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Design and Scale-Up of a Practical Enantioselective Route to 5-Phenylbicyclo[2.2.2]oct-5-en-2-one

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Supporting Information

ABSTRACT: A practical enantioselective route to chiral 5-phenylbicyclo[2.2.2]oct-5-en-2-one **1** has been designed and developed. The target compound has been obtained as colorless crystals in 22% yield from 2-cyclohexenone, with an enantiomeric ratio higher than 99.5:0.5 and notably high chemical purity (> 99%). Three intermediates out of nine chemical steps are isolated. It is noteworthy that this process is devoid of any chromatography or distillation although all but one intermediate are oils. Key to success was the optimization of an intramolecular aldol reaction of an in situ prepared ketone aldehyde leading to the solid intermediate (1*R*,4*R*,4*S*,6*S*)-6-hydroxybicyclo[2.2.2]octan-2-one **9a** that is isolated in very high chemical and chiral purity. This is an example of an intramolecular crystallization-induced diastereomer transformation (CIDT). The dehydration of this secondary alcohol to **1** required an extensive screen of reaction conditions to secure an excellent purity, essential for crystallization of this low-melting compound. The final process is simple and concentrated as demonstrated by an expeditious synthesis of 1 kg of **1** in a 30-L reactor in 10 working days.

INTRODUCTION

Enantiomerically pure (*R*,*R*)-phenylbicyclo[2.2.2]oct-5-en-2-one **1**[1] was required as key intermediate for an active pharmaceutical ingredient (API). Larger amounts (90 kg) were produced with an initial Diels–Alder step[2] and a final chromatographic separation of the enantiomers (Scheme 1). Bicyclo[2.2.2]-octenes are important skeletons in various fields of organic chemistry,[3] including chiral dienes as a new privileged class of ligands as pioneered by the groups of Hayashi[4] and Carreira.[5]

Although this route proved scalable and the separation was highly efficient, it suffered from some impediments in view of larger scales: (i) the diene **2** was prepared at low temperatures and required distillation, (ii) the Diels–Alder reaction was dependent on the quality of α-chloroacrylonitrile which might have to be distilled prior use, (iii) the intrinsic loss of more than half of the material in the final chiral separation without the possibility for racemization and recycling, and (iv) the moderate assay of the product (87% w/w) as obtained after preparative chromatography. The product was obtained in 16% overall yield as a waxy black solid. On the other hand, the published route to **1** suffers from a yield of <0.2% over nine steps, relying on an enantioselective host–guest complex formation, starting from hydroquinone and maleic anhydride.[1a] An enantioselective route was therefore required to secure the access to larger scales.[6] Besides the usual requirements like cost reduction including a low priced and early introduction of chirality, high throughput and short cycle times, this specific target placed a great demand on yields and selectivities, as purification of the liquid intermediates should be restricted to extraction only. Clearly, a solid intermediate as a cleanup stage was desired.

ALTERNATIVE ROUTES

The main retrosynthetic bond breaks are depicted in Figure 1. The retrosynthetic path A leads to a known precursor, ketal ketone **5**,[2a] which was thought to arise from intramolecular enolate alkylation.[7] Several adjustments of the oxidation stage would lead to a Michael adduct **7**, which is conceivably synthesized from malonate addition to 1,4-dioxaspiro[4.5]dec-6-en-8-one **8**, a transformation which is lacking an enantioselective example in literature. The intramolecular aldol reaction of a putative ketone aldehyde intermediate **10**,[8] path B, was perceived as feasible yet highly risky endeavor due to the many isomeric products which can evolve from such a seemingly labile substrate. Ketone aldehyde **10** or a masked form thereof was deemed accessible either via the nitrile **11** or the ester **12**, both being conceivably derived from asymmetric Michael additions of phenyl acetonitrile or malonates, respectively, onto cyclohexenone. There is ample precedence for the latter even on kilogram scale,[9] whereas the enantioselective Michael addition of phenyl acetonitrile to this acceptor was unprecedented.[10] These paths have been assessed in parallel, some first as a racemic proof-of-concept, in order to quickly sort out the best route for development of the enantioselective route.

Further alternative approaches to **1** were checked with racemates to assess the feasibility: (i) asymmetric 1,4-addition of organovinyl reagent onto cyclohexenone.[11] The ensuing epoxidation of the double bond failed, giving exclusively the Baeyer–Villiger lactone product. (ii) On paper, one of the shortest routes involves the Michael addition of (1-phenylvinyl)-magnesium bromide[12] onto cyclohexenone. However, in practice, the preparation of the Grignard reagent, the costs, and the lack of enantioselective examples caused us to leave this route.

Intramolecular Ketone Enolate Alkylation (Path A). Path A (Scheme 2) starts with 1,4-dioxaspiro[4.5]dec-6-en-8-one, **8**, which was best prepared from commercially available 1,4-dioxaspiro[4.5]decan-8-one.[13] Alternative syntheses of **8**

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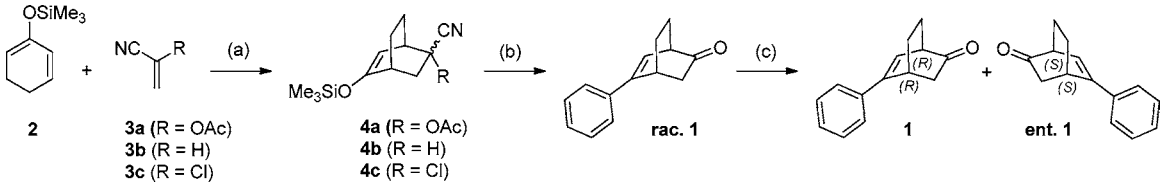
Scheme 1. Original route used for the first GMP campaign[2a]



Reagents and conditions: (a)[2a] 66% (R = OAc), 84% (R = H), >88% (R = Cl); (b)[2a] 4–5 steps, 86% (R = OAc), 39% (R = H), 44% (R = Cl); (c) preparative chiral chromatography, Chiralpak AS-V (20 μm, 250 mm × 80 mm), eluent: MeOH (0.1% Et_3N), er > 98:2, 85% recovery of both enantiomers; or Chiralpak IA (20 μm, 250 mm × 76 mm), eluent: heptane/EtOAc 75:25, er > 99:1, 82% recovery of both enantiomers.

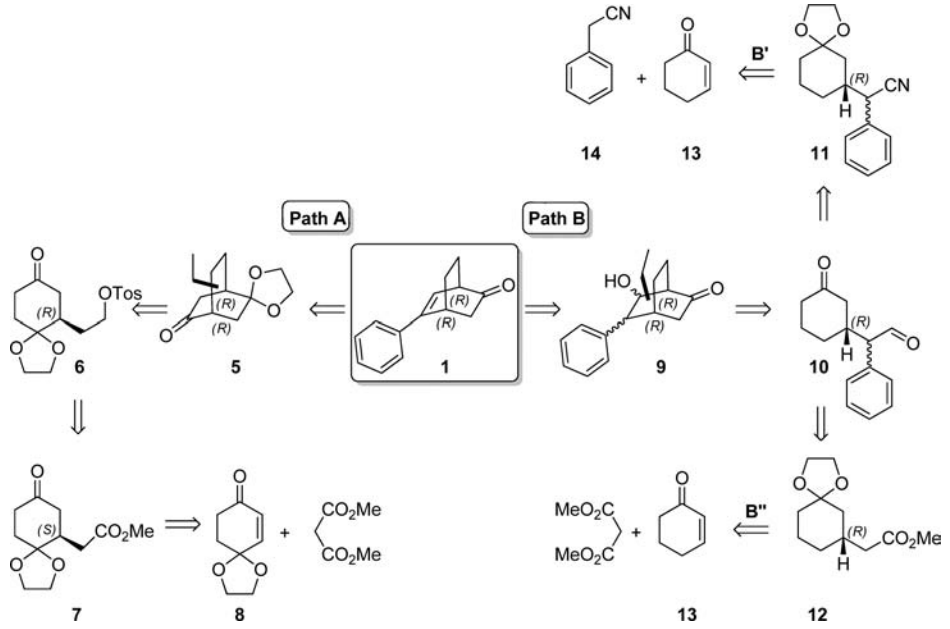
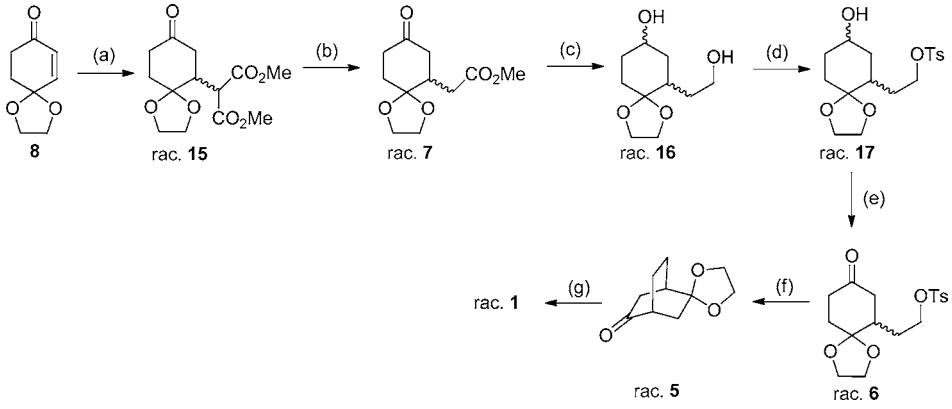


Figure 1. Proposed retrosyntheses of **1**.

Scheme 2. Intramolecular ketone enolate alkylation, racemic proof-of-concept (path A)



Reagents and conditions: (a) dimethyl malonate (1.5 equiv), Et_3N, LiCl (1 equiv), toluene, rt, 89%; (b) DABCO (4 equiv), H_2O (2 equiv), toluene, 110 °C, sealed vial, 73%; (c) 2 M $LiAlH_4$ in THF (2 equiv), THF, rt, 65%; (d) pTosCl (1 equiv), Et_3N (1 equiv), Bu_2SnO (0.02 equiv), rt, 84%; (e) SO_3.pyridine (1.5 equiv), Et_3N (3 equiv), DMSO (5 equiv), DCM, rt, 61%; (f) KO*t*Bu (1.2 equiv), THF, 5 °C, 60%. (g) ref 2a.

gave inferior results.[14] The crucial intermediate as probe for the cyclization (*rac*-**6**) was synthesized by a sequence of Michael addition of dimethyl malonate to **8**,[15] decarboxylation in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford *rac*-**7**,[16] exhaustive reduction with $LiAlH_4$ to the diol *rac*-**16** as isomeric mixture, selective monosulfonylation of the primary alcohol with *p*-toluenesulfonyl chloride (*p*TosCl) in the presence of catalytic dibutyltin oxide to get *rac*-**17**,[17] and a Parikh–Doering oxidation to yield *rac*-**6**.[18] Gratifyingly, the cyclization step proceeded dose-controlled at 5 °C by addition of KO*t*Bu in THF. The quality of ketone ketal *rac*-**5**, a key precursor of *rac*-**1**, was acceptable after comparison of the GC and NMR spectra with a known sample from another route.[2a] Due to expected high costs for the starting material **8**[19] and the need for a development of a new catalytic enantioselective addition to **8**, we focused on path B.

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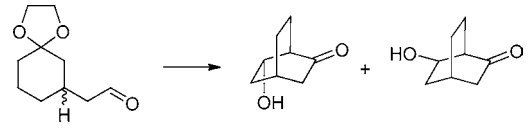
Intramolecular Aldol Reaction of Masked Ketone-Aldehyde 10 to 9 (path B). The intramolecular aldol cyclization was described for the des-phenyl derivative **18** by Mori,[20] Bettolo[21] and Mattay,[22] see Scheme 3.[23] The cyclization afforded an *endo*/*exo* mixture of ~85:15, and *rac*-**19a** was obtained in 61% yield after flash chromatography.[21a]

Scheme 3. Literature precedence for the racemic des-phenyl derivative 18[21a]



18 **19a** 85:15 **19b**

To probe the unprecedented cyclization to **9** we synthesized the required α-phenyl derivative *rac*-**21** as depicted in Scheme 4. Aldehyde *rac*-**21** was prepared according to published procedures. A Michael addition of phenylacetonitrile **14** to cyclohexenone **13** afforded *rac*-**20**,[24] which was protected as ketal *rac*-**11** and finally reduced to aldehyde **21**. Gratifyingly, the pivotal intramolecular aldol reaction proceeded with 5 M H_3PO_4 in quantitative (uncorrected) yield using crude *rac*-**21**.[22a] The dehydration was achieved by heating the intermediate mesylate *rac*-**22** in the presence of Li_2CO_3 and LiBr in DMF at 150 °C. It is noteworthy that all intermediates (oils) have been processed as crude products into the next stages without chromatography, the only purification being short-path distillation of *rac*-**1**.

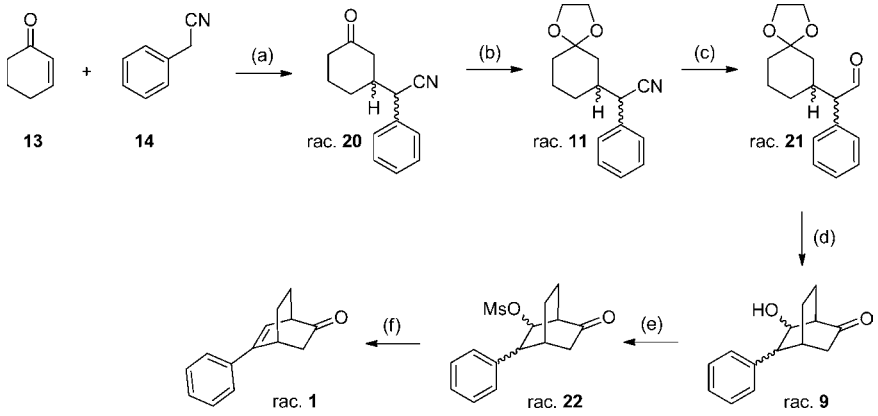
■ ENANTIOSELECTIVE ROUTE

With the racemic proof-of-concept for the crucial stereospecific C−C bond formation at hand and the availability of an efficient synthesis of the chiral starting material **23**,[16,25] we set out to develop a robust route building on the Shibasaki reaction as enantioselective step (Scheme 5). As a testimony to the practicality of this robust transformation, the enantiomerically pure malonate **23** was synthesized on multi kg scale, starting with a Michael addition of dimethyl malonate to cyclohexenone **13** catalyzed by (*R*)-ALB (Al−Li-bis(binaphthoxide complex); without crystallization the crude Michael adduct was telescoped into the ketal formation step with ethylene glycol to afford **23** as oil with an er > 99.5:0.5.[16,26]

Decarboxylation Step to 12. Initial runs with DABCO and water in toluene at reflux over 16 h led to a black oil of low purity requiring purification by distillation.[16] In practice, a mixture of malonate **23**, 2 equiv of LiCl and 1 equiv of water in 2 vol of DMAc was heated to 135−140 °C and stirred at this temperature for 4−5 h.[27] A white precipitate[28] was formed after reaching 120 °C, indicating the start of the decarboxylation. In contrast to reported procedures which rely on addition of water to dissolve the solids, we took advantage of this observation and removed the salts by a filtration of the reaction mixture at rt. This significantly reduced the volumes of both water and toluene for the workup with this dipolar aprotic solvent.[29] The filter cake was washed with 0.5 vol toluene, and the product **12** was obtained as low-viscosity oil in 88% yield[30] after a final water extraction step and solvent removal. In the absence of water, degradation occurred. Best conversion was achieved with 2 equiv of LiCl; the use of 1 equiv led to 20% conversion and degradation. Besides being operationally simpler, this process is faster than in published protocols.[31] Viable solvents are DMAc, NMP, DMF, and DMSO. DMSO was not judged as the ideal solvent due to its instability at elevated temperatures. The evolving chloromethane was trapped in a scrubber filled with a 1:1 mixture of ethanolamine and water.

α-Arylation to 24. The α-arylation of esters is an established method for larger scales as well[32] since the seminal work by the Hartwig and Buchwald groups.[33] We used lithium diisopropylamide (LDA) as base. $P(tBu)_3{\cdot}HBF_4$ was chosen as a hindered phosphine ligand due to its stability and ease of handling. $Pd(OAc)_2$ and $Pd_2(dba)_3$ gave similar results. Replacement of bromobenzene by chlorobenzene was only feasible with $Pd_2(dba)_3$ and gave similar yields.[34] Excess bromobenzene was difficult to remove from the oil; therefore, only 1 equiv was used.[35] The reaction displayed a slight delayed exotherm which did not vary much upon scale-up (internal temperature rose to 25−29 °C with a constant jacket temperature at 20 °C on 40 g-, 400 g-, and 4-kg scale); on the other hand, dosage to the enolate of bromobenzene alone or as a mixture with **12** at 40 °C led to byproducts. Dosage of a mixture of $Pd_2(dba)_3$ and $P(tBu)_3{\cdot}HBF_4$ in toluene did not seem advisable as this mixture gave a precipitation when

Scheme 4. Phenylacetonitrile route, racemic proof-of-concept (paths B, B′)



Reagents and conditions: (a)[24] 1:1 mixture of diastereoisomers; (b) ethylene glycol (10 equiv), $pTsOH{\cdot}H_2O$ (0.05 equiv), toluene, 110 °C, 1.5 h, 99%; (c) 1 M diisobutyl aluminium hydride in heptane (1.7 equiv), THF, 25 °C, 59%; (d) 5 M H_3PO_4 (6.5 equiv), THF, 80 °C 5 h, 101%; (e) Methanesulfonyl chloride (MsCl, 1.9 equiv), Et_3N (2.0 equiv), DCM, 10−20 °C, 1 h, 89%; (f) i) Li_2CO_3 (1.0 equiv), LiBr (1.0 equiv), DMF, 150 °C, 1 h, 91% crude, ii) distillation, 120 °C, 0.001 mbar, 37%.

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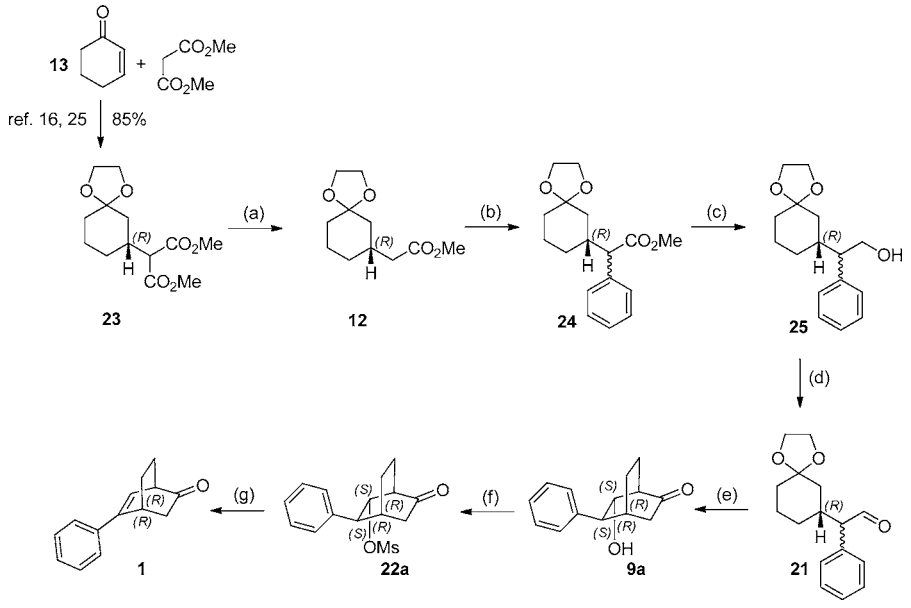
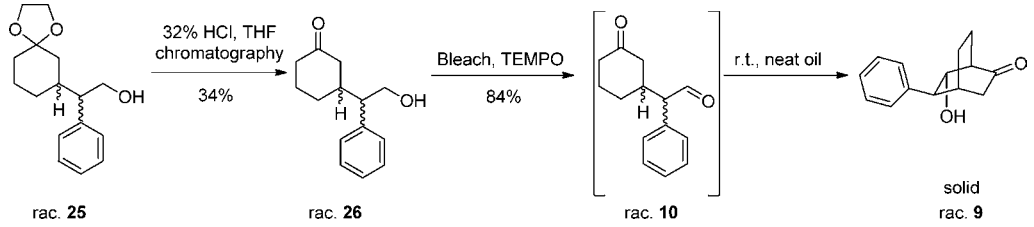
Scheme 5. Preferred route for scale up (paths B, B″)



Reagents and conditions. Yields are corrected for NMR assay of starting material and product: (a) LiCl (2.0 equiv), H_2O (1.0 equiv), dimethylacetamide (DMAc), 140 °C, 5 h, 88%; (b) i) 33% HexLi in hexane (1.1 equiv), diisopropylamine (DIPA, 1.2 equiv), toluene, 0−10 °C, 30 min, (ii) **12**, 5−10 °C, 45 min, iii) tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$, 0.01 equiv), P(*t*Bu)$_3$·HBF$_4$ (0.01 equiv), bromobenzene (1.0 equiv), 10−29 °C, 3 h, toluene-solution of **24** telescoped into next step; (c) 2.4 M $LiAlH_4$ in THF (0.55 equiv), toluene, 5−15 °C, 30 min, 84% (2 steps); (d) NaOCl solution (12% w/w, 1.2 equiv), aqueous sat. $NaHCO_3$ solution, KBr (0.1 equiv), 2,2,6,6-tetramethyl-piperidine-1-oxyl, (TEMPO, 0.01 equiv), 5−10 °C, 1 h, EtOAc-solution of **21** (2 vol) telescoped into next step; (e) 32% HCl (0.3 equiv), 50 °C, 2 h, 45% (2 steps); (f) MsCl (1.3 equiv), Et_3N (1.5 equiv), toluene, 10−20 °C, 10 min, telescoped into next step; (g) 2,4,6-collidine, 140−145 °C, 1.5 h, two crops, 79% (2 steps).

Scheme 6. Small-scale synthesis of unprotected keto-aldehyde *rac*-10 for initial test of cyclization



prepared separately. Once the catalytic cycle with the halobenzene was running—as judged by product formation according to HPLC—temperatures up to 50 °C were not detrimental. Excess of LDA (1.25 equiv) did not improve conversion. A concern was the removal of the color as no purification of the downstream intermediates by crystallization seemed possible at this stage. The black precipitation (Pd black and residues of the ligand) was triggered by lower pH. The best compromise between color removal and ease of phase split was accomplished by a citric acid quench, followed by a phase split, water extraction, and a final charcoal treatment of the organic layer.[36] Scavengers (Silicycle, Si-Diamine, 1.52 mmol/g)[37] were not superior for decoloration. On kilogram scale, neat **12** was added to freshly prepared LDA in hexane and toluene at 0−10 °C. After 10 min, $Pd_2(dba)_3$ and P(*t*Bu)$_3$·HBF$_4$ were added, followed by the dosage of bromobenzene. Following aqueous workup, the toluene solution was concentrated, thereby removing water by azeotropic distillation and adjusting the desired concentration of **24** for the next step.[38] Ester **24** consisted of a mixture of *like* and *unlike* epimers **24a** and **24b** in a ratio of 60:40 to 70:30 by GC, both epimers being productive substrates for downstream chemistry. For analytical purposes we isolated both racemic epimers **24a** and **24b** allowing for the determination of the relative configuration by X-ray structure analysis (*rac*-**24a**, Supporting Information [SI]).

Reduction to 25. The reduction of the ester **24** to the alcohol **25** was straightforward. We concentrated on streamlining the process and minimizing the equivalents of $LiAlH_4$ and solvent volumes. On 5-kg scale, 0.55 equiv of $LiAlH_4$ was dosed as 2.4 M solution in THF to the toluene stream of the preceding step, the exothermic reaction being dose controlled at 5−15 °C. The classical three-stage quench employing the least amount of water was employed, thus producing a nicely granulated suspension for easy filtration.[39] Simple removal of solvent afforded the product **25** as low-viscosity oil in 84% yield over two steps. Remarkably, this reduction is very concentrated, i.e. 4.2 vol solvent was required for reaction, including quench.

Oxidation/Cyclization Sequence to 9a. Oxidation to 21. The masked precursor for the cyclization **21** was accessed from **25** by the TEMPO-bleach oxidation protocol, see Scheme 5.[40] It was anticipated that cyclization would ensue directly after deketalization in a one-pot fashion.

We prepared the putative precursor for the intramolecular aldol reaction, the labile free ketone *rac*-**10**[41] via keto-alcohol *rac*-**26** to get more insight into this intramolecular aldol reaction (Scheme 6). In situ prepared *rac*-**10** cyclized spontaneously to

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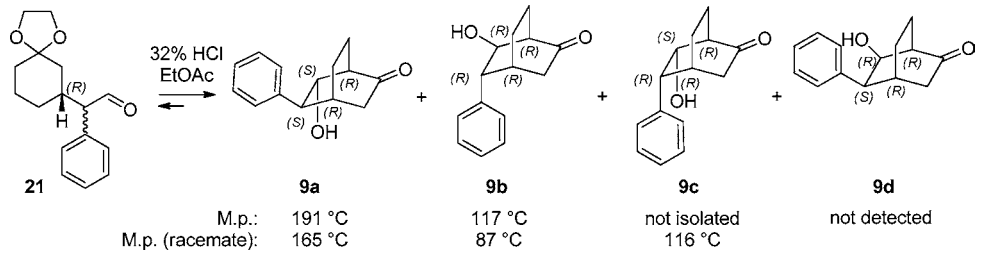
Scheme 7. Isomeric distribution of the products of the intramolecular aldol reaction



rac-**9** upon standing as neat oil at rt, one diastereoisomer being enriched. This made us confident to find mild conditions for the cyclization of **21**. It is noteworthy that basic conditions, too, were beneficial for the cyclization of *rac*-**10** to *rac*-**9**, for example KOH in aqueous MeOH, or KO*t*Bu in THF.

Some process parameters of the oxidation required optimization. Decomposition was observed with the less expensive 4-hydroxy-TEMPO.[42] Both DCM and EtOAc proved successful for this oxidation. Toluene in alcohol **25** slightly decreased both yield and assay purity. In practice, a freshly prepared bleach solution of pH 8−9.5, was dosed at 5−10 °C to a mixture of **25**, KBr (dissolved in water), and TEMPO in EtOAc. The concentrated (8.5 vol) exothermic oxidation was dose-controlled. After quench of excess bleach with sodium thiosulfate and an aqueous wash of the organic phase, the concentration for the next step (2 vol EtOAc) was adjusted by distillation under reduced pressure.[43] The ketal aldehyde **21** proved to be sufficiently stable to allow for an aqueous workup and a telescoping into the next stage, vide infra.[44]

Cyclization to 9. The projected cyclization was associated with the formation of many conceivable products and isomeric mixtures thereof. In addition to the four possible isomeric alcohols **9a−d** (Scheme 7) which could be produced by intramolecular attack of the ketone enolate onto the aldehyde, the following byproducts are conceivable: oligomers derived from intermolecular aldol reactions, ketals of all products, cyclobutanols[45] arising from cyclization to the opposite methylene of the keto group in **10**, and hemiacetals[45b] derived from an attack of the aldehyde enolate to the ketone. Original literature conditions for the racemic des-phenyl derivative **18** (Scheme 3) or for *rac*-**21** (Scheme 4) were quite harsh, employing either phosphoric acid[22] or 2 N HCl in refluxing THF[21a] for 4 and 24 h, respectively; the product was isolated after evaporation to dryness, aqueous workup, and chromatography. Employing these conditions our phenyl derivative **21** afforded semisolid material **9** as isomeric mixture that was used as such in the last two steps. For the first racemic batches on 100-g scale we applied a telescoped process: dosage of the DCM-solution containing the aldehyde *rac*-**21** to a solution of 32% HCl in 2-methyl-THF at 65−75 °C, affording **9** as a yellow, greasy solid in 80% assay-corrected yield. Residual 2-methyl-THF and ethylene glycol proved difficult to be removed and led to decreased purity in the ensuing stages.

A chromatographic separation of the three main (racemic) products allowed for the determination of the relative configuration by X-ray crystal structure analysis (Figure 2).[46]

In addition, the melting points of these bicyclic isomers led to a better understanding of the isomeric ratio in the reaction mixture, which is best rationalized as crystallization-induced diastereomer transformation (CIDT).[47] Key to success was the observation that the isomer **9a** (and *rac*-**9a**) was isolated with >99% diastereoisomeric purity after simple filtration of the reaction mixture (sum of isomers **9a** and **9b** was 70−85% a/a by LC−MS, with a best ratio of **9a** and **9b** of 85:15), when we turned to solvents like esters or toluene. The diastereomeric ratio of starting ketal aldehyde **21** was between 60:40 and 70:30 (by GC−MS) in favor of the isomer with *like* topicity (*R*,*R*).[48] However, in-process controls (IPC) by HPLC of the mixture indicated **9a** with (*S*)-configuration of the benzylic position as major isomer. We think that the equilibrium between these isomers is driven by the higher melting point—hence lower solubility—of **9a**, thus depleting the mixture in **9a**. Epimerization should occur via the reversible aldehyde enolate reprotonation (Figure 3).[49]

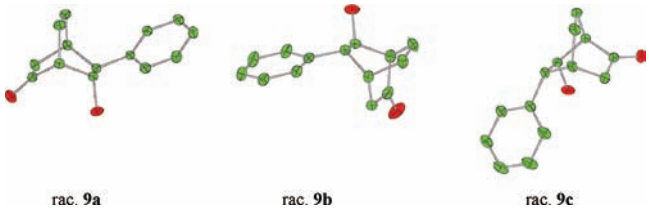


Figure 2. X-ray structures of *rac*-**9a**, *rac*-**9b**, and *rac*-**9c**.

To elucidate the utility of each single isomer for downstream chemistry we submitted these three diastereomerically pure racemic isomers separately to the elimination conditions of the next step (Scheme 5): whereas *rac*-**9a** and *rac*-**9b** displayed comparable kinetics and IPC purity, *rac*-**9c** turned out to be unproductive resulting in decomposition.

With these data at hand, a first specific goal for the optimization of the cyclization was to reach the highest possible isomeric ratio of diastereoisomer **9a** in the reaction mixture. The isomeric ratio was determined by chiral HPLC separating all six isomers.[50] Consistent purity indication was obtained by thin layer chromatography (TLC), whereas LC or GC often faked too high a purity which was not corroborated by NMR assay or TLC.[51] After having reached the highest possible ratio, the yield was to be optimized.

A set of experiments performed with **21** is presented in Table 1. Running the reaction more concentrated led to better results (entries 1 and 2). The kinetics were elucidated (entries 3, 4): an IPC at 20 min showed a multitude of products in addition to the three major isomers which coalesced to two products, **9a** and **9b**, after 100 min. Raising the temperature from 50 to 70 °C did not significantly improve the ratio of **9a** (entry 3, 5). 50 °C was found to be the optimum temperature considering the overall purity by HPLC which decreased with higher temperatures (not shown). In addition, important conclusions have been obtained from screening reaction conditions with racemic **21**[52] (1 equiv 32% HCl, 2 h, 20 °C): (i) the reaction requires temperatures higher than rt; the isomeric ratio

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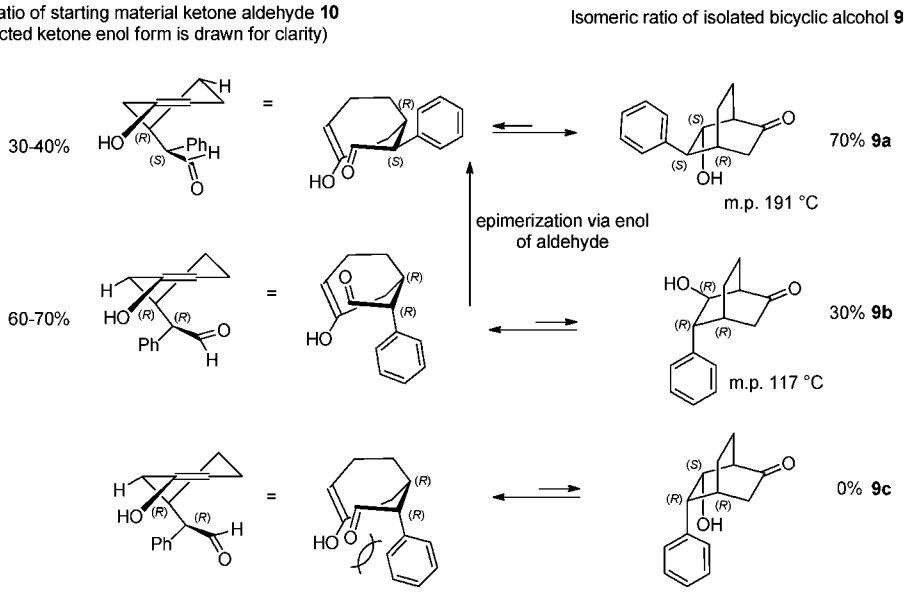


Figure 3. Tentative mechanistic explanation of the observed isomeric ratio by CIDT.

Table 1. [a] Optimization of cyclization conditions with enantiopure 21

entry	solvent	temp. °C	time	9a[b] %	9b[b] %	9c[b] %
1	2 vol EtOAc	50	2 h	85	15	0
2	5 vol EtOAc	50	2 h	68	25	7
3	1 vol EtOAc	50	20 min	78	13	9
4	1 vol EtOAc	50	100 min	86	14	0
5	1 vol EtOAc	70	20 min	80	15	5

[a]5−45 g scale (**21**), 32% HCl (0.3 equiv). [b]Ratio of each isomer normalized to the sum of **9a**, **9b**, and **9c** in the reaction mixture, by % a/a (chiral HPLC).

for *rac*-**9a**/*rac*-**9b**/*rac*-**9c** at 20 °C in EtOAc was 76:16:8; (iii) reactions in the following solvents gave a lower content of *rac*-**9a** and 5−20% unproductive *rac*-**9c** as compared to the results in EtOAc: acetone, toluene, isopropanol, THF, *tert*-butyl methyl ether (TBME). Clearly, EtOAc was the first choice to get both a high content of the desired isomer and a high-yielding reactive crystallization.[53]

We subjected the isomerically pure products **9a,b,c** to the best reaction conditions to shed light on their interconversion potential, to define the aging time prior to filtration, and to determine the limits of this process (Table 2). Both racemic (dr > 99:1) and enantiomerically pure (dr > 99:1, er > 99:1) isomers have been used and gave a similar trend. Gratifyingly, the diastereoisomer *rac*-**9a** was stable (entry 1), a third of *rac*-**9b** isomerized to the desired *rac*-**9a** (entry 2), and *rac*-**9c** led to a 1:1 mixture of *rac*-**9a** and *rac*-**9b** (entry 3). The enantiomer **9a** isomerized to a small extent (entry 4) and **9b** led to a similar ratio as its racemate (entry 5).

Table 2. [a] Isomerization studies with diastereomerically pure isomers of 9

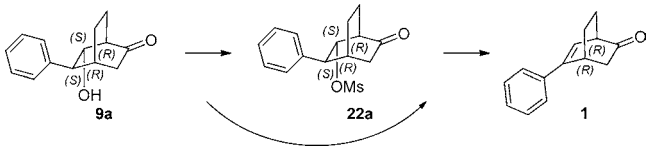
entry	starting material	solvent	*rac*-9a[b]	*rac*-9b[b]	*rac*-9c[b]
1	*rac*-**9a**	2 vol EtOAc	100	0	0
2	*rac*-**9b**	2 vol EtOAc	30	67	2
3	*rac*-**9c**	2 vol EtOAc	59	41	0
			9a[c]	9b[c]	9c[c]
4	**9a**	2 vol EtOAc	93	7	0
5	**9b**	2 vol EtOAc	49	51	0

[a]Conditions: 0.5 g scale, 32% HCl (0.3 equiv), 50 °C, 18 h. [b]Ratio of each isomer normalized to the sum of *rac*-**9a**, *rac*-**9b**, and *rac*-**9c** in the reaction mixture, by % a/a (chiral HPLC). [c]Ratio of each isomer normalized to the sum of **9a**, **9b**, and **9c** in the reaction mixture, by % a/a (chiral HPLC).

Following the optimized conditions (Table 1, entry 1), 32% HCl was added to the EtOAc-solution containing 3 kg of crude **21** from the oxidation. After stirring at 50 °C for 2 h (conversion to the sum of all three diastereoisomers of **9** was 97% by LC−MS) the suspension was aged first at 10 °C for 16 h, then at 0 °C for 1 h. The main diastereoisomer **9a** was isolated by filtration in 46% yield over two steps with er > 99.5:0.5 (HPLC).[54] We found that ∼10% toluene in **21** slightly decreased the yield: a second run on 1 kg scale with a toluene content of 2% w/w in **21** gave 51% corrected yield from **25** to **9a**. This telescoped oxidation/cyclization protocol is characterized by a highly concentrated CIDT protocol and a remarkably high diastereomeric purity (>99.5%).[55]

Elimination to 1. Originally (Scheme 4), we engaged crude **9** consisting of the three isomers (as greasy solid) with a moderate purity in the mesylate-elimination sequence. The poor quality of crude **1** hampered an efficient purification by crystallization or distillation. With **9a** of very high purity at hand, we now embarked on the stepwise optimization. The obvious one-step dehydration from **9a** to **1** was studied first (Scheme 8). Either no reaction (HOAc, with/without NaOAc; $BF_3{\cdot}Et_2O$ in DCM; SiO_2), decomposition (thionyl chloride in toluene; phosphoryl chloride; Ac_2O/HOAc; pTsOH in toluene; polyphosphoric acid; dicyclohexylcarbodiimide with

Scheme 8. Dehydration of 9a to 1



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catalytic CuCl[56]), or undesired product formation (*o*-formyl product with HCO_2H or trimethylorthoformiate; two undesired products with Burgess reagent[57]) was observed. Best IPC purity (55% a/a by LC−MS) was achieved by heating in neat thionyl chloride for 3 h, albeit with many byproducts. The ketone group was suspected of intervening in the skeletal rearrangements.[58,59] However, we could not protect **9a** as ketal without acid-catalyzed ring-opening and formation of a multitude of products. On the other hand, treatment of **9a** with NaH and benzyl bromide to protect the secondary alcohol led to isomerization yielding a 2:1 mixture of **9a** and **9b**.

We then turned to a two-stage process by first synthesizing the mesylate **22a** which was used as substrate for the subsequent screens. Optimization targets were the IPC purity of **1** by HPLC, followed by the color and the isolated yield. At first, the amidine bases DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), MTBD (7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene), TMPDA (*N*,*N*,*N*′,*N*′-tetramethylpropane-1,3-diamine), and DABCO (1,4-diazabicyclo[2.2.2]-octane) were examined for the eliminations in neat conditions or in THF, DMF, toluene, diglyme, *n*-butyronitrile, or acetonitrile at 85−150 °C (SI). These reactions either proved to be slow at lower temperatures or produced many byproducts, some arising from ring-opened amidine bases. The best result was obtained with 2 equiv of DBU in toluene at 140 °C (external temp.) for 1 h, with a purity of ca. 90% a/a of an IPC sample.

The risk of ring-opening of DBU and DBN at the required high temperatures directed us to screen inorganic bases such as Li_2CO_3, K_2CO_3 in *o*-xylene, DMF, NMP, DMSO, DBU, or toluene, with and without additives (NaI or LiBr). The elimination in the presence of Li_2CO_3 in DBU gave a high purity; however, degradation started already after 25 min. Alkoxides (NaOMe, NaO*t*Bu, and KO*t*Bu) in diglyme or THF led to a low purity of **1**. We were surprised to observe a decent purity (89% a/a) without *any* base, when running the reaction in the presence of silica gel. This finding drove the design of the next experiments in the absence of base.

Amongst the solvents tested (toluene, *o*-xylene, chlorobenzene, DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone), DMF, NMP, DMSO, sulfolane), NMP and sulfolane gave the highest purities (92−99% a/a **1**) the latter ending up in a black solution. We envisaged a melt process heating neat **22a** (melting point of 87 °C for mesylate **22a**), but this led to many byproducts.

The finding that the elimination of the mesylate **22a** worked well without base allowed for a hypothesis about the mechanism. With the E2 *anti* elimination being impeded by the bicyclic structure and the E1cb being ruled out by the observation above, the E2 *syn* mechanism seems to be prevalent with release of methanesulfonic acid and explains the observations that only the two isomers **22a** and **22b** with the required *cis*-stereochemistry of the OMs group and the β-H finally produced **1**.[60]

A one-pot elimination protocol was tempting; after formation of the mesylate **22a** in NMP with MsCl and Et_3N, salts were filtered off, and the filtrate was heated directly to 135 °C for 80 min. The product **1** was obtained as black oil in 91% yield, however, with a low assay of 51% w/w which was upgraded to only 66% and 84% w/w by short-path distillation[61] or chromatography, respectively.

We speculated that the less basic pyridines could play the role of both base and solvent. The pK_a and stability seemed ideal for the elimination and the boiling points of pyridine, 2,6-lutidine, and 2,4,6-collidine at 115, 144, and 171 °C, respectively, should enable an easy control of the process temperature (Table 3). Pyridine gave a spot-to-spot reaction on TLC; however, the temperature was obviously too low to achieve full conversion (entry 1). With 2,6-lutidine the purity was pushed up to 90% which guided us to use 2,4,6-collidine, the solvent of choice (entries 2, 3). Higher concentrations are favorable for conversion and purity (entries 3, 4). By LC−MS, the addition of NMP seemed favorable, but the TLC revealed a baseline spot and a trace of alcohol **9** as compared to a single spot for the run in neat collidine (entries 4, 5).

Table 3. [a] Eliminations of 22a in pyridine bases

entry	base	temp.[b] °C	time h	IPC % a/a	comments
1	5 vol pyridine	115	24	60	66% conversion
2	2 vol 2,6-lutidine	143	3	90	byproduct
3	2 vol 2,4,6-collidine	150	3	98	
4	1 vol 2,4,6-collidine	143	1.5	99	
5	0.5 vol 2,4,6-collidine	150	2	100	in 0.5 vol NMP

[a]0.5 g scale (**22a**), full conversion unless otherwise stated, IPC a/a of desired product **1** (LC method 1). [b]External temperature.

To assess the safety of these reactions at high temperature, differential scanning calorimetry (DSC) was performed, see Table 4. On the basis of these results, NMP and collidine were considered as acceptable solvents. The DSC charts of neat solvents and of **1** are disclosed in the SI.

Table 4. DSC data for the elimination of 22a

entry	sample	left limit °C	peak °C	exotherm kJ/kg
1	neat **22a**[a]	124	142	−549
2	**22a** in 2,4,6-collidine	149	177	−158
3	**22a** in NMP	100	146	−169
4	*rac*-**22a** in DMSO	176	249	−739

[a]Mp at 87 °C (peak).

Crystallization of **1** proved challenging due to the low melting point (66−68 °C) and its lipophilic and unpolar nature. Residual impurities and solvents combined with tar formation thwarted crystallization. Phenylketone **1** of inferior quality (i.e., < 90% a/a or w/w) was impossible to crystallize without oil formation. A breakthrough was obtained with heptane for the crystallization that not only removed most of the impurities but enabled as well an efficient removal of tarry byproduct accompanying all runs.[62] Alternative crystallization solvents were heptane/TBME 4:1 v/v or neat TBME, both very concentrated (1−3 vol).

Following the preferred protocol on 1.6-kg scale, mesylate **22a** was accessed in 30 min with MsCl and Et_3N in toluene from alcohol **9a**. After water extraction, toluene was removed under reduced pressure.[63] The mesylate **22a** was dissolved in 1 vol of 2,4,6-collidine and heated at 140−145 °C for 1.5 h. Heptane was added followed by an acidic aqueous workup. Concentration of the heptane solution to the desired dilution, seeding at 40 °C, aging, and filtration gave a first crop of **1** in 63% yield. A second crop was obtained from the mother liquor in 17% yield, both as an off-white crystalline solid with an er > 99.5:0.5.[64]

Even though the number of chemical steps of this new route increased from six (including chiral separation) to nine this process—starting from 2-cyclohexenone—is more cost-efficient as compared to the first Diels−Alder route (Scheme 1).[65]

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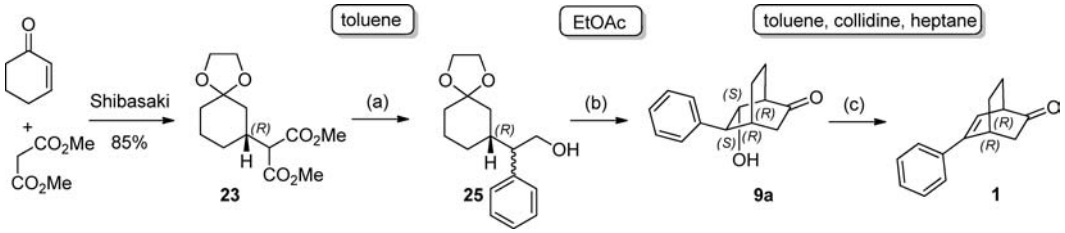
Scheme 9. Final process showing the three isolated intermediates; common solvents for telescoping are highlighted[a]



[a]Reagents and conditions, refer to Scheme 5 for more details. Yields are corrected for NMR assay of starting material and product: (a) i) LiCl, H_2O, DMAc, 140 °C, 5 h, toluene for workup, ii) HexLi, DIPA, hexane, toluene, $Pd_2(dba)_3$, $P(tBu)_3{\cdot}HBF_4$, bromobenzene, 10−20 °C, 3 h, toluene for workup, iii) $LiAlH_4$ in THF, toluene, 5−15 °C, 0.5 h, 74%; (b) i) NaOCl, $NaHCO_3$, KBr, TEMPO, water, EtOAc, 5−10 °C, 1 h, ii) 32% HCl, EtOAc, 50 °C, 2 h, 45%; (c) i) MsCl, Et_3N, toluene, 10−20 °C, 10 min, ii) 2,4,6-collidine, 140−145 °C, 1.5 h, 79%.

As compared to this preceding route, no time-consuming and expensive chiral separation is required, cyanides are omitted, and cryogenic conditions are no longer used. The overall yield increased from 16% to 22% (Scheme 9).

CONCLUSION

The enantioselective process as depicted in Scheme 9 yielded **1** in 22% overall yield starting from 2-cyclohexenone, as compared to < 1% yield following published protocols.[66,67] Essentially, this new route afforded **1** in > 99% chemical purity and er > 99.5:0.5 as crystalline solid. It is noteworthy that both enantiomers of **1** are accessible via this route by using either (*R*)- or (*S*)-BINOL in the powerful Shibasaki reaction. The intramolecular aldol reaction of ketal aldehyde **21** to secondary alcohol **9a** is a rare example of a practical intramolecular CIDT under mild conditions. Three major isomers of **9** have been isolated, and the relative configuration was unambiguously determined by single-crystal X-ray crystallography. A very concentrated elimination protocol from mesylate **22a** to **1** was designed, optimizing purity and color to enable an isolation of **1** by crystallization. The nine steps with three isolated intermediates enable a smooth and rapid scale-up to 1 kg of **1** with a high throughput.

EXPERIMENTAL SECTION

General remarks: 1 vol or 1 wt means 1 L of solvent or 1 kg of reagent, respectively, with respect to the reference starting material; er (enantiomeric ratio), dr (diastereomeric ratio); er and dr reported in this paper have not been validated by calibration.[68] Compounds are characterized by ^1H NMR (400 MHz, Bruker) or ^{13}C NMR (100 MHz, Bruker); internal standard for quantitative NMR was 1,4-dimethoxybenzene. Details for the GC−MS, LC−MS, and DSC methods are listed in the SI. All temperatures are internal temperatures, and yields are presented as is, unless otherwise stated.

Methyl 2-((*R*)-1,4-Dioxaspiro[4.5]decan-7-yl)-acetate (12). A 30-L steel-enameled reactor was charged with malonate **23** (5.99 kg, 85% w/w, 22 mol) and DMAc (15 L). Water (0.4 L, 1 equiv) and LiCl (1.872 kg, 2 equiv) were added. The solution was heated at 120−136 °C during 5 h. After reaching 120 °C, a precipitate formed, and gas evolution started without foaming. IPC by GC−MS showed more than 99% conversion. The mixture was cooled to 30 °C and filtered over a 10-L nutsche, filled with Celite (1.2 kg), and rinsed with toluene (3.5 L). The filtrate was washed with water (3 × 12 L). The organic phase was concentrated at 100 °C jacket temperature and 500−110 mbar to afford **12** as a low-viscosity oil. Yield: 4.2 kg (89%). Assay-corrected yield: 5.99 kg of **23** (85% w/w) gave 4.2 kg of **12** (84% w/w, 12% w/w toluene): 88% yield; Purity (GC−MS): 97% a/a, R_t 2.37 min, $[M + 1]^+$ = 215; ^1H NMR ($CDCl_3$): δ 3.95 (s, 4H), 3.68 (s, 3H), 2.26 (d, J = 6.9 Hz, 2H), 2.03−2.20 (m, 1H), 1.70−1.87 (m, 4H), 1.38−1.66 (m, 2H), 1.26 (t, J = 12.5 Hz, 1H), 0.86−1.06 (m, 1H).

Methyl 2-Phenyl-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (24, Mixture of Diastereoisomers). All liquids were degassed by three vacuum (500 mbar) − nitrogen purge (1 atm) cycles prior charging into the reactor. HexLi in hexane (33%, 8.3 L, 1.1 equiv) was added to a dry 30-L steel-enameled reactor, followed by toluene (16 L). Diisopropylamine (3.2 L, 1.2 equiv) was added at 0−10 °C over 30 min (*exothermic reaction*), followed by a toluene (0.5 L) rinse. Ketal **12** (4.0 kg, 86% w/w, 18.7 mol) was added neat at 5−10 °C over 45 min (*exothermic reaction*), followed by a toluene (1.5 L) rinse. The milky, light-yellow mixture was stirred for 10 min at 5−10 °C. $Pd_2(dba)_3$ (172 g, 0.01 equiv) and $P(tBu)_3{\cdot}HBF_4$ (55 g, 0.01 equiv) were added, followed by three cycles of evacuation to 500 mbar and nitrogen purge to 1000 mbar. Bromobenzene (2.94 kg, 1.0 equiv) was added at 10−15 °C over 15 min. The black mixture was warmed up to 20 °C by adjusting the jacket temperature to 20 °C and was stirred for 2 h 45 min (an *exotherm* occurred with a maximal internal temp. of 28.6 °C, see text, for larger scales reaction calorimetry is recommended). An IPC (GC) showed 99% conversion. A solution of citric acid monohydrate (2.4 kg, 0.6 equiv) in water (9.6 L) was added at 20−30 °C (*exothermic reaction*). After separation of the dark layers the organic phase was washed with water (2 × 12 L). Charcoal (0.4 kg) was added to the organic phase. After stirring at 20−30 °C for 30 min the organic phase was filtered over a pad of Celite (750 g) followed by a final rinse of the filter cake with toluene (2 L). Solvent (28.6 L) was removed from the organic phase by distillation at 60 °C jacket temperature and 210−58 mbar, then toluene (2.5 L) was added. This solution (8.85 kg, 0.9 vol per kg **24**) was used in the next step. An aliquot was withdrawn and evaporated to dryness (to a red-brown oil) for yield and purity determination. Yield: 4.97 kg content of **24** (exact yield was determined after the next step). NMR assay of aliquot: 82% w/w; purity (GC−MS): 96% a/a, R_t 3.34, 3.38 min (pair of diastereoisomers, 1:2), $[M + 1]^+$ = 291.

Analytical reference samples of *rac*-**24a** and *rac*-**24b** were obtained from a racemic run by chromatography on silica gel with toluene/EtOAc (95:5) as eluent. The more polar *rac*-**24a** (TLC) was further crystallized from TBME.

(*R)-Methyl 2-phenyl-2-((*R**)-1,4-dioxaspiro[4.5]-decan-7-yl)-acetate (*rac*-24a).** Colorless crystalline solid, *like* configuration as proven by single-crystal X-ray structure analysis; mp 87 °C (peak by DSC); TLC: R_f 0.30 (toluene/EtOAc 9:1);

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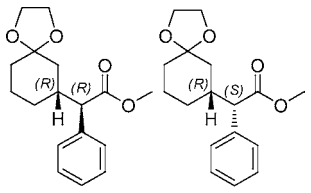

rac. **24a** rac. **24b**

purity (GC–MS): 97% a/a, R_t 3.43 min, $[M + 1]^+ = 291$; purity (LC–MS method 1): 100% a/a, R_t 1.74 min, $[M + 1]^+ = 291$; ^{1}H NMR ($CDCl_3$): δ 7.23–7.41 (m, 5H), 3.93–4.08 (m, 4H), 3.66 (s, 3H), 3.30 (d, J = 10.5 Hz, 1H), 2.33–2.46 (m, 1H), 1.84–1.93 (m, 1H), 1.61–1.80 (m, 2H), 1.26–1.56 (m, 4H), 0.70–0.85 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 173.7, 137.6, 128.6, 128.5, 127.3, 108.9, 64.3, 64.3, 58.1, 51.8, 40.0, 39.0, 34.8, 29.0, 22.7.

(*R)-Methyl 2-phenyl-2-((*S**)-1,4-dioxaspiro[4.5]-decan-7-yl)-acetate (*rac*-24b).** Yellow oil, *unlike* configuration by deduction with single-crystal X-ray structure analysis of *rac*-**24a**; TLC: R_f 0.33 (toluene/EtOAc 9:1); purity (GC–MS): 96% a/a, R_t 3.41 min, $[M + 1]^+ = 291$; purity (LC–MS method 1): 95% a/a, R_t 1.67 min, $[M + 1]^+ = 291$. ^{1}H NMR ($CDCl_3$): δ 7.23–7.39 (m, 5H), 3.72–3.95 (m, 4H), 3.66 (s, 3H), 3.31 (d, J = 10.5 Hz, 1H), 2.34–2.48 (m, 1H), 1.33–1.86 (m, 6H), 0.97–1.15 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 128.6, 127.3, 64.0, 64.2, 58.2, 51.8, 38.80, 38.6, 34.8, 30.5, 22.8.

2-Phenyl-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-ethanol (25, Mixture of Diastereoisomers). The reactor was charged with toluene (5.9 L) and a solution of 2.4 M $LiAlH_4$ in THF (3.9 L, 0.55 equiv). The feed tank was charged with the toluene solution (8.85 kg) of **24** (4.914 kg, 82% w/w of aliquot stripped to dryness, 17.1 mol) and additional toluene (3.9 L) to adjust to the target concentration of 1.6 vol per kg **24**. This solution was added to the $LiAlH_4$ solution at 5–15 °C over 1 h (*very exothermic reaction*). The reaction was stirred at 10–20 °C for 30 min. IPC (GC–MS) indicated > 99% conversion. A mixture of water (350 mL, 0.07 vol) and THF (990 mL) was added at 13–22 °C over 40 min (*exothermic* reaction *with evolution of* H_2). 15% NaOH-solution (350 mL, 0.07 vol) was added at 10–20 °C over 20 min (*exothermic reaction*). Water (1.1 L, 0.22 vol) was added at 10–20 °C over 5 min (*exothermic reaction*). Charcoal (0.5 kg, granulated, 0.1 wt.) was added, and the mixture was stirred at 20 °C for 2 h prior to filtration over Celite (0.6 kg, 0.2 wt.). The filter cake was washed with toluene (2 L). The filtrate was concentrated at 50–55 °C batch temperature and 500–25 mbar to afford **25** as a low-viscosity dark oil. Yield: 4.4 kg (98%). Assay-corrected yield over two steps: 4 kg of **12** (86% w/w) gave 4.4 kg of **25** (81% w/w, 11% w/w toluene): 84% yield; purity (GC–MS): 96% a/a, R_t 3.40, 3.49 min (30:70), $[M - 18 + 1]^+ = 245$.

2-Phenyl-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-acetaldehyde (21). Preparation of a bleach solution with pH 8.5–9.5: commercial bleach (12–15% aqueous NaOCl solution) was titrated with the KI/Na_2SO_3 couple to determine its hypochlorite content: 1.9 N, 12% w/w. This bleach solution (65 mL, 1.1 equiv) was diluted with aqueous sat. $NaHCO_3$ solution (26.4 mL) to achieve pH 8.7. Alcohol **25** (28.9 g, 89% w/w, 0.11 mol) was dissolved in EtOAc (110 mL). A solution of KBr (0.993 g, 0.08 equiv) in water (2.2 mL) was added at 0 °C, followed by TEMPO (130 mg, 0.008 equiv). The freshly prepared bleach solution was added at 0–10 °C over 20 min (*exothermic reaction*). IPC (GC and LC–MS method 1) showed >98% conversion. Aqueous sat. $Na_2S_2O_3$ solution (0.3 mL) was added at 10–15 °C until the test against KI (0.5 N solution)/starch (1% aqueous solution) was negative. Water (65 mL) was added and the mixture filtered over Celite (30 g). The organic phase was extracted with 1/2-sat. NaCl solution (2 × 60 mL). Total mass of the light-red EtOAc solution was 134 g. An aliquot was withdrawn and evaporated to dryness at 40 °C under reduced pressure during 15 min for purity and yield determination. Estimated yield of **21**: 27.4 g (85%, corr. for NMR assay). Analytical data for aliquot (yellow oil): NMR assay: 79% w/w; purity (GC–MS): 96% a/a, R_t 3.25, 3.29 min (40:60), $[M + 1]^+ = 261$. ^{1}H NMR ($CDCl_3$,): δ 9.71 (d, J = 3.2 Hz, 0.6H), 9.70 (d, J = 3.3 Hz, 0.4H), 7.29–7.42 (m, 3H), 7.18–7.24 (m, 2H), 3.77–4.04 (m, 4H), 3.30–3.36 (m, 1H), 2.42–2.57 (m, 1 H), 1.23–0.90 (m, 8H).

(1*R*,4*R*,5*S*,6*S*)-6-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (9a). Preparation of a bleach solution with pH 8.5–9.5: Commercial bleach (12–15% aqueous NaOCl solution) was titrated with the KI/Na_2SO_3 couple to determine its hypochlorite content: 1.92 N, 12% w/w. This bleach solution (7.2 L, 1.2 equiv) was diluted with aqueous sat. $NaHCO_3$ solution (2.9 L) to achieve pH 9.3. Alcohol **25** (3 kg, 81% w/w, 11.4 mol) was dissolved in EtOAc (15 L). A solution of KBr (136.1 g, 0.1 equiv) in water (300 mL) was added at 20 °C, followed by TEMPO (17.9 g, 0.01 equiv). The freshly prepared bleach solution was added at 4–8 °C over 45 min (*exothermic reaction*). IPC (GC–MS and LC–MS method 1) showed >98% conversion. Aqueous sat. $Na_2S_2O_3$ solution (50 mL, 0.02 equiv) was added at 10–15 °C until the test against KI (0.5 N solution)/starch (1% aqueous solution) was negative. The organic phase was washed with water (9 L) and 1/2-sat. NaCl solution (2 × 4 L). Solvent (9 L) was removed by distillation at 50 °C jacket temperature at 250–150 mbar. The target concentration (2 vol with respect to **21**) was adjusted by the addition of EtOAc (2 L) to get a total vol of 9 L. An aliquot (138.67 g) was withdrawn and evaporated to dryness (29.33 g, yellow oil) for purity and yield determination. Estimated crude mass was 3.095 kg of aldehyde **21** with an ^{1}H NMR assay of 61% w/w (14% w/w EtOAc) corresponding to 1.86 kg **21** (78% yield, corr. for NMR assay).

An aqueous solution of HCl (32%, 333 mL, 0.3 equiv) was added at 25 °C to the EtOAc solution of **21** and the mixture was stirred at 50 °C for 2 h. IPC (LC–MS method 1) showed > 97% conversion. The mixture was cooled to 10 °C, stirred at this temp. for 16 h, then further cooled to 0 °C and stirred at this temp. for 1 h. The suspension was filtered and washed with EtOAc (2 × 1.5 L). The filter cake was dried by applying vacuum for 2 h to afford **9a** as colorless crystalline solid. Yield: 0.921 kg. Assay-corrected yield: 3 kg of **25** (81% w/w) gave 0.921 kg **9a** (98% w/w): 45% yield. Mp 191 °C; relative configuration as proven by single-crystal X-ray structure analysis of *rac*-**9a**; chiral HPLC method: er > 99.5:0.5, diastereomeric purity: >99.5%; purity (LC–MS method 1): 100% a/a, R_t 1.23 min, $[M - 18 + 1]^+ = 199$; ^{1}H NMR ($CDCl_3$): δ 7.34–7.42 (m, 4 H), 7.27–7.32 (m, 1 H), 4.48 (t, J = 3.7 Hz, 1 H), 2.93–2.97 (m, 1 H), 2.58 (q, J = 3.1 Hz, 1 H), 2.49–2.56 (m, 1 H), 2.35–2.44 (m, 2 H), 1.87–1.95 (m, 3 H), 1.72–1.83 (m, 1 H), 1.42–1.53 (m, 1 H); ^{13}C NMR ($CDCl_3$): δ 215.4, 142.2, 128.6, 127.6, 126.6, 74.4, 52.8, 51.5, 45.6, 34.4, 20.2, 18.2.

(1*R*,2*S*,3*S*,4*R*)-6-Oxo-3-phenylbicyclo[2.2.2]octan-2-yl Methanesulfonate (22a). Bicyclic alcohol **9a** (25 g, 0.12 mol) was dissolved in DCM (125 mL) followed by Et_3N (24 mL, 1.5 equiv). The suspension was cooled to 0 °C and MsCl (11.6 mL, 1.3 equiv) was added at 10–20 °C. After 1.5 h, the mixture was filtered and the filtrate washed with water

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(125 mL) and 1/2-sat. NaCl solution (2 × 125 mL). The organic phase was dried over Na_2SO_4 and concentrated to dryness under reduced pressure to afford **22a** as a yellow oil, which solidified at rt. Yield: 32.5 g (96%). Twenty grams thereof was dissolved in heptane (350 mL) and EtOAc (350 mL) at 50 °C and filtered over silica gel (15 g). The filtrate was cooled to 0 °C and filtered, and the filter cake was washed with heptane (100 mL) to afford a first crop of **22a** as a colorless solid. Yield first crop: 8.33 g (42% recovery). Additional crystals were filtered off from the mother liquor to afford a second crop of **22a** as a colorless solid. Yield of second crop: 2.75 g (14% recovery). Mp 87 °C (peak by DSC); purity (LC−MS method 1): 100% a/a, R_t 1.4 min, $[M - 96 + 1]^+ = 199$; ^{1}H NMR ($CDCl_3$): δ 7.38−7.49 (m, 2H), 7.30−7.38 (m, 3H), 5.45 (t, J = 3.8 Hz, 1H), 3.22−3.30 (m, 1H), 2.88−3.00 (m, 4H), 2.54−2.63 (m, 1H), 2.44−2.53 (m, 1H), 2.35−2.42 (m, 1H), 1.96−2.08 (m, 2H), 1.71−1.88 (m, 1H), 1.43−1.60 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 211.0, 140.0, 129.0, 127.3, 82.6, 50.6, 48.6, 45.5, 39.5, 35.4, 20.2, 18.0.

(1*R*,4*R*)-5-Phenylbicyclo[2.2.2]oct-5-en-2-one (1). Telescoped Process. MsCl (0.56 L, 1.3 equiv) was added at 10−20 °C to a suspension of **9a** (1.2 kg, 5.55 mol) in toluene (6 L) and Et_3N (1.15 L, 1.5 equiv) (*exothermic reaction*). IPC (LC−MS method 1) showed >99% conversion after 10 min. The mixture was washed with water (2 × 3 L) and concentrated to dryness under reduced pressure to afford compound **22a** as a yellow oil, which solidified at rt. Yield of crude **22a**: 1.6 kg (99%). NMR assay: 95% w/w; purity (LC−MS method 1): 98% a/a, R_t 1.44 min, $[M - 96 + 1]^+ = 199$. ^{1}H NMR data in $CDCl_3$ correspond to the structure. Mesylate **22a** (1.6 kg, 5.50 mol) was dissolved in 2,4,6-collidine (1.2 L) and stirred at 140−145 °C for 1.5 h. IPC (LC−MS method 1) showed > 99% conversion. HCl (1 N, 3 L) and heptane (19 L) were added, and the layers were separated. The organic phase was washed with 1 N HCl (3 L), then with water (2 × 3 L) and filtered over Na_2SO_4 (1.7 kg).[69] The cake was washed with heptane (3 L). Solvent (11.5 L) was removed from the filtrate at 110 °C jacket temp. under reduced pressure. Seed crystals of **1** (300 mg) were added at 40 °C, the mixture was stirred at 39−40 °C for 1 h, cooled to 0 °C within 0.5 h, and stirred at 0 °C for 10 min. The suspension was filtered and the filter cake washed with heptane (1 L) to afford **1** as a beige crystalline solid. Yield first crop: 0.69 kg (63%). Mp 66.3−67.5 °C; $[\alpha]^{26}_D$ = +547° (c = 1; $CDCl_3$) ($[\alpha]^{19}_D$ = +447° (c = 1; $CDCl_3$));[1a] NMR assay: 100% w/w; chiral HPLC method: er > 99.5:0.5, diastereomeric purity: >99.5%; purity (LC−MS method 1): 100% a/a, R_t 1.60 min, $[M + 1]^+ = 199$. ^{1}H NMR ($CDCl_3$): δ 7.44−7.49 (m, 2H), 7.36−7.43 (m, 2H), 7.29−7.36 (m, 1H), 6.46 (dd, J_1 = 6.7 Hz, J_2 = 2.2 Hz, 1H), 3.53−3.58 (m, 1H), 3.30−3.35 (m, 1H), 2.19−2.23 (m, 2H), 1.97−2.06 (m, 1H), 1.83−1.96 (m, 1H), 1.64−1.80 (m, 2H); ^{1}H NMR (CD_3OD): δ 7.48−7.55 (m, 2H), 7.34−7.43 (m, 2H), 7.22−7.33 (m, 1H), 6.49 (d, J = 6.4 Hz, 1H), 3.55−3.62 (m, 1H), 3.22−3.30 (m, 1H), 2.09−2.30 (m, 2H), 1.88−2.04 (m, 2H), 1.59−1.83 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 212.4, 148.0, 137.6, 128.7, 127.8, 124.9, 122.1, 49.2, 40.4, 35.4, 24.6, 23.2.

The mother liquor was evaporated to dryness to get a red, oily residue (310 g). This was dissolved in heptane (1 L) at 50 °C, cooled down to 20 °C, and filtered to get a second crop of **1** as a light-brown crystalline solid. Yield: 0.186 kg (17%). NMR-assay: 94% w/w. Corrected yield: 16%. Chiral HPLC method: er > 99.5:0.5; purity (LC−MS method 1): 100% a/a.

The structure was proven by single-crystal X-ray analysis. **1** was processed to a crystalline intermediate with a residue of known chirality. X-ray crystal structure analysis of this intermediate allowed for the determination of the absolute configuration.

■ ASSOCIATED CONTENT

Supporting Information

Details for the GC−MS, LC−MS, and DSC methods. Experimental data for the reactions as depicted in Scheme 4. Tables with screening results of the cyclization and elimination step. ^{1}H- and ^{13}C NMR data (**12**, *rac*-**24**, **25**, **21**, **9a**, **22a**, **1**), GC−MS (**12**, **24**, *rac*-**24a**, **25**, **21**), LC−MS (**9a**, **22a**, **1**), chiral HPLC (**9a**, mixture of *rac*-**9a**, *rac*-**9b**, and *rac*-**9c**, **1**, mixture of **1** and ent-**1**), DSC (**22a**), X-ray crystal structure analysis for *rac*-**24a**, *rac*-**9a**, *rac*-**9b**, *rac*-**9c**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(51) Material with 100% a/a purity by GC or LC−MS could still show a baseline spot on TLC.

(52) As the selectivity seemed to be driven partially by the solubility differences, the results obtained by racemic compounds were not representative for the enantiomerically pure compounds, although we expected a similar distribution due to the same trend of melting points, see Scheme 7.

(53) We did not quantify the amount of HOAc which might be formed by hydrolysis of EtOAc at 50 °C.

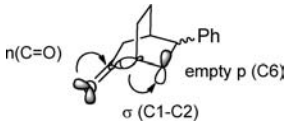
(54) A rework of the mother liquor (**9a**/**9b** 30:70, 60% a/a chiral HPLC) by extraction with $NaHCO_3$-solution and crystallization from either TBME or EtOAc gave an additional 3% yield.

(55) The assay-corrected yield for the cyclization was 60%.

(56) Miller, M. J. *J. Org. Chem.* **1980**, *45*, 3131−3132.

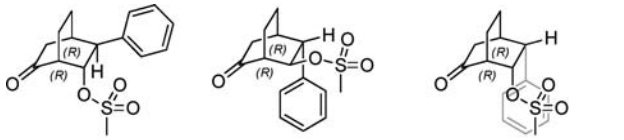
(57) Methyl-*N*-(triethylammoniumsulfonyl)carbamate, see: Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744−4745.

(58) A hyperconjugative interaction was postulated between the n(C═O), the σ(C1)−(C2), and the forming empty p orital, see: Carrupt, P.-A.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 1008−1028.



(59) Skeletal rearrangements of bicyclo[2.2.2]octyl cation, see: Walborsky, H. M.; Baum, M. E.; Youssef, A. A. *J. Am. Chem. Soc.* **1961**, *83*, 988−993.

(60) Mesylates **22a**, **22b**, and **22c** showing their suitability for a *syn*-elimination.



(61) VKL 70-4 SKR (VTA), at jacket temp. 137 °C, condenser 25 °C, dropping funnel temp. 60 °C, pressure ∼0.002 mbar.

(62) Solubilities of **1**: toluene: 66−100 g/L, heptane: 40−50 g/L, EtOAc and iPrOAc: > 200 g/L.

(63) The mesylate **22a** was obtained as oil which solifidied at rt. The two steps could be telescoped for larger scales. Toluene must be removed completely as a run with 30% v/v toluene made removal of black particles more difficult.

(64) In view of a nearly quantitative yield (for the sum of the three isomers of **9**) of the cyclization, in a separate experiment starting from ketal aldehyde **21**, the crude product **9** (a mixture of oil and waxy solid) was processed as is to **1**: the assay-corrected yield for the three steps with crude **9** and crystallized **9a** was 37% and 51%, respectively. In addition, the material from the crude run was colored and could not be purified with one crystallization. Hence, the isolation of a single isomer **9a** prior to the last steps is favored.

(65) Pd and ligand were the major cost drivers. The same yield was obtained with 0.2 mol % $Pd(OAc)_2$ and $Pd_2(dba)_3$ on 5-g scale.

(66) (a) Reference 1a. (b) Alternatively, chiral bicyclo[2.2.2]octane-2,5-dione, an intermediate of Takeuchi's synthesis was obtained in ∼0.45% yield by chromatographic separation of tartrate-derived monoketals of bicyclo[2.2.2]oct-7-ene-2,5-dione, see: Hill, R. K.; Morton, G. H.; Peterson, J. R.; Walsh, J. A.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 5528−5533.

(67) The chiral intermediate bicyclo[2.2.2]octane-2,5-dione (2.3% yield) was obtained by fractional crystallization of the (*R*)-5-(1-phenylethyl)semioxamazide, see: Otomura, Y.; Okamoto, K.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503−2508.

(68) Wernerova, M.; Hudlicky, T. *Synlett* **2010**, 2701−2707.

(69) Na_2SO_4 can be replaced by Celite. This polish filtration removes some residual black particles.

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