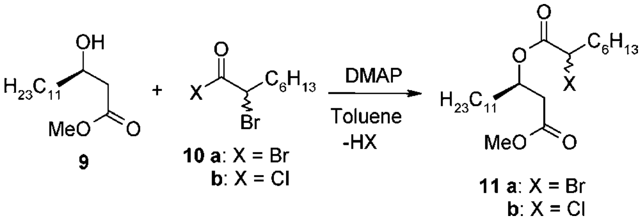
***Table 2.*** **Influence of diphosphine ligand**[a]

| entry | diphosphine | conversion (%) 1 h | 4 h | 16 h | **9**, % ee |
|---|---|---|---|---|---|
| 1 | **7a** | 45 | >99.9 | | 99 |
| 2 | **7b** | 26 | 94 | >99.9 | 99 |
| 3 | **7c** | 66 | >99.9 | | 99 |
| 4 | **7d** | 98 | >99.9 | | 94 |
| 5 | **7e** | 32 | 99.7 | >99.9 | 96 |
| 6 | **7f** | 1 | 2 | 4 | n.d. |
| 7[b] | **7g** | <1 | <1 | 1 | n.d. |
| 8 | **7h** | 1 | 5 | 20 | 99 |
| 9 | **7i** | 8 | 45 | 99.9 | 97 |
| 10[b] | **7j** | 7 | 34 | 91 | 64 |
| 11 | **7k** | 2 | 10 | 60 | 72 |
| 12 | **7l** | 9 | 13 | 22 | 39 |
| 13[c] | **7m** | <1 | <1 | <1 | n.d. |
| 14[d] | **7b** | 56 | 99.9. | >99.9 | 96 |

[a] [Ru(OAc)$_2$(diphosphine)]/20 HCl$_{aq}$, S/C 50 000, 70 bar H$_2$, 60 °C, MeOH (30 wt %, argon distilled); 15 g scale. [b] S/C 5000. [c] [RuCl(*p*-cy-mene)(**7m**)]Cl/18 HCl$_{aq}$ used as catalyst (S/C 5000). [d] [RuCl(*p*-cy-mene)(**7b**)]Cl/18 HCl$_{aq}$ used as catalyst (S/C 50 000).

***Scheme 5.*** **Synthesis of (*R*)-bromodiester 11a**



50 000) contained the very sterically demanding (*R*)-3,5-*t*-Pe-MeOBIPHEP **7d** as the chiral diphosphine ligand. However, with this catalyst the ee of **9** dropped to 94%. Due to the large-scale accessibility of the parent diphosphine (*R*)-MeOBIPHEP, **8b** was selected as the pre-catalyst for the asymmetric hydrogenation of **6**. The intermediate **8b** proved to be remarkably air stable. Storage of **8b** on the bench at room temperature for 6 months caused neither decrease in catalytic activity nor enantioselectivity at S/C 50 000 compared with freshly prepared **8b** or a sample of **8b**, which had been stored at room temperature under an argon atmosphere for 6 months. The $^{31}$P NMR spectra of air-exposed **8b** showed the formation of a small amount of the bis-oxide of **7b** (bis-oxide of **7b**/**8b** ~1:10). Evidently, this impurity had no influence on the formation of the catalytically active species. In contrast, the catalyst formed in solution by treatment of **8b** with HCl in methanol was highly air sensitive: stirring this catalyst solution for 10 min in air caused a total loss of activity. Therefore, total exclusion of air during both the catalyst formation step and the hydrogenation was crucial for high catalyst performance. Notwithstanding, complete conversion and 99% ee were achieved with an S/C ratio as high as 250 000 (40 bar H$_2$, 22 h), no matter if high-purity[18] or technical-grade gases[19] and solvents were used, thus indicating the commercial potential and the robustness of the asymmetric hydrogenation step. Finally, in order to achieve a high throughput on a large scale, an S/C ratio of 50 000 at 40 bar hydrogen pressure, which led to complete conversion within ca. 4 h, was selected for scale-up. The hydrogenation also proceeded selectively at a lower hydrogen pressure (e.g., 5 bar), but a 5-fold amount of **8b**, i.e., S/C 10 000, had to be employed to achieve complete conversion. In contrast, at a hydrogen pressure of 70 bar the hydrogenation rate increased, but the enantioselectivity slightly decreased. Surprisingly, a substrate concentration of 40−60 wt % was necessary for both a high reaction rate and a high enantioselectivity. Even at a concentration of 96 wt %, the hydrogenation reached 99% conversion within 16 h (S/C 50 000) and yielded **9** with 97% ee. On a large scale, the hydrogenation was carried out preferentially at concentrations between 40 and 60 wt %. As expected, a further increase of the reaction temperature brought about an increase of the reaction rate but also a decrease of the enantioselectivity. Finally, a process temperature of 80 °C was selected.

Under the best conditions, the hydrogenation of 200 g of **6** (2-L autoclave) ran to completion within 4 h, affording **9** with >99% purity and >99% ee. A total of greater than 2 tons of **9** in up to multi-100 kg batches have been produced accordingly. All batches met set specifications (>99.9% conversion, >99% ee).

**b. Acylation of 9:** The reaction of (*R*)-hydroxyester **9** with 2-bromooctanoyl halide **10** in toluene under modified Schotten−Baumann[20] conditions provided a 95% yield of (*R*)-bromodiester **11a**, which was a new, nonracemic intermediate for the subsequent synthesis of Orlistat **1**.

Initial laboratory preparations of **11a** involved adding pyridine in a 10 mol % excess to a hexane solution of **9** and **10** at 0 °C. This process was modified successfully to run in toluene with the addition of **10** to **9** in the presence of pyridine. However, use of pyridine on a large scale was undesirable due to odor concerns. Early attempts to use Schotten−Baumann conditions in which aqueous K$_2$CO$_3$ was added last to a toluene solution of reactants, or to use solid K$_2$CO$_3$ with a hexane solution of reactants, were unsuccessful. Pyridine was successfully replaced with 4-dimethylaminopyridine (DMAP) in a 2-mol % excess. Attempts to reduce the amount of DMAP using additional NaHCO$_3$ or KHCO$_3$ led to the finalized conditions employing 5-mol % DMAP and 1.5 equiv of KHCO$_3$.

The 2-bromooctanoyl bromide **10** was initially prepared by conversion of octanoic acid to octanoyl chloride using thionyl chloride, followed by bromination. Different bromination conditions produced varying amounts of **10a** and **10b** ranging from 60/40 to 98/2 (Scheme 5). The influence of the ratio **10a**/**10b** was investigated in the next reaction of the process: **10a**/**10b** containing as much as 18 wt % of **10b** has been used successfully, with less than 1% **11b** being formed. The level of **11b** present in the subsequent,

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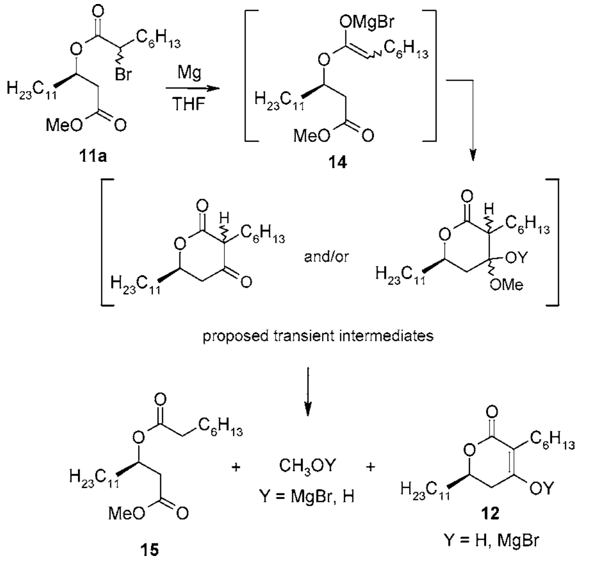
(17) (a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897. (b) Cereghetti, M.; Foricher, J.; Heiser, B.; Schmid, R. Eur. Pat. Appl. EP 398132, 1990. (c) Foricher, J.; Schmid, R. World Pat. Appl. WO 9315090, 1993. (d) Foricher, J.; Schmid, R. Eur. Pat. Appl. EP 0926152, 1998. (e) Foricher, J.; Heiser, B.; Schmid, R. Eur. Pat. Appl. EP 0530335, 1992.

(18) Nitrogen and hydrogen ex Carbagas 60 (≥99.99990% purity).

(19) Nitrogen and hydrogen ex Carbagas 25 (99.5% purity).

(20) (a) Schotten, C. *Ber.* **1884**, *17*, 2544. (b) Baumann, E. *Ber.* **1886**, *19*, 3218. (c) For a review see: Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 237.

***Scheme 6.*** **Intermediates and major products of the magnesium−metal reaction to 12**



magnesium-mediated ring closure to **12** was a concern since the presence of **11b** could significantly decrease the reaction rate and lead to a much reduced yield.

The commercially available 2-bromooctanoyl bromide **10a** contained variable amounts of **10b** typically ranging from 2−4%. The commercial **10a** was used on a large-scale producing ca. 2 tons of **11a**. The overall yield for the four batch campaign was 100.9% with an assay of 95.0% illustrating the excellent yields and robustness required for a large-scale process.

**c. Cyclization of 11:** The initial approach was to carry out the ring closure by treatment of a solution of (*R*)-bromodiester **11a** in tetrahydrofuran with magnesium metal as shown simplistically in Scheme 6. Maintaining a clean magnesium surface by the addition of 1,2-dibromoethane was required to consistently achieve yields in the 40−50% range. The major side product was the (*R*)-diester **15**, which could arise from protonation of the magnesium enolate **14** by either **12** or the methanol generated as a cyclization byproduct (Scheme 6). The R-diester could also be generated by equilibrium between the two possible enolates of **15** or from an intermolecular equilibrium between the various esters and their enolates. Although their yields were modest, these early experiments clearly indicated the potential of a second-generation process. The next stage of development work was to expand efforts to increase the yield from the initial 40−50% range.

**c.1. Screening Studies.** The first priority was to look at the main aspects of the reaction, such as (a) the best metal reagent; (b) the appropriate functional group(s) on **11** to facilitate ring closure; and (c) potentially large solvent effects. A quick screening of zinc, manganese, lithium, and magnesium showed that magnesium had the best potential. In an attempt to increase the cyclization rate and enhance the yield of **12**, potential alternatives to the methyl ester function of **11a** such as the corresponding morpholino amide, the *N*,*O*-dimethylhydroxylamide, the nitrile, the acid chloride, and the mixed pivaloyl anhydride were tested. However, none of these derivatives brought about an improved selectivity to **12**. Several solvents were investigated as potential alternatives to tetrahydrofuran. The use of toluene, diisopropyl ether, dimethylformamide, or 1,4-dioxane resulted in no formation of **12**. In ethers such as methyl *tert*-butyl ether, di-*n*-butyl ether, 1-methyltetrahydrofuran, 1,2-dimethoxyethane, and diethyl ether, **12** was formed, but yields were lower than those in tetrahydrofuran. All of these screening investigations resulted in lowering the yield of **12**.

**c.2. Activation of 11a by Magnesium Metal.** The second phase of exploration investigated more closely the magnesium-metal parameters such as particle size,[21] entraining reagents,[22] and reagent additives.[23] A too small magnesium particle size (both powders and flakes) resulted in the formation of thick, unmanageable slurries, and yields were not improved. In contrast, coarse magnesium chips (approximately $^{1}/_{8}$ to$^{1}/_{4}$ inch turnings) were most convenient for large scale production and allowed the reuse of any remaining magnesium metal as a heel left in the reactor. Magnesium-metal reactions typically require a surface activator or entrainment reagent to maintain optimum reaction activity. Other entraining reagents were investigated in an attempt to avoid the use of the toxic 1,2-dibromoethane. The use of trace amounts of cyclopentadiene, iodine, zinc chloride, or iron (III) bromide all appeared to increase the rate of Grignard formation as confirmed in the $^1$H NMR analysis indicated by the loss of the bromine after quenching the reaction mixture. However, in no instance was a significant increase in the isolated yield of **12** observed. Evidently, the key rate-limiting reaction of this step was slow ring closure.

Various additives were investigated in an attempt to either increase the cyclization rate or to minimize protonation of the intermediate magnesium enolate **14**. The reaction of 1,2-dibromoethane with magnesium not only furnishes a clean metallic surface on which **11a** can react but also results in the formation of ethylene and magnesium bromide. Since experiments in which all the 1,2-dibromoethane was added prior to the addition of **11a**, which is a less-effective surface-cleaning mode of addition, gave yields of approximately 48%, the presence of magnesium bromide was suspected to be enhancing the desired cyclization. Experiments using either magnesium chloride or magnesium iodide in the absence of 1,2-dibromoethane produced yields comparable to experiments performed in the presence of 1,2-dibromoethane alone. However, the addition of numerous other Lewis acids produced no significant yield increases beyond 50%. Some of the studied Lewis acids were zinc bromide, zinc chloride, magnesium chloride, magnesium bromide, magnesium iodide, copper(I) bromide, and diethylaluminum chloride. Addition of chlorotrimethylsilane or acetic anhydride as a prequench to react preferentially with the methanol

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reaction side product did not afford any yield benefits. The same held true for the addition of amine bases such as diisopropylethylamine and triethylamine. Apparently, these hindered bases did not effectively prevent a labile proton from causing side products. None of these additives aided in the ring-closure reaction or in stopping the side-reaction protonation to **15.**

**c.3. Fine-Tuning of the Magnesium-Metal Process Parameters.** Thus far, investigations had failed to increase the yield of **12**. By timed quench studies, the formation of the Grignard **14** from **11** was observed to be faster than the ring closure to **12**. Decreasing the production of **15** should result in an improved yield of **12**. A closer study of the reaction parameters, such as temperature, stoichiometry, order of addition and workup procedures, was initiated. A study of various reaction temperatures indicated that cyclization rates were optimal at 60 °C. Since a reasonable alternative to 1,2-dibromoethane was not found, a study was done to minimize the 1,2-dibromoethane amounts required for Grignard initiation and formation of the magnesium enolate **14**. It was found that once a magnesium heel had been formed, whether it was initiated by iodine or 1,2-dibromoethane, the reaction proceeded reasonably well. 1,2-Dibromoethane (1 equiv) added with the **11a** solution gave the best results with isolated **12** yields of about 50%. A 0.5 equiv amount of 1,2-dibromoethane resulted in an approximately 5−10% lower yield. No 1,2-dibromoethane gave 10−20% lower yield. It was observed that **11b** reacted at a much slower rate in the Grignard reaction than **11a**. The use of less than 1 molar equiv of 1,2-dibromoethane and 15−20 mol % **11b** (relative to **11a**) resulted in the yield decreasing from 45−50% to approximately 35%. However, the yield in the presence of 15−20% **11b** could be increased to 45−50% by using 1 molar equiv of 1,2-dibromoethane. Although the mechanistic reason for this yield dependency on the 1,2-dibromoethane charge is unclear, the additional 1,2-dibromoethane might be causing the conversion of **11b** to **11a** and, therefore, a **10b** limit of <2% in **10a** was set to have a consistent parameter. Although these parameter changes did not increase yields, close observations gave a hint as to how to increase the yield above 50%.

**c.4. Activation of 11a by Grignard Reagents.** The key hint on improving **12** yields was that somehow the magnesium-metal was affecting the reaction. The **11a** substrate was complicating the situation due to having other enolizable carbonyls that could complex with the magnesium metal and having easily detached protons that were available for intramolecular reduction of the **14** intermediate to **15**. Fortunately, no double addition side products were observed. Magnesium-metal insertion reactions into carbon−halogen bonds were first reported by Victor Grignard around 1900.[24] The reduction of a carbon−magnesium−bromide bond to a carbon−hydrogen bond and the double addition of a Grignard reagent to an ester are common problems with magnesium-metal reactions. Although the history of Grignard reactions is long, the mechanism of Grignard reactions is still not well understood.[25] Recent reviews still indicate some controversy on whether this pathway may be a radical-type reaction (single electron transfer) or quenched by an available labile proton (two electron transfer).[26] The presence of a competitive Grignard reagent, which could also react with the acidic protons in **11a**, a transient intermediate, **12**, or the methanol byproduct, might possibly decrease production of **15**. A study of several simple Grignard reagents (methyl, isopropyl, *sec*-butyl, and *tert*-butyl) did result in reduction of **15** as a side product and with optimized conditions improved yields of **12** up to the 60−75% range. Since the reaction of **11a** occurred rapidly with magnesium metal even at low temperatures, an experiment was performed without the magnesium metal. Interestingly, the reaction produced the same yields when using 2 to 3 equiv of the Grignard reagent. This development removed the complexities of maintaining a clean metal surface with the toxic 1,2-dibromoethane. Analyses of periodic, quenched-reaction samples suggested that although all of the **11a** was being immediately consumed through rapid metal−halogen exchange, the cyclization product was being formed at a much slower rate. Although the trans-metalation from *tert*-butyl magnesium chloride to **14** was rapid even at −78 °C, acceptable cyclization rates of the intermediate enolate **14** still required temperatures of approximately 60 °C. The *tert*-butyl Grignard reagent gave superior product yields over longer times than other comparable Grignard reagents due to less decomposition once the reaction approached completion. The proposed mechanism for the reaction of *tert*-butyl magnesium chloride with **11a** is shown in Scheme 7.

The apparent lower propensity of *tert*-butyl magnesium chloride to form side products may be due to its steric bulk, which decreases its nucleophilicity and its propensity to react with the *tert*-butyl bromide byproduct. Since solutions of *tert*-butyl magnesium chloride in tetrahydrofuran are commercially available or can readily be prepared from *tert*-butyl chloride and magnesium-metal, this Grignard reagent was chosen for further development. This new variation does not fit into either of the traditional zinc Reformatsky[27] or magnesium Barbier[28] reactions. The utilization of this different halogen−magnesium exchange reaction seems to be part of a growing field.[29]

The commercial solutions of ca. 1 M *tert*-butyl magnesium chloride showed a very low propensity to form a precipitate upon storage at 20−25 °C. Since the proposed cyclization mechanism suggested that 3 molar equiv of Grignard reagent were required, a series of experiments was performed by the slow addition of **11a** to 2.5−5.0 equiv of *tert*-butyl magnesium chloride at 60 °C. With the slow addition no exothermic reaction was observed, even on scale-

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***Scheme 7.*** **Simplified reaction pathway for the halogen−magnesium exchange reaction to 12**

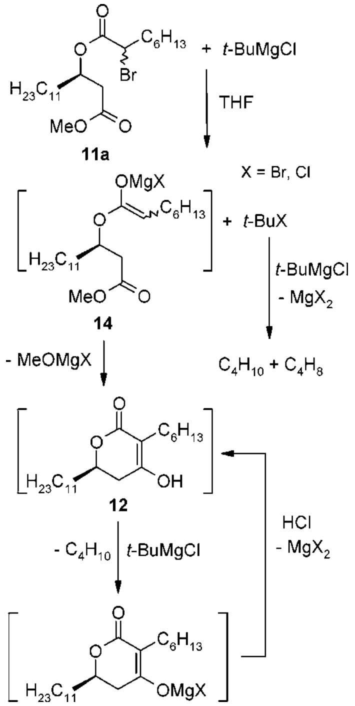

***Table 3.*** **Influence of *t*-BuMgCl/11a molar ratio**

| entry | *t*-BuMgCl/**11a** (mol/mol) | isolated yield (%) |
|---|---|---|
| 1 | 2.50 | 66.4 |
| 2 | 2.75 | 74.0 |
| 3 | 3.00 | 78.4 |
| 4 | 3.25 | 74.5 |
| 5 | 3.50 | 72.9 |
| 6 | 5.00 | 72.6 |

up. The results (Table 3) show that the yield was fairly constant when a range of 2.75−5.0 equiv of Grignard reagent was used.

The final major yield-enhancing breakthrough was the discovery that simultaneous addition of *tert*-butyl magnesium chloride and a solution of **11a** in tetrahydrofuran to a small amount of tetrahydrofuran at 60 °C produced yields of approximately 85%. It was unclear why this mode of addition was so beneficial, but apparently, this addition mode further decreased undesired side reactions due to excess Grignard reagent. The reverse addition of *tert*-butyl magnesium chloride to **11a** minimized excess Grignard reagent but resulted in a yield decrease of 5−10%.

**c.5. Workup of the Cyclization Mixture.** Concurrent with alterations in the cyclization step itself, the subsequent workup procedure underwent numerous modifications throughout both the research and development phases. The initial workup of the Grignard process involved decanting the product-containing tetrahydrofuran solution away from the magnesium-metal heel, distilling off the tetrahydrofuran, dissolving the residue in ethyl acetate, and washing the organic phase with hydrochloric acid followed by water. Finally, removal under a vacuum of all the ethyl acetate produced a residue, which was then slurried in hexane. The product was isolated after filtering and drying.

***Table 4.*** **Quench study**

| | | | | wt % yield of **12** in solution after | | | |
|---|---|---|---|---|---|---|---|
| entry | acid | equiv | pH | 0 h | 3 h | 22 h | 48 h |
| 1 | HCl | 3.2 | 0 | 88 | 89 | 88 | 86 |
| 2 | citric | 3.1 | 1.3 | 86 | 90 | 91 | 91 |
| 3 | citric | 2.1 | 7 | 87 | 90 | 87 | |
| 4 | citric | 1.5 | 8 | 89 | 89 | 75 | 67 |

The workup procedure required both an extraction solvent system and a crystallization solvent system. The presence of magnesium salts in the reaction mixture necessitated an aqueous-acid workup and, consequently, displacement of tetrahydrofuran with a relatively water-immiscible extraction solvent. A crystallization-solvent system which did not involve distillation of the product to dryness was also needed. Ideally, a single-solvent system could satisfy all requirements. A number of potential extraction solvents were studied, including ethyl acetate, isopropyl acetate, methylene chloride, methyl *tert*-butyl ether, and toluene. All of these solvents worked fairly well with the main differences being the amount of solvent required to completely dissolve **12**. Since methyl *tert*-butyl ether and heptane were utilized in the first-generation process, these two solvents were ultimately selected as the extraction and crystallization solvents, respectively.

Since the instability of **12** to either strongly acidic or strongly basic conditions was known, citric acid, which is a relatively weak acid, was investigated as an alternative to hydrochloric acid. In a laboratory stability study, a methyl *tert*-butyl ether/tetrahydrofuran slurry of a crude reaction mixture was transferred into various quench mixtures as shown in Table 4. When 3.1−3.2 equiv of acid were utilized, the 48 h samples indicated that approximately a 5% extra yield loss was suffered in the hydrochloric acid experiment relative to citric acid. As expected, it was found that quenching with only 1.5 equiv of citric acid resulted in significant degradation of **12** within 22 h, while using 2.1 equiv of citric acid resulted in stable assays of **12** out to at least 22 h. The final use of 3 equiv of citric acid (relative to **11a**) represented an attempt to build robustness into the process by keeping the pH slightly on the acidic side. A second citric acid wash (0.5 equiv) was found to significantly decrease the amount of magnesium salts remaining in the organic phase.

Since the hydrogenation of **12** to **13** in the first-generation process had been shown to be highly sensitive to salts entrained in **12**, numerous water washes were required to decrease these salts to an acceptable level. The citric acid workup typically required five water washes to decrease the conductivity of the last aqueous phase to <200 $\mu$ siemens, which was a level that had been shown to ensure acceptable hydrogenation rates. As the water washing progressed, the pH of the aqueous washes gradually increased from approximately 2.5 to approximately 3.5.

Several experiments, which utilized various batches of both *tert*-butyl Grignard reagent and **11a**, were performed under the final conditions. Data from these experiments confirmed that the process was capable of producing 80–88% yields of **12** having 99–100% purity. A large-scale production campaign produced ca. 760 kg of **12**. The overall average large-scale yield from **11a** was 83.7% with a purity of >99.5%.

**Synthesis of (3*S*,4*S*,6*R*)-$\delta$-Lactone 13.** In the second reaction sequence, no major changes from the first-generation process were needed to diastereoselectively reduce enantiomerically pure **12** to enantiomerically pure **13**.[3u] A large-scale production campaign using the Raney Nickel catalyzed heterogeneous hydrogenation of **12** afforded ca. 360 kg of **13** in 86% yield with an average purity >98%. No other diastereomer was observed above 1.5%.

**Synthesis of PEA-Salt 4.** The subsequent third reaction sequence was also carried out in analogy to the first-generation process.[3u] Hydroxy-$\delta$-lactone **13** was first THP-protected, followed by saponification of the $\delta$-lactone, selective benzylation of the $\delta$-hydroxy group, and deprotection of the THP-ether. After treatment with (*S*)-phenylethylamine, the enantiomerically pure PEA-salt **4** was isolated in double the yield of **4** to that produced by the first-generation optical resolution based process. Isolation of **4** via crystallization remained necessary to meet the previously set purity specifications and to ensure a substrate quality suitable for further transformation into **1**. A large-scale production of the PEA-salt **4** produced over 250 kg in 88% yield.

**Final Steps to Orlistat.** There were virtually no differences in the last reaction sequence between the first- and second-generation Orlistat processes for the conversion of **4** to **1**.[3u] Benzenesulfonyl chloride promoted $\beta$-lactonization of **4** and subsequent debenzylation afforded the (*S*,*S*,*R*)-oxetanone **5** in 85% yield (Step 4). In the last step (Step 5), the *N*-formyl-L-leucine building block was introduced using Mitsunobu conditions to yield Orlistat **1** on a multi-10 kg scale in 80% yield. The second-generation process produced **1** that was equivalent and met all first-generation specifications.

## Conclusion

The comparison of first- and second-generation Orlistat processes shows significant improvements for the new synthetic route. The overall yield of the enantioselective, second-generation process for **1** from **6** amounts to 41–48%, which compares very favorably with the 18–22% achieved with the first-generation, optical resolution based process of **4**. Particularly, the herein described hydrogenation process proved to be highly robust, such that the large-scale production of $\beta$-hydroxyester **9** with very high ee (>99%) and purity (>99%) by asymmetric hydrogenation of $\beta$-ketoester **6** was straightforward and practical. The acylation of **9** and subsequent cyclization of **11** to the single enantiomer **12** proved to be a robust and high yielding process also. The new enantioselective synthesis utilized the same chemistry for the later steps as the original process. The key aspect of the improved enantioselective synthesis was that now the resulting **12** was enantiomerically pure and not a racemate (as in **2**). This improvement removed the late stage resolution required at **4** in the original synthesis and allowed doubling the throughput in the later steps. In summary, the goal set at the beginning of the work, i.e., to create a significantly more efficient process by obviating the late-stage resolution present in the first-generation process, was achieved using inexpensive commercially available starting materials.

## Experimental Section

**General.** All reagents and solvents, if not otherwise noted, were obtained from commercial suppliers and used without further purification. All gases used in the large-scale production runs were of technical grade (99.5% purity). The diphosphines and ruthenium complexes were either purchased from Strem (**7e**,**g**,**j**–**m**) or prepared according to or in analogy to, respectively, the literature (**7a**–**d**,**f**,**h**,[17]**i**,[30] **8a**–**m**).[4,13] Melting points were determined on a Büchi 510 and are uncorrected. $^1$H NMR spectra (at 250 MHz on a Bruker AC 250E spectrometer or at 300 MHz on a General Electric QE300 spectrometer) were recorded by using TMS as an internal standard. Chemical shifts are given in ppm ($\delta$), and *J* values, in hertz. ESI-MS spectra were measured on a Perkin-Elmer Sciex API III. Elemental analyses were carried out on a Carlo Erba 1160 elemental analyzer.

For the determination of conversion and chemical purity of **9** (both enantiomers) by GC (column: DB-1, injector: 280 °C, detector: 330 °C, oven: 50–320 °C/5 °C per min, carrier gas: He (70 kPa)); a sample of the methanolic reaction mixture was evaporated to dryness, 2 mg of the residue were dissolved in 500 $\mu$L of pyridine and 500 $\mu$L of BSTFA/1% TMCS, and the mixture was stirred for 1 h at room temperature. GC retention times: 22.8 min, **8** (both enantiomers); 23.5 and 23.7 min **6** (i.e., *cis* and *trans* silylenol ethers of **6**).

For enantiomeric purity determination of **9** by GC (column: Optima-240, injector: 280 °C, detector: 300 °C, oven: 200–290 °C/3 °C per min, carrier gas: He (80 kPa)); a 2 mg sample of the evaporated residue from above was dissolved in 1 mL of dichloromethane, and then 10 mg of (*S*)-Trolox-methyl ether, 15 mg of 1,3-dicyclohexylcarbodiimide, and 0.1 g of 4-dimethylaminopyridine were added to the solution. The resulting mixture was stirred for 30 min at 60 °C and filtered (Acrodisc PFTE 0.45 $\mu$m). GC retention times: 26.8 min, (*S*)-enantiomer of **9**; 27.6 min, **9**.

**Methyl (*R*)-3-Hydroxytetradecanoate (9):** A 200-mL stainless steel addition device which was connected to a 2-L autoclave was charged in the air with 1 N aqueous hydrogen chloride (0.62 mL, 0.62 mmol) and methanol (100 mL). The addition device was sealed and purged with nitrogen. Afterwards, the autoclave was charged in the air with **8b** (27.9 mg, $31.2 \times 10^{-6}$ mol, S/C $5 \times 10^4$), **6** (400 g, 1.56 mol), and methanol (658 mL). The autoclave was sealed and purged with nitrogen. The bottom valve of the addition device was opened, and the aqueous-methanolic solution of hydrogen chloride was introduced into the autoclave. The

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reaction mixture was stirred for 30 min at 20 °C. Nitrogen was then replaced by hydrogen (30 bar), and the mixture was heated to 80 °C. After 25 min at a reaction temperature of 80 °C, the pressure had reached 31 bar. The hydrogen pressure was set to a constant 40 bar. After 4 h, the conversion was complete (>99.9%, 99.0% ee), and the autoclave was cooled to 20 °C. The hydrogen pressure was released, and the autoclave was purged with nitrogen. The slightly yellow solution was transferred to a 2-L Erlenmeyer flask, and the autoclave was washed with methanol (300 mL). The methanolic solutions were combined. If desired, the methanol solution of **9** can be utilized directly in the next step.

Rotatory evaporation of the combined methanolic solution to dryness at 50 °C/30 mbar gave crude **9** (397.1 g) as a white, waxy solid. Crude **9** (10.9 g) was dissolved in hexane (52 mL) at 30 °C and then cooled in an ice bath. At 15 °C, a few seed crystals of pure **9** were added to promote crystallization. The resulting suspension was stirred for 4 h at 0−5 °C and then stored overnight at −15 °C. The white precipitate was filtered off, washed with ice-cold hexane (20 mL), and dried under a vacuum (0.1 bar) for 6 h at room temperature to yield pure **9** (10.2 g, 92% yield) as white crystals with 99.7% purity (GC %AN) and 99.7% ee. Mp 40 °C. MS (EI): 259 ($M + H^+$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 4.10−3.90 (m, 1H), 3.71 (s, 3H), 2.84 (d, 1H, $J = 2.5$ Hz), 2.52 (dd, 1H, $J = 10.3, 1.7$ Hz), 2.41 (dd, 1H, $J = 10.3, 5.5$ Hz), 1.6−1.2 (m, 20H), 0.88 (t, 3H, $J = 4.2$ Hz). Anal. calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.57; H, 11.79. Ru content (X-ray fluorescence): 6 ppm.

Alternatively, a 2000-L autoclave was charged with a methanolic solution of **6** and the pre-catalyst **8b** (S/C 50 000). After the autoclave was purged with technical grade nitrogen, 1 N HCl (20 equiv relative to **8b**) in methanol was added through a 3-L autoclave-addition device previously purged with technical grade nitrogen to form the air-sensitive catalyst. Nitrogen was replaced by technical grade hydrogen (40 bar), and the temperature was set to 40 °C. After 4−16 h the conversion was complete, and the methanolic solution of **9** was used directly in the next step.

**(*R*)-3-[(2-Bromo-1-oxo-octyl)oxy]-tetradecanoic Acid Methyl Ester (11a).** (*R*)-hydroxyester **9** (351.1 g, 547.6 mmol, 40.3 wt % solution in methanol) was added to a 1-L, three-neck, jacketed, round-bottom flask, which was equipped with a distillation condenser, an addition funnel, a nitrogen inlet, a thermocouple, and a mechanical stirrer. Most of the methanol was removed by vacuum distillation. Toluene (360 mL) was added to the residue, and solvents were again removed by vacuum distillation. 4-Dimethylaminopyridine (3.3 g, 27 mmol), $KHCO_3$ (78.75 g, 786.5 mmol), water (40 mL), and toluene (25 mL) were added to the reaction mixture. The mixture was stirred and cooled to 11 °C. 2-Bromooctanoyl bromide (173.4 g, 602 mmol, 96.4 wt % 2-bromooctanoyl bromide, 2.5 wt % 2-bromooctanoyl chloride) was added to the stirred, reaction mixture at approximately 100 mL/h over 1.5 h. The mixture was stirred for 2 h at 10 °C and then sampled for reaction completion (0.07 wt % **9**). Water (108 mL) was added, and the mixture was stirred for 15 min at 10 °C. The mixture was allowed to settle, and the phases were separated. The organic phase was washed with water (2 × 108 mL, 10 °C). Solvents and residual water were removed by vacuum distillation and gave **11a** as an orange oil (261.8 g, 103% yield, typically 4−5 wt % toluene). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.28 (dt, 1H, $J = 6.4$ Hz), 4.17 (dd, 1H, $J = 7.5$ Hz, $J = 7.5$ Hz), 3.67 (s, 3H), 2.60 (m, 2H), 2.00 (m, 2H), 1.65 (m, 2H), 1.25 (m, 26H), 0.88 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.60, 170.56, 169.26, 169.15, 72.15, 72.10, 51.91, 51.83, 46.18, 46.12, 46.05, 38.92, 38.87, 35.12, 34.96, 34.92, 34.17, 33.95, 32.01, 31.62, 31.45, 29.96, 29.72, 29.60, 29.54, 29.45, 29.36, 29.14, 28.82, 28.64, 27.29, 25.08, 25.00, 22.79, 22.60, 14.20, 14.09.

**(*R*)-3-Hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2*H*-pyran-2-one (12).** Tetrahydrofuran (60 mL) was added to a 2-L, three-neck, jacketed, round-bottom Morton flask, which was equipped with a distillation condenser, two syringe pumps, a nitrogen inlet, a thermocouple, and a mechanical stirrer. The mixture was heated to 60 °C. (*R*)-Bromo diester **11a** (89.7 g, 95.0 wt %, 184 mmol) was placed into one of the syringe pumps. *tert*-Butyl magnesium chloride/tetrahydrofuran (685 mL, 1.02 M total base, 0.94 M active base, 645 mmol) was placed into the other syringe pump. Both solutions were added simultaneously over a 5-h addition period (addition rates of 17.2 mL/h and 137 mL/h, respectively). Once the additions were complete, the reaction mixture was held at 60 °C for 2 h, cooled to 20 °C over 3 h, and held at 20 °C for 12.5 h. The reaction mixture was sampled for reaction completion (glc analysis). The reaction mixture was concentrated by vacuum distillation to ca. 400 mL (ca. 50% of the original volume). *tert*-Butyl methyl ether (275 mL) was added to the mixture to produce a fluid, cream-colored suspension. Tetrahydrofuran (17.5 mL) was added to the suspension. Another 2-L, three-neck, jacketed, round-bottom Morton flask, which was equipped with a distillation condenser, a nitrogen inlet, a thermocouple, and a mechanical stirrer, was used to prepare a solution of citric acid (43.32 g) and water (142 mL). The cream-colored suspension was slowly pumped into the stirred, aqueous citric acid solution over 60 min via Teflon tubing. The suspension flask was rinsed through the tubing into the quench vessel with 17.5 mL of tetrahydrofuran. The resulting reaction mixture was heated to 30 °C, and 75 mL of *tert*-butyl methyl ether were added. Stirring was continued for ca. 2 h. After the mixture was allowed to settle, the lower aqueous phase was drained from the upper product-containing organic layer. A solution of citric acid (6.75 g) and water (111 mL) was added to the remaining organic layer. The mixture was stirred and allowed to settle, and the aqueous layer was separated from the product-containing organic phase. The remaining organic layer was washed with water (5 × 88 mL). The mixture was concentrated by vacuum distillation to ca. 400 mL. *n*-Heptane (460 mL) was added over ca. 1 h resulting in a very thin suspension. The mixture was concentrated again by vacuum distillation to ca. 400 mL, and *n*-heptane (184 mL) was added slowly. The suspension was stirred for 2 h at 25 °C, cooled to 5 °C over 1 h, and then held at 5 °C for 13.5 h. The slurry was filtered, rinsed with cold *n*-heptane (184 mL), and dried. The product **12** was isolated as a white solid (56.12

g, 86.5% yield, 99.99% purity (GC wt/wt)). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (keto form) 4.68 (m, 1H), 3.41 (t, 1H, $J = 5.6$ Hz), 2.72 (dd, 1H, $J = 3.0$ Hz, $J = 15.9$ Hz), 2.42 (dd, 1H, $J = 11.5$ Hz, $J = 18.8$ Hz), 2.00−1.49 (m, 6H), 1.49−1.20 (m, 24H), 0.88 (m, 6H); (enol form) 8.07 (s, 1H), 4.32 (m, 1H), 2.51 (m, 2H), 2.27 (m, 2H), 1.75 (m, 1H), 1.61 (m, 1H), 1.52−1.15 (m, 26H), 0.88 (m, 6H).

Typically, the magnesium route generated a 1:1 mixture of the enol and keto forms. The enol form slowly equilibrated to the keto form in $CDCl_3$, which contained a trace of hydrogen chloride. The keto-form NMR spectrum was identical to that found in the literature.[31] The ratio of the keto/enol forms was solvent dependent. The NMR data for the enol-form was obtained using a malonate synthetic route.[6]

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