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Converting a Birch Reduction Product into a Polyketide: Application to the Synthesis of a C^1–C^{11} Building Block of Rimocidin

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Dedicated to Professor Herbert Mayr on the occasion of his 65th birthday

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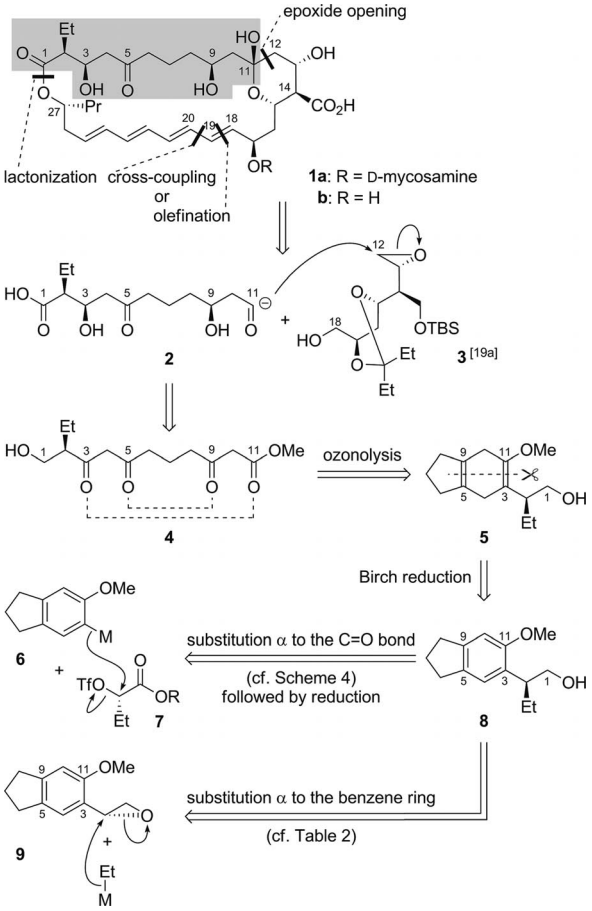
A stereoselective synthesis of a C^1–C^{11} building block for the polyol-polyene antibiotic rimocidin has been developed. Its functional groups originate from a disubstituted indane, which underwent Birch reduction, and oxidative cleavage. This provided a dihydropyranone with a β-keto ester side-chain. The latter was subjected to a Noyori hydrogenation (*ds* > 97:3). An oxy-Michael addition gave a mixture of two spiroketals. Luche reduction then led to three spiroketals in an 80:10:10 ratio. The major spiroketal became isolable by separating one of the by-products chromatographically and the other by a diastereomer-selective thioketalization. The remaining spiroketal was ring-opened to give a dithiolane. Its CO_2Me group was converted into the 1,3-dithiane unit of the target compound (i.e., **47**) using an odor-reducing work-up procedure, which should prove to be generally useful.

Introduction

Rimocidin (**1a**) is a polyol-polyene macrolide that was isolated from *Streptomyces rimosus* in 1951.[1] The presence of a through-conjugated tetraene moiety and an aminoglycoside – derived from D-mycosamine – were recognized by Cope et al.[2] (Scheme 1). Work by the groups of Rinehart[3] and Borowski[4] culminated in a proof of the complete structural formula of rimocidin (**1a**) in 1995. A tetrahydropyrancarboxylic acid moiety (C^{12}–C^{18} fragment) is a noteworthy substructure of rimocidin because it is also present in several other polyol-polyene macrolides,[5] namely in amphotericin B,[6] nystatin A_1,[7] candidin,[8] and pimaricin.[9,10] Each of these compounds shows antifungal activity.[11] Nonetheless – and in contrast to amphotericin B, nystatin A_1, and pimaricin – rimocidin (**1a**) is used neither in human therapy[12] nor in food preservation.[13]

Total syntheses of the aglycon (i.e., **1b**) of rimocidin (**1a**) have been achieved in the laboratories of Rychnovsky[14a] and Smith III.[14b] Similar successes have been reported concerning amphotericin B,[15] nystatin A_1,[16] candidin,[17] and pimaricin.[18] Our group has studied several variations of the preparation of the common tetrahydropyrancarboxylic acid moiety (C^{12}–C^{18} fragment) mentioned above.[19,20] In this paper, we report how this activity has been extended



Scheme 1. Retrosynthetic analysis of C^1–C^{11} synthon **2** of the polyol-polyene antibiotic rimocidin (**1a**) and its aglycon **1b**.

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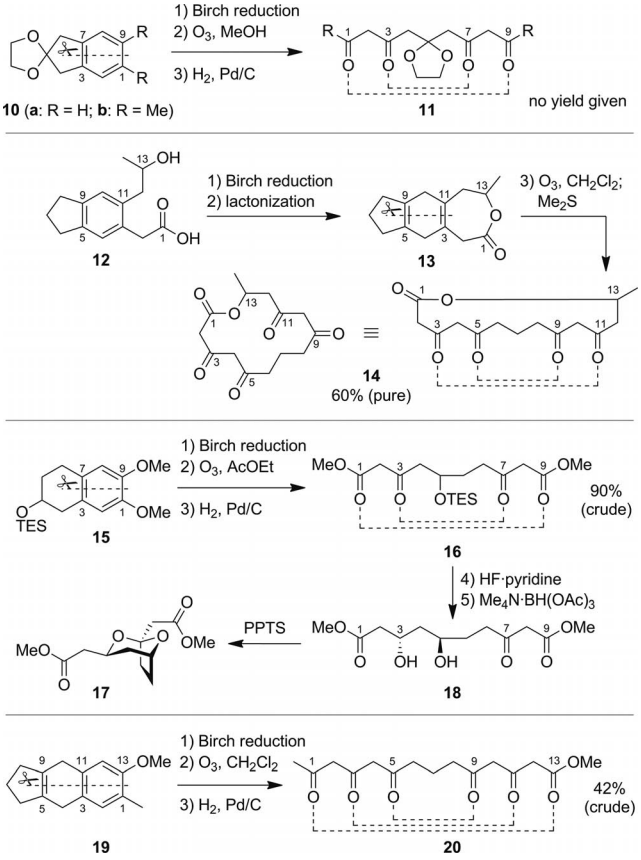
to the stereoselective synthesis of the equivalent (i.e., **47**; Scheme 9) of a C^1–C^{11} synthon **2** (Scheme 1) for rimocidin (**1a**).

Retrosynthetic Analysis

Macrolides are usually obtained by the Yamaguchi or a related macrolactonization of an appropriately protected *seco*-hydroxy acid.[21] As a rule, such macrolactonizations rely on a convergent approach, in which a number of building blocks are first assembled independently and joined later. Envisaging a synthesis of rimocidin (**1a**) in that manner, we identified three appealing precursors (Scheme 1): (1) a C^{20}–C^{30} or C^{19}–C^{30} fragment (not shown) for establishing the tetraene scaffold through a cross-coupling or an olefination; (2) a C^{12}–C^{19} (not shown) or C^{12}–C^{18} counterpart that represents the "eastern" moiety (e.g., the epoxy alcohol **3**, which is reported elsewhere[19a]); and (3) a synthetic equivalent of C^1–C^{11} synthon **2**. The latter was conceived as an aldehyde derivative with umpolung reactivity that would be able to attack an epoxide (e.g., **3**) at C^{12} nucleophilically. Thus, we planned to install a 1,3-dithiane instead of the aldehyde function[22] in the synthetic equivalent **46** of synthon **2** (cf. Scheme 9).

It was planned that the hydroxylated stereocenters of C^1–C^{11} synthon **2** would come from the regio- and stereoselective bis-reduction of hydroxy-triketo ester **4** (Scheme 1). The C=O bonds of **4** were envisaged to be the result of a double oxidative cleavage of the alkene *and* enol ether moieties of substituted cyclohexa-1,4-diene **5**. This compound looked like the product of a Birch reduction[23] of disubstituted indane **8**. Its stereocenter was deemed to be accessible by stereoselective alkylation of arylmetal **6** by enantiomerically pure triflate **7**, or of an ethylmetal by enantiomerically pure epoxide **9**.

Our Birch reduction/ozonolysis approach is unusual. This is because it uses *both* entities that result from the C=C bond cleavage. In ozonolyses of "standard" Birch reduction products, the cyclohexa-1,4-dienes do not have an annulated ring. Such an ozonolysis completes the conversion of an aromatic precursor into a 1,3-diketone or a β-keto ester.[24] In contrast, a Birch reduction product like **5** (Scheme 1), which contains an annulated ring, gives a tethered ozonolysis product. Such a product contains twice the number of C=O groups compared to an untethered ozonolysis product from a non-annulated Birch product.[25] This suggests that the synthesis of polyoxygenated molecules might become advantageous by such an approach. Despite this, it has not been used extensively. Pertinent examples of which we are aware are compiled in Scheme 2. The substrates are three indanes (i.e., **10a**,**b**[26] and **12**[27]), one tetralin (i.e., **15**[28]), and a cyclopentane-annulated dialin (i.e., **19**).[29] These precursors yield Birch reduction/ozonolysis products with four new carbonyl groups (**10a**,**b**→**11**, **12**→**14**), with two new carbonyl groups and two new ester functionalities (**15**→**16**), or with five new carbonyl groups and one new ester functionality (**19**→**20**). An ester results from a C_{Ar}–OMe motif in the starting material. It is noteworthy that alcohol, silyl ether, ketal, and carboxylic acid moieties survive the combined reaction conditions of Scheme 2.



Scheme 2. Previously obtained[26–29] polyfunctional building blocks for polyketide synthesis from sequences starting with a Birch reduction, which delivers an annulated cyclohexa-1,4-diene, and ending by an ozonolysis. Heteroatom-free non-oxygenated aromatics lead to polycarbonyl compounds, while mono- and dimethoxy-substituted aromatics contribute one ester group or two, respectively.

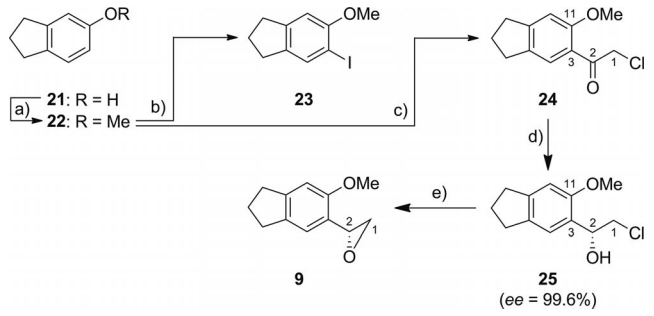
The literature precedent shown in Scheme 2 encouraged our belief that the Birch reduction/ozonolysis sequence **8**→**4** that *we* planned (Scheme 1) stood a fair chance of success – even though **4** was a triketo ester, and no such species had been obtained by this methodology prior to our work. On the other hand, the precedent shown in Scheme 2 alerted us to the fact that the sensitivity of polycarbonyl compounds akin to **11**,[26] **14**,[27] **16**,[28] and **20**[29] – i.e., in our case **4** – towards decomposition, particularly in the presence of acid or base, was not to be underestimated.

In addition we were conscious of a difficulty that would have to be faced once we were in possession of triketo ester **4**: the need to differentiate the carbonyl groups at C^3, C^5, and C^9. The C^3=O and C^9=O bonds would have to be reduced by hydride additions from the top face (with respect to the orientation of formula **4** in Scheme 1) without affecting the C^5=O bond. We were confident that the C^{11}=O bond, which is part of an ester, would not compete for the reductants. Finally, we were aware of the possibility of par-

ticipation by a neighbouring functional group at the stage of the anticipated Birch reduction/ozonolysis product **4**. Its OH group looked to be poised to add to the C^5=O bond and form a hemiketal. When we reduced first the C^9=O and then the C^3=O bond, we were in fact able to exploit this hemiketal formation to protect the C^5=O bond.

Synthesis of the Enantiomerically Pure Indane

Scheme 3 shows how we bridged the gap between 5-hydroxyindane (**21**), which is commercially available, and iodine-substituted indane **23**, which we considered as a precursor of metalated indane **6** (see Scheme 1). Hydroxyindane **21** was methylated with Me_2SO_4 in the presence of aqueous KOH. The resulting methoxyindane (i.e., **22**; 91% yield) reacted with iodine monochloride in AcOH[30] to give an 83:17 mixture of monoiodo derivatives in favor of the *ortho*-substitution product **23**. This ratio was improved to 95:5 by recrystallization.

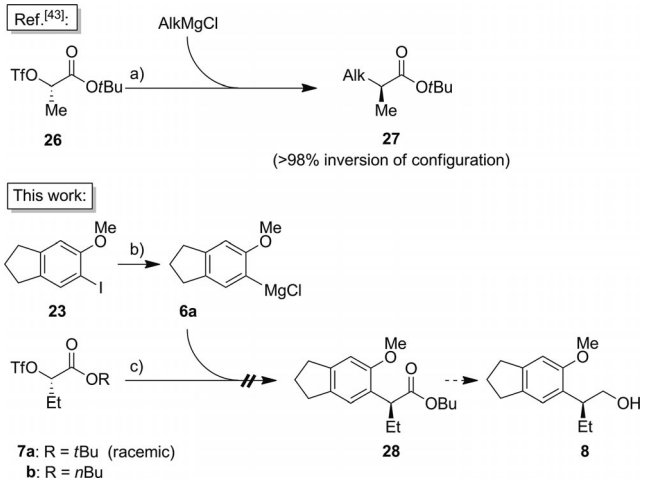


Scheme 3. Synthesis of indanes **23** and **9** for the **6** + **7** and the **9** + EtM approaches to the indane core, as shown in Scheme 1. *Reagents and conditions:* a) Me_2SO_4 (1.2 equiv.), KOH (50% aq.; 4.0 equiv.), acetone, reflux, 1 h; 91%. b) ICl (1.3 equiv.), AcOH, room temp., 2 h; 49%, *dr* = 95:5 after recrystallization. c) Chloroacetonitrile (6.0 equiv.), $ZnCl_2$ (2.5 equiv.), HCl_g, 85 °C, 2 h; HCl (concd. aq.), reflux, 30 min; 60%. d) BH_3·THF (1.0 equiv.), (*R*)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (2 mol-%), THF, room temp., 5 h; 76%. e) NaOH (aq.; 7.0 equiv.), *i*PrOH, room temp., 1.5 h; 96%.

Scheme 3 also shows how we converted the same commercially available indane (i.e., **21**) into indane-substituted epoxide **9**, which we needed for the preparation of indane-substituted alcohol **8** (see Scheme 1). To this end, we subjected methoxyindane **22** to a regioselective *ortho*-(chloroacetylation) to give chloroacetophenone **24**. Attempted Friedel–Crafts acylations with chloroacetyl chloride and $AlCl_3$ (1.1 equiv.) at various temperatures (0 °C, 20 °C, 40 °C) in CH_2Cl_2, CS_2 or nitrobenzene resulted mostly in demethylation.[31,32] Generating the chloroacetylating agent in situ from chloroacetic acid and either P_2O_5/$MeSO_3H$[33] or P_2O_5/SiO_2[34] allowed access to acetophenone derivative **24** without removing the methyl group. However, by-products formed that were hard to remove by flash chromatography on silica gel[35] and subsequent recrystallizations from *n*-hexane. The issue was solved with a Houben–Hoesch acylation[36], i.e., using chloroacetonitrile, $ZnCl_2$, and HCl gas as the source of the electrophile. This procedure had previously been used for acylations, including a chloroacetylation, of aromatics with at least *two* hydroxy or methoxy groups.[37] We adopted the Houben–Hoesch method to our *mono*methoxylated aromatic **22** by using chloroacetonitrile (6 equiv.) as the solvent and heating the mixture at 85 °C. The resulting iminium chloride was hydrolyzed at reflux temperature after adding concentrated aqueous HCl. Chloroacetophenone **24** was isolated in 60% yield after a single recrystallization from *n*-hexane.

A modified[38] Corey[39]–Itsuno[40] reduction[41] of ketone **24** gave chlorohydrin **25** (Scheme 3). Compound **25** was isolated in 76% yield by extractive work-up and recrystallization from *n*-hexane. It had an *ee* of 99.6%.[42] Treatment of this chlorohydrin with a suspension of K_2CO_3 in MeOH (room temp., 2 h) induced ring-closure. The crude product (≈ 92% yield) consisted predominantly of the desired epoxide (i.e., **9**). However, it contained up to 20% of a by-product, which we interpreted as resulting from an epoxide-ring opening by MeO^-. As epoxide **9** decomposed on silica gel,[35] removal of the by-product was impossible. In contrast, treatment of chlorohydrin **25** with aqueous NaOH in *i*PrOH (room temp., 1.5 h) gave epoxide **9** cleanly in 96% yield.

Our first attempt towards indane-substituted alcohol **8** followed the **6** + **7** strategy outlined in Scheme 1, and is shown in detail in Scheme 4. It was based on the recently described[43] stereoselective substitutions of the triflate group of enantiomerically pure α-(trifluoromethanesulfonyl)carboxylic esters **26** upon treatment with an alkylmagnesium chloride and a catalytic amount of $ZnCl_2$ (→ **27**; Scheme 4, top). We tried an analogous substitution reaction between arylmagnesium chloride **6a**, catalytic $ZnCl_2$, and racemic α-(trifluoromethanesulfonyl)carboxylic ester **7a**, which had not been studied in ref.[43] Arylmagnesium com-

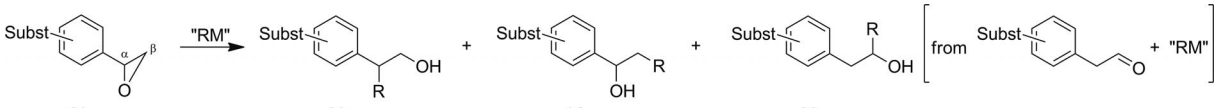


Scheme 4. Testing the **6** + **7** approach to the indane core, as shown in Scheme 1. *Reagents and conditions:* a) Ref.[43] **6**, THF, 0 °C; addition of AlkMgCl (1.4 equiv.), $ZnCl_2$ (5 mol-%), 2.5 h; > 70%. b) **23** (1.4 equiv. relative to **7**), *i*PrMgCl (1.4 equiv.), THF, –25 °C, 1.5 h; 86% conversion into **6a**.[44] c) *Either* **7a** (racemic, 1.0 equiv.), $ZnCl_2$ (10 mol-%), THF, 0 °C; addition of **6a**, 4 h, then room temp., 16 h; *or* **7b** (*ee* > 99.5%, 1.0 equiv.), $ZnCl_2$ (15 mol-%), THF, 0 °C; addition of **6a**, 2.5 h (cf. footnote[46]).

pound **6a** was prepared in 86% yield[44] by an iodine/magnesium exchange reaction[45] between *i*PrMgCl and iodoindane **23**. However, several combinations of triflate **7a** and **6a** did not give the desired substitution product (i.e., **28**), but led instead to the decomposition of the triflate. We wondered whether Grignard reagent **6a** was too sterically hindered (because **6a** is α-branched, whereas other Grignard reagents that were used to form substitution products **27**[43] were not), not nucleophilic enough (because its carbanionic center is sp^2- rather than sp^3-hybridized), or stabilized by the methoxy group (through electron withdrawal from the carbanionic center and/or by complexation of the Mg atom). As a compensatory measure, we tried to couple arylmagnesium reagent **6a** with triflate **7b** (Scheme 4, bottom). The latter compound contains a CO_2nBu group. Hence, it should be less sterically hindered than the previously used triflate (i.e., **7a**), which contained a CO_2tBu group. The new reactant combination failed to give the substitution product **28**. However, the diminished steric hindrance of triflate **7b** resulted in an entirely different reaction, albeit one that was useless for our purposes.[46] The same undesired reaction occurred when we omitted the $ZnCl_2$ or replaced it by LiCl·CuCl (10 mol-%).

Our second attempt towards indane-substituted alcohol **8** followed the **9** + "EtM" strategy outlined in Scheme 1. The aim was to open styrene oxide **9** by an ethyl nucleophile regioselectively and stereoselectively. Regarding regiocontrol, the desired α-attack should be favored by benzylic activation, but an undesired β-attack might compete because of a lower steric hindrance. Regarding stereocontrol, first principles suggested that observing 100% inversion of configuration would be more likely than 100% retention. For this reason, we had synthesized *R*-configured styrene oxide **9**, not its enantiomer. Table 1 provides an overview of the regioselectivity of styrene oxide reactions from the literature using organometallic reagents not too different from "EtM". Table 1 also compiles observations concerning their stereoselectivity. Last but not least, Table 1 covers a chemoselectivity issue that arises when a a styrene oxide **29** isomerizes into an arylacetaldehyde by a semipinacol rearrangement,[47,48] and the latter compound reacts with the organometallic reagent to give a non-benzylic secondary alcohol **32**. Grignard reagents attack styrene oxides **29** selectively at C^α to give primary alcohols **30** (Table 1, entries 1, 2).[49,50] However, they cause some epoxide rearrangement (→ non-benzylic secondary alcohols **32**).[49,50] This side-reaction was circumvented by using Et_2Mg (Table 1, entry 3),[49] plausibly because the Lewis acidity of the metal was attenuated. Me_3Al (Table 1, entries 4–6) gave no rearrangement/addition product **32**.[51,52] Et_3Al gave a little (Table 1, entry 7), but not if PPh_3 was present (Table 1, entry 8).[53] $LiAlBu_4$ did not give **32** either (Table 1, entry 9).[54] Each of these reagents opened styrene oxides **29** selectively at C^α. Surprisingly, in the cases studied (Table 1, entries 4, 5),

Table 1. Ring-opening reactions of various styrene oxides **29** with organometallics collected from the literature.



29 **30** **31** **32**

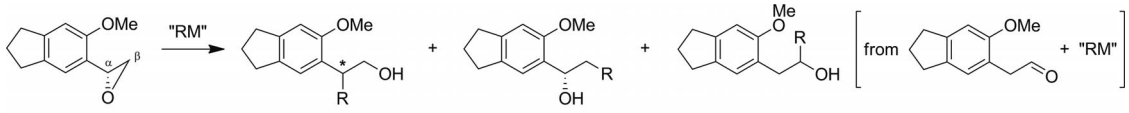
Entry	Ref.	Subst	*ee*	"RM"	Solvent	Yield of **30**	*ee* of **30**	Yield of **31**	Yield of **32**
1	[49]	H		EtMgBr	Et_2O	38%		–	38%
2	[50]	2,5-OMe-4-Me		MeMgI	Et_2O	51%		not reported	not reported
3	[49]	H		Et_2Mg	Et_2O	75%		–	–
4	[51]	H	100%	Me_3Al	*n*-hexane	85%	85%[a]	–	–
5	[51]	2,3,4,5-F	97%	Me_3Al	*n*-hexane/CH_2Cl_2 (2:1)	94%	63%[a]	–	–
6	[52]	2-OAr-4-I	93%	Me_3Al	hexanes	75%	89%[a]	15%	–
7	[53]	H		Et_3Al	toluene	50%		–	25%
8	[53]	H		Et_3Al, 5 mol-% PPh_3	toluene	93%		–	2%
9	[54]	H		$LiAlBu_4$	toluene	92%		–	–
10	[55]	H		BuCu	Et_2O	11%		19%	–
11	[55]	H		Bu_2CuLi	Et_2O	32%		48%	–
12	[55]	H		BuCu(CN)Li	Et_2O	28%		4%	–
13	[56]	H		BuCu(CN)Li	Et_2O	74%		21%	–
14	[55]	H		$Bu_2Cu(CN)Li_2$	Et_2O	29%		40%	–
15	[57]	H		$Bu_2Cu(CN)Li_2$	THF	8%		85%	–
16	[58]	H		$Me_2Cu(CN)Li_2$	Et_2O	65%		13%	–
17	[58]	H		$Me_2Cu(CN)Li_2$	THF	33%		60%	–
18	[59]	H	98%	$Hex_2CuMgBr$	not reported	67%	96%[b]	33%	–
19	[62]	H	96%	MeCu(CN)Li, BF_3·Et_2O	THF	75%	96%[b]	–	–
20	[52]	2-OAr-4-I	93%	MeCu(CN)Li, BF_3·Et_2O	THF	70%	91%[b]	–	–

[a] The major enantiomer resulted from substitution with retention of configuration. [b] The major enantiomer resulted from substitution with inversion of configuration.

Me_3Al gave the product with 60–85% retention of configuration.[51,52] This was rationalized by a two-step S_Ni-mechanism.[51] Organocopper reagents ring-open styrene oxides **29** with little preference for C^α or for C^β attack (Table 1, entries 9–18).[55–59] This observation is valid for alkylcopper reagants, Gilman cuprates, Normant cuprates,[60] "lower-order cyanocuprates", and "higher-order cyano cuprates".[61] The highest proportions of C^α attack were seen with BuCu(CN)Li (Table 1, entry 13) and $Me_2Cu(CN)Li_2$ (Table 1, entry 16) in diethyl ether rather than THF solutions. However, full regioselectivity could be reached with MeCu(CN)Li in THF in the presence of $BF_3{\cdot}Et_2O$ (Table 1, entries 19, 20), and in these reactions, complete inversion (95–100%) of configuration was observed.[52,62] An advantage of the organocopper reagents was that none of them induced a semipinacol rearrangement that could have led to the formation of alcohol **32**.

Table 2 describes our efforts to open indane-substituted epoxide **9** with vinylmagnesium bromide (Table 2, entry 1) and with a variety of ethylmetal reagents (Table 2, entries 2–13). Vinylmagnesium bromide caused somewhat less semipinacol rearrangement (Table 2, entry 1; →**36**) than did ethylmagnesium iodide (Table 2, entry 2; →**37**), while diethylmagnesium caused none (Table 2, entry 3). The major reaction mode of these reagents was to open epoxide **9** with perfect α- vs. β-selectivity. Nonetheless, they were useless for our purposes, because they eroded ca. 60–80% of the stereointegrity of substrate **9**.[63] They substituted preferentially with retention of configuration. So, too, did $AlEt_3$ and $LiAlEt_4$, but again with a considerable loss of stereointegrity (Table 2, entries 4, 5). Moreover, epoxide rearrangement[47] was more prominent than with the Grignard reagents (Table 2, entries 1, 2), and it became worse when we used $EtAlO/(Et_2Al)_2O$[64] as an ethyl donor (Table 2, entry 6). Overall these observations can be explained – and put in perspective in the context of the results of Table 1 – by considering the Lewis acidities of Mg^{II} and Al^{III}, and the +M effect of the methoxy group in the indane-moiety of

Table 2. Ring-opening reactions of indane-substituted epoxide **9** with C_2H_n-transferring organometallics.



9 (*ee* = 96.6%) R = Vin: **33**, R = Et: **8**; R = Vin: **34**, R = Et: **35**; R = Vin: **36**, R = Et: **37**

Entry	"RM"	Reaction conditions (possibly including the preparation of "RM")	**33** or **8** : **34** or **35** : **36** or **37**	Yield of **33** or **8**	*ee*[a] of **33**[b] or **8**[c]
1	VinMgBr	VinylMgBr (2.0 equiv.), Et_2O/THF (2:1), 0 °C, 15 min; H_2 (1 atm.), $Pd(OH)_2$/C, EtOAc	93 : 0 : 7	68%	–15%[d]
2	EtMgI	EtMgI (2.0 equiv., 1.5 M in Et_2O), Et_2O, 0 °C to 40 °C, 1 h	89 : 0 : 11	55%	–39%[d]
3	Et_2Mg[49]	$MgEt_2$ (1.1 equiv.), Et_2O, 0 °C to room temp., 15 min	100 : 0 : 0	70%	–29%[e]
4	$AlEt_3$, cat. PPh_3[53]	$AlEt_3$ (2.0 equiv.), PPh_3 (5 mol-%), toluene, 0 °C, 15 min	66 : 0 : 34	43%	–31%[d]
5	$LiAlEt_4$[54]	$AlEt_3$ (1.5 equiv.), EtLi (1.5 equiv.), *n*-hexane, 0 °C, 15 min	78 : 0 : 22	61%	–25%[d]
6	$EtAlO/(Et_2Al)_2O$[64]	$AlEt_3$ (10 equiv.), H_2O (6.0 equiv.), CH_2Cl_2, –20 °C, 30 min	49 : 0 : 51	27%	not determined
7	EtLi[65]	EtLi (2.0 equiv.), Et_2O, 0 °C to room temp., 1 h	complex mixture	12%	+5%[d]
8	EtCu	EtLi (2.0 equiv.), CuI (2.0 equiv.), Et_2O, –40 °C to –20 °C, 30 min, 0 °C, 3 h, room temp., 16 h	complex mixture	19%	0%[e]
9	Et_2CuLi	EtLi (3.0 equiv.), CuI (1.5 equiv.), Et_2O, –40 °C to –20 °C, 30 min, 0 °C to room temp., 30 min	38 : 62 : 0	24%	+91%[d]
10	$Et_2Cu(CN)Li_2$[61]	EtLi (3.0 equiv.), CuCN (1.5 equiv.), Et_2O, –40 °C, 4 h, room temp., 16 h	77 : 23 : 0	56%	+89%[d]
11	EtCu(CN)Li[56]	EtLi (1.2 equiv.), CuCN (1.2 equiv.), THF, –40 °C to –20 °C, 2 h, room temp., 18 h	no conversion; epoxide **9** was reisolated in quantitative yield		
12	EtCu(CN)Li/ $BF_3{\cdot}Et_2O$[56]	EtLi (1.5 equiv.), CuCN (1.5 equiv.), $BF_3{\cdot}Et_2O$ (1.5 equiv.), THF, –78 °C, 15 min	80 : 0 : 20	30%	+3%[d]
13[f]	EtCu(CN)Li[56]	EtLi (1.7 equiv.), CuCN (1.7 equiv.), Et_2O, –40 °C to 0 °C, 4 h, room temp., 16 h	100 : 0 : 0	76%	+95%[d]

[a] In this column, each *ee* value is preceded by the sign of the optical rotation of a $CDCl_3$ solution (20 °C) of the isolated sample of **8** (it must be noted that the ring-opening products **33** and **36** were hydrogenated to give **8** and **37** prior to isolating **8**). Levorotatory samples of **8** resulted from substitutions with more retention than inversion of configuration, dextrorotatory samples of **8** from substitutions with inversion of configuration. [b] We determined the preponderant absolute configuration of ring-opening product **33** after hydrogenation of the olefinic C=C bond (→**8**); see footnote [c]. [c] We established that the preponderant absolute configuration in the dextrorotatory sample of ring-opening product **8**, which emerged from the experiment from entry 13 was (*S*) (cf. Scheme 5). [d] Determined by chiral HPLC (details: ref.[63]). [e] Determined by measuring $[\alpha]_D^{20}$. [f] The epoxide **9** used in this experiment had 99.6% *ee*.

epoxide **9**. These reagents favor the formation of a benzylic cation, which persists until it picks up an ethyl residue from a face almost at random, or until it rearranges.

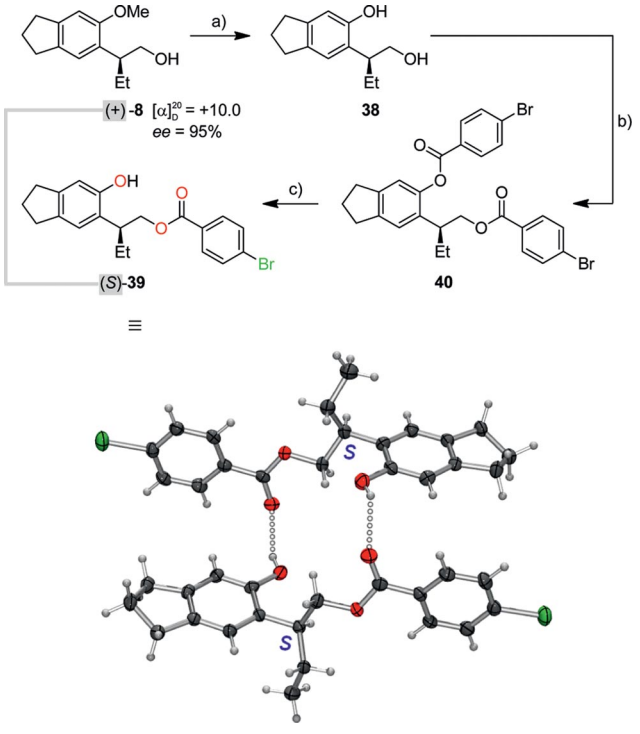
EtLi, which is probably less Lewis acidic than Mg- or Al-based organometallics, and which is known to open aliphatic terminal epoxides nucleophilically,[65] did not not react cleanly with indane-substituted epoxide **9**. A mixture of many compounds resulted, from which we isolated just 12% of the desired alcohol (i.e., **8**) (Table 2, entry 7). However, this material was almost racemic: a 5% nett inversion of the configuration had occurred.

Our interpretation of the absence of type-**32** alcohols from the relevant product portfolios in Table 1 (i.e., entries 10–20) had been that the reactions of organocopper reagents with styrene oxides **29** do not tend to proceed via benzyl cations. This prospect encouraged us to try such reagents for the ring-opening of epoxide **9** (Table 2, entries 8–13). The ethyl Gilman cuprate, however, shared the weakness of its butylated counterpart (Table 1, entry 11), attacking at C^{α} rather than at C^{β} (Table 2, entry 9). The ethyl-containing "higher order cyanocuprate"[61] showed a 77:23 bias in favor of the required β-attack (Table 2, entry 10). The ethyl-containing "lower order cyanocuprate" remained inert when it was exposed to epoxide **9** in THF solution at –20 °C (Table 2, entry 11). However, the same cuprate reacted smoothly with epoxide **9** (99.6% *ee*) in diethyl ether solution at 0 °C (Table 2, entry 13). The regioselectivity for α-attack was perfect. The stereochemical outcome was tantamount to 97.7% inversion and 2.3% retention, as concluded from isolating alcohol (+)-**8** (76% yield) as an (*S*)-enantiomer with 95.1% *ee*.

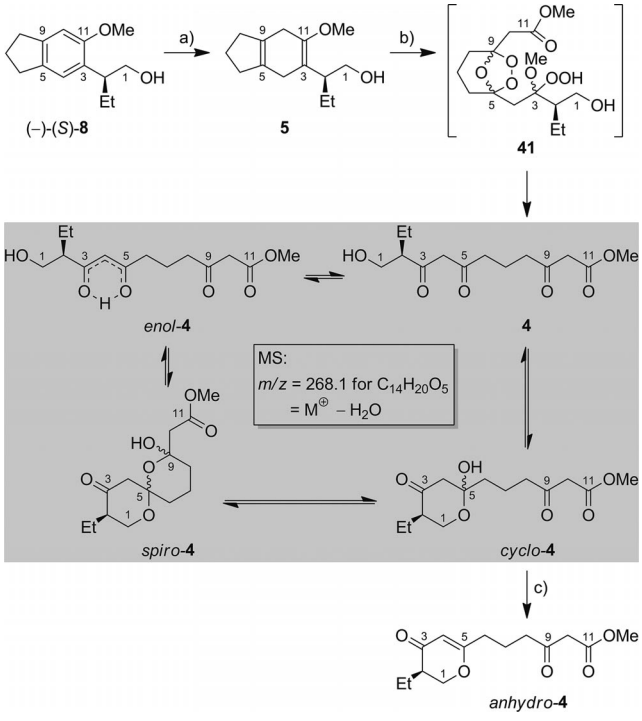
The absolute configuration of ring-opening product (+)-**8** was established as *S* by X-ray crystallography[66,67] of bromine-containing[68] ester (*S*)-**39** (Scheme 5). Compound **39** was prepared from (+)-**8** in three steps and 24% overall yield. First, we demethylated the ether moiety of (+)-**8** cleanly at 180 °C, by heating it with $MeMgI{\cdot}Et_2O$ (20 equiv.).[69] Phenol **38** was formed in almost quantitative yield. Double esterification provided bis(*p*-bromobenzoate) **40**. Treatment of **40** with a suspension of $NaHCO_3$ in methanol selectively removed the aryl ester by transesterification to give the desired monoester (i.e., **39**).

Conversion of the Indane into the C[1]–C[11] Building Block

Having achieved the synthesis of indane-substituted alcohol (+)-(*S*)-**8** with 95% *ee*, our synthetic design (Scheme 1) called for its subjection to a Birch reduction/ozonolysis sequence in order to release the hydroxy-triketocarboxylic ester **4**. Scheme 6 shows how this transformation was executed. Deferring a detailed discussion to the next paragraph, it is first worthwhile to appreciate the final

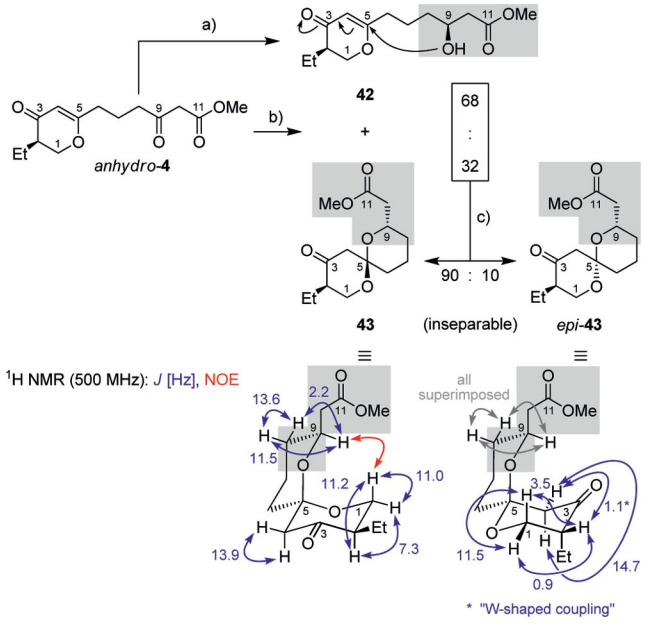


Scheme 5. Conversion of (+)-**8** into *p*-bromobenzoate (*S*)-**39**. Configuration-proving ORTEP plot of the unit cell of an X-ray structure analysis of a single crystal of (*S*)-**39** at 173 K.[67] *Reagents and conditions:* a) MeMgI (3 M in Et_2O, 20 equiv.), neat, 180 °C, 30 min; 94%. b) *p*-Bromobenzoyl chloride (3.0 equiv.), pyridine (as solvent), room temp., 24 h; 64%. c) $NaHCO_3$ (3.0 equiv.), MeOH/THF (1:1), reflux, 3 h; 62%.



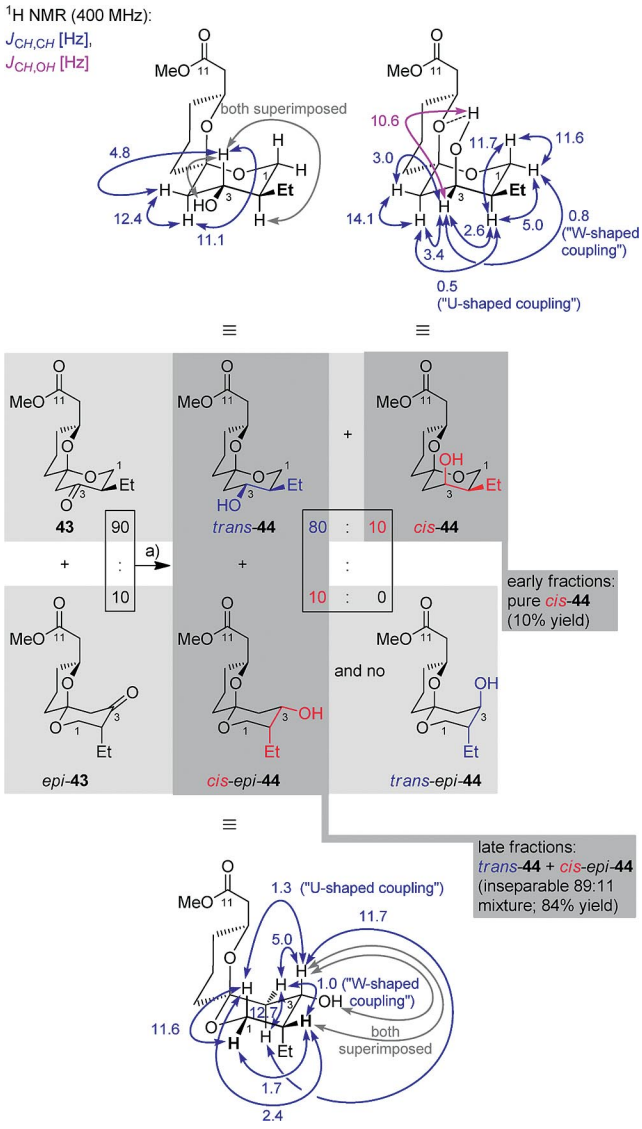
Scheme 6. Realization of the Birch reduction/ozonolysis strategy "**8**→**4**" shown in Scheme 1. *Reagents and conditions:* a) Li (12 equiv.), liq. NH_3/THF/*t*BuOH (6:1:1), –33 °C, 1 h; addition of NH_4^+ $^-$OAc; extractive work-up; 95%. b) Stream of O_3 in O_2, MeOH/CH_2Cl_2 (2:1), –78 °C, 45 min; PPh_3 (2.2 equiv.), room temp., 15 h; the product was not purified. c) Camphorsulfonic acid (20 mol-%), THF, room temp., 22 h; addition of Na_2SO_4 (anhydrous), 4 h; 50% over the two steps from **5**.

product shown in Scheme 6. It is dihydropyranone-containing β-keto ester *anhydro*-**4**. We obtained it almost effortlessly from **4**, which had been the key compound in our synthetic plan (Scheme 1). The advantage of dealing with *anhydro*-**4** from then on rather than dealing with **4** was that *anhydro*-**4** protected the former C^5=O group as an enol ether. Moreover, *anhydro*-**4** attenuated the electrophilicity of the former C^3=O group because it was integrated into a push-pull olefin. The unaltered C^9=O group of *anhydro*-**4** was part of a β-keto ester moiety. Thus only C^9=O, and no other structural motif, was susceptible to a Noyori hydrogenation,[70] as Scheme 7 shows. Thereafter, the C^3=O moiety of the push-pull olefin substructure was reduced by a metal hydride (Scheme 8). Scheme 9 details the concluding steps towards synthetic equivalent **47** of C^1–C^{11} synthon **2** (Scheme 1) of rimocidin (**1a**).



Scheme 7. Stereoselective carbonyl group reduction I: Noyori hydrogenation of β-keto ester *anhydro*-**4** and spiroketal ketone formation.[75] *Reagents and conditions:* a) H_2 (4.0 bar), $Me_2NH_2^+$ $[RuCl(S)\text{-}(BINAP)]_2(\mu\text{-}Cl)_3^-$ (0.5 mol-%), EtOH, room temp., 16 h; **42**:**43** = 80:20 in the crude product; 67% **42** after flash chromatography on silica gel (**43** was not isolated).[35] b) Same as (a), then H_2 replaced by N_2 (1 bar), room temp., 72 h; 68:32 mixture of **42** and **43**. c) Camphorsulfonic acid (5 mol-%), $CHCl_3$, room temp., 16 h; 90:10 mixture of **43** and *epi*-**43**, 66% over the two steps.

The Birch reduction of indane (+)-(*S*)-**8** was performed under conditions that we deemed typical for anisols,[23] i.e., using lithium[71] in a mixture of liquid ammonia, THF, and *tert*-butanol[72] (Scheme 6). Without purification, cyclohexa-1,4-diene **5** was isolated in 95% yield. It had to be handled under an atmosphere of argon because of its pronounced propensity to rearomatize (→**8**). Bearing this in mind, **5** was obtained remarkably pure, as shown by its 300 MHz ^{1}H NMR spectrum in $CDCl_3$. This revealed four allylic protons ($\delta \approx 2.3$ ppm) and four bisallylic protons ($\delta = 2.57$ and 2.84 ppm) as required, and there was no indication of any sizeable amounts of contaminants.



Scheme 8. Stereoselective carbonyl group reduction II: Luche reduction of spiroketal ketones **43** and *epi*-**43**.[84] *Reagents and conditions:* a) $NaBH_4$ (1.1 equiv.), $CeCl_3 \cdot 7H_2O$ (1.1 equiv.), MeOH, –78 °C to room temp., 2 h; yields: 84% (*trans*-**44** + *cis*-*epi*-**44**) separated from 10% (*cis*-**44**).

Ozonolysis of Birch reduction product **5** seemed frustrating (Scheme 6). According to TLC and ^{1}H NMR analyses, a plethora of products formed in the reaction, and they did not include the desired hydroxy-triketocarboxylic ester (i.e. **4**). Mindful of the tendency[26,28,29] of polycarbonyl compounds to form ketals in an uncontrolled fashion, we tried hard to effect the C=C cleavages in **5** step by step. We monitored the ozonolysis by TLC, performed it in the presence of the Sudan dyes Solvent Black 3, Solvent Red 19, and Solvent Red 23 (in decreasing order of reactivity towards O_3),[73] or added 2-methylbut-2-ene or 2,3-dimethylbut-2-ene to the substrate in order to stop the reaction after the C^3=C^{11} bond had been broken and while the C^5=C^9 bond was still intact. This was the order of reactivity that would be favored on the basis that "the methoxy-substituted C^3=C^{11} bond reacts first because it is more electron rich".

The opposite expectation would have been that "the tetrasubstituted C^5=C^9 bond reacts first because it is less sterically hindered". In fact, there seemed to be no overall effect, as we never isolated a cyclopentene.

Eventually, we returned to the initially attempted "complete ozonolysis" of Birch reduction product (+)-(*S*)-**8** (Scheme 6). It was carried out in MeOH/CH_2Cl_2 (2:1) at –78 °C. The surmised diastereomeric mixture of secondary ozonides **41** was destroyed by the addition of PPh_3, and not Me_2S, which did not bring about a complete conversion. Reevaluating the ^{1}H NMR spectrum of the resulting mixture, we ignored the apparent absence of hydroxy-triketocarboxylic ester **4**, and wondered whether it showed instead the various plausible isomers of **4** – e.g. *enol*-**4**, *cyclo*-**4**, and/or *spiro*-**4** and their diastereomers. A mass spectrum (EI, 70 eV) of the mixture showed a 33% peak at *m*/*z* = 268.1, which is the value calculated for $C_{14}H_{20}O_5^+$. This was encouraging, since the latter might be the $[M - H_2O]^+$ peak formed from the molecular ion M^+ of any of the isomers **4**, *enol*-**4**, *cyclo*-**4**, or *spiro*-**4**. This interpretation was corroborated when we managed to converge the mixture into a single product, namely dihydropyranone-containing β-keto ester *anhydro*-**4**. This compound was formed in 50% overall yield from **5** when the ozonolysate was reduced with PPh_3 and then exposed in THF solution to camphorsulfonic acid for 1 d. *Anhydro*-**4** is a dihydropyranone-containing β-keto ester. It was identified by singlets due to the O=C–CH_2–C=O unit (δ = 3.45 ppm) and the olefinic proton of the pyranone moiety (δ = 5.27 ppm) in its ^{1}H NMR spectrum (500 MHz, $CDCl_3$).[74]

The β-keto ester moiety of dihydropyranone *anhydro*-**4** was subjected to a Noyori hydrogenation[70] in ethanol. Using $Me_2NH_2^+$ $[RuCl(S)\text{-}(BINAP)]_2(\mu\text{-}Cl)_3^-$ as a catalyst,[76] 4 bar hydrogen pressure was sufficient to effect complete conversion at room temp. within 16 h (Scheme 7). Flash chromatography on silica gel[35] gave *S*-configured[77] β-hydroxy ester **42** in 67% yield. This was a lower yield than expected.[78] We blamed this discrepancy on having lost some **42** because it had cyclized *under the reaction conditions*[79] to give spiroketal **43**. This compound had been detected as a pure epimer (i.e., free from *epi*-**43**) as a minor constituent in the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the crude hydrogenation product (**42**:**43** = 80:20).

Spiroketal **43** appeared more attractive as a synthetic intermediate than its precursor, pyranone-containing β-hydroxy ester **42**. This is because the forthcoming reduction of the C^3=O group would give a more stable alcohol starting from **43** (→**44**; cf. Scheme 8) than starting from **42**.[80] For this reason, we tried to drive the β-hydroxy ester **42** deliberately (cf. ref.[79]) towards spiroketalization (→**43**). For instance, we left the crude hydrogenation product(s) **42** (+ **43**) for three extra days [Scheme 7, experiment (b) vs. (a)] in the HCl-containing[79] solvent. The 300 MHz ^{1}H NMR spectrum of the crude product mixture revealed a 68:32 ratio of β-hydroxy ester **42** and spiroketal **43** (without any *epi*-**43**). Exposing the crude hydrogenation product(s) **42** (+ **43**) to the ethanolic HCl[79] for 5 d allowed the yield of formation of **43** to reach 68%.

Spiroketal formation could be driven to completion only when we isolated the mentioned 68:32 mixture of **42** and **43**, and restarted the cyclization **42**→**43** once more. $ZnBr_2$[81] (1.2 equiv., CH_2Cl_2, room temp., 20 h) in CH_2Cl_2, $BF_3{\cdot}Et_2O$ (1.2 equiv., room temp., CH_2Cl_2, 16 h) in CH_2Cl_2, or pyridinium *p*-toluenesulfonate in $CDCl_3$ were ineffective for this cyclization. A 5% solution of concd. HCl in THF/CH_3CN (1:1)[82] effected it at room temp. within 2 h (84% yield). Unfortunately, this occurred with concomitant epimer formation – **43**:*epi*-**43** = 86:14 – and the epimers were inseparable by flash chromatography on silica gel.[35] The best **43**:*epi*-**43** ratio (90:10) was obtained when a chloroform solution of the **42**:**43** mixture was treated with camphorsulfonic acid. The yield of **43**/*epi*-**43** then was 66% over the two steps.

The three-dimensional structures of spiroketal epimers **43** and *epi*-**43** were resolved mainly through analysis of the vicinal H,H coupling constants within the tetrahydropyran-4-one (as opposed to tetrahydropyran) moieties (500 MHz, $CDCl_3$; Scheme 7, bottom). Such an analysis was feasible, even though none of the spiroketals was isolated pure. Our configurational proofs consisted of pinpointing axially orientated protons – those protons showing diaxial couplings (> 10 Hz). This let us assign the major spiroketal (i.e., **43**) as an equatorially ethylated tetrahydropyran-4-one and the minor spiroketal (i.e., *epi*-**43**) as an axially ethylated tetrahydropyran-4-one. The configuration of the spirocenter in the major spiroketal **43** followed from the equatorial orientation of its CH_2CO_2Me group [which, in turn, was deduced from the magnitudes of the "endocyclic" vicinal coupling constants ($J_{axial,axial}$ = 11.5 Hz; $J_{axial,equatorial}$ = 2.2 Hz) of the neighboring ring proton (9-H; cf. Scheme 7)]. An NOE observed in the major spiroketal **43** confirmed this conclusion (cf. Scheme 7). Because of signal overlap, the configuration of the spirocenter in the minor spiroketal *epi*-**43** was not proved.[83]

The next step was the reduction of the inseparable 90:10 mixture of spiroketal tetrahydropyranones **43** and *epi*-**43** (Scheme 8). The desired configuration of the stereocenter formed at C^3 would result from reduction of the major isomer (i.e., **43**) by axial attack. Such a selectivity is known using $NaBH_4$,[85] SmI_2,[86] or potassium dissolving in NH_3/MeOH[87] as a reductant. We used $NaBH_4/CeCl_3$[88] and obtained three out of the maximum of four possible diastereomers. The major spiroketal (i.e., **43**) was reduced to give spiroketal alcohols *trans*-**44** and *cis*-**44**. The minor spiroketal (i.e., *epi*-**43**) gave the spiroketal alcohol *cis*-*epi*-**44**, selectively. Flash chromatography allowed the separation of these products into an 89:11 mixture of *trans*-**44** and *cis*-*epi*-**44** (84% yield), and pure *cis*-**44** (10% yield).

Diastereomer *cis*-**44** was analyzed by ^{1}H NMR spectroscopy (Scheme 8) and X-ray crystallography (Figure 1).[67] Its 3D structure originated (1) from the configuration of spiroketal tetrahydropyranone **43**, in which the ethyl group at C^2 was equatorial, and (2) from an equatorial attack of hydride.

Spiroketal alcohol *trans*-**44** must have originated from spiroketal tetrahydropyranone **43** for mass balance reasons.

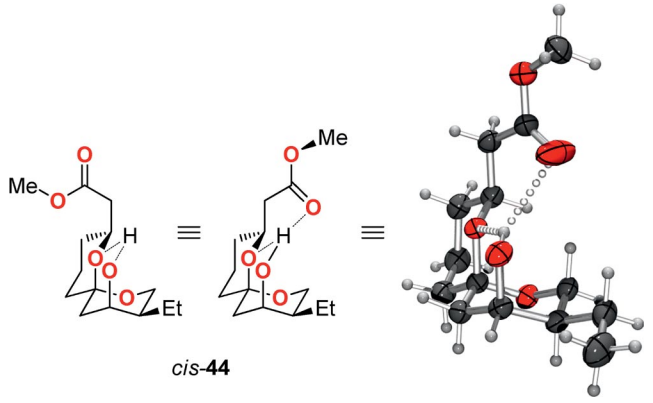
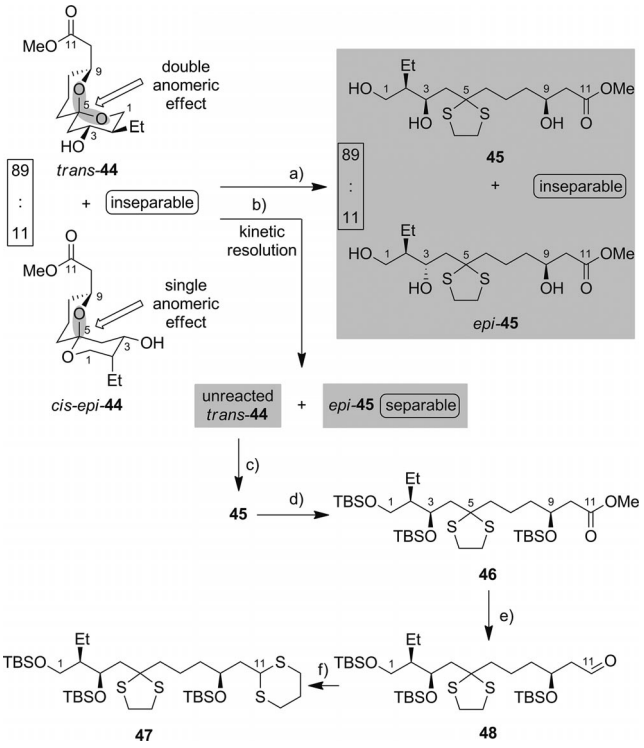


Figure 1. ORTEP plot of an X-ray structure analysis of a single crystal of spiroketal *cis*-**44** (recorded at 173 K).[67] The axial OH group is stabilized by two hydrogen bonds.

This is because the former was the major *product* and the latter the predominant component of the *starting material*. Hence, like tetrahydropyranone precursor **43**, spiroketal alcohol *trans*-**44** contains an equatorial ethyl group at C^2. The OH group at C^3 of *trans*-**44** is also equatorial, because 3-H ($\delta_{in\ C6D6}$ = 0.96 ppm) is axial, as deduced from the magnitude of the coupling constant $J_{3,4}$ of 11.1 Hz,[89] which indicates a diaxial coupling (Scheme 8). The axial orientation of 3-H in the major reduction product (i.e., *trans*-**44**) of tetrahydropyranone **43** gives evidence for the preponderance of an equatorial rather than an axial hydride attack.

Having identified *cis*-**44** *and trans*-**44** as reduction products with equatorial ethyl groups, and thus products of the reduction of spiroketal tetrahydropyranone **43**, it was clear that the third spiroketal alcohol shown in Scheme 8 stemmed from the minor tetrahydropyranone precursor (i.e., *epi*-**43**) and therefore contained an axial ethyl group (and an equatorial 2-H bond[90]). The OH group in this spiroketal alcohol is equatorial, and 3-H is axial. This was concluded from the fact that the high-field proton at C-4 ($\delta_{in\ C6D6}$ = 1.41 ppm) shows a diaxial coupling constant (11.7 Hz) for $J_{4,3}$.[91] Thus, we assigned stereostructure *cis-epi*-**44** to the third spiroketal alcohol shown in Scheme 8.

In spiroketal alcohol *trans*-**44**, the stereocenters at C^2, C^3, and C^9 were correctly installed. The refunctionalization of the polyketide chain by breaking the spiroketal open was effected by an O,O→S,S transketalization with ethane-1,2-dithiol[92] (Scheme 9). This reaction required a large excess of both the dithiol (100 equiv.) and $BF_3{\cdot}Et_2O$ (60 equiv.) to reach completion within 3 d at –40 °C.[93] An inseparable 89:11 mixture of epimers **45** and *epi*-**45** resulted (63% yield). The minor spiroketal (i.e., *cis-epi*-**44**) reacted more quickly, with its conversion being complete after 24 h. The rate order of formation of *epi*-**45** > **45** was plausible, because *cis-epi*-**44** is stabilized by one anomeric effect and *trans*-**44** by two. The difference in their transthioketalization rates opened the possibility of differentiating the sprioketal alcohols by effecting a partial transthioketalization, i.e., a "kinetic resolution" of sorts. Indeed, milder transthioketalization conditions [ethane-1,2-dithiol (10 equiv.), $BF_3{\cdot}Et_2O$ (10 equiv.), –40 °C, 7 h] than before allowed the conversion of *cis-epi*-**44** into *epi*-**45** without affecting *trans*-**44** at all. Compound *trans*-**44** was reisolated free of its epimer in quantitative yield. Subjecting the reisolated *trans*-**44** to the earlier described "harsher" transthioketalization conditions [ethane-1,2-dithiol (100 equiv.), $BF_3{\cdot}Et_2O$ (60 equiv.), –40 °C, 3 d] gave a single thioketal, polyketide **45** (81% yield). Its alcohol functionalities were silylated with TBSOTf and 2,6-lutidine (→**46**, 85% yield).[94,95] Reduction of the ester group with DiBAH (1.2 equiv.) in CH_2Cl_2 yielded aldehyde **48** without overreduction so cleanly (90% yield) that purification by flash chromatography[35] could be omitted.



Scheme 9. Separation of reduction products *trans*-**44** and *cis-epi*-**44** (89:11 mixture) by an epimer-selective trans(thio)ketalization. Conversion of *trans*-**44** into C^1–C^{11} building block **47**. *Reagents and conditions:* a) $HS(CH_2)_2SH$ (100 equiv.), $BF_3{\cdot}Et_2O$ (60 equiv.), –40 °C, 72 h; 63% of an 89:11 **45**:*epi*-**45** mixture. b) $HS(CH_2)_2SH$ (10 equiv.), $BF_3{\cdot}Et_2O$ (10 equiv.), –40 °C, 7 h; 98% *trans*-**44** reisolated; the yield of *epi*-**45** was not determined. c) Same conditions as (a); 81%. d) TBSOTf (3.5 equiv.), 2,6-lutidine (7.0 equiv.), CH_2Cl_2, –78 °C to room temp., 30 min, 85%. e) DiBAH (1.2 equiv.), CH_2Cl_2, –78 °C, 30 min; 90%. f) $HS(CH_2)_3SH$ (3.5 equiv.), $LiClO_4$ (3.0 equiv.), Et_2O, room temp., 24 h; 63%. TBS = *tert*-butyldimethylsilyl; DiBAH = diisobutylaluminum hydride.

The formation of 1,3-dithiane **47** from aldehyde **48** required a careful search for appropriate conditions (Scheme 9). This was because a Lewis acid was required as a catalyst, but this risked cleaving the silyl ethers.[96] Indeed, the use of $BF_3{\cdot}Et_2O$ or $TiCl_4$[97] at –78 °C resulted in the decomposition of substrate **48**. Neither was thioacetalization feasible using $SOCl_2/SiO_2$[98] nor trimethylsilyl-protected propane-1,3-dithiol/ZnI_2 without jeopardizing the

silyl ether moieties.[99] Finally, propane-1,3-dithiol in conjunction with the mildly Lewis acidic $LiClO_4$ in Et_2O[100] delivered the desired dithiane (i.e., **47**) without by-products in 63% yield. Compound **47** is a protected C^1–C^{11} fragment of aglycon **1b** of rimocidin (**1a**).

For an experimentalist, making dithianes (here: **47**) from carbonyl compounds (here: **48**) and propane-1,3-dithiol is not a well-liked transformation because of the nauseous and intense smell of the thiol. We worked up the reaction for the synthesis of dithiane **47** using a procedure that should be welcomed by many others, because it scavenges the propane-1,3-dithiol and so keeps it from evaporating. In the case at hand, this innovation was not for olfactory concerns but simply because it was troublesome to separate excess propane-1,3-dithiol (in the earlier fractions) from the desired dithiane (i.e., **47**; in the later fractions) by flash chromatography on silica gel.[35] We avoided this problem by liberating the *crude* dithiane **47** from excess propane-1,3-dithiol. We did so by pouring the ethereal reaction mixture into a separatory funnel and shaking it vigorously with an aqueous $CuSO_4$ solution, which had been buffered to pH ≈ 5 by $NaHCO_3$. The thiol and Cu^{II} formed a yellow precipitate, which was easily filtered off. This work-up procedure is likely to be unknown to many in the synthetic community if not all, and it should be broadly welcomed as it can reduce a classic malodor.

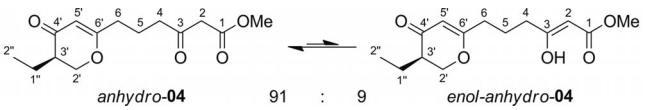
Conclusions

Starting from 5-indanol (**21**), we synthesized a fully functionalized and differentially protected C^1–C^{11} building block **47** for the polyol-polyene macrolide rimocidin (**1a**). The total yield was 2.3% over 16 steps, the average yield 79% per step. 5-Methoxyindane (**22**) was acylated regioselectively by using a nitrile as both solvent and electrophile; this was the only way to preserving the methoxy group. The first stereocenter (at C^2) was introduced with 99.6% *ee* by a Corey–Itsuno reduction of acetophenone **24**. The resulting chlorohydrin (i.e., **25**) cyclized under basic conditions to give styrene oxide **9**. This compound was ring-opened [→(+)-(*S*)-**8**] with high chemo-, regio-, and stereoselectivity only by the lower-order cyanocuprate EtCu(CN)Li in Et_2O solution, but not by the many other organometallics we tried. Since ring-opening product **8** was an indane, too, it was susceptible to a Birch reduction. A double ozonolysis of the resulting cyclopentane-annulated cyclohexadiene (i.e., **5**) delivered a hydroxy-triketo ester **4**. It cyclocondensed to give β-keto ester-substituted dihydropyranone *anhydro*-**4**. The C^3=O, C^5=O, and C^9=O groups of precursor **4** were differentiated in such a way that a Noyori hydrogenation of the C^9=O group followed by a Luche reduction of the C^3=O group completed the stereogenic centers in the spiroketal alcohol *trans*-**44**. The latter compound could not be freed from a small amount of its undesired epimer *cis*-*epi*-**44** by flash chromatography,[35] but the epimers were separated by an *isomer-selective transthioketalization* with 1,2-ethanedithiol/BF_3·Et_2O. This reaction affected only *cis*-*epi*-**44** (→*epi*-**45**), allowing the reisolation of spiroketal alcohol *trans*-**44** as a pure compound. It was then transthioketalized (→**45**) itself, which set the stage for DiBAH reduction and dithiane formation. This reaction had to occur in the presence of three TBS ether groups, and proved to be possible by using 1,3-propanedithiol under $LiClO_4$ catalysis. This step delivered the C^1–C^{11} building block (i.e., **47**) of rimocidin (**1a**) and its aglycon **1b**.

Experimental Section

General Information: Reactions were performed under N_2 in glassware that had been freshly dried with a heat-gun under vacuum. THF was freshly distilled from K, Et_2O was freshly distilled from Na/K, CH_2Cl_2 and NEt_3 were distilled from CaH_2. Petroleum ether refers to distillates with a boiling point of 30–50 °C. Products were purified by flash chromatography[35] on Merck silica gel 60 (0.040–0.063 mm). Fraction numbers are given (#). Unless otherwise stated, yields refer to analytically pure samples. ^{1}H NMR spectroscopy [TMS (tetramethylsilane; δ = 0.00 ppm) as internal standard in $CDCl_3$; C_6HD_5 (δ = 7.16 ppm) as internal standard in C_6D_6]: Varian Mercury VX 300, Bruker Avance 400, and Bruker DRX 500. ^{13}C NMR spectroscopy [TMS (δ = 0.00 ppm) as internal standard in $CDCl_3$; CHD_5 (δ = 128.06 ppm) as internal standard in C_6D_6]: Bruker Avance 400 and Bruker DRX 500. Assignments of ^{1}H NMR and ^{13}C NMR resonances refer to the IUPAC nomenclature except within substituents (where primed numbers are used). MS: Dr. J. Wörth, C. Warth, Institut für Organische Chemie und Biochemie, University of Freiburg. Combustion analyses: F. Tönnies and A. Siegel, Institut für Organische Chemie und Biochemie, Universität Freiburg. IR spectra: Perkin–Elmer Paragon 1000. Optical rotations were measured with a Perkin–Elmer polarimeter 341 at 589 nm and 20 °C, and were calculated by the Drude equation $\{[\alpha]_D = (\alpha_{exp} \times 100)/(c \times d)\}$; rotational values are the average of five measurements of α_{exp} in a given solution of the respective sample. Melting points were measured on a Dr. Tottoli apparatus (Büchi). The *ee* values were determined by chiral HPLC with a Chiralcel OD-H (0.46×25 cm, Daicel Chemical Ind. Ltd.) column by G. Fehrenbach, Institut für Organische Chemie und Biochemie, Universität Freiburg. X-ray data for **23** and *cis*-**52**[67] were recorded at 173 K by Dr. M. Keller, Institut für Organische Chemie und Biochemie, Universität Freiburg.

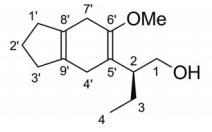
Methyl (*R*)-6-(3-Ethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-yl)-3-oxohexanoate (*anhydro*-4) Equilibrating with Methyl (*R*,*Z*)-6-(3-Ethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-yl)-3-hydroxyhex-2-enoate (*enol-anhydro* 4):



Dihydroarene **5** (2.42 g, 10.9 mmol, 1.0 equiv.) was dissolved in $MeOH/CH_2Cl_2$ (3:1, 80 mL). A stream of O_3/O_2 was passed through the solution at –78 °C for 45 min, until a blue color persisted. Excess O_3 was removed by passing a stream of N_2 through the reaction mixture at –78 °C for 20 min. After addition of PPh_3

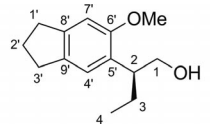
(6.28 g, 23.9 mmol, 2.2 equiv.), the mixture was allowed to reach room temp. and stirred for 1 h. The solvent was evaporated under reduced pressure, the residue was dissolved in THF (60 mL), and camphorsulfonic acid (506 mg, 2.18 mmol, 0.2 equiv.) was added. After stirring at room temp. for 18 h, dry Na_2SO_4 (1.55 g, 10.9 mmol, 1 equiv.) was added. The reaction was continued for 4 h. NEt_3 (1.5 mL, 10.9 mmol, 1.0 equiv.) was added, and all volatiles were evaporated under reduced pressure. Flash chromatography[35] (8 cm, fraction volume 100 mL, Et_2O) of the residue gave a 91:9* mixture of *anhydro*-**4** and *enol-anhydro*-**4** as a colorless oil (#11–17, 1.46 g, 50%). * This ratio was determined from the ^1H NMR integrals of the signals at δ = 5.27 (s, 1 H, 5′-H, *anhydro*-**4**) and 5.28 (s, 1 H, 5′-H, *enol-anhydro*-**4**) ppm. $[\alpha]_D^{20}$ = –4.7 (*c* = 1.30 in $CHCl_3$, 10 cm). ^1H NMR (499.6 MHz, $CDCl_3$/TMS): *anhydro*-**4**: δ = 0.98 (dd, $J_{2'',1''A} = J_{2'',1''B}$ = 7.5 Hz, 3 H, 2′′-H_3), 1.44 (ddq, $^2J_{1''A,1''B}$ = 14.4, $J_{1''A,5'}$ = 7.6, $J_{1''A,2''}$ = 7.2 Hz, 1 H, 1′′-H^A), 1.82 (ddq, $^2J_{1''B,1''A}$ = 13.8, $J_{1''B,2''}$ = 7.6, $J_{1''B,5'}$ = 5.6 Hz, 1′′-H^B), 1.88 (tt, $J_{5,4} = J_{5,6}$ = 7.3 Hz, 2 H, 5-H_2), 2.26 (t, $J_{6,5}$ = 7.3 Hz, 2 H, 6-H_2), overlapping with 2.23–2.30 (m, 1 H, 3′-H), 2.60 (t, $J_{4,5}$ = 7.1 Hz, 2 H, 4-H_2), 3.45 (s, 2 H, 2-H_2), 3.74 (s, 3 H, OCH_3), 4.21 (dd, $^2J_{6'A,6'B}$ = 11.4, $J_{6'A,5'}$ = 8.4 Hz, 1 H, 6′-H^A), 4.44 (dd, $^2J_{6'B,6'A}$ = 11.4, $J_{6'B,5'}$ = 4.75 Hz, 1 H, 6′-H^B), 5.27 (s, 1 H, 5′-H) ppm; *enol-anhydro*-**4**: δ = 5.00 (s, 1 H, 2-H), 5.27 (s, 1 H, 5′-H), 12.03 (s, 1 H, 3-OH) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$/TMS): δ = 11.5 (C-2′′), 19.97 (C-5), 20.11 (C-1′′), 33.54 (C-6), 41.69 (C-4), 45.39 (C-3′), 49.06 (C-2), 52.44 (OCH_3), 71.25 (C-2′), 104.05 (C-5′), 167.48 (C-1), 175.61 (C-6′), 195.10 (C-4′), 201.63 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3465, 2965, 2880, 1745, 1715, 1665, 1610, 1450, 1440, 1405, 1365, 1325, 1205, 1170, 1110, 1010, 900, 825 cm^{-1}. $C_{14}H_{20}O_5$ (268.31): calcd. C 62.67, H 7.51; found C 62.41, H 7.65.

(*S*)-2-(6-Methoxy-4,7-dihydroindan-5-yl)butan-1-ol (5):



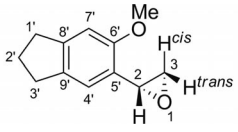
Ammonia (approx. 300 mL) was condensed into a three-necked round-bottomed flask at –78 °C. Small pieces (approx. 2 × 2 × 2 mm) of lithium (2.00 g, 286 mmol, 12 equiv.) were added under vigorous stirring. After they had dissolved, a solution of **8** (5.25 g, 23.8 mmol, 1.0 equiv.) in THF/*t*BuOH (1:1, 50 mL) was added dropwise. The resulting mixture was stirred at –33 °C for 1 h. Excess reductant was destroyed by adding wet ammonium acetate (25 g) in five portions such that the mixture became colorless and stayed so. The ammonia was allowed to evaporate at room temp. H_2O (100 mL) was added. The resulting mixture was extracted with Et_2O (3 × 50 mL). The extracts were combined and washed with H_2O (50 mL) and brine (50 mL), dried with $MgSO_4$, and evaporated under reduced pressure. A colorless oil (5.03 g, 95%) was obtained. It was stored without purification – because the ^1H NMR spectrum showed that the sample was pure **5** – at 4 °C under an argon atmosphere. In this manner, re-aromatization was avoided until the compound was submitted to ozonolysis. ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.88 (dd, $J_{4,3A} = J_{4,3B}$ = 7.4 Hz, 3 H, 4-H_3), AB signal (δ_A = 1.31, δ_B = 1.41, J_{AB} = 13.4 Hz, in addition split by $J_{A,2}$ = 9.5, $J_{A,4}$ = 7.3, $J_{B,2}$ = 5.8, $J_{B,4}$ = 7.6 Hz, 2 H, 3-H_2), 1.60 (br. s, 1 H, 1-OH), 1.90 (tt, $J_{2',1'}$ = 8.1,* $J_{2',3'}$ = 6.8 Hz,* 2 H, 2′-H_2), 2.23–2.34 (m, 4 H, 1′-H_2, 3′-H_2), 2.57 and 2.84 (2 m, 4 H, 4′-H_2, 7′-H_2), 3.00 (dddd, $J_{2,3A} = J_{2,1A}$ = 9.5, $J_{2,3B} = J_{2,1B}$ = 5.5 Hz, 1 H, 2-H), 3.44–3.62 (m, 2 H, 1-H_2), overlapping with 3.54 (s, 3 H, OCH_3) ppm; * values interchangeable.

(*S*)-2-(6-Methoxyindan-5-yl)butan-1-ol (8):



EtLi (1.74 M in nBu_2O, commercially available at ACROS, 35 mL, 61.1 mmol, 1.7 equiv.) was added at –40 °C to a stirred suspension of CuCN (5.47 g, 61.1 mmol, 1.7 equiv.) in Et_2O (180 mL). After the addition was complete, stirring was continued at –20 °C for 30 min. The black solution was cooled to –40 °C. The neat epoxide **9** (6.84 g, 36.0 mmol, 1.0 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for 4 h, and at room temp. for 16 h. Buffer solution [prepared from NH_4Cl (satd. aq.), NH_3 (25% aq.), and H_2O (4:3:1); 120 mL] was added slowly. The resulting mixture was stirred vigorously for 2 h at room temp while being exposed to the ambient atmosphere. After extraction with Et_2O (3 × 50 mL), the combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The residue was purified by flash chromatography[35] (8 cm, fraction volume 100 mL, cyclohexane/EtOAc, 7:1) to yield **8** as a colorless oil (#10–20, 6.04 g, 76%). The *ee* of (*S*)-**8** was determined by chiral HPLC as specified in ref.[63] $[\alpha]_D^{20}$ = +10.0 (*c* = 1.04 in $CHCl_3$, 10 cm). ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.86 (dd, $J_{4,3A} = J_{4,3B}$ = 7.4 Hz, 3 H, 4-H_3), AB signal (δ_A = 1.61, δ_B = 1.74, J_{AB} = 13.5 Hz, in addition split by $J_{A,4} = J_{B,4}$ = 7.4, $J_{A,2}$ = 8.7, $J_{B,2}$ = 6.1 Hz, 2 H, 3-H_2), 2.07 (tt, $J_{2',1'} = J_{2',3'}$ = 7.4 Hz, 2 H, 2′-H_2), 2.84 (t, $J_{3',2'}$ = 7.7 Hz, 2 H, 3′-H_2),* 2.88 (t, $J_{1',2'}$ = 7.7 Hz, 2 H, 1′-H_2),* 3.18 (dddd, $J_{2,3A}$ = 8.7, $J_{2,1A}$ = 7.0, $J_{2,1B} = J_{2,3B}$ = 6.0 Hz, 1 H, 2-H), AB signal (δ_A = 3.72, δ_B = 3.75, J_{AB} = 10.5 Hz, in addition split by $J_{A,2}$ = 7.1, $J_{B,2}$ = 5.8 Hz, 2 H, 1-H_2), 3.79 (s, 3 H, OCH_3), 6.79 (s, 1 H, 7′-H),* 7.01 (s, 1 H, 4′-H)* ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 12.17 (C-4), 24.07 (C-3), 25.67 (C-2′), 32.26 (C-3)′,* 33.21 (C-1′),* 42.92 (C-2), 55.76 (OCH_3), 66.67 (C-1), 107.34 (C-7′),* 132.53 (C-4′),* 128.24 (C-6′), 136.04 (C-9′), 143.26 (C-8′), 156.80 (C-5′) ppm; * these assignments were corroborated by an HMBC experiment. IR (film): $\tilde{\nu}$ = 3365, 2955, 2870, 1615, 1490, 1465, 1415, 1300, 1260, 1195, 1170, 1080, 1040, 915, 840, 745 cm^{-1}. $C_{14}H_{20}O_2$ (220.31): calcd. C 76.33, H 9.15; found C 76.13, H 9.36.

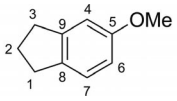
(*R*)-2-(6-Methoxyindan-5-yl)oxirane (9):



Aqueous NaOH (2 M, 130 mL, 260 mmol, 7.0 equiv.) was added at 10 °C to a solution of chlorohydrin **25** (8.55 g, 37.7 mmol, 1.0 equiv.) in *i*PrOH (130 mL) while stirring. Stirring was continued vigorously at room temp. for 1.5 h. The resulting mixture was extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), aq. phosphate buffer (pH = 7.1, 0.5 M, 100 mL), and brine (100 mL). They were dried with Na_2SO_4, filtered, and evaporated in vacuo. The resulting yellowish oil (6.85 g, 96%) was not purified, since it decomposed on silica gel. A ^1H NMR spectrum of **9** revealed no impurities. Compound **9** was stored at 4 °C, where it crystallized slowly. ^1H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 2.06 (tt, $J_{2',1'} = J_{2',3'}$ = 7.4 Hz, 2 H, 2′-H_2), 2.70 (dd, $^2J_{3cis,3trans}$ = 5.7, $J_{3cis,2}$ = 2.7 Hz, 1 H, 3-H^{cis}), 2.81 and 2.89 (2 t, $J_{1',2'} = J_{3',2'}$ = 7.4 Hz, 4 H, 1-H_2, 3′-H_2), 3.84 (s, 3 H, OCH_3),

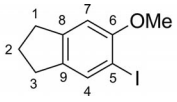
3.11 (dd, $^2J_{3trans,3cis}$ = 5.7, $J_{3trans,2}$ = 4.1 Hz, 1 H, 3-H^{trans}), 4.17 (dd, $J_{2,3trans}$ = 4.0, $J_{2,3cis}$ = 2.8 Hz, 1 H, 2-H^{cis}) ppm.

5-Methoxyindane (22):[101]



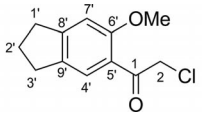
Aqueous KOH [KOH (100 g) in H_2O (100 mL), 1.55 mol, 4.0 equiv.] was added to a solution of 5-indanol (**21**; 50.7 g, 378 mmol, 1.0 equiv.) in acetone (600 mL). Me_2SO_4 (41 mL, 54.7 g, 453 mmol, 1.2 equiv.) was added dropwise over 1 h while stirring, which resulted in the acetone refluxing gently. A precipitate of K_2SO_4 was filtered off. The aqueous phase was separated and extracted with acetone (50 mL). The combined organic extracts were concentrated in vacuo. Fractional distillation of the residue (65–67 °C, 1 mbar) yielded the title compound as a yellowish oil (50.9 g, 91%). ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 2.07 (tt, $J_{2,1} = J_{2,3}$ = 7.4 Hz, 2 H, 2-H$_2$), 2.84 and 2.88 (2 t, $J_{1,2} = J_{3,2}$ = 7.3 Hz, 4 H, 1-H$_2$, 3-H$_2$), 3.78 (s, 3 H, OCH_3), 6.69 (dd, $J_{6,7}$ = 8.3, $^4J_{6,4}$ = 2.5 Hz, 1 H, 6-H), 6.78 (d, $^4J_{4,6}$ = 2.4 Hz, 1 H, 4-H), 7.10 (d, $J_{7,6}$ = 8.1 Hz, 1 H, 7-H) ppm.

5-Iodo-6-methoxyindane (23):[102]



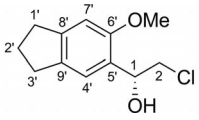
A solution of iodine monochloride (3.1 mL, 60.9 mmol, 1.3 equiv.) in AcOH (50 mL) was added dropwise to a solution of indane **22** (6.94 g, 46.8 mmol, 1.0 equiv.) in AcOH (100 mL) at room temp. The reaction mixture was stirred at room temp. for 2 h, and then it was extracted with petroleum ether (3× 100 mL). The combined organic extracts were carefully washed with $NaHCO_3$ (satd. aq.; 2× 100 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was a solid, which was recrystallized from wet EtOH to give **23** as a white crystalline solid (6.31 g, 49%, 95:5 mixture with 4-iodo-5-methoxyindane), m.p. 38–40 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 2.07 (tt, $J_{2,1}$ = 7.2,* $J_{2,3}$ = 7.5 Hz,* 2 H, 2-H$_2$), 2.83 and 2.86 (2 t, $J_{1,2} = J_{3,2}$ = 7.4 Hz, 4 H, 1-H$_2$, 3-H$_2$), 3.84 (s, 3 H, OCH_3), 6.74 (s, 1 H, 7-H), 7.59 (s, 1 H, 4-H) ppm; * assignments interchangeable.

2-Chloro-1-(6-methoxyindan-5-yl)ethanone (24):



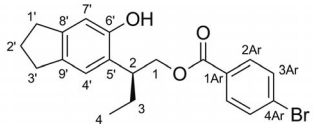
A suspension of $ZnCl_2$ (23 g, 858 mmol, 2.5 equiv.) in $SOCl_2$ (25 mL) was heated at reflux for 0.5 h. Most of the $SOCl_2$ was distilled off at atmospheric pressure, and the rest was removed in vacuo (6 h). The residue of dry $ZnCl_2$ was dissolved in chloroacetonitrile (26 mL, 139 mmol, 6.0 equiv.). 5-Methoxyindane **22** (10.3 g, 69.3 mmol, 1.0 equiv.) was added. The resulting mixture was stirred vigorously at 85 °C for 2 h, while a stream of dry HCl gas[103] was bubbled through. A dark-red viscous mass formed. It was cooled to room temp. HCl (concd. aq.; 50 mL) was added dropwise (***caution:*** gaseous HCl was liberated). The resulting suspension was heated at reflux for 1 h in order to hydrolyze the imine intermediate. After cooling to room temp., the reaction mixture was extracted with EtOAc (3× 100 mL). The combined organic extracts were washed with H_2O (2× 100 mL) and brine (2× 100 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The residue was recrystallized from *n*-hexane to yield **24** as a brownish crystalline solid (9.33 g, 60%), m.p. 62–64 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 2.10 (tt, $J_{2',1'} = J_{2',3'}$ = 7.5 Hz, 2 H, 2′-H$_2$), 2.85 and 2.93 (2 t, $J_{1',2'} = J_{3,2}$ = 7.4 Hz, 4 H, 1′-H$_2$, 3′-H$_2$), 3.91 (s, 3 H, OCH_3), 4.77 (s, 2 H, 1′-H$_2$), 6.86 (s, 1 H, 7′-H), 7.71 (s, 1 H, 4′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 25.69 (C-2′), 31.74 and 33.70 (C-1′, C-3′), 51.27 (C-2), 55.82 (OCH_3), 107.76 (C-7′), 123.24 (C-5′), 126.59 (C-4′), 136.93 (C-9′), 152.67 (C-8′), 158.59 (C-6′), 192.24 (C-1) ppm. IR (film): $\tilde{\nu}$ = 2950, 2840, 1680, 1615, 1570, 1485, 1465, 1415, 1255, 1200, 1165, 1145, 1100, 1025, 875, 845, 790, 745 cm^{-1}. $C_{12}H_{13}ClO_2$ (224.68): calcd. C 64.15, H 5.83; found C 64.10, H 5.99.

(*R*)-2-Chloro-1-(6-methoxyindan-5-yl)ethanol (25):



BH_3·THF complex (1.0 M in THF, 50 mL, 49.8 mmol, 1.0 equiv.) was added to a solution of (*R*)-5-(hydroxydiphenylmethyl)pyrrolidine-2-one[38] (266 mg, 1.00 mmol, 2 mol-%) in THF (80 mL) while stirring at room temp. After stirring for a further 5 min, a solution of ketone **24** (11.2 g, 49.8 mmol, 1.0 equiv.) in THF (80 mL) was added dropwise over 3 h. After allowing the reduction to proceed for a further 2 h, excess reductant was destroyed at 0 °C by the slow addition of aq. HCl (2 M, 100 mL). The resulting mixture was extracted with Et_2O (2× 100 mL). The combined organic extracts were washed with H_2O (100 mL), satd. aq. $NaHCO_3$ (100 mL), aq. phosphate buffer (pH = 7.1, 0.5 M, 100 mL), and brine (100 mL). They were then dried with Na_2SO_4 and filtered, and the solvents were evaporated in vacuo. The resulting residue was recrystallized from *n*-hexane. This yielded **25** as a white crystalline solid (8.55 g, 76%), m.p. 92–94 °C. The *ee* of **25** was determined by chiral HPLC: Chiralcel OD-H column, *n*-heptane/EtOH (97:3), 0.8 mL min^{-1}, 20 °C isothermal; $\lambda_{detector}$ = 285 nm; $t_{r\,(R)\text{-}\mathbf{25}}$ = 12.6 min, $t_{r\,(S)\text{-}\mathbf{25}}$ = 11.6 min [(*R*)-**25**:(*S*)-**25** = 99.8:0.2 (99.6% *ee*)]. $[\alpha]_D^{20}$ = –34.9 (*c* = 1.04 in $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 2.07 (tt, $J_{2',1'} = J_{2',3'}$ = 7.4 Hz, 2 H, 2′-H$_2$), 2.85 and 2.89 (2 t, $J_{1',2'} = J_{3',2'}$ = 7.7 Hz, 4 H, 1′-H$_2$, 3′-H$_2$), 2.91 (d, $J_{1\text{-}OH,1}$ = 2.9 Hz, 1 H, 1-OH), AB signal (δ_A = 3.62, δ_B = 3.82, J_{AB} = 10.9 Hz, in addition split by $J_{A,1}$ = 8.5, $J_{B,1}$ = 3.6 Hz, 2 H, 2-H$_2$), 3.82 (s, 3 H, OCH_3), 5.07 (ddd, $J_{1,2A}$ = 8.2, $J_{1,2B}$ = 4.0, $J_{1,1\text{-}OH}$ = 3.7 Hz, 1 H, 1-H), 6.78 (s, 1 H, 7′-H), 7.26 (s, 1 H, 4′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 25.68, (C-2′), 31.96 and 32.13 (C-1′, C-3′), 49.75 (C-2), 55.47 (OCH_3), 70.75 (C-1), 106.93 (C-7′), 122.84 (C-4′), 125.71 (C-5′), 136.14 (C-8′), 145.36 (C-9′), 155.22 (C-6′) ppm. IR (film): $\tilde{\nu}$ = 3445, 2955, 2905, 2845, 1615, 1585, 1490, 1465, 1430, 1320, 1300, 1275, 1255, 1165, 1080, 1060, 1025, 915, 870, 840, 735, 700 cm^{-1}. $C_{12}H_{15}ClO_2$ (226.70): calcd. C 63.57, H 6.83; found C 63.58, H 6.67.

(*S*)-2-(6-Hydroxyindan-5-yl)butyl 4-Bromobenzoate (39)



Cleavage of the Methyl Ether Moiety of Compound 8: Under an atmosphere of N_2, a mixture of indane **8** (300 mg, 1.36 mmol, 1.0 equiv.) and MeMgI (3 M in Et_2O, 9.0 mL, 27 mmol, 20 equiv.)

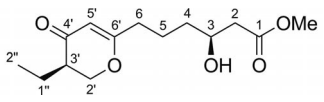
was heated at 180 °C for 30 min. The residue was cooled to –20 °C. H_2O (10 mL) was added slowly and with vigorous stirring. After extraction with Et_2O (3× 5 mL), the combined organic extracts were washed with NH_4Cl (satd. aq.; 3 mL) and brine (3 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The resulting colorless oil (262 mg, 94%) was not purified, since a ^1H NMR spectrum revealed that it was essentially pure.

Formation of a Bis(4-bromobenzoate): The aforementioned residue (50 mg, 0.24 mmol, 1.0 equiv.) was dissolved in pyridine (1 mL). *p*-Bromobenzoyl chloride (160 mg, 0.727 mmol, 3.0 equiv.) was added at room temp. After having been stirred for 24 h, the reaction mixture was poured into aq. $CuSO_4$ (1 M, 3 mL). The resulting mixture was extracted with Et_2O (3× 3 mL). The combined organic extracts were washed with aq. $CuSO_4$ (1 M, 3 mL) and brine (3 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The residue, a colorless oil (88 mg, 64%), was used in the next step without purification.

Monohydrolysis of the Bis(4-bromobenzoate): A mixture of all of this aforementioned residue, powdered $NaHCO_3$ (39 mg, 460 mmol, 3.0 equiv.), and MeOH/THF (1:1, 3 mL) was heated under reflux. After extraction with Et_2O (3× 5 mL), the combined organic extracts were washed with H_2O (2 mL) and brine (2 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated. The residue was purified by flash chromatography[35] [1.5 cm, fraction volume 10 mL, petroleum ether/Et_2O 20:1→4:1 (#12)] and yielded **39** (#18–23, 62%; 37% for the three steps from **8**) as a white solid. Recrystallization from *n*-hexane gave monocrystals (m.p. 95–98 °C) that were suitable for X-ray diffraction analysis (cf. Scheme 5).

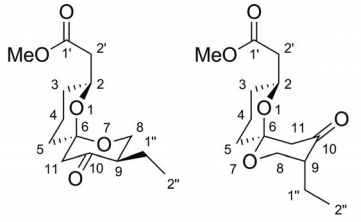
The *ee* of (*S*)-**39** was determined by chiral HPLC: Chiralcel AD-H column, *n*-heptane/EtOH (85:15), 1.0 mL min^{-1}, 20 °C isothermal; $\lambda_{detector}$ = 245 nm; $t_{r\,(S)\text{-}39}$ = 14.7 min, $t_{r\,(R)\text{-}39}$ = 10.5 min [(*S*)-**39**:(*R*)-**39** = 96.6:3.4 (93.2% *ee*)]. $[\alpha]_D^{20}$ = –14.6 (*c* = 1.12 in $CHCl_3$, 10 cm). ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.92 (dd, $J_{4,3A}$ = $J_{4,3B}$ = 7.4 Hz, 3 H, 4-H_3), AB signal (δ_A = 1.79, δ_B = 1.91, J_{AB} = 13.5 Hz, in addition split by $J_{A,2}$ = 9.2, $J_{A,4}$ = 7.4 Hz,$J_{B,4}$ = 7.5, $J_{B,2}$ = 5.9 Hz, 2 H, 3-H_2), 2.05 (tt, $J_{2',1'}$ = $J_{2',3'}$ = 7.3 Hz, 2 H, 2′-H_2), 2.79–2.86 (m, 4 H, 1-H_2, 3-H_2), 3.30 (dddd, $J_{2,3A}$ = 9.2, $J_{2,1A}$ = 7.3, $J_{2,1B}$ = $J_{2,3B}$ = 5.7 Hz, 1 H, 2-H), AB signal (δ_A = 4.34, δ_B = 4.45, J_{AB} = 10.9 Hz, in addition split by $J_{A,2}$ = 7.4, $J_{B,2}$ = 5.7 Hz, 2 H, 1-H_2), 5.28 (s, 1 H, 5′-OH), 6.70 (s, 1 H, 7′-H),* 7.00 (s, 1 H, 4′-H),* AABB signal centered at δ = 7.56 (2 H, 3^{Ar}-H)* and δ = 7.86 (2 H, 2^{Ar}-H)* ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 12.17 (C-4), 24.21 (C-3), 25.78 (C-2′), 32.27 (C-3′),* 32.90 (C-1′),* 39.81 (C-2), 69.43 (C-1), 112.04 (C-7′), 123.29 (C-4′), 124.71 (C-5′), 128.20 (C-1^{Ar}),* 129.29 (C-4^{Ar}),* 131.24 (C-2^{Ar}),** 131.81 (C-3^{Ar}),** 136.39 (C-8′),* 143.91 (C-9′),* 152.81 (C-6′),* 166.49 (*C*O_2Ar) ppm; * assignment corroborated by an HMBC experiment; ** assignment corroborated by an HSQC experiment. IR (film): $\tilde{\nu}$ = 3440, 2960, 2845, 1700, 1590, 1430, 1400, 1275, 1175, 1120, 1105, 1010, 955, 850, 755, 685 cm^{-1}. $C_{20}H_{21}BrO_3$ (389.28): calcd. C 61.71, H 5.44; found C 61.48, H 5.45. The crystallographic data of this compound are available (ref.[67]).

Methyl (3*S*)-6-[(3*R*)-3-Ethyl-4-oxo-3,4-dihydro-2*H*-pyran-6-yl]-3-hydroxyhexanoate (42):



(*S*)-{[RuCl(BINAP)]$_2$(μ-Cl)$_3$}·NH_2Me_2 (38 mg, 23 μmol, 0.5 mol-%; purchased from ABCR) was added to a solution of β-keto ester *anhydro*-**4** (1.21 g, 4.51 mmol, 1.0 equiv.) in degassed EtOH (35 mL) at room temp. The mixture was stirred for 17 h in an autoclave under an atmosphere of H_2 (4.0 bar). The autoclave was vented, and the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography[35] (4 cm, fraction volume 20 mL, cyclohexane/EtOAc, 5:8) to yield the title compound as a colorless oil (#11–27, 812 mg, 67%). $[\alpha]_D^{20}$ = +3.8 (*c* = 1.18 in $CHCl_3$, 10 cm). ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.98 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.5 Hz, 3 H, 2′′-H_3), 1.45 (ddq, $^2J_{1''A,1''B}$ = 15.2, $J_{1''A,3'}$ = $J_{1''A,2''}$ = 7.3 Hz, 1 H, 1′′-H^A), overlapping with 1.42–1.59 (m, 2 H, 5-H_2), overlapping with 1.58 –1.70 (m, 1 H, 4-H^A), 1.71–1.81 (m, 1 H, 4-H^B), overlapping with 1.82 (ddq, $^2J_{1''B,1''A}$ = 14.0, $J_{1''B,3'}$ = 5.6, $J_{1''B,2''}$ = 7.6 Hz, 1 H, 1′′-H^B), 2.26 (dddd, $J_{3',1''A}$ = 8.7, $J_{3',2'A}$ = 8.2, $J_{3',2'B}$ ≈ $J_{3',1''B}$ ≈ 4.7 Hz, 1 H, 3′-H), 2.27 (dd, $J_{6,5A}$ = $J_{6,5B}$ = 7.5 Hz, 2 H, 6-H_2), AB signal (δ_A = 2.43, δ_B = 2.51, J_{AB} = 16.5 Hz, in addition split by $J_{A,3}$ = 8.8, $J_{B,3}$ = 3.4 Hz, 2 H, 2-H_2), 2.99 (d, $J_{3\text{–}OH,3}$ = 4.0 Hz, 1 H, 3-OH), 3.72 (s, 3 H, OCH_3), 4.01 (ddddd, $J_{3,2A}$ ≈ $J_{3,4}$ ≈ 8.3, $J_{3,2B}$ ≈ $J_{3,3\text{-}OH}$ ≈ $J_{3,4}$ ≈ 4.0 Hz, 1 H, 3-H), AB signal (δ_A = 4.21, δ_B = 4.43, J_{AB} = 11.4 Hz, in addition split by $J_{A,3'}$ = 8.3, $J_{B,3'}$ = 4.7 Hz, 2 H, 2′-H_2), 5.28 (s, 1 H, 5′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 11.56 (C-2′′), 20.21 (C-1′′), 22.46 (C-4), 34.39 (C-6), 35.70 (C-5), 41.14 (C-2), 45.48 (C-3′), 51.87 (OCH_3), 67.56 (C-3), 71.26 (C-2′), 103.89 (C-5′), 173.36 (C-1), 176.46 (C-6′), 195.24 (C-4′) ppm. IR (film): $\tilde{\nu}$ = 3435, 2960, 2935, 2880, 1735, 1660, 1605, 1460, 1440, 1405, 1365, 1205, 1170, 1010, 905, 825 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{14}H_{22}O_5$ $[M]^+$ 270.14672; found 270.14700 (Δ = +1.0 ppm).

Methyl 2-[(2*S*,6*R*,9*R*)-9-Ethyl-10-oxo-1,7-dioxaspiro[5.5]undecan-2-yl]acetate (43) as a 90:10 mixture with Methyl 2-[(2*S*,6*S*,9*R*)-9-Ethyl-10-oxo-1,7-dioxaspiro[5.5]undecan-2-yl]acetate (*epi*-43)



90 : 10

43 *epi*-**43**

In-Situ Generation of Compounds 42 and 43: (*S*)-{[RuCl(BINAP)]$_2$(μ-Cl)$_3$}·NH_2Me_2 (45 mg, 27 μmol, 0.5 mol-%; purchased from ABCR) was added to a solution of β-keto ester **42** (1.46 g, 5.44 mmol, 1.0 equiv.) in degassed EtOH (50 mL) at room temp. The mixture was stirred for 16 h in an autoclave under an atmosphere of H_2 (4.0 bar). H_2 was replaced by N_2 (1.0 bar), and the solution was stirred for a further 72 h. The solvent was evaporated under reduced pressure. ^1H NMR analysis of the residue revealed the presence of a 68:32 mixture of spiroketal **43** and β-hydroxy ester **42**; spiroketal *epi*-**43** was not detected.

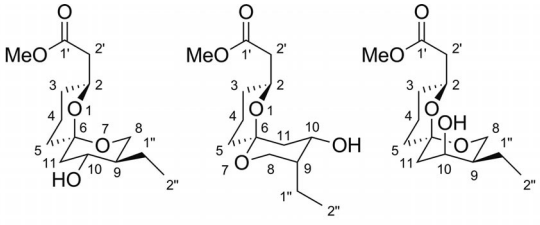
Completion of Spiroketal Formation: A solution of the crude product from the preceding paragraph and camphorsulfonic acid (63 mg, 0.27 mmol, 5 mol-%) in $CHCl_3$ (15 mL) was stirred for 16 h at room temp. After addition of $NaHCO_3$ (satd. aq.; 20 mL), the mixture was extracted with CH_2Cl_2 (3× 15 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography[35] (5 cm, fraction volume 50 mL, cyclohexane/EtOAc, 5:1) to yield a 90:10-mixture* of

43 and *epi*-**43** as a colorless oil (#9–13, 965 mg, 66%); *this ratio was determined from the ^{1}H NMR integrals of the signals at δ = 3.63 (s, 3 H, OCH_3, **43**) and 3.65 (s, 3 H, OCH_3, *epi*-**43**) ppm.

43: ^{1}H NMR (499.6 MHz, $CDCl_3$/TMS): δ = 0.92 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.5 Hz, 3 H, 2′′-H_3), 1.18 (ddq, $^2J_{1''A,1''B}$ = 14.3, $J_{1''A,9}$ = $J_{1''A,2''}$ = 7.2 Hz, 1 H, 1′′-H^A), 1.24 (dddd, $^2J_{3ax,3eq}$ = $J_{3ax,4ax}$ = 13.5, $J_{3ax,2}$ = 11.5, $J_{3ax,4eq}$ = 4.2 Hz, 1 H, 3-H^{ax}), 1.43 (ddd, $^2J_{5ax,5eq}$ = $J_{5ax,4ax}$ = 13.4, $J_{5ax,4eq}$ = 4.6 Hz, 1 H, 5-H^{ax}), 1.60–1.68 (2 m, 2 H, 3-H^{eq}, 4-H^{eq}), 1.72–1.85 (m, 2 H, 1′′-H^B, 5-H^{eq}), 1.89 (ddddd, $^2J_{4ax,4eq}$ = $J_{4ax,3ax}$ = $J_{4ax,5ax}$ = 13.4, $J_{4ax,3eq}$ = $J_{4ax,5eq}$ = 4.1 Hz, 1 H, 4-H^{ax}), 2.34–2.44 (m, 1 H, 9-H), overlapping with AB signal (δ_A = 2.36, δ_B = 2.44, J_{AB} = 15.2 Hz, in addition split by $J_{A,2}$ = 4.4, $J_{B,2}$ = 9.2 Hz, 2 H, 2′-H_2), overlapping with AB signal (δ_A = 2.39, δ_B = 2.44, J_{AB} = 13.9 Hz, 2 H, 11-H_2), 3.63 (s, 3 H, OCH_3), 3.69 (dd, $^2J_{8ax,8eq}$ = $J_{8ax,9}$ = 11.2 Hz, 1 H, 8-H^{ax}), 3.98 (dd, $^2J_{8eq,8ax}$ = 11.0, $J_{8eq,9}$ = 7.3 Hz, 1 H, 8-H^{eq}), 4.08 (dddd, $J_{2,3ax}$ = 11.5, $J_{2,2'B}$ = 9.2, $J_{2,2'A}$ = 4.4, $J_{2,3eq}$ = 2.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$/TMS): δ = 11.64 (C-2′′), 17.71 (C-1′′), 18.64 (C-4), 29.81 (C-3), 34.13 (C-5), 40.83 (C-2′), 50.83 (C-9), 51.58 (OCH_3), 52.35 (C-11), 64.07 (C-8), 66.99 (C-2), 100.68 (C-6), 171.81 (C-1′), 206.54 (C-10) ppm; a NOE was observed between δ = 8-H^{ax} and 2-H. IR (film): $\tilde{\nu}$ = 2950, 2875, 1735, 1720, 1440, 1385, 1290, 1260, 1240, 1195, 1180, 1080, 1030, 995, 970, 835 cm^{-1}. $C_{14}H_{22}O_5$ (270.32): calcd. C 62.20, H 8.20; found C 61.99, H 8.27.

***epi*-43:** ^{1}H NMR (499.6 MHz, $CDCl_3$/TMS): δ = 0.92 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.5 Hz, 3 H, 2′′-H_3), 2.14 (ddddd, $J_{9,1''A}$ = $J_{9,1''B}$ = 7.8, $J_{9,8ax}$ = 3.3, $J_{9,8eq}$ = $J_{9,11eq}$ = 1.3 Hz, 1 H, 9-H), 2.30 (dd, $^2J_{11eq,11ax}$ = 14.7, $^4J_{11eq,9}$ = 1.1 Hz, 1 H, 11-H^{eq}), 2.49 (d, $^2J_{11ax,11eq}$ = 14.7 Hz, 1 H, 11-H^{ax}), 3.65 (s, 3 H, OCH_3), 3.76 (dd, $^2J_{8eq,8ax}$ = 11.6, $J_{8eq,9}$ = 0.9 Hz, 1 H, 8-H^{eq}), 4.13 (dd, $^2J_{8ax,8eq}$ = 11.5, $J_{8ax,9}$ = 3.5 Hz, 1 H, 8-H^{ax}) ppm. ^{13}C NMR (125.6 MHz, $CDCl_3$/TMS): δ = 11.81 (C-2′′), 18.66 (C-4), 23.81 (C-1′′), 34.24 (C-5), 40.77 (C-2′), 49.48 (C-11), 51.61 (OCH_3), 52.00 (C-9), 62.66 (C-8), 67.06 (C-2), 99.90 (C-6), 208.79 (C-10) ppm.

Methyl 2-[(2*S*,6*R*,9*R*,10*R*)-9-Ethyl-10-hydroxy-1,7-dioxaspiro[5.5]-undecan-2-yl]acetate (*trans*-44) in a 89:11 Mixture with Methyl 2-[(2*S*,6*S*,9*R*,10*S*)-9-Ethyl-10-hydroxy-1,7-dioxaspiro[5.5]undecan-2-yl]acetate (*cis-epi*-44); and Methyl 2-[(2*S*,6*R*,9*R*,10*S*)-9-Ethyl-10-hydroxy-1,7-dioxaspiro[5.5]undecan-2-yl]acetate (*cis*-44) (separately isolated):



At –78 °C, powdered $NaBH_4$ (134 mg, 3.54 mmol, 1.1 equiv.) was added in 10 portions at intervals of 1 min to a stirred solution of $CeCl_3 \cdot 7H_2O$ (1.32 g, 3.54 mmol, 1.1 equiv.) and spiroketals **43** and *epi*-**43** (90:10 mixture; 869 mg, 3.21 mmol, 1.0 equiv.) in MeOH (20 mL). The reaction mixture was stirred at –78 °C for a further 2 h, and at room temp. for 30 min. It was then poured into $NaHCO_3$ (satd. aq.; 30 mL). After extraction with EtOAc (3× 30 mL), the combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. The residue consisted of a 80:10:10-mixture of *trans*-**44**, *cis-epi*-**44**, and *cis*-**44** [this ratio was determined from the ^{1}H NMR integrals over the following resonances of the crude product: 3.36 (dd, $J_{8ax,8eq}$ = $J_{8ax,9}$ = 11.5 Hz, 1 H, 8-H^{ax}, *trans*-**44**), 3.75 (ddd, $J_{8ax,8eq}$ = 11.7, $J_{8ax,9}$ = 2.4, $^4J_{8ax,10}$ = 1.4 Hz, 1 H, 8-H^{ax}, *cis-epi*-**44**), and 3.86 (ddddd, $J_{10,10\text{-}OH}$ = 10.6, $J_{10,11ax}$ = 3.4, $J_{10,11eq}$ = 3.1, $J_{10,9}$ = 2.6, $^4J_{10,8eq}$ = 0.5 Hz, 1 H, 10-H, *cis*-**44**) ppm]. This mixture was separated by flash chromatography[35] [5 cm, fraction volume 50 mL, cyclohexane/EtOAc 4:1→3:1 (#8)→2:1 (#15)→1:1 (#30)] to give pure *cis*-**44** as a white crystalline solid (#12–15, 86 mg, 10%), and an 89:11 mixture of *trans*-**44** and *cis-epi*-**44** as a colorless oil (#20–35, 735 mg, 84%).

***trans*-44:** ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.83 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.5 Hz, 3 H, 2′′-H_3), 0.96 (dddd, $^2J_{3ax,3eq}$ = $J_{3ax,4ax}$ = 13.1, $J_{3ax,2}$ = 11.5, $J_{3ax,4eq}$ = 3.9 Hz, 1 H, 3-H^{ax}), 1.09 (ddq, $^2J_{1''A,1''B}$ = 13.7, $J_{1''A,9}$ = 8.1, $J_{1''A,2''}$ = 7.5 Hz, 1 H, 1′′-H^A), 1.22 (ddd, $^2J_{5ax,5eq}$ = $J_{5ax,4ax}$ = 13.2, $J_{5ax,4eq}$ = 4.8 Hz, 1 H, 5-H^{ax}), 1.22–1.42 (3 m, 3 H, 3-H^{eq}, 4-H^{eq}, and 9-H), overlapping with 1.27 (dd, $^2J_{11ax,11eq}$ = 12.5, $J_{11ax,10}$ = 11.1 Hz, 1 H, 11-H^{ax}), 1.57 (dddd, $^2J_{5eq,5ax}$ = 13.0, $J_{5eq,4ax}$ = 4.1, $J_{5eq,4eq}$ = 2.4, $^4J_{5eq,3eq}$ = 1.4 Hz, 1 H, 5-H^{eq}), 1.73 (dqd, $^2J_{1''B,1''A}$ = 13.7, $J_{1''B,2''}$ = 7.7, $J_{1''B,9}$ = 3.5 Hz, 1 H, 1′′-H^B), 1.92 (dd, $^2J_{11eq,11ax}$ = 12.4, $J_{11eq,10}$ = 4.9 Hz, 1 H, 11-H^{eq}), 1.94 (ddddd, $^2J_{4ax,4eq}$ = $J_{4ax,3ax}$ = $J_{4ax,5ax}$ = 13.2, $J_{4ax,3eq}$ = $J_{4ax,5eq}$ = 4.1 Hz, 1 H, 4-H^{ax}), AB signal (δ_A = 2.09, δ_B = 2.37, J_{AB} = 15.0 Hz, in addition split by $J_{A,2}$ = 4.0, $J_{B,2}$ = 9.6 Hz, 2 H, 2′-H_2), 3.57 (dd, $^2J_{8ax,8eq}$ = $J_{8ax,9}$ = 11.4 Hz, 1 H, 8-H^{ax}), 3.37 (s, 3 H, OCH_3), 3.66–3.75 (m, 1 H, 10-H), 3.70 (dd, $^2J_{8eq,8ax}$ = 11.3, $J_{8eq,9}$ = 5.0 Hz, 1 H, 8-H^{eq}), 4.13 (dddd, $J_{2,3ax}$ = 11.6, $J_{2,2'B}$ = 9.5, $J_{2,2'A}$ = 4.0, $J_{2,3eq}$ = 2.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = 11.40 (C-2′′), 18.98 (C-4), 21.36 (C-1′′), 30.62 (C-3), 34.90 (C-5), 41.28 (C-2′), 45.55 (C-9), 45.60 (C-11), 50.94 (OCH_3), 63.06 (C-8), 66.38 (C-2), 68.29 (C-10), 98.05 (C-6), 171.36 (C-1′) ppm.

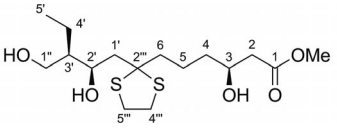
***cis-epi*-44:** δ = 0.89 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.4 Hz, 3 H, 2′′-H_3), 1.41 (dd, $^2J_{11ax,11eq}$ = 12.8, $J_{11ax,10}$ = 11.7 Hz, 1 H, 11-H^{ax}), 1.67 (ddd, $^2J_{11eq,11ax}$ = 12.7, $J_{11eq,10}$ = 5.0, $J_{11eq,9}$ = 1.0 Hz, 1 H, 11-H^{eq}), AB signal (δ_A = 2.09, δ_B = 2.37, J_{AB} = 15.0 Hz, in addition split by $J_{A,2}$ = 4.0, $J_{B,2}$ = 9.6 Hz, 2 H, 2′-H_2), 3.64 (dd, $^2J_{8eq,8ax}$ = 11.6, $J_{8eq,9}$ = 1.7 Hz, 1 H, 8-H^{eq}), 3.38 (s, 3 H, OCH_3), 3.90 (ddd, $^2J_{8ax,8eq}$ = 11.6, $J_{8ax,9}$ = 2.4, $^4J_{8ax,10}$ = 1.3 Hz, 1 H, 8-H^{ax}), 4.13–4.20 (m, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = 11.52 (C-2′′), 15.12 (C-1′′), 19.02 (C-4), 30.62 (C-3), 34.99 (C-5), 41.28 (C-2′), 40.42(C-11), 41.24 (C-9), 50.92 (OCH_3), 60.47 (C-8), 66.29, and 66.35 (C-2 and C-10), 97.80 (C-6), 171.40 (C-1′) ppm. IR (film): $\tilde{\nu}$ = 3435, 2955, 2875, 1740, 1440, 1385, 1290, 1225, 1200, 1180, 1045, 1025, 980, 935, 880, 835, 765, 680 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{14}H_{24}O_5$ $[M]^+$ 272.16237; found 272.16250 (Δ = +0.5 ppm).

***cis*-44:** m.p. 101–103 °C. $[\alpha]_D^{20}$ = +108 (*c* = 1.15 in $CHCl_3$, 10 cm). ^{1}H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.93 (dd, $J_{2'',1''A}$ = $J_{2'',1''B}$ = 7.4 Hz, 3 H, 2′′-H_3), 1.24–1.33 (m, 1 H, 3-H^{ax}), overlapping with 1.23 (ddq, $^2J_{1''A,1''B}$ = 13.8, $J_{1''A,9}$ = 7.3, $J_{1''A,2''}$ = 7.0 Hz, 1 H, 1′′-H^A), 1.42 (ddq, $^2J_{1''B,1''A}$ = 13.5, $J_{1''B,9}$ = $J_{1''B,2''}$ = 7.5 Hz, 1 H, 1′′-H^B), 1.47–1.65 (4 m, 4 H, 9-H, 3-H^{eq}, 4-H^{eq}, and 5-H^{eq}), overlapping with 1.46 (ddd, $J_{5ax,4ax}$ = 13.5, $^2J_{5ax,5eq}$ = 13.0, $J_{5ax,4eq}$ = 4.2 Hz, 1 H, 5-H^{ax}), 1.62 (ddd, $^2J_{11ax,11eq}$ = 14.1, $J_{11ax,10}$ = 3.4, $^4J_{11ax,9}$ = 0.5 Hz, 1 H, 11-H^{ax}), 1.90 (ddddd, $^2J_{4ax,4eq}$ ≈ $J_{4ax,3ax}$ ≈ $J_{4ax,5ax}$ ≈ 13.4, $J_{4ax,3eq}$ ≈ $J_{4ax,5eq}$ ≈ 4.1 Hz, 1 H, 4-H^{ax}), 1.96 (dd, $^2J_{11eq,11ax}$ = 14.2, $J_{11eq,10}$ = 3.0 Hz, 1 H, 11-H^{eq}), AB signal (δ_A = 2.43, δ_B = 2.49, J_{AB} = 14.9 Hz, in addition split by $J_{A,2}$ = 4.3, $J_{B,2}$ = 9.3 Hz, 2 H, 2′-H_2), 3.46 (d, $J_{10\text{-}OH,10}$ = 10.6 Hz, 1 H, 10-OH), 3.51 (ddd, $^2J_{8eq,8ax}$ = 11.4, $J_{8eq,9}$ = 4.8, $^4J_{8eq,10}$ = 0.8 Hz, 1 H, 8-H^{eq}), 3.62 (dd, $^2J_{8ax,8eq}$ = $J_{8ax,9}$ = 11.7 Hz, 1 H, 8-

H^{ax}), 3.71 (s, 3 H, OCH_3), 4.06 (ddddd, $J_{10,10\text{-}OH}$ = 10.6, $J_{10,11eq}$ = 3.4, $J_{10,11ax}$ = 3.1, $J_{10,9}$ = 2.6, $^4J_{10,8eq}$ = 0.5 Hz, 1 H, 10-H), 4.13 (dddd, $J_{2,3ax}$ = 11.5, $J_{2,2'B}$ = 9.3, $J_{2,2'A}$ = 4.2, $J_{2,3eq}$ = 2.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 11.23 (C-2′′), 18.27 (C-4), 20.73 (C-1′′), 30.49 (C-3), 34.47 (C-5), 41.14 (C-2′), 41.30 (C-11), 41.36 (C-9), 51.92 (OCH_3), 60.23 (C-8), 66.13 (C-10), 67.31 (C-2), 98.00 (C-6), 172.04 (C-1′) ppm. IR (film): $\tilde{\nu}$ = 3525, 2955, 2940, 2875, 1740, 1440, 1390, 1290, 1200, 1175, 1150, 1075, 1050, 1030, 990, 865, 840, 805 cm^{-1}. $C_{14}H_{24}O_5$ (272.34): calcd. C 61.74, H 8.88; found C 61.29, H 8.92. The crystallographic data of compound *cis*-**44** are available (ref.[67]).

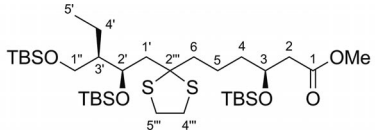
Isolation of Pure *trans*-44: At –40 °C, BF_3·Et_2O (3.3 mL, 27 mmol, 10 equiv.) was added dropwise to a solution of spiroketals *trans*-**44** and *cis-epi*-**44** (89:11 mixture; 735 mg, 2.70 mmol, 1.0 equiv.) in ethanedithiol (2.7 mL, 27 mmol, 10 equiv.). After 7 h of vigorous stirring, $NaHCO_3$ (satd. aq.; 20 mL) was added carefully, while stirring vigorously. The mixture was allowed to reach room temp. After extraction with Et_2O (3× 10 mL), the combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, and filtered. The Et_2O was distilled off at atmospheric pressure. Ethanedithiol was removed under high vacuum at room temp. The residue was purified by flash chromatography[35] (4 cm, fraction volume 20 mL, cyclohexane/EtOAc, 2:1). The title compound (#7–16, 642 mg, 87% relative to all of the 89:11 diastereomeric mixture; 98% relative to the fraction of *trans*-**44** in the 89:11 mixture) was isolated as a colorless oil.

(*S*)-Methyl 3-Hydroxy-6-{2-[(2*R*,3*R*)-2-hydroxy-3-(hydroxymethyl)-pentyl]-1,3-dithiolan-2-yl}hexanoate (45):



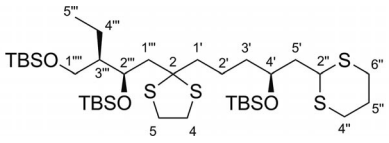
At –40 °C, BF_3·Et_2O (16.8 mL, 137 mmol, 60 equiv.) was added to a well-stirred solution of spiroketal *trans*-**44** (620 mg, 2.28 mmol, 1.0 equiv.) in ethanedithiol (23 mL, 228 mmol, 100 equiv.). After stirring for 2 d, $NaHCO_3$ (satd. aq.; 100 mL) was added. The mixture was allowed to reach room temp. After extraction with Et_2O (3× 20 mL), the combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, and filtered. The Et_2O was distilled off at atmospheric pressure. Ethanedithiol was removed under high vacuum at room temp. The residue was dissolved in MeOH (30 mL), and combined with alumina (super I B, 15 g). After stirring for 1.5 h, the solvent was evaporated under reduced pressure. The residue was packed onto a column filled with silica gel. Flash chromatography[35] [4 cm, fraction volume 20 mL, cyclohexane/EtOAc 1:1→1:2 (#11)→2:1 (#27)→EtOAc (#33)→EtOAc/MeOH, 3:1 (#38)] gave the title compound as a colorless oil (#11–40, 678 mg, 81%). $[\alpha]_D^{20}$ = +6.5 (*c* = 1.11 in $CHCl_3$, 10 cm). ^{1}H NMR (499.6 MHz, $CDCl_3$/TMS): δ = 0.97 (dd, $J_{5',4'A}$ = $J_{5',4'B}$ = 7.5 Hz, 3 H, 5′-H_3), 1.25–1.41 (m, 2 H, 4′-H_2), 1.43–1.59 (m, 2 H, 5-H_2), 1.61–1.69 (m, 1 H, 3′-H), overlapping with 1.59–1.74 (m, 2 H, 4-H_2), AB signal (δ_A = 1.95, δ_B = 2.05, J_{AB} = 13.8 Hz, in addition split by $J_{A,5}$ = 11.7, $J_{A,5}$ = 4.5, $J_{6B,5}$ = 11.9, $J_{6B,5}$ = 4.5 Hz, 2 H, 6-H_2) overlapping with 1.99 (br. d, $^2J_{1'A,1'B}$ = 14.7, $J_{1'A,2'}$ < 0.5 Hz, 1 H, 1′-H^A), 2.18 (dd, $^2J_{1'B,1'A}$ = 15.1, $J_{1'B,2'}$ = 8.8 Hz, 1 H, 1′-H^B), AB signal (δ_A = 2.44, δ_B = 2.51, J_{AB} = 16.3 Hz, in addition split by $J_{A,3}$ = 8.8, $J_{B,3}$ = 3.4 Hz, 2 H, 2-H_2), 3.08–3.12 (2 m, 2 H, 3-OH, 1′′-OH),* 3.28–3.36 (m, 4 H, 4′′′-H_2, 5′′′-H_2), 3.77 (s, 3 H, OCH_3), 3.72–3.76 (m, 2 H, 1′′-H_2), 3.91 (d, $J_{2'\text{-}OH,2'}$ = 2.2 Hz, 1 H, 2′-OH),* 4.05 (ddddd, $J_{3,2A}$ = $J_{3,4}$ = 8.1, $J_{3,2B}$ = $J_{3,4}$ = $J_{3,3\text{-}OH}$ = 4.1 Hz, 1 H, 3-H), 4.29 (ddd, $J_{2',1'A}$ = 8.7, $J_{2',2'\text{-}OH}$ = $J_{2',3}$ = 2.3 Hz, 1 H, 2′-H) ppm; * assignment corroborated by an HMBC experiment. ^{13}C NMR (125.6 MHz, $CDCl_3$/TMS): δ = 12.37 (C-5′), 18.89 (C-4′), 22.64 (C-4), 36.28 (C-5), 39.99 and 40.16 (C-4′′′, C-5′′′), 41.28 (C-2), 45.02 (C-1′), 45.33 (C-6), 47.11 (C-3′), 51.85 (OCH_3), 64.32 (C-1′′), 67.55 (C-3), 70.74 (C-2′′′), 73.49 (C-2′), 173.36 (C-1) ppm. IR (film): $\tilde{\nu}$ = 3415, 2950, 2925, 2875, 1735, 1435, 1280, 1200, 1160, 1100, 1040, 920, 850, 730 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{16}H_{30}O_5S_2$ $[M]^+$ 366.15347; found 366.15450 (Δ = +2.8 ppm).

(*S*)-Methyl 3-(*tert*-Butyldimethylsiloxy)-6-(2-{(2*R*,3*R*)-2-(*tert*-butyldimethylsiloxy)-3-[(*tert*-butyldimethylsiloxy)methyl]pentyl}-1,3-dithiolan-2-yl)hexanoate (46):



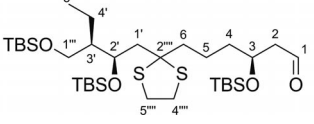
At –78 °C, TBSOTf (440 µL, 1.91 mmol, 3.5 equiv.) was added dropwise to a solution of triol **43** (200 mg, 0.546 mmol, 1.0 equiv.) and 2,6-lutidine (450 µL, 3.82 mmol, 7.0 equiv.) in CH_2Cl_2 (6 mL). The resulting mixture was stirred for a further 20 min. The reaction was quenched by the addition of MeOH (3 drops). The mixture was allowed to reach room temp. After adding H_2O (6 mL), it was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[35] [1.5 cm, fraction volume 10 mL, petroleum ether/Et_2O 24:1→19:1 (#9)] to yield the title compound as a colorless oil (#14–20, 320 mg, 83%). $[\alpha]_D^{20}$ = +11.6 (*c* = 0.90 in $CHCl_3$, 10 cm). ^{1}H NMR (499.6 MHz, C_6D_6): δ = 0.110, 0.112, 0.12, 0.17, 0.24, and 0.27 [6 s, 6× 3 H, 3 $Si(CH_3)_2$], 1.00, 1.02, and 1.04 [3 s, 3× 9 H, 3 $SiC(CH_3)_3$], 1.06 (dd, $J_{5',4'A}$ = $J_{5',4'B}$ = 7.6 Hz, 3 H, 5′-H_3), 1.48 (ddq, $^2J_{4'A,4'B}$ = 14.9, $J_{4'A,3'}$ = 7.4, $J_{4',5'}$ = 7.4 Hz, 1 H, 4′-H^A), 1.53–1.66 (m, 3 H, 4′-H^B, 4-H_2), 1.73–1.86 (m, 2 H, 5-H_2), 1.89 (ddddd, $J_{3',1''B}$ = $J_{3',4'A}$ = 7.5, $J_{3',1''A}$ = $J_{3',4'B}$ = 5.1, $J_{3',2'}$ = 2.3 Hz, 1 H, 3′-H), 2.02–2.14 (m, 2 H, 6-H_2), 2.30 (dd, $^2J_{1'A,1'B}$ = 14.9, $J_{1'A,2'}$ = 5.1 Hz, 1 H, 1′-H^A), AB signal (δ_A = 2.39, δ_B = 2.51, J_{AB} = 14.7 Hz, in addition split by $J_{A,3}$ = 5.0, $J_{B,3}$ = 7.4 Hz, 2 H, 2-H_2), 2.51 (dd, $^2J_{1'B,1'A}$ = 14.9, $J_{1'B,2'}$ = 5.9 Hz, 1 H, 1′-H^B), 2.75–2.89 (m, 4 H, 4′′′-H_2, 5′′′-H_2), 3.37 (s, OCH_3), AB signal (δ_A = 3.72, δ_B = 3.77, J_{AB} = 9.7 Hz, in addition split by $J_{A,3'}$ = 5.5, $J_{B,3'}$ = 7.1 Hz, 2 H, 1′′-H_2), 4.28 (dddd, $J_{3,2B}$ = 7.3, $J_{3,2A}$ = $J_{3,4A}$ = $J_{3,4B}$ = 5.6 Hz, 1 H, 3-H), 4.44 (ddd, $J_{2',1'A}$ = $J_{2',1'B}$ = 5.5, $J_{2',3'}$ = 2.0 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125.6 MHz, C_6D_6): δ = –5.25, –5.24, –4.55, –4.48, –3.98, and –3.37 [3 $Si(CH_3)_2$], 13.07 (C-5′), 18.26, 18.45, and 18.48 [3 $SiC(CH_3)_3$], 19.83 (C-4′), 23.20 (C-5), 26.08, 26.20, and 26.35 [3 $SiC(CH_3)_3$], 38.13 (C-4), 39.49 and 39.75 (C-4′′′, C-5′′′), 42.82 (C-2), 44.53 (C-6), 47.54 (C-1′), 49.44 (C-3′), 50.97 (OCH_3), 62.53 (C-1′′), 69.98 (C-3), 70.98 (C-2′′′), 71.15 (C-2′), 171.50 (C-1) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2855, 1745, 1470, 1465, 1435, 1360, 1255, 1090, 1050, 1005, 940, 835, 775, 665 cm^{-1}. $C_{34}H_{72}O_5S_2Si_3$ (709.32): calcd. C 57.57, H 10.23, S 9.04; found C 57.65, H 10.17, S 8.97.

2-[(*S*)-4-(*tert*-Butyldimethylsiloxy)-5-(1,3-dithian-2-yl)pentyl]-2-{(2*R*,3*R*)-2-(*tert*-butyldimethylsiloxy)-3-[(*tert*-butyldimethylsiloxy)-methyl]pentyl}-1,3-dithiolane (47):



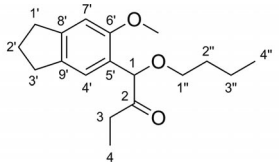
$LiClO_4$ (28 mg, 260 μmol, 3.0 equiv.) was dried under vacuum (0.2 mbar) for 6 h at room temp. It was then added in one portion to a solution of aldehyde **48** (59 mg, 86.8 μmol, 1.0 equiv.) and 1,3-propanedithiol (30 μL, 304 μmol, 3.5 equiv.) in Et_2O (1 mL). The resulting suspension was stirred for 3 d. $CuSO_4$ (1 M, aq., pH adjusted to 5 by adding a few drops of satd. aq. $NaHCO_3$; 2 mL) was added with stirring. The supernatant liquid was decanted from a solid, which we assumed was a complex formed from Cu^{II} and 1,3-propanedithiol. The solution was extracted with petroleum ether (4× 1.5 mL). The combined organic extracts were washed with $CuSO_4$ (1 M aq., pH adjusted to 5 by adding a few drops of satd. aq. $NaHCO_3$, 2 mL) and with brine (2 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[35] [1.5 cm, fraction volume 10 mL, petroleum ether/Et_2O 100:1→75:1 (#13)→60:1 (#25)] to yield the title compound as a colorless wax (#29–39, 39 mg, 63%). $[\alpha]_D^{20}$ = +1.31 (c = 0.933 in $CHCl_3$, 10 cm). ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.03, 0.04, 0.08 (double intensity), 0.10, and 0.11 [5 s, 6× 3 H, 3 $Si(CH_3)_2$], 0.88, 0.89, and 0.90 [3 s, 3× 9 H, 3 $SiC(CH_3)_3$], 0.95 (dd, $J_{5''',4'''A}$ = $J_{5''',4'''B}$ = 7.5 Hz, 3 H, 5′′′-H_3), 1.24–1.40 (m, 2 H, 4′′′-H_2), 1.40–1.50 (m, 2 H, 3′-H_2), 1.50–1.61 (m, 2 H, 2′-H_2), 1.65 (ddddd, $J_{3''',4'''A}$ = 7.7, $J_{3''',1''''B}$ = 6.6, $J_{3''',1''''A}$ = $J_{3''',4'''B}$ = 5.7, $J_{3''',2'''}$ = 2.1 Hz, 1 H, 3′′′-H), 1.80–1.85 (m, 2 H, 5′-H_2), 1.85–1.94 (m, 3 H, 1-H_2, 5′′-H^{ax}), 2.00 (dd, $^2J_{1''',A,1''',B}$ = 14.8, $J_{1''',A,2'''}$ = 5.5 Hz, 1 H, 1′′′-H^A), 2.11 (ddddd, $^2J_{5''eq,5''ax}$ = 13.9, $J_{5''eq,6''eq}$ = 4.8 Hz,* $J_{5''eq,4''eq}$ = 4.2 Hz,* $J_{5''eq,6''ax}$ = 3.3, $J_{5''eq,6''ax}$ = 2.8 Hz, 1 H, 5′′-H^{eq}), 2.25 (dd, $^2J_{1''',B,1''',A}$ = 14.9, $J_{1''',B,2'''}$ = 5.6 Hz, 1 H, 1′′′-H^B), 2.65–2.75 (m, 4′′-H^{eq}, 2 H, 6′′-H_2), 2.89 (ddd, $^2J_{4''ax,4''eq}$ = 14.0, $J_{4''ax,5''ax}$ = 11.3, $J_{4''ax,5''eq}$ = 2.7 Hz, 1 H, 4′′-H^{ax}), 3.19–3.29 (m, 4 H, 4-H_2 and 5-H_2), AB signal (δ_A = 3.53, δ_B = 3.59, J_{AB} = 9.6 Hz, in addition split by $J_{A,3'''}$ = 5.8, $J_{B,3'''}$ = 6.8 Hz, 2 H, 1′′′′-H_2), 3.95 (dddd, $J_{4',5'A}$ ≈ $J_{4',5'B}$ ≈ $J_{4',3'A}$ ≈ $J_{4',3'B}$ ≈ 6.0 Hz, 1 H, 4′-H), 4.10 (dd, $J_{2'',5'A}$ ≈ $J_{2'',5'B}$ ≈ 7.2 Hz, 1 H, 2′′-H), 4.16 (ddd, $J_{2''',1'''A}$ ≈ $J_{2''',1'''B}$ ≈ 5.5, $J_{2''',3'''}$ = 2.3 Hz, 1 H, 2′′′-H) ppm; * values interchangeable. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = –5.31, –5.27, –4.39, –4.16, –4.13, and –3.58 [6 $Si(CH_3)_2$], 12.83 (C-5′′′), 18.19, 18.28, and 18.30 [3 $SiC(CH_3)_3$], 19.62 (C-4′′′), 22.56 (C-2′), 26.05, 26.05, and 26.18 [3 $SiC(CH_3)_3$], 30.18 and 30.69 (C-4′′, C-6′′), 37.74 (C-3′), 39.46 and 39.66 (C-4, C-5), 42.82 (C-5′), 43.94 (C-6′), 44.22 (C-2′′), 46.86 (C-1′′′), 48.99 (C-3′′′), 62.15 (C-1′′′′), 68.76 (C-4′), 70.72 (C-2′′′), 70.77 (C-2) ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2895, 2855, 1470 1465, 1255, 1090, 1050, 935, 835, 775, 670 cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{32}H_{67}O_3S_4Si_3$ $[M]^+$ 711.32809; found 711.32840 (Δ = +0.4 ppm).

(*S*)-3-(*tert*-Butyldimethylsiloxy)-6-(2-{(2*R*,3*R*)-2-(*tert*-butyldimethylsiloxy)-3-[(*tert*-butyldimethylsiloxy)methyl]pentyl}-1,3-dithiolan-2-yl)hexanal (48):



At –78 °C, DiBAH (1 M in *n*-hexane, 470 μL, 470 μmol, 1.2 equiv.) was added dropwise to a solution of ester **46** (279 mg, 393 μmol, 1.0 equiv.) in CH_2Cl_2 (5 mL). The resulting mixture was stirred for a further 30 min. The reaction was quenched by the addition of aq. phosphate buffer (pH = 7.1 Hz, 1 M, 3 mL) and potassium sodium tartrate (satd. aq., 10 mL). After stirring vigorously for 1.5 h without cooling, the mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The oily residue (**48**, 239 mg, 90%) was not purified, but was used directly to synthesize dithiane **47**. ^1H NMR (300.1 MHz, $CDCl_3$/TMS): δ = 0.04 (double intensity), 0.06, 0.08, 0.09, and 0.10 [5 s, 6× 3 H, 3 $Si(CH_3)_2$], 0.88, 0.88, and 0.89 [3 s, 3× 9 H, 3 $SiC(CH_3)_3$], 0.95 (dd, $J_{5',4'A}$ = $J_{5',4'B}$ = 7.5 Hz, 3 H, 5′-H_3), 1.23–1.41 and 1.48–1.70 (m, 7 H, 4-H_2, 5-H_2, 3′-H, 4′-H_2), 1.86–1.96 (m, 2 H, 6-H_2), 2.52 (dd, $J_{2,3}$ = 5.7, $J_{2,1}$ = 2.5 Hz, 2 H, 2-H_2), 3.20–3.30 (m, 4 H, 4′′′-H_2, 5′′′-H_2), AB signal (δ_A = 3.54, δ_B = 3.59, J_{AB} = 9.7 Hz, in addition split by $J_{A,3'}$ = 5.8, $J_{B,3'}$ = 6.7 Hz, 2 H, 1′′-H_2), 4.10–4.23 (m, 2 H, 2′-H, 3-H), 9.81 (t, $J_{1,2}$ = 2.5 Hz, 1 H, 1-H) ppm.

1-Butoxy-1-(6-methoxyindan-5-yl)butan-2-one (52):



At –30 °C, *i*PrMgCl (2.0 M in THF, 400 μL, 781 μmol, 1.4 equiv.) was added dropwise to a solution of aryl iodide **23** (214 mg, 781 μmol, 1.4 equiv.) in THF (2 mL). The resulting mixture was stirred for 1.5 h, and then it was added dropwise to a solution of triflate **7b** (163 mg, 558 μmol, 1.0 equiv.) and $ZnCl_2$ (11 mg, 83.7 μmol, 15 mol-%) in THF (2 mL) at 0 °C. The mixture was stirred for a further 2.5 h. The reaction was quenched by the addition of NH_4Cl (half-saturated aq., 4 mL). The resulting mixture was extracted with petroleum ether (3× 5 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography[35] (2 cm, fraction volume 20 mL, petroleum ether/Et_2O, 19:1) to yield the title compound as a colorless oil (#11–14, 38 mg, 23%). $[\alpha]_D^{20}$ = +67.5 (c = 0.80 in $CHCl_3$, 10 cm). ^1H NMR (400.1 MHz, $CDCl_3$/TMS): δ = 0.89 (t, $J_{4',3'}$ = 7.4 Hz, 3 H, 4′-H_3), 0.99 (t, $J_{4,3}$ = 7.4 Hz, 3 H, 4-H_3), 1.38 (m, 2 H, 3′-H), 1.59 (m, 2 H, 2′-H), 2.06 (tt, $J_{2'',1''}$ = $J_{2'',3''}$ = 7.4 Hz, 2 H, 2′′-H_2), AB signal (δ_A = 2.44, δ_B = 2.49, J_{AB} = 17.5 Hz, in addition split by $J_{A,4'}$ = 7.4, $J_{B,4'}$ = 7.7 Hz, 2 H, 3-H_2), 2.83 (t, $J_{1'',2''}$ = 7.4 Hz, 2 H, 1′′-H_2), 2.88 (t, $J_{3'',2''}$ = 7.4 Hz, 2 H, 3′′-H_2), AB signal (δ_A = 3.40, δ_B = 3.43, J_{AB} = 9.0 Hz, in addition split by $J_{A,2'}$ = $J_{B,2'}$ = 6.8 Hz, 2 H, 1′-H_2), 3.81 (s, 3 H, OCH_3), 5.15 (s, 1 H, 1-H), 6.79 (s, 1 H, 4′-H), 7.17 (s, 1 H, 7′-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS): δ = 7.71 (C-4), 13.97 (C-4′), 19.39 (C-3′), 25.73 (C-2), 31.90 (C-3), 32.07 (C-2′), 32.17 (C-1′′), 33.41 (C-3′′), 55.89 (OCH_3), 69.43 (C-1′), 81.26 (C-1), 107.39 (C-4′′), 123.50 (C-6′′), 123.90 (C-7′′), 136.34 (C-9′′), 145.77 (C-8′′), 156.18 (C-5′′), 209.45 (C-2) ppm; an HMBC experiment (100.6 MHz/400.1 MHz, $CDCl_3$/TMS) showed long-range C,H correlations: (1) of C-5 with 1-H; (2) of C-5 with 1-H; (3) of C-2 with 3-H_2; (4) of C-6′ with 1-H; and (5) of C-1′′ with 1-H. A NOESY experiment (400.1 MHz) revealed spatial proximities (1) between 1-H and 3-H_2; and (2) between 1-H and 1′-H_2.

Supporting Information (see footnote on the first page of this article): Experimental procedure and characterization for triflates *rac*-**7a** and (*S*)-**7b**, copies of the ^1H and ^{13}C NMR spectra for the synthesized compounds, determination of the enantiopurity of the X-rayed crystal of (*S*)-**39**, and X-ray crystallography of compounds (*S*)-**39** and *cis*-**44**.

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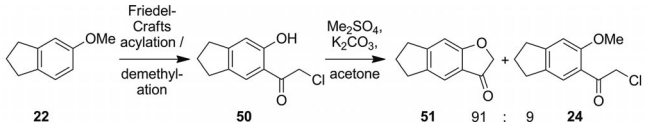

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[42] The *ee* of (*R*)-**25** was determined by chiral HPLC: Chiralcel OD-H column, *n*-heptane/EtOH (97:3), 0.8 mL min^{-1}, 20 °C isothermal; $\lambda_{detector}$ = 285 nm; $t_{r\,(R)\text{-}25}$ = 12.6 min, $t_{r\,(S)\text{-}25}$ = 11.6 min [(*R*)-**25**: (*S*)-**25** = 99.8:0.2 (99.6% *ee*)].
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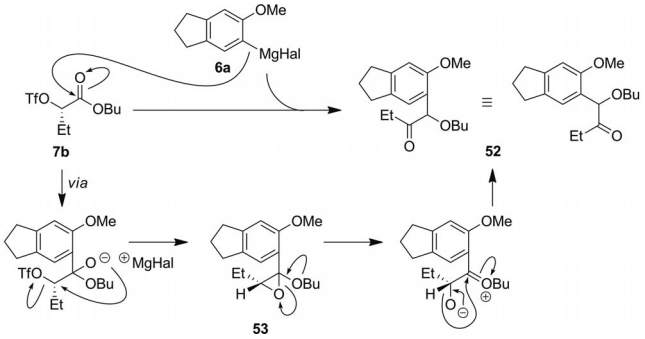
[46] A reaction between triflate **7b** and Grignard reagent **6a** occurred nevertheless. It provided 61% of a product whose ^{1}H NMR spectrum indicated an indane scaffold and a butoxy chain. We assign this compound to be α-butoxy ketone **52**. We interpret this transformation as being the result of an initial attack of the Grignard reagent at the C=O bond of the ester rather than at the C–O bond of the triflate. Subsequent ring-closure leads to an epoxide (i.e., **53**). The latter undergoes a semipinacol rearrangement,[47,48] which creates an ether and a carbonyl group simultaneously.



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[61] For the introduction of "higher-order cuprates", see: a) B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**,

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[63] The *ee* of (*S*)-**8** was determined by chiral HPLC: Chiralcel OD-H column, *n*-heptane/*i*PrOH (200:1), 0.8 mL min^{-1}, 15 °C isothermal; $\lambda_{detector}$ = 230 nm; $t_{r\,(S)\text{-}\mathbf{8}}$ = 21.2 min, $t_{r\,(R)\text{-}\mathbf{8}}$ = 23.6 min [for entry 13 in Table 2: (*S*)-**8**:(*R*)-**8** = 97.6:2.4 (95.1% *ee*)].

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[66] Compound **39** formed triclinic crystals. Starting from the non-centrosymmetric (or acentric) space group $P\bar{1}$, the structure of **39** could be accomodated assuming that there are two differently orientated yet identically configured molecules per unit cell. Combined with the anomalous dispersion[68] of the diffraction measurement, the absolute configuration of **39** was inferred to be (*S*). Alternatively, we could accommodate the X-ray data of **39** – albeit not quite as well – assuming that it crystallized in the centrosymmetric space group $P\bar{1}$. This would have implied that **39** formed a true racemate, i.e., that **39** was racemic. We discarded that interpretation because the X-rayed crystals revealed a 93.2% *ee* when we subjected them to chiral HPLC (for more details, see Supporting Information).

[67] CCDC-883615 (for **39**) and -883616 (for *cis*-**44**) contain the crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre* via www.ccdc.cam.ac.uk/data_request/cif.

[68] The presence of a heavy atom – like bromine in **39** – gives rise to an anomalous X-ray diffraction, and thereby allows the determination of the absolute configuration of an optically active sample, see: J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature* **1951**, *168*, 271–272.

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[72] For the earliest report – to the best of our knowledge – in which *tert*-butyl alcohol is used as a co-solvent for Birch reductions, see: H. I. Drydes Jr, G. M. Webber, R. R. Burtner, J. A. Cella, *J. Org. Chem.* **1961**, *26*, 3237–3245.

[73] These dyes are O_3-sensitive, and so are capable of scavenging O_3 when it is faced with less reactive C=C bonds. When another C=C bond is reactive enough to react with O_3 faster than the dye does, selective ozonolyses are feasible: T. Veysoglu, L. A. Mitscher, J. K. Swayze, *Synthesis* **1980**, 807–810.

[74] The enol tautomer of dihydropyranone-containing β-keto ester *anhydro*-**4** was admixed in a 9:91 ratio in $CDCl_3$. It was recognized by the olefin singlet at δ = 5.00 ppm and enol singlet at δ = 12.03 ppm.

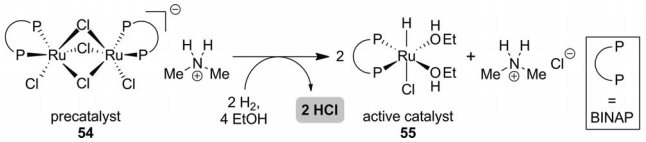
[75] In Scheme 7, the positional numbers of spiroketal ketones **43** and *epi*-**43** use the numbering of rimocidin (**1a**). In contrast, the Exp. Section features positional numbers in accordance with the IUPAC nomenclature.

[76] According to L. DiMichele, S. A. King, A. W. Douglas, *Tetrahedron: Asymmetry* **2003**, *14*, 3427–3430, $Et_2NH_2^+$ [RuCl(*S*)-(BINAP)]$_2$(μ-Cl)$_3^-$ is the structure of a catalyst commonly referred to as "[$RuCl_2$(*S*)-(BINAP)]$_2$·NEt_3". Accordingly, we write $Me_2NH_2^+$ [RuCl(*S*)-(BINAP)]$_2$(μ-Cl)$_3^-$.

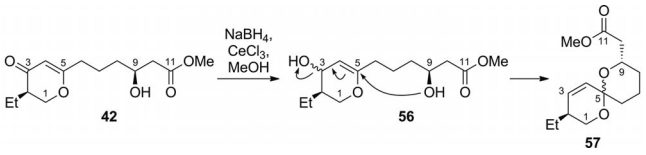
[77] An *S* configuration was expected for the newly formed stereocenter in β-hydroxy ester **42**, since (*S*)-BINAP-based Noyori hydrogenations of β-keto esters always deliver this configuration.[70]

[78] Usually Noyori hydrogenations proceed with 90% yield or more.[70]

[79] We suppose that pyranone-containing β-hydroxy ester **42** cyclizes to give spiroketals **43** and *epi*-**43** by an HCl-catalyzed intramolecular Michael addition. HCl is a stoichiometric by-product of the formation of active Ru^{II} complex **55** from its precursor **54**, see ref.[70b] Accordingly, 0.5 mol-% **54** in the reaction mixture should have given 1 mol-% **55** + 1 mol-% HCl.



[80] A Luche reduction of pyranone-containing β-hydroxy ester **42** delivered a 80:20 mixture of epimeric but unassigned alcohols **56** and *epi*-**56**:



This was judged from the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of the product mixture, specifically by determining the integral ratio of the resonances appearing at δ = 4.81 (d, $J_{4,3}$ = 5.7 Hz, 1 H, 4-H, **56**) and 4.67 (d, $J_{4,3}$ = 4.7 Hz, 1 H, 4-H, *epi*-**56**) ppm. Even under neutral conditions, this mixture decomposed within a few hours to form what we assume to be spiroketal **57**. While the ^{1}H NMR signals (300 MHz, $CDCl_3$) of the decomposition product(s) were severely overlapping, the olefin resonances δ = 5.58 (dd, $J_{3,4}$ = 10.0, $J_{3,2}$ = 2.6 Hz, 1 H, 3-H) and 5.81 (d, $J_{4,3}$ = 10.1 Hz, 1 H, 4-H) ppm appeared to be assignable as indicated.

[81] For $ZnBr_2$-induced spiroketal formation from a 1,9-dihydroxyalkan-5-one in CH_2Cl_2, see: M. M. Claffey, C. J. Hayes, C. H. Heathcock, *J. Org. Chem.* **1999**, *64*, 8267–8274.

[82] For spiroketal formation from a 1,9-dihydroxyalkan-5-one in the presence of THF/CH_3CN/HCl (12 M aq.) (10:10:1), see: J. L. Hubbs, C. H. Heatrock, *J. Am. Chem. Soc.* **2003**, *125*, 12836–12843.

[83] ^{1}H NMR spectra of a 80:20-mixture of **43** and *epi*-**43** recorded at 300 vs. 313 vs. 333 K were identical. This observation is consistent with the interpretation that *epi*-**43** is a diastereomer of **43**, and not a conformer.

[84] In Scheme 8, the positional numbers of the spiroketal alcohols *trans*-**44**, *cis*-**44**, and *cis*-*epi*-**44** use the numbering of rimocidin (**1a**). In contrast, the Exp. Section features positional numbers in accordance with IUPAC nomenclature.

[85] M. T. Crimmins, W. G. Hollis Jr., D. M. Bankaitis-Davis, *Tetrahedron Lett.* **1987**, *28*, 3651–3654.

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Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031; c) J. D. White, R. Hanselmann, R. W. Jackson, W. J. Porter, Y. Ohba, T. Tiller, S. Wang, *J. Org. Chem.* **2001**, *66*, 5217–5231.

[87] a) Y.-b. Zhao, N. E. Pratt, M. J. Heeg, K. F. Albizati, *J. Org. Chem.* **1993**, *58*, 1300–1301; b) Y.-b. Zhao, K. F. Albizati, *Tetrahedron Lett.* **1993**, *34*, 575–578.

[88] For the reduction of a 1,7-dioxaspiro[5.5]undecan-4-one analogous to substrate **43** using $NaBH_4/CeCl_3$, see ref.[82]

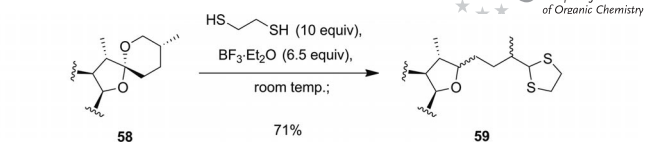
[89] The coupling constant $J_{3,4}$ in spiroketal-alcohol *trans*-**44** could not be read from the 3-H resonance since the latter was overlapping the resonance of 1-H^{eq}. However, $J_{4ax,3}$ = 11.1 Hz could be identified from the resonance of 4-H^{ax} ($\delta_{in\ C6D6}$ = 1.27 ppm, dd, J_{gem} = 12.5, $J_{4ax,3}$ = 11.1 Hz), and the 12.5 Hz splitting was atributed to J_{gem} because it also appeared in the 4-H^{eq} resonance ($\delta_{in\ C6D6}$ = 1.92 ppm, dd, J_{gem} = 12.4, $J_{4eq,3}$ = 4.9 Hz).[84]

[90] These *J* values were extracted from the hyperfine splitting of the resonances of 1-H^{ax} at δ = 3.90 (ddd, J_{gem} = 11.6, $J_{1ax,2}$ = 2.4, $^4J_{1ax,3}$ = 1.3 Hz) ppm, and 1-H^{eq} at δ = 3.64 (dd, J_{gem} = 11.6, $J_{1eq,2}$ = 1.7 Hz) ppm. The resonance of 2-H was a dddddd at δ = 1.29–1.36 ppm; due to overlapping resonances by 4-H^{ax} (*trans*-**44**) and 2-H (*cis*-*epi*-**44**), we could not extract $^3J_{2,1ax}$, $^3J_{2,1eq}$, $^3J_{2,3ax}$, $^3J_{2,1'A}$, $^3J_{2,1'B}$, or $^4J_{2,4eq}$.

[91] These *J* values were extracted from the hyperfine splitting of the resonances of 4-H^{ax} at δ = 1.41 (ddd, J_{gem} = 12.8, $J_{4ax,3}$ = 11.7 Hz, 1 H) ppm, and 4-H^{eq} at δ = 1.68 (ddd, J_{gem} = 12.7, $J_{1eq,2}$ = 5.0, $^4J_{1eq,3}$ = 1.0 Hz, 1 H) ppm. The resonance of 3-H was a ddddd at δ = 4.13–4.20 ppm; due to superimposing resonances by 9-H (*trans*-**44**) and 9-H (*cis*-*epi*-**44**), we could not decipher $^3J_{3,2eq}$, $^3J_{3,3\text{-}OH}$, $^3J_{3,4ax}$, $^3J_{3,4eq}$ or $^4J_{3,1ax}$.

[92] Procedure: R. E. Ireland, J. P. Daub, *J. Org. Chem.* **1983**, *48*, 1303–1312.

[93] It is known that spiroketals and ethane-1,2-dithiol may undergo side-reactions as well as the transketalization to give a 2,2-disubstituted 1,3-dithiolane, because at "higher temperatures" such mixtures are suceptible to oxidation-state changes through formal [1,*n*] hydride shifts. For instance, sapogenins, which contain substructure **58** and ethane-1,2-dithiol (10 equiv.)/$BF_3{\cdot}Et_2O$ (6.5 equiv.) furnished tetrahydrofuran derivative **59** in 71% yield, even at room temp.; see: C. Djerassi, O. Halpern, G. R. Pettit, G. H. Thomas, *J. Org. Chem.* **1959**, *24*, 1–6.



[94] For the method, see: E. J. Corey, H. Cho, C. Rücker, D. H. Hua, *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

[95] TBSCl and imidazole in DMF (see E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191) were too unreactive to silylate the sterically hindered OH group at C^3.

[96] For example, $BF_3{\cdot}Et_2O$ was used for the cleavage of TBS to their respective alcohols, see: a) D. R. Kelly, S. M. Roberts, R. F. Newton, *Synth. Commun.* **1979**, *9*, 295–299; b) S. A. King, B. Pipik, A. S. Thompson, A. DeCamp, T. R. Verhoeven, *Tetrahedron Lett.* **1995**, *36*, 4563–4566; c) for the use of Lewis acids for the cleavage of silyl ethers, see: A. D. Cort, *Synth. Commun.* **1990**, *20*, 757–760.

[97] This method was described for the conversion of an aldehyde into a 1,3-dithiane in the presence of two TBS ethers, see: F. Eustache, P. I. Dalko, J. Cossy, *J. Org. Chem.* **2003**, *68*, 9994–10002.

[98] Method: Y. Kamitori, M. Hojo, R. Masuda, T. Kimura, T. Yoshida, *J. Org. Chem.* **1986**, *51*, 1427–1431.

[99] Method: D. A. Evans, L. K. Truesdale, K. G. Grimm, S. L. Nesbitt, *J. Am. Chem. Soc.* **1977**, *99*, 5009–5017.

[100] Method: L. F. Tietze, B. Weigand, C. Wulff, *Synthesis* **2000**, 69–71.

[101] For the preparation and full characterization of 5-methoxyindane (**22**), see: H. O. House, C. J. Blankley, *J. Org. Chem.* **1968**, *33*, 53–60.

[102] For the elemental analysis of 5-iodo-6-methoxyindane (**23**), see: a) C. A. Panetta, S. C. Bunce, *J. Org. Chem.* **1961**, *26*, 4859–4866. For ^1H NMR spectroscopic data for 5-iodo-6-methoxyindane (**23**), see: b) A. Ali, Z. Lu, P. J. Sinclair, Y.-H. Chen, C. J. Smith, H. Li, C. F. Thompson, *U.S. Patent*, 7910592, **2011**. (http://appft1.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PG01&p=1&u=/netahtml/PTO/srchnum.html&r=1&f=G&l=50&s1=20090042892.PGNR).

[103] Dry HCl gas was generated by addition of concd. aq. HCl to $CaCl_2$; see: F. J. Arnáiz, *J. Chem. Educ.* **1995**, *72*, 1139–1139.

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