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Development of a Scalable Synthesis of (*S*)-3-Fluoromethyl-γ-butyrolactone, Building Block for Carmegliptin's Lactam Moiety‖

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ABSTRACT: Several new routes are reported for the synthesis of (*S*)-3-fluoromethyl-γ-butyrolactone. An asymmetric hydrogenation-based synthesis was chosen as the enabling route to produce the lactone on a 10-kg scale. A superior stereoselective route starting from (*S*)-*tert*-butyl glycidyl ether which afforded the desired lactone in three steps with ∼50% overall yield was finally selected for further development and production.

1. INTRODUCTION

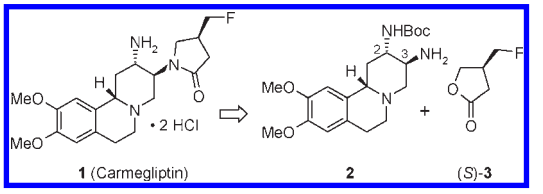
Carmegliptin (**1**) is a potent and long-acting DPP-IV inhibitor which in clinical studies has proven its suitability as a safe oral antidiabetic agent with once-daily administration.[1] Carmegliptin belongs to a new, structurally distinct class of DPP-IV inhibitors featuring a tricyclic 2-amino-hexahydro-benzo[*a*]quinolizine core bearing heteroaromatic, aromatic, or nonaromatic substituents in the 3-position.[2] Specifically, the substituent consists of a five-membered fluoromethyl-substituted lactam in the case of **1**. The preceding paper in this issue describes process research and development work for the synthesis of the Boc-protected 2,3-diamino-hexahydro-benzo[*a*]quinolizine core **2** and its conversion into the active pharmaceutical ingredient (API) by coupling with (*S*)-3-fluoromethyl-γ-butyrolactone ((*S*)-**3**, Scheme 1).[3] In the present contribution the process chemistry for the synthesis of fluoromethyl lactone (*S*)-**3** is reported.[4]

In the initial discovery chemistry work, fluoromethyl lactone *rac*-**3** was prepared from 1,3-diacetoxyacetone (**4**) by a sequence of Horner−Wadsworth−Emmons olefination with triethyl phosphonoacetate, acid-catalyzed transesterification−lactonization to provide the hydroxymethyl butenolide **6**,[5] double bond hydrogenation, and final deoxyfluorination with diethylaminosulfur trifluoride (DAST, Scheme 2). Fluoromethyl lactone *rac*-**3** was used in the coupling with enantiomerically pure tricyclic core **2**, an approach requiring diastereomer separation on the way to the API.[3]

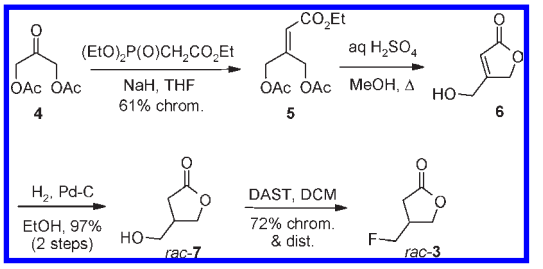
In subsequent discovery chemistry work, fluoromethyl lactone (*S*)-**3** was prepared from (*S*)-paraconic acid ((*S*)-**11**) which was obtained by a literature-known route involving Evans' alkylation chemistry as key step (Scheme 3).[6] Borane reduction of (*S*)-**11** followed by deoxyfluorination of (*R*)-**7** with DAST produced (*S*)-**3**, ready for use in the coupling with **2**.[3]

Limitations of this synthesis of (*S*)-**3** towards scale-up were its high number of steps, the low overall yield, and the known propensity of the intermediate (*R*)-**7** to racemize.[7] The limited thermal stability and the high costs of DAST used in the deoxyfluorination reaction were also of some concern. A new route to (*S*)-**3** should preferably be shorter, avoid (*R*)-**7** as intermediate, and use an inexpensive fluorination reagent. Various approaches towards these goals were evaluated in the course of the project, among them approaches involving asymmetric catalysis, enzymatic desymmetrization, and syntheses from readily available enantiopure precursors.

Scheme 1. Assembly of carmegliptin



Scheme 2. Synthesis of fluoromethyl lactone *rac*-3



2. ASYMMETRIC HYDROGENATION-BASED SYNTHESIS

Asymmetric reduction of fluoromethyl butenolide **13** (Scheme 4) could provide an attractive and straightforward access to (*S*)-**3** using asymmetric hydrogenation,[8] hydrosilylation,[9] conjugate hydride addition,[10] or yeast reduction[11] that have been reported for the reduction of butenolides, specifically also for 3-alkyl-, 3-acetoxymethyl-, and 3-benzyloxymethyl-butenolides.[12] Asymmetric reductions of 3-halomethyl-butenolides, though, have not yet been described to the best of our knowledge. Process research work commenced with the search for an efficient synthesis of

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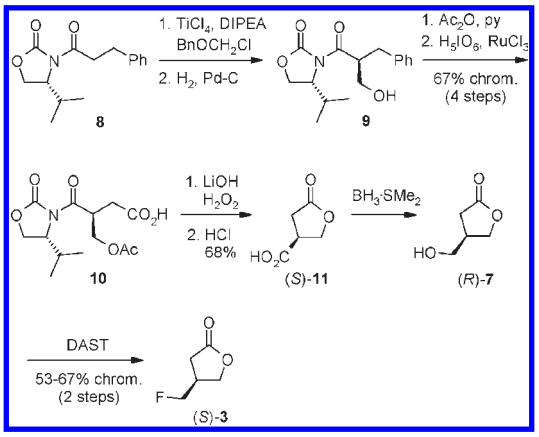
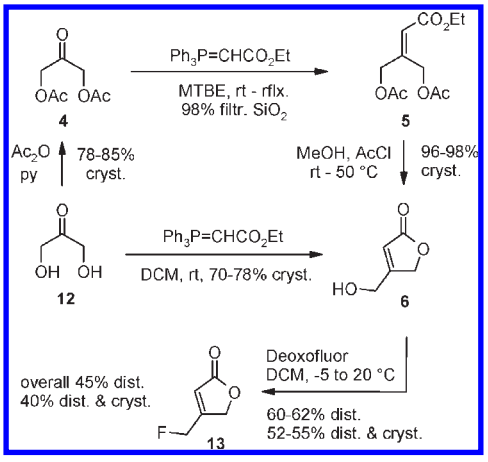
Scheme 3. Synthesis of fluoromethyl lactone (*S*)-3



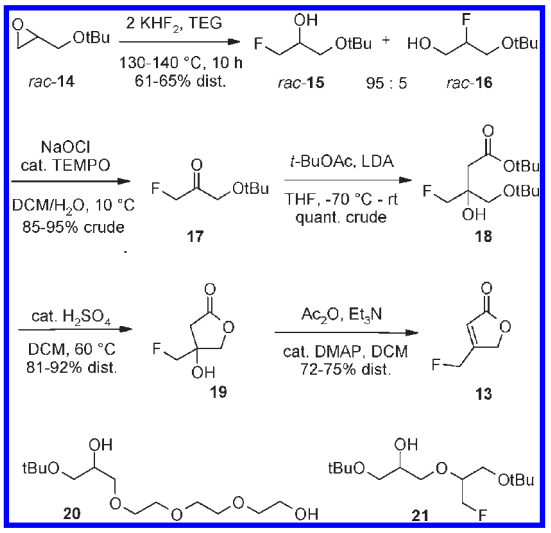
Scheme 4. Wittig route to fluoromethyl butenolide 13



fluoromethyl butenolide **13**. Several routes towards **13** were investigated (Schemes 4 and 5).

2.1. Wittig Route to Fluoromethyl Butenolide 13. In analogy to the first steps of the initial discovery chemistry route to *rac*-**3**, 1,3-diacetoxyacetone (**4**) was subjected to Wittig reaction with $Ph_3P{=}CHCO_2Et$ (1.2 equiv)[13] in methyl *tert*-butyl ether (MTBE) to afford the α,β-unsaturated ester **5** in 98% yield after filtration over silica gel (Scheme 4). The Wittig reaction replaced the less selective, chromatography-requiring, and lower-yielding Horner–Wadsworth–Emmons reaction previously used. The requisite diacetate **4** was produced by acetylation (3 equiv Ac_2O, pyridine) of inexpensive 1,3-dihydroxyacetone (**12**) in nonoptimized yields of 78–85% after crystallization.[14] Treatment of **5** with dry HCl in methanol resulted in clean deacetylation–lactonization to afford the hydroxymethyl butenolide **6** in 96–98% yield after crystallization from heptane/dichloromethane (DCM).[15] Proof of concept was also demonstrated for a one-step Wittig access to **6**. Reaction of **12** with $Ph_3P{=}CHCO_2Et$ (1.2 equiv) in DCM followed by spontaneous cyclization provided **6** in an isolated yield of 70–78%.[14] Workup consisted in separation of the water-soluble **6** from the DCM-soluble triphenylphosphine oxide (TPPO) and crystallization. Product purity, however, was unsatisfactory and further work would have been required to optimize this one-step access to **6**.[16]

Scheme 5. *tert*-Butyl glycidyl ether route to 13



Deoxyfluorination of **6** was performed with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor, 1.1 equiv), a reagent reported to be thermally more stable than DAST.[17] Fluoromethyl butenolide **13** was obtained in 60–81% yield after distillation. Crystallization of the low-melting **13** (mp 28–29 °C) from MTBE or MTBE/heptane was used to ensure a quality suitable for asymmetric hydrogenation. Some efforts were undertaken to replace the expensive Deoxofluor reagent. Reaction of **6** with inexpensive perfluoro-1-butanesulfonyl fluoride (PBSF, 2 equiv) in the presence of diisopropylethylamine (DIPEA, 6 equiv) and DIPEA·3HF (2 equiv)[18] afforded **13** in 76% yield on small scale after silica gel chromatography and distillation. However, on larger scale yields dropped despite extensive parameter variation (stoichiometry, order of reagent addition, solvent), and chromatographic purification remained unavoidable, leading to discontinuation of this deoxyfluorination protocol.

2.2. *tert*-Butyl Glycidyl Ether Route to Fluoromethyl Butenolide 13. The approaches reported above relied on DAST or Deoxofluor as nucleophilic fluorine source and an activated alcohol as electrophilic reaction partner. In our search for more economical fluoride sources we shifted our focus to epoxides as electrophiles. Their propensity to undergo ring-opening with various HF-delivering reagents is well documented.[19] *tert*-Butyl glycidyl ether (*rac*-**14**, Scheme 5) was selected as the starting epoxide because of its ready availability as a cheap bulk chemical and the expected stability of the *tert*-butyl ether under ring-opening conditions. In the event, the previously unreported fluorinative ring-opening of *rac*-**14** was accomplished with potassium hydrogen difluoride (KHF_2) in triethylene glycol (TEG) analogous to a protocol devised for other epoxides.[20] Thus, heating *rac*-**14** in a suspension of KHF_2 in TEG (130 °C, mol ratio *rac*-**14**/KHF_2/TEG = 1:2:1.5) provided the regioisomeric fluorohydrins *rac*-**15** and *rac*-**16** (~70%) in a 95:5 ratio. Major byproducts were diol **20** (~25%), originating from competing epoxide opening with TEG, and ether **21** (~3%), the secondary product from epoxide opening with *rac*-**15**. Distillation afforded *rac*-**15**/*rac*-**16** mixtures with slightly improved ratios of up to 98:2 in yields of 61–65% based on *rac*-**14**.[21] Replacing the TEG solvent by diethylene glycol (DEG) or ethylene glycol (EG) led to lower yields due to increased formation of solvolysis products, while tetraethylene glycol (TEEG) required a higher reaction temperature

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Table 1. Fluorinative ring-opening of epoxide *rac*-14

#	reagent (equiv)	solv.	cond. °C/h	rac-**15**/rac-**16**[a]	yield dist. (%)
1	KHF_2 (2.5)	TEG	130/10	95:5	64
2	KHF_2 (2)[b]	TEG	130/6	95:5	63
3	KHF_2 (2)	DEG	130/5	95:5	54
4	KHF_2 (2)	EG	130/4	92:8	30
5	KHF_2 (2)	TEEG	150/7	95:5	58
6	$Et_3N\cdot 3HF$ (2)	neat	110/2	79:21	53
7	DIPEA·3HF (2)	neat[c]	110/2	82:18	nd[d]
8	$Et_3N\cdot 2HF$ (2.7)	neat	110/4	86:14	nd[d]

[a] By GC analysis; conversion >90% unless otherwise noted. [b] KHF_2 was finely ground. [c] Conversion 76%. [d] nd = not distilled.

of 150 °C (Table 1, entries 1−5).[22] HF-delivering agents other than KHF_2 such as $Et_3N\cdot 3HF$, DIPEA·3HF, or $Et_3N\cdot 2HF$[23] proved inferior in terms of regio- and/or chemoselectivity (Table 1, entries 6−8). TEMPO-catalyzed bleach oxidation of the mixture *rac*-**15**/*rac*-**16** provided ketone **17** in 84−95% crude yield, whereby the minor fluorohydrin *rac*-**16** was oxidized to the corresponding water-soluble acid which was washed out in the workup.

Addition of the Li-enolate of *tert*-butyl acetate to **17** (THF, −70 °C) produced hydroxy ester **18** which upon heating in 1,2-dimethoxyethane (DME) in the presence of catalytic amounts of conc. H_2SO_4 underwent ester and ether cleavage and subsequent lactonization providing hydroxy lactone **19** in virtually quantitative yield.[24] Dehydration of **19** was accomplished preferably with acetic anhydride/triethylamine in the presence of a catalytic amount of DMAP to give **13** in 72−75% yield after distillation and crystallization from MTBE.[25]

2.3. Asymmetric Hydrogenation of Fluoromethyl Butenolide 13. Microbial reduction, hydrosilylation, and hydrogenation were evaluated for the asymmetric reduction of **13**. Microbial reduction was abandoned early on because only 1 out of 1200 strains provided the desired (*S*)-configuration, and moreover, enantioselectivity (89% ee) and rate were unsatisfactory.[26] In Cu-catalyzed hydrosilylations of **13** using Buchwald conditions[9] (1 mol % bisphosphine ligand, 2.5 mol % $CuCl_2\cdot H_2O$, 0.2 equiv NaO*t*-Bu, 4 equiv polymethylhydrosiloxane) the atropisomeric bisphosphine (*R*)-BIPHEMP (**22a**, Figure 1) was identified to be the best ligand leading to (*S*)-**3** with up to 91% ee. However, preparative runs pointed to difficulties in the workup and purification at larger-scale, prompting us to search for a viable asymmetric hydrogenation protocol.

In the asymmetric hydrogenation of **13**, Rh, Ir, and Ru catalysts derived from a variety of bisphosphine ligands **22a**−**t** (Figure 1) were evaluated, and two effective catalysts were identified, one Rh- the other Ru-based (Scheme 6).[27] In the Rh domain (Table 2, left column) the highest ee of 93% was achieved with the catalyst derived from the bithiophene−bisphosphine ligand (*S*)-TMBTP (**22l**).[28] This catalyst was moderately active and substrate/catalyst ratios (*S*/*C*) of up to 1000 were reached (50 bar H_2, DCM, 40 °C).[29] Among the Ru catalysts[30] tested (Table 2, right column), the complex [$Ru(OAc)_2$((*R*)-3,5-*t*-Bu-MeOBIPHEP)] (**23**) derived from the sterically demanding bisphosphine **22f** was highly active (*S*/*C* up to 15,000). It proved most suitable, affording (*S*)-**3** in 92% ee under screening conditions and in 96−97% ee under optimized conditions (5−10 bar H_2, MeOH, 30 °C, substrate conc. 24% w/w).[31] Solvent effects

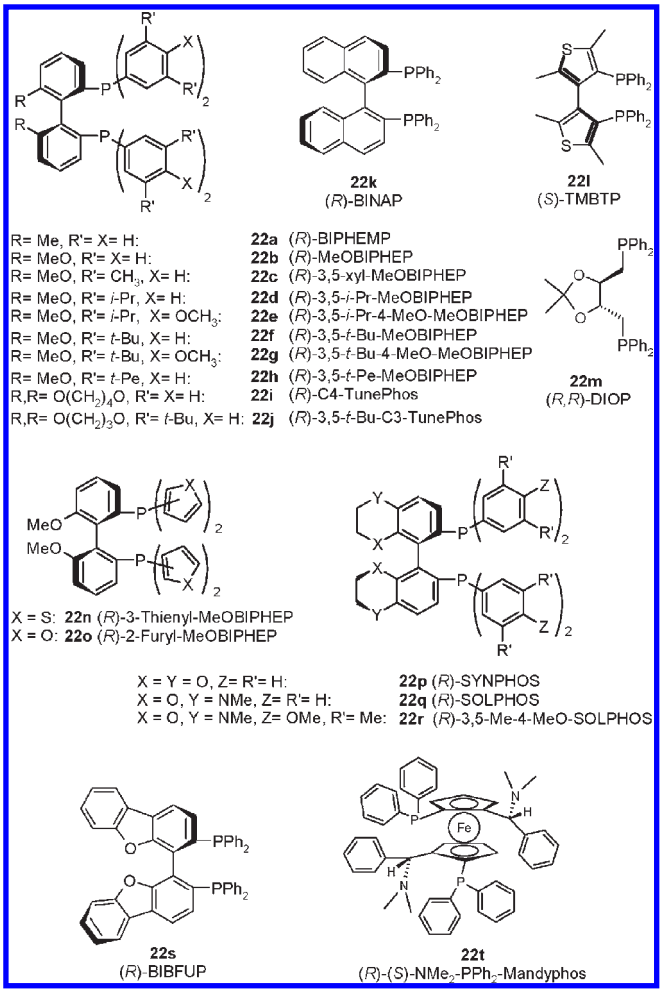
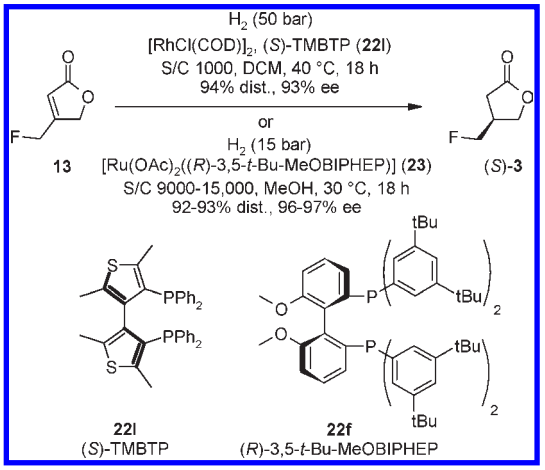


Figure 1. Bisphosphine ligands evaluated in the asymmetric hydrogenation of **13**.

Scheme 6. Asymmetric hydrogenation of fluoromethyl butenolide 13



observed in the hydrogenation of **13** with catalyst **23** are shown in Table 3. Although the highest enantioselectivity was obtained in 2,2,2-trifluoroethanol (TFE, >99% ee, entry 1), methanol was selected as solvent for cost reasons.

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Table 2. Influence of bisphosphine ligand in the Rh- and Ru-catalyzed hydrogenation of 13 to (*S*)-3

	Rh-cat.[a]		Ru-cat.[b]	
#	P^P	% ee	P^P	% ee
1	*ent*-**22a**	52	**22a**	76
2	*ent*-**22b**	55	**22b**	68
3	*ent*-**22c**	45	**22c**	81
4			**22d**	92
5			*ent*-**22e**	91[c]
6	*ent*-**22f**	43	**22f**	92
7	*ent*-**22g**	43	*ent*-**22g**	87[c]
8			**22h**	95
9			**22i**	65
10			*ent*-**22j**	82[c]
11	*ent*-**22k**	59	**22k**	77
12	**22l**	92[d]	**22l**	37[c,e]
13	**22m**	55[c]		
14	*ent*-**22n**	47	**22n**	69
15			**22o**	58
16	*ent*-**22p**	56		
17	*ent*-**22q**	54		
18			**22r**	82
19			**22s**	63
20	**22t**	70		

[a] $[RhCl(COD)]_2$ + P^P, *S*/*C* 100, 50 bar H_2, 40 °C, DCM, 10% w/v, 16−20 h, 0.1-g scale; conversion >99%. [b] Catalyst $[Ru(OAc)_2(P^P)]$ preformed, or in situ formed ($[Ru(OAc)_2(COD)]$, P^P, 40 °C, 2 h), *S*/*C* 100, 40−50 bar H_2, 40 °C, MeOH, 7−10% w/v, 18−20 h, 0.1−0.2 g scale; conversion >99%. [c] (*R*)-**3** was formed. [d] 93% ee at *S*/*C* 1000 and 1-g scale. [e] Experiment in DCM, *S*/*C* 50.

Table 3. Influence of solvent in the hydrogenation of 13 to (*S*)-3 with Ru catalyst 23[a]

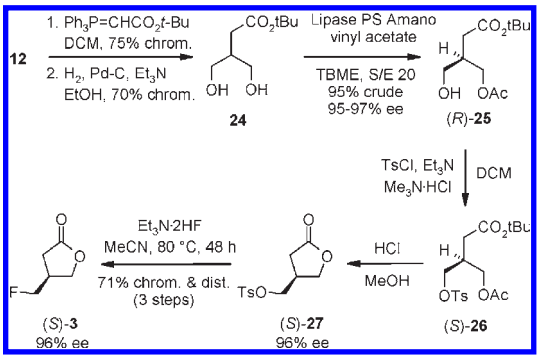
#	solvent	*S*/*C*	*c* (% w/w)	% ee
1	TFE	1000	15	99.5
2	EtOH	1000	24	93
3	PrOH	1000	24	93
4	MeOH	1000	20	93
5	MeOH	100	11	92
6	*i*-PrOH	100	11	90
7	DCM	100	7	90
8	EtOAc	100	10	51
9	toluene	100	10	51
10	THF	100	10	47

[a] 50 bar H_2, 40 °C; experiments with *S*/*C* 100 at 0.1-g scale, with *S*/*C* 1000 at 1-g scale; conversion >99%.

3. ENZYMATIC DESYMMETRIZATION ROUTE

Proof of concept was established for a desymmetrization approach based on the literature-known enzymatic monoacetylation of diol **24** (Scheme 7).[32] Diol **24** was synthesized from 1,3-dihydroxyacetone (**12**) by Wittig olefination with $Ph_3P{=}CHCO_2t$-Bu followed by Pd-catalyzed double bond hydrogenation in the presence of Et_3N (0.2 equiv) to avoid hydrogenolytic deoxygenation. The enzymatic monoacetylation of **24**

Scheme 7. Enzymatic desymmetrization route



with Lipase PS Amano was established under technically relevant conditions (20% w/v substrate concentration in vinyl acetate/MTBE 1:1) affording monoacetate (*R*)-**25** with 95−97% ee and in yields of 90−95%. The major byproduct (~3%) was the corresponding diacetate. Tosylation of (*R*)-**25** (catalyzed by 0.1 equiv $Me_3N{\cdot}HCl$)[33] followed by HCl/MeOH-mediated ester cleavage−lactonization furnished the tosyloxymethyl lactone (*S*)-**27**[34] which was readily transformed into (*S*)-**3** by reaction with $Et_3N{\cdot}2HF$ (6 equiv, in situ prepared from 4 equiv $Et_3N{\cdot}3HF$ and 2 equiv Et_3N).[23] Configurational integrity was maintained over the three steps and the overall yield of (*S*)-**3** amounted to 71% after final chromatography and distillation. Both the acyclic and the cyclic tosylates (*S*)-**26** and (*S*)-**27** proved to be crystalline compounds and the former one allowed for upgrading of enantiomeric purity by crystallization, albeit with considerable loss of yield. Attempts to perform fluorine introduction at the stages of monoacetate (*R*)-**25** or the acyclic tosylate (*S*)-**26** failed.

Overall this enzyme-based route to (*S*)-**3**, which is attractive due to the ease and efficiency of the introduction of the stereogenic center, afforded ~35% yield based on **12** over six steps. Shortcomings of the route are the unsatisfactory synthesis of diol **24** and the required chromatographic purifications. Consequently, this route could not compete with other routes described herein.

4. SYNTHESES OF (*S*)-3 USING STARTING MATERIALS FROM THE CHIRAL POOL

4.1. The Malonate Route. Inspired by the regioselective epoxide ring-opening with KHF_2 in the asymmetric hydrogenation route, a stereoselective synthesis starting from optically active *tert*-butyl glycidyl ether (*S*)-**14** was designed (Scheme 8). In contrast to *rac*-**14**, the enantiomer (*S*)-**14** was expensive and commercially available only in small quantities (10 g).[35] Thus at the outset of our investigation (*S*)-**14** was secured in sufficient amounts (100 g) by hydrolytic kinetic resolution (HKR) of *rac*-**14** using the method of Jacobsen.[36] Enantioselective epoxide ring-opening with 0.55 equiv water in presence of 0.5 mol % (*R*,*R*)-(Salen)Co^{III}acetato complex (rt, 20 h) provided the enantiopure (*S*)-**14** with 99.8% ee in 44% yield after distillation.[37] Bulk quantities of (*S*)-**14** with ee ≥98% were later offered by external suppliers. The formation of the fluorohydrin (*R*)-**15** was accomplished as described above for the racemic series (Scheme 5) by epoxide opening with KHF_2 and TEG. Reducing the amount of TEG (mol ratio (*S*)-**14**/KHF_2/TEG = 1:2:0.8) and adding a catalytic amount of tetrabutylammonium hydrogensulfate

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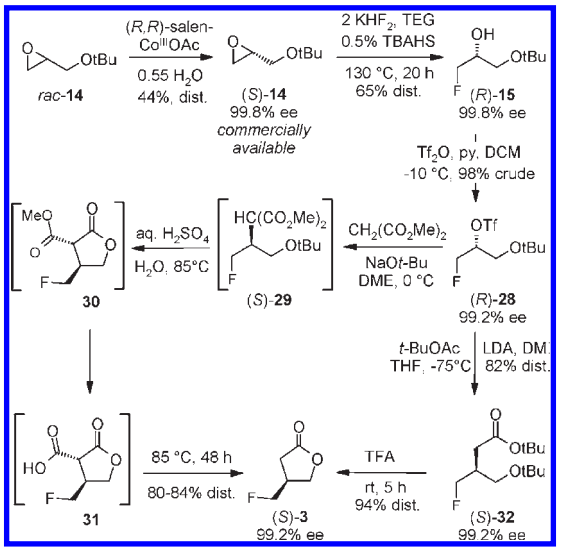
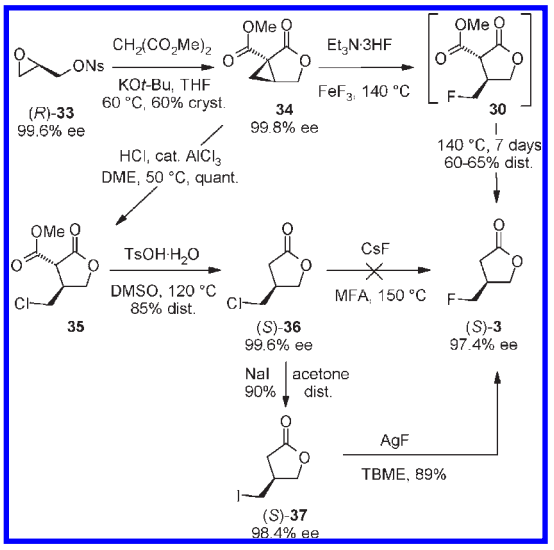
Scheme 8. Malonate route to fluoromethyl lactone (*S*)-3



Scheme 9. HF and HCl addition to cyclopropanolactone 34



(TBAHS) led to a slightly improved yield of a 95:5 mixture of the two regioisomeric fluorohydrins. The major regioisomer (*R*)-**15** was isolated by distillation over a Fenske ring-packed column with ~99% regioisomeric purity (GC) in ~65% yield. Subsequent treatment of (*R*)-**15** with triflic anhydride and pyridine in DCM gave the crude triflate (*R*)-**28** with negligible racemization (≤0.3%). In order to avoid racemization, the triflate formation as well as the hydrolysis were performed at −10 °C.[38] Since the neat triflate (*R*)-**28** was only marginally stable at rt, it was either used immediately after isolation or stored at −20 °C.[39]

The ensuing substitution of (*R*)-**28** with sodium dimethyl malonate in DME proceeded with full inversion of configuration providing the intermediate (*S*)-**29** which was transformed in situ into lactone (*S*)-**3** by treatment with 2 M H_2SO_4 (85 °C, 48 h).[40,41] While the *tert*-butyl ether cleavage and the lactonization ((*S*)-**29** → **30**) was effected at reflux temperature in <0.5 h, the hydrolysis of the methyl ester and the subsequent decarboxylation (**30** → **31** → (*S*)-**3**) required up to 2 days. Extraction with DCM followed by distillation delivered (*S*)-**3** in 80−84% yield with ≥99% chemical and enantiomeric purity (GC). Starting from commercially available (*S*)-**14** with 98.0% ee, (*S*)-**3** with 97.8% ee was obtained in three steps with 50−55% overall yield. Consequently this short and efficient malonate route was considered most suitable for further development.

A somewhat less efficient alternative involved the substitution of the triflate (*R*)-**28** with the Li-enolate of *tert*-butyl acetate providing the *tert*-butyl ester (*S*)-**32**. In order to obtain high selectivity and yield, this S_N2 substitution had to be performed at low temperature (THF, −75 °C) and in the presence of an additive like 1,3-dimethyl-2-imidazolidinone (DMI, 3 equiv).[42] Lactonization of (*S*)-**32** was effected after deprotection with TFA and provided (*S*)-**3** in 94% yield (GC 99.3%, 99.4% ee).

4.2. The Cyclopropanolactone Route. In a further approach we have envisaged to establish the fluoromethyl group by HF-addition to cyclopropanolactone **34** to provide the fluoromethyl lactone **30** (Scheme 9) which can be converted into (*S*)-**3** by hydrolysis and decarboxylation as was already demonstrated in the malonate route (cf. Scheme 8). The literature-known cyclopropanolactone **34** was synthesized from commercially available glycidyl nosylate (*R*)-**33**[43] in a single step by malonate substitution followed by an intramolecular epoxide−cyclopropane ring rearrangement.[44]

The HF-addition to the cyclopropane ring in **34** proved to be much more difficult than expected. Thus, treatment of **34** with HF delivering reagents such as $Et_3N \cdot 3HF$, 70% HF pyridine, and even 100% HF under various conditions (<100 °C) did not provide any of the desired fluoromethyl lactone **30**. Finally, and surprisingly, treatment of **34** with neat $Et_3N \cdot 3HF$ (12 equiv)[45] and FeF_3 (2 equiv) at 140 °C for 7−9 days directly afforded (*S*)-**3**. Apparently, under these drastic reaction conditions **30**, which was detected only in traces (GC and DC, 1−2%),[46] was converted into (*S*)-**3** by an unexpected demethoxycarbonylation reaction. After workup and distillation, (*S*)-**3** was isolated in up to 65% yield (GC 96.8%, 97.4% ee). Despite the shortness and good overall yield of 35−40%, this two-step cyclopropanolactone route was not considered for scale-up due to the harsh reaction conditions in the second step and the corrosive nature of the $Et_3N \cdot 3HF$ reagent.[47]

On the other hand, HCl added smoothly to **34** in presence of a catalytic amount of $AlCl_3$ (2 equiv HCl, 2 mol % $AlCl_3$, DME, 50 °C)[48] furnishing the chloromethyl lactone **35**. Subsequent demethoxycarbonylation using $TsOH \cdot H_2O$ in DMSO (2 equiv, 120 °C, 3 h) gave (*S*)-**36** which was converted into the iodomethyl lactone (*S*)-**37** by a Finkelstein reaction with NaI. While (*S*)-**37** was successfully converted into (*S*)-**3** with AgF, the substitution of (*S*)-**36** and (*S*)-**37** with less expensive fluoride salts such as CsF in polar solvents like *N*-methylformamide (MFA), DMSO or MeCN failed.

5. SCALE-UP OF THE ASYMMETRIC HYDROGENATION-BASED SYNTHESIS

The asymmetric hydrogenation route, being the earliest one available, was used as enabling route for the production of API on the 10-kg scale. Initially, the Wittig route (Scheme 4) served to prepare the hydrogenation substrate **13** and first batches of (*S*)-**3** were obtained by the Rh process which subsequently was replaced by the Ru process. Later, the glycidyl ether route to **13** (Scheme 5) and the Ru process were used. Such rapid changes of routes and processes are not atypical for project situations in which API supply is on the critical path.

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The Wittig route was scaled without optimization and provided **13** in an overall yield of 40% after distillation and crystallization. The Deoxofluor-mediated transformation **6** → **13** was performed at temperatures not exceeding 25 °C without further safety measures. The glycidyl ether route to **13** was readily scaled up to 20 kg. For the fluorinative epoxide opening a mode involving addition of *rac*-**14** to the KHF_2/TEG mixture at 125 °C over 1 h (mol ratio *rac*-**14**/KHF_2/TEG = 1:2:1.5) was shown to be unproblematic by a calorimetric investigation (ΔH = −46 kJ/mol, $\Delta_{adia}T_{max}$ = 43 °C, $\Delta_{adia}T_{accu}$ = 36 °C). In the event the reaction was performed by addition of *rac*-**14** over 15 min at 140 °C and a reaction time at 140 °C of 5 h to provide a yield of 64% for the distilled *rac*-**15**/rac-**16** 97:3 mixture. In the subsequent steps yields of 84% for crude ketone **17** and 67% for distilled and crystallized fluoromethyl butenolide **13** were obtained. The final crystallization was necessary to obtain a high-quality material for the asymmetric reduction. An overall yield of 36% thus was achieved for the *tert*-butyl glycidyl ether route to the hydrogenation substrate **13**.

Not unexpectedly, the quality of **13** played an important role in the development of efficient hydrogenation processes. In the Rh process *S*/*C* ratios of 1000 were reached in small-scale experiments, but only 400−500 were realized upon upscaling, even after 2-fold distillation of **13**. Nevertheless, more than 0.5 kg of (*S*)-**3** with an ee of 93% were prepared in 94% yield after distillation. The Ru-catalyzed hydrogenation of substrate **13**, prepared by the Wittig route and purified by distillation followed by crystallization, proceeded smoothly at the kg-scale at *S*/*C* ratios of 12,500 affording (*S*)-**3** with 95% ee in 98−99% yield after distillation. More than 5 kg of (*S*)-**3** were prepared with an overall yield of 39% over the five steps starting from dihydroxyacetone (**12**). The quality of **13** prepared by the *tert*-butyl glycidyl ether route was even more critical. A purification protocol involving decolorization with charcoal, filtration over silica gel, distillation, and final crystallization was necessary to produce material of adequate quality for the hydrogenation. Preparative 5-kg batch hydrogenations of **13** purified in this way proceeded efficiently at *S*/*C* ratios of 9000 providing (*S*)-**3** with ee values in the range of 96.3−96.8% in average 93% yield after distillation corresponding to an overall yield of 33% over the six steps starting from *rac*-**14**.

Occasionally, catalyst inhibition was observed, for which the reasons remained unclear. Acetic acid, a potential contaminant, was demonstrated to have no inhibitory effect up to 2 mol % (∼240 equiv based on Ru catalyst). Triethylammonium acetate which might have been entrained from step **19** → **13** was found to stop the hydrogenation reaction completely at the 0.2 mol % level. However, there was no clear evidence for the presence of this contaminant in substrate batches showing reduced hydrogenation rates. Substrate batches of suboptimal quality sometimes showed a tendency to trigger hydrodefluorination leading to 3-methyl-γ-butyrolactone as byproduct accompanied by acidic vapors most probably from HF.

The enantiomeric purity of the (*S*)-**3** materials produced in the asymmetric hydrogenations (93% ee Rh-catalyzed, 96−97% ee Ru-catalyzed) was sufficient for use in the API synthesis. The minor diastereomer formed in the coupling with aminobenzoquinolizine **2** was readily removed in the crystallizations towards the API.

6. SCALE-UP OF THE MALONATE ROUTE

The malonate route to (*S*)-**3**, once available, was considered the most suitable for development to technical scale. Accordingly, starting from commercial epoxide (*S*)-**14** of 99.4% ee, a production process was developed for the synthesis sequence via (*S*)-**29** (Scheme 8), and the process was scaled to a batch size of >100 kg of (*S*)-**14** or 100 kg of isolated (*S*)-**3**. The conversion of (*S*)-**14** to the fluorohydrin (*R*)-**15** was accomplished within 24 h at 135−140 °C. A Hastelloy vessel had to be employed due to the corrosive nature of the KHF_2 reagent and the harsh reaction conditions. The extended reaction time was required due to the low solubility of KHF_2. A reaction protocol involving mixing all components at rt (mol ratio (*S*)-**14**/KHF_2/TEG = 1:2:0.8) and subsequent heating to 135 °C was demonstrated to be safe by a calorimetric investigation (ΔH = −50 kJ/mol, $\Delta_{adia}T_{max}$ = 88 °C). The bulk amount of insoluble inorganic salts was filtered off, and the crude step product was rectified using a distillation column giving (*R*)-**15** in 59% yield. Major focus for process development was to circumvent the isolation of the unstable triflate (*R*)-**28**. This was achieved by developing a telescoped process in which (*R*)-**15** was reacted with triflic anhydride at −10 to −20 °C in the presence of pyridine, filtering off the pyridinium triflate precipitation formed at −15 °C, and dosing the solution of (*R*)-**28** in DCM at −5−0 °C directly into a solution of sodium dimethyl malonate in DME. For the subsequent H_2SO_4-promoted deprotection−lactonization−hydrolysis−decarboxylation sequence the reaction time could be reduced from 48 h to 18−20 h by working at 92−94 °C and at higher concentration. Also this step had to be conducted using a Hastelloy vessel as the reaction mixture was highly corrosive due to traces of fluoride formed combined with the acidic reaction conditions at elevated temperatures.[49] The crude product was purified by distillation to give (*S*)-**3** in a yield of 73%, an assay of 98−100% (w/w), and an ee of 99.3%. Using this process a total of >500 kg of (*S*)-**3** was produced in an overall yield of 43% based on (*S*)-**14**.

7. CONCLUSION

In summary, route exploration for optically active fluoromethyl lactone (*S*)-**3** has resulted in the identification of four new pathways to synthesize this small molecule: (a) the five- or six-step Ru-catalyzed asymmetric hydrogenation route—in which the butenolide substrate **13** was prepared either from dihydroxyacetone or, more favorably, from *tert*-butyl glycidyl ether (*rac*-**14**)—leading to (*S*)-**3** with 96−97% ee in 33−39% overall yield; (b) a six-step enzymatic desymmetrization route starting from 1,3-dihydroxyacetone (95−97% ee, 35% overall); (c) the three-step malonate route starting from optically active *tert*-butyl glycidyl ether (*S*)-**14** (98−99% ee, overall 50−55% lab scale, and 43% technical scale); and (d) the two-step cyclopropanolactone route starting from optically active glycidyl nosylate (*R*)-**33** (97.5% ee, 35−40% overall). In the routes selected for scale-up the stereogenic center was established either by asymmetric hydrogenation or by using an enantiopure starting material, i.e. (*S*)-**14**. In both scaled routes the very inexpensive fluorine-introducing reagent KHF_2 was used to establish the primary fluoride functionality, thus replacing the initially used expensive DAST and Deoxofluor reagents, respectively, and greatly contributing to lower chemical costs. Finally, the three-step malonate route was selected for technical development and for API production at larger scale on the basis of its shortness, its highest yield, the commercial availability of enantiopure starting material, and its estimated lowest process costs.

8. EXPERIMENTAL SECTION

8.1. General Remarks. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All reactions were carried out under argon or nitrogen atmosphere. Column chromatography on silica gel 60 (mesh 70-230, Merck) was used to provide reference samples for analytical purposes of products and byproducts. Yields are weight-based and not corrected for assays unless otherwise noted. The chemical purity and conversions were determined by gas chromatography (GC, area %). The enantiomeric excess (ee) was determined by chiral GC using a cyclodextrin-based BGB-176 column (30 m × 0.25 mm; BGB-Analytik Ltd.) for (*S*)-**14**, (*R*)-**15**, and (*R*)-**28**, and a cyclodextrin-based BGB-175 column (30 m × 0.25 mm, BGB-Analytik Ltd.) for (*S*)-**3**. NMR spectra were recorded using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and coupling constants (J)—determined assuming first-order behavior—are given in ppm and hertz (Hz). ^{19}F NMR chemical shifts are calculated on the basis of $CFCl_3$ as standard. Low-resolution electron impact mass spectra (EI-MS) were obtained at an ionization voltage of 70 eV or by positive or negative ion spray ionization (ESI-MS). Data are reported in the form of m/z (intensity relative to base = 100).

8.2. Wittig Route to 13. *8.2.1. Acetic Acid 3-Acetoxy-2-oxo-propyl Ester (**4**).* A 500-L reactor was charged with 1,3-dihydroxyacetone (**12**, 25 kg, 277.5 mol) and pyridine (81 L). To the suspension obtained was added acetic anhydride (81 L, 862 mol) over 40 min (exothermic!), maintaining the jacket temperature (T_j) between 15 and 22 °C. The resultant reddish solution was stirred at 20 °C for 3 h and then concentrated at 50−55 °C/≥10 mbar. The oily residue was dissolved in DCM (250 L) and the solution washed with 25% hydrochloric acid (2 × 125 L) and water (125 L). The organic layer was concentrated (40 °C/≥10 mbar), and the dark-red, oily residue (120 L) was dissolved in toluene (144 L) at ∼30 °C. Crystallization was induced by addition of heptane (125 L) over 15 min followed by seeding with pure diacetate **4**. After stirring for 1 h, additional heptane (125 L) was added to improve stirrability, and the suspension was stirred at 20 °C overnight and at 0 °C for 2 h. The suspension was filtered, and the filter cake was washed with precooled heptane (150 L) and dried (30−35 °C/≥10 mbar), affording diacetate **4** (37.5 kg, 77.6%) as white powder, GC 100%. An analogous smaller-scale reaction starting from 4.0 kg (44.4 mol) **12** gave 6.26 kg (81%) **4**, GC 99.7%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17 (s, 6H, CH_3CO_2), 4.75 (s, 4H, CH_2CO). EI-MS (m/z) 102.2 (7), 101.1 (100), 73.1 (34), 43.3 (93). Anal. Calcd for $C_7H_{10}O_5$ (174.15): C 48.28; H 5.79; O 45.93. Found: C 48.28; H 5.78.

*8.2.2. 4-Acetoxy-3-acetoxymethyl-but-2-enoic Acid Ethyl Ester (**5**).* A 60-L reactor was charged with diacetate **4** (2.25 kg, 12.9 mol), MTBE (35 L), and $Ph_3P{=}CHCO_2Et$ (5.45 kg, 15.6 mol). The solution was stirred under reflux for 5 h and allowed to cool to rt during 14 h. MTBE was exchanged with heptane (40 L, 45 °C/450−170 mbar), and the resulting suspension was stirred at rt overnight. After addition of toluene (7 L) and additional stirring at rt for 1 h and at 0−4 °C for 2 h, the suspension was filtered and the filter cake (TPPO) washed with precooled toluene (10 L). The filtrate was concentrated (45 °C/110 mbar) to give 3.25 kg crude α,β-unsaturated ester **5** as reddish oil. This material, combined with 3.25 kg **5** from a duplicate reaction, was dissolved in a 3:1 mixture of heptane/ethyl acetate (8 L) and chromatographically filtered over a column containing 15 kg silica gel 60 using heptane/ethyl acetate 3:1 as the eluent. Seventeen fractions of 5 L were collected and evaporated (45 °C/≥2 mbar) to give **5** (6.20 kg, 98%) as colorless oil, GC 99.9%.[5] IR (film): ν 2982, 1741, 1713, 1370, 1207, 1145, 1028 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 2.08 and 2.12 (s, 3H each, $C(O)CH_3$), 4.20 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.72 and 5.26 (s, 2H each, CH_2OAc), 6.00 (quint, J = 1.6 Hz, 1H, =C*H*−). EI-MS (m/z) 185.2 (48), 171.1 (12), 157.2 (48), 142.1 (100), 129.1 (19), 113 (15), 97.1 (39).

*8.2.3. 4-Hydroxymethyl-5H-furan-2-one (**6**).* In a 60-L reactor ester **5** (6.10 kg, 25.0 mol) was dissolved in methanol (28 L), and acetyl chloride (177 mL, 2.5 mol) was added over 10 min under cooling, maintaining the temperature at 22−23 °C. After stirring at 22 °C for 18 h and at 50 °C for 2 h, the reaction mixture was concentrated (45 °C/≥10 mbar), and the residual yellowish oil (2.80 kg) was azeotroped with toluene (3 × 19 L, 45 °C/≥10 mbar). The crude yellow oil was dissolved in DCM (6 L), and crystallization was effected by slowly cooling to −5 °C followed by addition of heptane (22 L) over 30 min. After additional stirring at −5 °C for 30 min, the suspension was filtered. The filter cake was washed with cold heptane (4 L) and dried (rt/10 mbar/16 h) to give hydroxymethyl butenolide **6** (2.75 kg, 96.5%) as white powder, GC 98.6%.[5] IR (Nujol): ν 3419, 3115, 2954, 1743, 1450, 1370, 1254, 1140, 1066, 1012 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.55 (t, J = 5 Hz, 1H, O*H*), 4.60 (d, J = 5 Hz, 2H, CH_2OH), 4.88 (s, 2H, CO_2CH_2), 6.04 (t with fine structure, 1H, =C*H*−). EI-MS (m/z) 96 (10), 85 (100), 84 (61), 70 (25), 68 (13), 67 (10), 57.1 (16), 56.1 (13), 55 (49), 39.1 (32), 38.1 (11), 31.2 (24), 29.3 (44). Anal. Calcd for $C_5H_6O_3$ (114.10): C 52.63; H 5.30; O 42.07. Found: C 52.39; H 5.21; H_2O 0.23.

*8.2.4. 4-Fluoromethyl-5H-furan-2-one (**13**).* A 160-L reactor was charged with hydroxymethyl butenolide **6** (10.35 kg, 90.7 mol) and DCM (42 L), and the solution was cooled to −10 °C. Bis-(2-methoxyethyl)aminosulfur trifluoride (23.5 kg, 95%, 101 mol, Deoxofluor, Matrix Scientific) was added over 50 min, maintaining the temperature strictly between −5 and −10 °C. During the addition, a yellowish emulsion was obtained which turned into an orange-red solution after completion of the addition. After stirring at 15−20 °C for 2 h, a solution of water (5 L) in ethanol (25 L) was added over 30 min, maintaining the temperature between −5 and −10 °C, and the mixture was allowed to reach rt. After concentration (40 °C/650−120 mbar) to a volume of ∼30 L, the residue was dissolved in DCM (42 L), and the solution was washed with 1.0 M hydrochloric acid (3 × 83 L). The aqueous layers were back-extracted with DCM (3 × 30 L), and the combined organic layers were evaporated to dryness. The resulting dark-brown liquid (8.32 kg) was distilled in four portions (4-L pear-shaped flask, 20-cm Vigreux column) providing fluoromethyl butenolide **13** (6.30 kg) as colorless liquid, bp 73−80 °C/∼0.1 mbar, GC 97.7%. IR (film): ν 1778, 1738, 1448, 1133, 1040, 1003 cm^{-1}. The distillate was dissolved in MTBE (7 L) and crystallized under stirring at 0 °C (2 h) and −20 °C (3 h). Filtering over a precooled filter, washing with precooled MTBE (4 L, −20 °C), and drying (rt/≥1 mbar/24 h) provided fluoromethyl butenolide **13** (5.69 kg, 54%) as white crystalline powder, mp 30−40 °C, GC 99.8%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.89 (s with fine structure, 2H, CH_2O), 5.33 (d with fine structure, $^2J_{HF}$ = 46 Hz, 2H, CH_2F), 6.11 (s with fine structure, =C*H*−); 1.60 (s, ∼0.2 H, ∼10 mol % H_2O,). EI-MS (m/z) 116.2 (7), 87.2 (100), 86.3 (7), 59.2 (25), 58.3 (12), 57.1 (17), 39.3 (11), 29.4 (5). An analytical sample of **13** obtained

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by three-fold crystallization from MTBE showed a mp of 28−29 °C, colorless needles. According to ^{1}H NMR this material contained about 5 mol % H_2O.

8.3. *tert*-Butyl Glycidyl Ether Route to 13. *8.3.1. 1-tert-Butoxy-3-fluoro-propan-2-ol (rac-**15**).* A 630-L Hastelloy reactor was charged with triethylene glycol (115 L, 129 kg, 859 mol) and potassium hydrogen difluoride (89 kg, 1140 mol), and the resulting suspension was heated to 140 °C. *tert*-Butyl glycidyl ether (*rac*-**14**, 75 kg, GC 98%, 565 mol) was added over 45 min, and the suspension was stirred at 140 °C for 5 h, cooled to rt, and treated with water (330 L). After stirring for 30 min, the pH was adjusted to 7−7.5 by addition of 28% sodium hydroxide (58 L), and the reaction mixture was extracted with MTBE (3 × 400 L). The organic phases were washed with brine (80 kg sodium chloride in 185 L water), combined, and concentrated (45 °C/≥10 mbar) to a volume of ∼100 L. After removal of insoluble particles by filtration through a Teflon membrane filter, the residual oil was purified by short path distillation to yield 54.1 kg (64%) of a colorless liquid, bp 68 °C/20 mbar, GC 95.2% *rac*-**15** and 3.7% *rac*-**16**. IR (film): ν 3422 (br), 2975, 1474, 1390, 1365, 1195, 1085, 1015 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (s, 9H, C(CH_3)$_3$), 2.43 (d, J = 5.3 Hz, 1H, OH), 3.45 (m, 2H, CH_2O), 3.94 (dm, $^3J_{HF}$ = 17.7 Hz, 1H, CHOH), 4.45 (dm, $^2J_{HF}$ = 47.3 Hz, 2H, CH_2F). EI-MS (m/z) 135.2 (11), 100.3 (10), 59.3 (63), 57.3 (100), 41.4 (19), 29.5 (14).

*8.3.2. 3-tert-Butoxy-2-fluoro-propan-1-ol (rac-**16**).* A reference sample of fluorohydrin *rac*-**16** was obtained by chromatography as colorless oil. IR (film): ν 3402 (br), 2975, 1475, 1364, 1195, 1076, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (s, 9H, C(CH_3)$_3$), 2.23 (t, J = 6.3 Hz, 1H, OH), 3.62 and 3.85 (m, 2H each, CH_2O), 4.63 (dm, $^2J_{HF}$ = 48 Hz, 1H, CHF). EI-MS (m/z) 135 (70), 59 (100), 57.1 (69), 41.1 (13).

*8.3.3. 1-tert-Butoxy-3-fluoro-propan-2-one (**17**).* A 630-L reactor was charged with DCM (145 L), water (145 L), sodium bicarbonate (11.5 kg), potassium bromide (4 kg), *rac*-**15**/*rac*-**16** mixture (54.1 kg, GC 95.2% *rac*-**15** and 3.7% *rac*-**16**, 360 mol), and after cooling to 0 °C, with TEMPO (275 g). Bleach (245 L, 301 kg, ∼10% active Cl, ∼400 mol) was added to the two-phase mixture under vigorous stirring over a period of 1.5 h while maintaining the temperature below 10 °C. After stirring for an additional 15 min, the reaction mixture remained dark-red, indicating that the oxidation was complete (potassium iodide−starch test positive). A solution of saturated sodium bisulfite solution (∼1 L) was added until the reaction mixture was fully discolored (potassium iodide−starch test negative). The two phases were allowed to separate, and the aqueous phase was extracted with DCM (2 × 95 L). The combined organic phases were washed with brine (31 kg sodium chloride dissolved in 73 L water) and concentrated (25 °C/≥50 mbar) to minimum stir volume. THF (46 L) was added, and the reactor content was again concentrated to minimum stir volume. The THF charge/concentration process was repeated another time to ensure complete azeotropic removal of DCM. The residual crude ketone **17** was dissolved in THF (30 L) and the solution carried on into the next step. A yield of 84% was determined for crude **17** based on evaporation of an aliquot of the solution, GC purity 97.6%. IR (film): ν 2976, 1746, 1367, 1193, 1099, 1063 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (s, 9H, C(CH_3)$_3$), 4.15 (d, $^4J_{HF}$ = 1.3 Hz, 2H, CH_2O), 5.13 (d, $^2J_{HF}$ = 47.5 Hz, 2H, CH_2F). EI-MS (m/z) 133.1 (6), 115.3 (5), 87.3 (30), 59.3 (13), 57.3 (100).

*8.3.4. 3-tert-Butoxymethyl-4-fluoro-3-hydroxybutyric Acid tert-Butyl Ester (**18**).* A 630-L Hastelloy reactor was charged with diisopropylamine (34.4 kg, 47.7 L, 340 mol) and dry THF (162 kg). The mixture was cooled to −60 °C, and butyl lithium (1.6 M in hexane, 138 kg, 203 L, 325 mol) was slowly added. After stirring at −60 °C for 45 min, the light-yellow solution was cooled to −70 °C, and *tert*-butyl acetate (39 kg, 45 L, 335.5 mol) was added within 5 min at below −65 °C. Stirring was continued at −70 °C for 45 min, and the above THF solution of ketone **17** (theoretically 302 mol corresponding to 44.8 kg) was added within 5 min. The reaction mixture was allowed to warm to 0 °C and was treated with saturated ammonium chloride solution (480 L), and the phases were separated. The organic layer was washed successively with 10% ammonium chloride solution (2 × 180 L) and 10% sodium chloride solution (90 L). The slightly yellow organic layer was dried by passage through a column filled with sodium sulfate (95 kg) and evaporated to dryness (40 °C/≥50 mbar). The oily residue was dissolved in ethyl acetate (100 L) and again evaporated to dryness, providing crude hydroxy ester **18** as slightly yellow oil which was left in the reactor for the next step, GC 98.4%. IR (film): ν 3476 (br), 2975, 1727, 1706, 1366, 1155, 1084, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 and 1.47 (s, 9H each, C(CH_3)$_3$), 2.54 (m, 2H, CH_2CO_2), 3.37 (d, J = 2.3 Hz, 2H, CH_2O), 3.87 (s, 1H, OH), 4.38 (dm, $^2J_{HF}$ = 47 Hz, 2H, CH_2F). EI-MS (m/z) 177.2 (24), 153.3 (10), 135.2 (65), 134.2 (30), 121.2 (39), 119.1 (11), 102.2 (34), 59.4 (10), 57.3 (100).

*8.3.5. 4-Fluoromethyl-4-hydroxy-dihydro-furan-2-one (**19**).* The 630-L reactor containing crude hydroxy ester **18** from the previous step was charged with DME (60 L) and 96% sulfuric acid (0.79 kg, 430 mL, 7.7 mol). The two-phase mixture was heated under stirring at 55−60 °C (T_j 80 °C; caution: very strong gas evolution!) for 4 h. After cooling to rt, sodium acetate trihydrate (4.0 kg, 29.4 mol) was added to the dark-brown solution and the mixture was vigorously stirred for 30 min. Ethyl acetate (64 L) was added and the resulting suspension passed through a column filled with sodium sulfate (20 kg). The column was rinsed with ethyl acetate (30 L) and the combined eluents were evaporated to dryness (45 °C/≥40 mbar) to provide crude lactone **19** (41.6 kg, 102% by weight) as dark-brown oil, GC 98%, 1.4% w/w residual DME, 0.2% w/w residual ethyl acetate. An analytical sample was obtained by bulb-to-bulb distillation providing a yellow oil, bp ∼150 °C/0.1 mbar. IR (film): ν 3420 (br), 2968, 1760, 1295, 1184, 1021, 1000 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.63 and 2.74 (AB with fine structure, J = 18 Hz, 1H each, CH_2CO_2), 2.85 (br s, 1H, OH), 4.27 and 4.34 (AB with fine structure, J = 10.2 Hz, 1H each, CH_2O), 4.47 (d, $^2J_{HF}$ = 47 Hz, 2H, CH_2F). EI-MS (m/z) 135.2 (15), 106.2 (16), 101.2 (6), 76.2 (100), 43.3 (7).

*8.3.6. 4-Fluoromethyl-5H-furan-2-one (**13**).* A 630-L Hastelloy reactor was charged with crude hydroxy lactone **19** (39.9 kg, derived from theoretically 290 mol **17**) and DCM (190 L), and the solution was cooled to −10 °C. Acetic anhydride (36.0 kg, 33.3 L, 352 mol) and triethylamine (35.4 kg, 48.8 L, 350 mol) were added, each over 15 min, followed by a solution of 4-dimethylaminopyridine (0.73 kg, 6.0 mol) in DCM (10 L) over 10 min (exothermic!) resulting in a temperature increase to 0 °C. The brownish-black reaction mixture was stirred at 0 °C for 1 h and at rt for 8 h. After quenching with ethanol (4 L) and stirring for 15 min, the mixture was diluted with DCM (100 L), washed in two portions with a ∼1 N HCl solution saturated with sodium chloride (prepared from 122 L water, 40 kg sodium chloride and 13.5 kg 37% HCl), and with brine (3 × 80 L). The combined aqueous phases were back-extracted with DCM

(2 × 100 L). The combined organic phases were evaporated, and the residue was azeotropically dried with toluene (2 × 110 L, 40−45 °C/≥25 mbar). The residual oily suspension was taken up in MTBE (160 L), the suspension was stirred at rt for 30 min and centrifuged, and the cake was washed with MTBE (100 L). The combined filtrate and wash solution were evaporated, and the residue was azeotroped with toluene (3 × 30 L) to ensure complete removal of acetic acid. The dark-brown residue was dissolved in DCM (120 L), the solution filtered through a pressure filter filled with Norit SA II charcoal (1.7 kg) and Dicalite (5 kg), the filter washed with DCM (35 L), and the filtrate evaporated to dryness (25−50 °C/≥4 mbar). The material, after dissolution in ethyl acetate (60 L), was chromatographically filtered over silica gel (100 kg) using heptane/ethyl acetate 2:1 (total 1600 L), and the fractions containing **13** were collected and evaporated (45 °C/≥12 mbar). The residue was dissolved in DCM (100 L) and the solution again filtered through a pressure filter filled with Norit SA II charcoal (1.7 kg) and Dicalite (5 kg). The filter cake was washed with DCM (70 L) and the filtrate evaporated (45 °C/≥15 mbar) affording crude **13** (28.0 kg, GC 97.3%, assay 93.6%) as oil (caution: tendency for crystallization!). The material was distilled in four portions (Büchi rotavapor R-220) to yield **13** (24.7 kg, 73%) as colorless oil, bp 78−83 °C/0.2−0.1 mbar. For further purification the distilled product that meanwhile had solidified was dissolved in MTBE (75 L), the solution cooled to 16−18 °C, seeded with 10 g of **13**, and stirred for 4 h. Seeding was repeated with 10 g of **13** and the mixture cooled to 5−0 °C over a period of 4 h in which crystallization occurred exothermically. The suspension was stirred at 0 °C for 12 h, cooled to −15 °C over a period of 3 h, and stirred for 3 h. Filtering over a precooled suction-filter, washing with cold MTBE (25 L, −15 °C), and drying (rt/<30 mbar/24 h) provided fluoromethyl butenolide **13** (22.6 kg, 67% based on **19**, 36% overall based on *rac*-**14**) as white crystalline powder, GC 100%, assay 98.9%, 0.2% w/w residual MTBE.

8.4. Asymmetric Hydrogenation of 13. *8.4.1. (S)-4-Fluoromethyl-dihydro-3H-furan-2-one ((S)-**3**) by Ru-Catalyzed Hydrogenation.* In a glovebox (O_2 content < 2 ppm), an Erlenmeyer flask was charged with [Ru(OAc)$_2$((*R*)-3,5-*t*-Bu-MeOBIPHEP)] (**23**, 6.50 g, 5.2 mmol) and methanol (250 mL). The mixture was stirred for 20 min at rt and transferred into a stainless steel catalyst addition device. The device was sealed, pressurized with argon (7 bar), and connected to a 50-L Hastelloy C22 autoclave. Under an argon atmosphere the autoclave was charged with a solution of fluoromethyl butenolide **13** (5.40 kg, 46.5 mol, material prepared by *tert*-butyl glycidyl ether route) in methanol (11.5 L). Methanol (10.2 L) was added, and the autoclave was sealed, evacuated, and pressurized with argon at 1 bar. This procedure was repeated seven times, and then the catalyst solution was introduced into the autoclave. Argon was replaced with hydrogen (15 bar), and the reaction mixture was hydrogenated under vigorous stirring (600 rpm) at 30 °C for 18 h; hydrogen uptake ≥99% after 4 h, conversion by GC 100% after 18 h. The hydrogen atmosphere was replaced with argon, and the orange reaction solution was transferred to a 20-L flask (using methanol (8 L) for rinsing) and concentrated (40 °C/≥20 mbar). The residue (5.18 kg) was distilled (Büchi rotavapor R-220, pressure at vacuum pump ∼0.5 mbar, bp 85−90 °C) to provide fluoromethyl lactone (*S*)-**3** (5.10 kg, 93%) as colorless liquid, GC 99.4%, 96.8% ee, Ru not detectable by X-ray fluorescence (<10 ppm). Yields of 92−93% and ee values of 96.3−96.8% were obtained in four further hydrogenation runs at the 4−5 kg scale. IR (film): ν 1766, 1169, 1020, 946 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.43 and 2.68 (*ABC*, J_{AB} = 17.8 Hz, J_{AC} = 6.5 Hz, J_{BC} = 9.1 Hz, 1H each, CH_2CO$_2$), 2.96 (m, 1H, CHCH$_2$F), 4.24 and 4.45 (*ABX*, J_{AB} = 9.4 Hz, J_{AX} = 5.7 Hz, J_{BX} = 7.7 Hz, 1H each, CH_2O), 4.47 (dm, $^2J_{HF}$ = 47 Hz, 2H, CH_2F). ^{13}C NMR ($CDCl_3$, 150 MHz, ^{1}H-decoupled): δ 29.73 (d, $^3J_{CF}$ = 6.7 Hz, CH_2CO_2), 35.66 (d, $^2J_{CF}$ = 20.3 Hz,$CHCH_2F$), 69.18 (d, $^3J_{CF}$ = 5.8 Hz, CH_2O), 82.67 (d, $^1J_{CF}$ = 172.2 Hz, CH_2F), 175.85 (s, C=O). ^{19}F NMR ($CDCl_3$, 377 MHz, ^{1}H-coupled): δ −224.98 (td, $^2J_{FH}$ = 46.8 Hz, $^3J_{FH}$ = 18.7 Hz). EI-MS (*m*/*z*) 118.3 ($M^{+\bullet}$, 22), 74.3 (33), 73.3 (11), 60.3 (67), 59.3 (100), 41.4 (43), 39.2 (25), 32.4 (55), 29.4 (18).

*8.4.2. (S)-4-Fluoromethyl-dihydro-3H-furan-2-one ((S)-**3**) by Rh-Catalyzed Hydrogenation.* In a glovebox (O_2 content < 2 ppm), an Erlenmeyer flask was charged with [RhCl(COD)]$_2$ (716.7 mg, 1.454 mmol), (*S*)-TMBTP (**22l**, 1.889 g, 3.198 mmol), and DCM (135 mL). The mixture was stirred at rt for 15 min and transferred into a stainless steel catalyst addition device. The device was sealed, pressurized with argon (7 bar), and connected to a 2-L Hastelloy C4 autoclave, previously charged with fluoromethyl butenolide **13** (135 g, 1.163 mol, material prepared by the Wittig route) and DCM (877 mL). The autoclave was sealed and purged with argon, and the catalyst solution was introduced into the autoclave. Argon was replaced with hydrogen (50 bar), and the reaction mixture was vigorously stirred (800 rpm) at 40 °C for 18 h; conversion 100%. The hydrogen atmosphere was replaced with argon, and the orange reaction solution was combined with the solution of an identical second batch and concentrated (40 °C/≥20 mbar). The residue was distilled through a 15-cm Vigreux column affording fluoromethyl lactone (*S*)-**3** (260 g, 94%) as colorless liquid, bp 70−72 °C/0.04 mbar, GC 96.6%, 93.2% ee.

8.5. Malonate Route. *8.5.1. (S)-tert-Butyl Glycidyl Ether (S)-**14**.* A 500-mL round-bottomed flask equipped with an air balloon, a magnetic stirrer, and an ice bath was charged with (1*R*,2*R*)-(−)-1,2-cyclohexanediamino-*N*,*N*′-bis-(3,5-di-*tert*-butylsalicylidene) cobalt(II) (6.04 g, 10 mmol), *tert*-butyl glycidyl ether *rac*-**14** (260.4 g, 2000 mmol), acetic acid (2.40 g, 40 mmol), and THF (20 mL). After cooling to 0 °C, deionized water (19.8 g, 1100 mmol) was added all at once under stirring and cooling in an ice bath. The dark-red reaction mixture was stirred under an air atmosphere at 0 °C for 0.5 h and then at rt for 20 h. The round-bottomed flask was equipped with a Fenske ring-packed column (20 cm × 2 cm), and the product was separated from the higher-boiling (*R*)-*tert*-butyl glyceryl ether by distillation at reduced pressure affording (*S*)-**14** (113.2 g, 43.5%) as colorless liquid, bp 84−86 °C/100 mbar, GC 99.8%, >99.9% ee. $[\alpha]^{20}_{365}$ = −23.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21 (s, 9H, C(CH_3)$_3$), 2.62 and 2.80 (*ABC*, J_{AB} = 5.1 Hz, J_{AC} = 2.7 Hz, J_{BC} = 4.3 Hz, 1H each, CH_2 epoxide), 3.10 (m, 1H, CHOCH$_2$), 3.42 and 3.53 (*ABC*, J_{AB} = 10.7 Hz, J_{AC} = 5.3 Hz, J_{BC} = 3.9 Hz, 1H each, CH_2O*t*-Bu).

*8.5.2. (R)-1-tert-Butoxy-3-fluoro-propan-2-ol ((R)-**15**).* A white suspension of *tert*-butyl glycidyl ether (*S*)-**14** (195.3 g, 1500 mmol, 98.0% ee, commercial source), triethylene glycol (150 mL), potassium hydrogen difluoride (234.3 g, 3000 mmol), and tetrabutylammonium hydrogen sulfate (2.6 g, 7.5 mmol) was stirred at 130 °C for 20 h. After cooling to rt the brown suspension was diluted with DCM (300 mL) and washed with water (1.0 L), 5% $NaHCO_3$ (300 mL), and 10% brine (200 mL). All aqueous layers were extracted sequentially with DCM (150 mL), and the combined organic

layers were dried over K_2CO_3. After removal of the main part of the solvent by distillation at normal pressure, the residue (~300 mL) was distilled over a Fenske ring-packed column (20 cm × 2 cm) affording fluorohydrin (*R*)-**15** (149.2 g, 66%) as colorless liquid, bp 104−105 °C/100 mbar, GC 99.2%, 98.0% ee. $[\alpha]^{20}_{365}$ = +12.0 (*c* 1.0, $CHCl_3$). IR (film): ν 3420 (br), 1475, 1365, 1197, 1089, 1019 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20 (s, 9H, $C(CH_3)_3$), 2.47 (d, *J* = 5.4 Hz, 1H, O*H*), 3.45 (m, 2H, CH_2O), 3.95 (dm, $^3J_{HF}$ = 17.7 Hz, 1H, C*H*OH), 4.45 (dm, $^2J_{HF}$ = 47.3 Hz, 2H, CH_2F). ESI-MS (*m*/*z*) 151 ($[M+H]^+$, 20), 95 ($[M+H-C_4H_8]^+$, 35). Anal. Calcd for $C_7H_{15}FO_2$ (150.19): C 55.98; H 10.07; F 12.65; O 21.31. Found: C 55.72; H 9.89; F 12.44; O 21.45.

*8.5.3. Trifluoromethanesulfonic Acid (R)-1-tert-butoxymethyl-2-fluoro-ethyl ester ((R)-**28**).* To a colorless solution of fluorohydrin (*R*)-**15** (30.0 g, 200 mmol) and pyridine (32 mL, 400 mmol) in DCM (300 mL) at −10 °C was added trifluoromethanesulfonic anhydride (34.6 mL, 210 mmol) over 1 h. Stirring at −10 °C was continued for 1 h, and the yellow, cold suspension was washed with 1.0 M HCl (200 mL), 10% brine (120 mL), and 10% Na_2CO_3 (120 mL). The aqueous layers were extracted with DCM (80 mL), and the combined organic layers were dried over K_2CO_3 and filtered. After the addition of K_2CO_3 (1.4 g, 10 mmol), the solvent was evaporated (20 °C/≥10 mbar) affording crude triflate (*R*)-**28** (56.9 g) as yellow oil (GC 98.5%, 97.8% ee) which was used without purification in the next step. $[\alpha]^{20}_D$ = −22.8 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20 (s, 9H, $C(CH_3)_3$), 3.66 (d, *J* = 5.5 Hz, 2H, CH_2O), 4.67 (dd, $^2J_{HF}$ = 47.0 Hz, *J* = 4.2 Hz, 2H, CH_2F), 5.05 (dm, $^3J_{HF}$ = 19.0 Hz, 1H, C*H*OTf).

*8.5.4. (S)-4-Fluoromethyl-dihydro-3H-furan-2-one ((S)-**3**).* Sodium *tert*-butoxide (21.1 g, 220 mmol) was dissolved in DME (200 mL) and dimethyl malonate (31.7 g, 240 mmol) was added at 20 °C over 15 min. After cooling to 0 °C, the triflate (*R*)-**28** (56.9 g, ~195 mmol) was added at 0 °C over 15 min, and the orange solution was stirred at 0 °C for 7 h. The cooling bath was removed, 2.0 M H_2SO_4 (200 mL) was added all at once, and the yellow reaction mixture was heated under reflux for 48 h (isobutylene and CO_2 gas evolution at ≤85 °C). After cooling to rt, the reaction mixture was extracted with DCM (3 × 200 mL), and the organic layers were washed with 2% $NaHCO_3$ (100 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed by rotary evaporation (35 °C/≥10 mbar) affording 22.1 g brown oil. Purification by distillation over a Vigreux column provided fluoromethyl lactone (*S*)-**3** (19.8 g, 84% based on (*R*)-**15**) as colorless oil, bp 68−69 °C/0.5 mbar, GC 99.2%, 97.8% ee. $[\alpha]^{20}_D$ = −37.3 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_5H_7FO_2$ (118.11): C 50.85; H 5.97; F 16.09. Found: C 50.42; H 5.90; F 15.92.

*8.5.5. Preparation of (S)-3 without Isolation of Triflate (R)-**28**.* A 2-L jacketed glass reactor was charged with sodium *tert*-butoxide (38.4 g, 400 mmol) and DME (335 mL). To the yellowish solution at 3−10 °C was added dimethyl malonate (57.2 g, 433 mmol) over 15 min (exothermic). Separately, a 0.5-L jacketed glass reactor was charged with fluorohydrin (*R*)-**15** (50.0 g, 333 mmol, obtained from (*S*)-**14** of 99.4% ee), DCM (350 mL) and, at 5 °C, with pyridine (31.0 mL, 30.5 g, 383 mmol). To the clear colorless solution was added at −17 to −7 °C trifluoromethanesulfonic anhydride (56.8 mL, 97.7 g, 346 mmol) over 45 min using an infusion pump. The resultant suspension was stirred at −20 to −15 °C until a conversion of >99.7% was reached (~1 h). The cold suspension was passed through a pressure filter (charged with a 9 cm paper filter) and the reactor and the filter cake were washed with DCM (2 × 50 mL). The cold (−15 °C) filtrate and wash solutions were added to the 2-L reactor containing the deprotonated malonate at 0−5 °C over a period of 1 h. The reaction mixture, initially an orange solution and, transiently, towards the end of the addition, an orange gel-like suspension, was stirred at 0 °C for 19 h. Sulfuric acid (2.0 M, 300 mL) was added to the now clear, orange solution at <10 °C (exothermic) and the solvent (DCM) was distilled off (T_j 80 °C, reaction temperature up to 94 °C, strong isobutylene and CO_2 gas evolution). The remaining reaction mixture (~400 mL) was heated under reflux at 92−94 °C (T_j 110 °C) for 20 h upon which the remaining solvent (DME) and excess dimethyl malonate were removed by distillation (bp ~85 °C/630 mbar). The residue was treated with water (100 mL) and DCM (700 mL), the organic layer was separated and washed with 8% $NaHCO_3$ (100 mL), and the aqueous layers were back-extracted with DCM (400 mL each). The combined organic layers were evaporated (50 °C/200 mbar), and the residue was distilled to provide fluoromethyl lactone (*S*)-**3** (32.0 g, 81% based on (*R*)-**15**) as a colorless liquid, bp 72−74 °C/0.5 mbar, GC 98.6%, 99.3% ee.

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Notes

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(12) Asymmetric hydrogenation of hydroxymethyl butenolide **6** was reported to lead to material of very low ee, likely due to the propensity of the optically active product **7** to racemize (cf. reference 8c).

(13) Commercial material was used, or the ylide was prepared and isolated from [(ethoxycarbonyl)methyl]triphenylphosphonium bromide in a NaOH/DCM two-phase system.

(14) 1,3-Dihydroxyacetone (**12**) in substance exists mainly in the dimeric hemiacetal form unless freshly distilled; see: (a) Fischer, H. O. L.; Mildbrand, H. *Ber. Dtsch. Chem. Ges. B* **1924**, *57B*, 707. (b) Davies, L. *Bioorg. Chem.* **1973**, *2*, 197. (c) Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855. The monomer/dimer ratio had no influence on the reaction.

(15) The formerly used aqueous protocol (10% H_2SO_4 in MeOH) was less selective and led to material that was difficult to purify by distillation or crystallization.

(16) An alternative two-step access to **6** involved reaction of **12** with $Ph_3P{=}CHCO_2t$-Bu and ester cleavage−cyclization with 0.25 M HCl in methanol. Hydroxymethyl butenolide **6** was obtained in 73% yield over two steps after chromatography which proved inevitable.

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(21) The primary alcohol *rac*-**16** is slightly less volatile than the secondary alcohol *rac*-**15**. Pure samples of *rac*-**15** and *rac*-**16** were obtained by chromatography.

(22) Further polar solvents such as DMF, DMA, NMP, DMPU, and DMSO proved poor in terms of chemoselectivity and yields and/or rates.

(23) $Et_3N{\cdot}2HF$ has been reported to be more nucleophilic than $Et_3N{\cdot}3HF$, see: (a) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527. (b) Chou, T. S.; Becke, L. M.; O'Toole, J. C.; Carr, M. A.; Parker, B. E. *Tetrahedron Lett.* **1996**, *37*, 17.

(24) The use of catalytic amounts of conc. H_2SO_4 allowed for a nonaqueous workup (quenching with solid NaOAc followed by filtration over Na_2SO_4), hence, avoiding extractive isolation of the rather water-soluble hydroxy lactone **19**. Use of excess of conc. H_2SO_4 necessitated an aqueous workup and exhaustive extraction of **19** with ethyl acetate leading to high volume factors.

(25) Other conditions such as $SOCl_2$/pyridine, $POCl_3$/pyridine, and the Vilsmeier and Burgess reagents provided also good conversions and yields. MsCl/Et_3N, DEAD/PPh_3, and $SO_3{\cdot}NEt_3$ led to unsatisfactory conversions and/or yields.

(26) More than 250 strains produced the undesired enantiomer (*R*)-**3**, many with 100% conversion and ee values >98%. Screenings were performed in a 24 deep-well format at 0.1% w/v substrate concentration.

(27) Iridium catalysts in a short screening afforded only low conversions and enantioselectivities.

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(29) A solvent screening in the Rh-catalyzed hydrogenation with **22l** as the ligand showed DCM (92−93% ee) and trifluoromethylbenzene (91% ee) to be preferred solvents. Toluene (73% ee) and the group of methanol, isopropanol, THF and ethyl acetate (≤33% ee) turned out to be vastly inferior. Whether traces of HX (X = halogen) released from the solvent contributed to the higher ee's in the halogenated solvents—as suggested by a reviewer—was not investigated.

(30) Preformed Ru catalysts were prepared as described; cf.: (a) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.(b) Cereghetti, M.; Foricher, J.; Heiser, B.; Schmid, R. (F. Hoffmann-La Roche Inc.). U.S. Patent 5,488,172, 1996. (c) Chan, A. S. C.; Laneman, S. *Inorg. Chim. Acta* **1994**, *223*, 165. Other Ru catalysts were made in situ from $[Ru(OAc)_2(COD)]$ and the bisphosphine ligand in the presence of the starting material **13** and MeOH (40 °C, 2 h). Only marginal ee differences were observed in cases where both the preformed and the in situ prepared catalyst were evaluated.

(31) At this point, it may be of interest to note that hydrogenation of the analogous nonfluorinated compound 3-methyl-2-buten-4-olide with Ru catalyst **23** provided (*S*)-3-methyl-γ-butyrolactone with ee values of only 77% and 59% ee at *S*/*C* 100 and 5000, respectively (50 bar H_2, 40 °C, 20 h, MeOH). On the other hand, the Rh-catalyzed hydrogenation of 3-methyl-2-buten-4-olide ($[RhCl(COD)]_2$ + **22l**, *S*/*C* 100, 50 bar H_2, 40 °C, 20 h, DCM) provided 92% ee, equal to the ee obtained for **13**.

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(34) For an independent synthesis based on a microbial Bayer−Villiger oxidation of 3-benzyloxy-cyclobutanone see: Mazzini, C.; Lebetron, J.; Alphand, V.; Furstoss., R. *J. Org. Chem.* **1997**, *62*, 5215. For a synthesis of (*R*)-**27** starting from (*R*)-paraconic acid ((*R*)-**11**) see: Mori, K. *Tetrahedron* **1983**, *39*, 3107.

(35) For the preparation of optically active (*S*)-*tert*-butyl glycidyl ether see: (a) Thakur, S. S.; Li, W.-J.; Shin, C.-K.; Kim, G.-J. *Chirality* **2005** (Volume Date 2006), *18*, 37. (b) Kim, M.-J.; Lim, I. T.; Choi, G.-B.; Whang, S.-Y.; Ku, B.-C.; Choi, J.-Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 71. (c) Kotik, M.; Brichac, J.; Kyslik, P. *J. Biotechnol.* **2005**, *120*, 364.

(36) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307 and references cited therein.

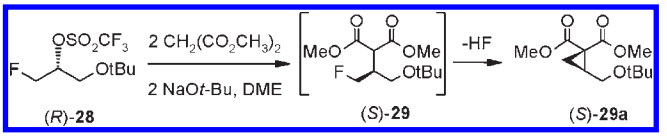
(37) The lower boiling (*S*)-**14** was separated from the higher-boiling (*R*)-*tert*-butyl glyceryl ether by distillation.

(38) When the reaction mixture was warmed up and stirred at ambient temperature, increasing racemization was observed (1 h: 0.75%; 24 h: 23% (*S*)-**28** formation).

(39) At ambient temperature the stability of the neat triflate (*R*)-**28** could be extended to 1−2 days by the addition of solid K_2CO_3 or DIPEA (5 mol%). As solution in DCM (*R*)-**28** was stable at ambient temperature for two days without any additive. Although the corresponding mesylate, tosylate and nosylate derivatives were stable compounds, only the triflate (*R*)-**28** was sufficiently reactive to effect a selective and efficient malonate substitution.

(40) In order to minimize HF elimination to the cyclopropane side product (*S*)-**29a**, the excess of sodium dimethyl malonate (1.1 equiv)

was kept as low as possible. With ≥2 equiv sodium dimethyl malonate, the intermediate (*S*)-**29** was completely converted into (*S*)-**29a**.



(41) The triflate substitution with sodium dimethyl malonate (generated either with NaH or preferably with NaO*t*-Bu) was tested in the solvents DME (0 °C, ∼7 h) and THF (0 °C, ∼20 h). DME was preferred over THF due to the higher boiling point (86 vs 66 °C) allowing a higher reflux temperature and accelerating the hydrolysis of the malonic ester and the subsequent decarboxylation with aq H_2SO_4.

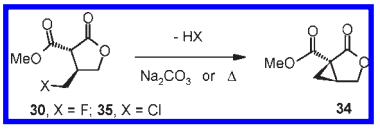
(42) The additive DMI was superior to DMPU and preferred over the highly toxic HMPA; cf.: Al Abed, Y.; Zaman, F.; Shekhani, M. S.; Fatima, A.; Voelter, W. *Tetrahedron Lett.* **1992**, *33*, 3305.

(43) (*R*)-Glycidyl 3-nitrobenzenesulfonate (*R*)-**33** was offered in bulk quantity by an external supplier.

(44) (a) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. (b) Kitaori, K.; Mikami, M.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Synlett* **1998**, 499. (c) Mikami, M.; Furukawa, Y.; Oodera, J.; Yoshimoto, P. H. (Daiso Co., Ltd.). Jpn. Pat. JP 10059955, 1998.

(45) $Et_3N \cdot 3HF$ (37% HF in Et_3N), Honeywell No. 1790. For HF addition to activated cyclopropane rings see: Cotterill, I. C.; Finch, H.; Highcock, R. M.; Holt, R. A.; Mahon, M. F.; Molloy, K. C.; Morris, J. G.; Roberts, S. M.; Short, K. M.; Sik, V. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1353.

(46) It is noteworthy that under basic (Na_2CO_3) or thermal conditions (GC, ≥200 °C) the lactones **30** and **35** partially eliminate HX providing cyclopropanolactone **34**.



(47) Experiments with corrosive HF reagents such as $Et_3N \cdot 3HF$ were performed in HF-resistant perfluoro-alkoxy-copolymer PFA-flasks (Supplier: Bohlender GmbH, Waltersberg 8, D-97947 Grünsfeld).

(48) Cf. Steffen K.-D. (Hüls AG). U.S. Patent 5,463,111, 1995.

(49) The main source of fluoride is the formation of cyclopropane (*S*)-**29a** in the malonate substitution reaction (cf. reference[40]). In the ensuing treatment with 2 M H_2SO_4 (*S*)-**29a** is further converted into cyclopropanolactone **34** and hydroxymethyl lactone **7** which were observed as trace byproducts.

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