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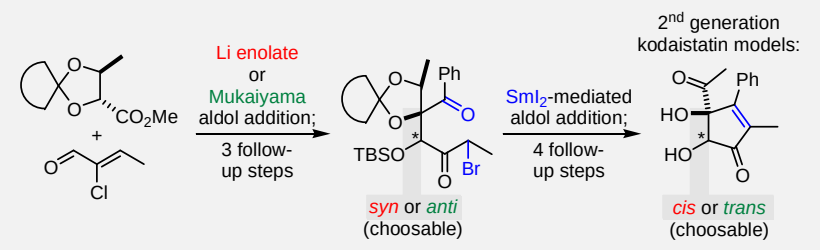

Aldols are the key: We determined the relative configuration in the diol moiety of the natural product kodaistatin A, an anti-diabetic lead, being *trans*. This follows from NMR comparisons with *cis*,*trans*-isomeric models, which we synthesized in 11-12 steps. Early-stage aldolizations ensured stereocomplementarity by using either a lithium enolate or an enol silane. Cyclopentanone formations by intra-molecular aldol additions of a samarium enolates ensued.

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A New Approach to Models of the 4,5-Dihydroxycyclopentenone Core of the Kodaistatins A–D. Elucidation of the Diol Configuration in Kodaistatin A

David Peter[a] and Reinhard Brückner*[a]

Dedicated to Professor Lutz F. Tietze at the occasion of his 75th birthday

Abstract: *The kodaistatins are natural products from* Aspergillus terreus*. Being strongly anti-diabetic they hold some promise of a novel diabetes cure. However, considerations of that kind face two drawbacks. (1) The kodaistatins contain a heavily substituted pulvinone/cyclopentenone combination. (2) The kodaistatins are 1,2-diols, whose 3D structure have not been assigned yet. However, we can exclude two of the four possible stereostructures. We conclude that kodaistatin A is a* trans*-, not a* cis*-diol, from NMR comparisons with a pair of* cis,trans*-isomeric kodaistatin models, which we synthesized in 11 and 12 steps, respectively. The stereocenters of the diol moiety arose from stereocomplementary, highly diastereoselective aldol additions of a lithium enolate or the corresponding silyl ketene acetal. The cyclopentenone moieties stemmed from intramolecular aldol additions and ensuing dehydrations. The requisite enolates were obtained by the reduction of α-bromoketones with samarium diiodide.*

Diabetes mellitus has become a major health threat. It affects 415 million people around the world.[1] Patients suffering from type 2 diabetes exhibit reduced insulin activity.[2] As a consequence, gluconeogenesis in their livers is increased.[3] This leads to an excessive release of glucose into the blood stream.[3] Drugs promoting lower glucose concentrations there might alleviate the resulting disorders. The natural products kodaistatin A–D (**1**–**4**; Figure 1a) are potential leads for such a medication.[4,5] They inhibit the transport protein glucose-6-phosphate T1 translocase in the nM range. This protein is indispensable for transporting glucose-6-phosphate from the cytoplasm into the endoplasmatic reticulum of hepatocytes. This is the site of the last step both of gluconeogenesis and glycogenolysis, the conversion glucose-6-phosphate → glucose + P_i.[2]

The kodaistatins A–D (**1**–**4**; Figure 1a) were isolated by a group from Hoechst Marion Roussel Deutschland GmbH (now Sanofi-Aventis) from the soil mold *Aspergillus terreus*.[4,5] They comprise a pulvinone unit, a dienone side-chain with one stereocenter, and a dihydroxycyclopentenone core with two stereocenters. Originally, all stereocenters were left unassigned. Kaczybura and Wüster from our group determined the *S*-configuration of the side-chain stereocenter of kodaistatin A (**1**).[6] They ozonolyzed the natural product, worked up reductively, and identified the resulting alcohol *S*-**5** (Figure 1b) by chiral GLC. Wüster implemented this finding in a synthesis of the "first generation kodaistatin model" *cis*-**6** (Figure 1b).[6] Its *cis*-dihydroxycyclopentenone moiety displayed ^{13}C NMR resonances, which hinted at kodaistatin A being *trans*-dihydroxylated. Unfortunately, this inference was negative evidence because Wüster´s route failed to provide a "correctly" configured model *trans*-**6** besides the "incorrectly" configured *cis*-isomer. Here we make up for that deficit by synthesizing a "second generation kodaistatin model" **7** (Figure 1c) both as the *cis*- and the *trans*-isomer. This succeeded by a completely different strategy.

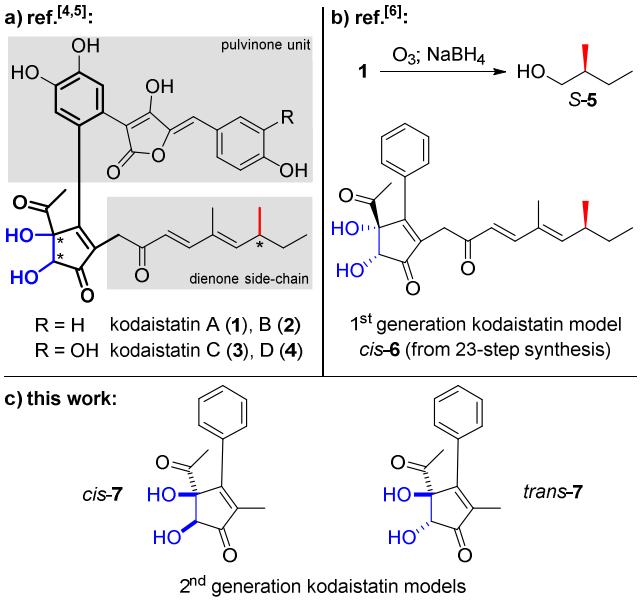

Figure 1. a) Structures of the kodaistatins A–D (**1**–**4**).[4,5] b) Degradation product *S*-**5**[6] obtained from the side-chain of kodaistatin A (**1**) by ozonolyis and $NaBH_4$ reduction;[6] our 1st generation kodaistatin model *cis*-**6**.[6] c) The 2nd generation kodaistatin model targets *cis*- and *trans*-**7** of the present study.[7]

Our route to the second generation kodaistatin models *cis*- and *trans*-**7** should entail a cyclopentenone-forming Wittig reaction. It is sketched as the transformation **8** → **7** in our retrosynthetic analysis (Scheme 1, at left). Such ring-closures are known.[8] The phosphonium salt **8** should result from tributyl- or triphenylphosphane and an α-haloketone **9** (Hal = Cl, Br). We deemed to obtain the latter by a brominating hydrolysis[9] of the chloroolefin

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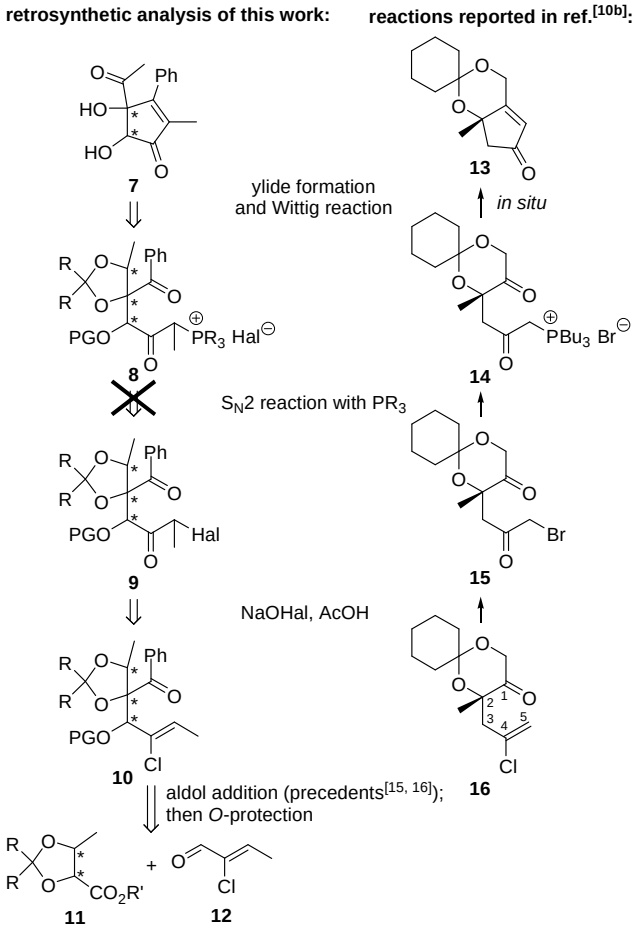
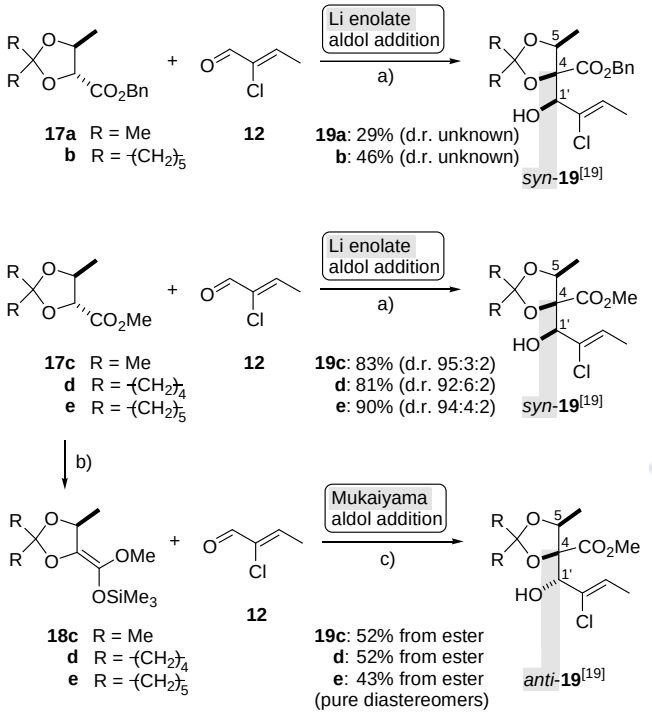


Scheme 1. Left: Joint retrosynthesic analysis of the *cis*- and the *trans*-isomer of the 2nd generation kodaistatin model **7**. Right: A related 4-chloropent-4-en-1-one → cyclopentenone transformation by Stoltz et al.[10b] – Eventually, we could not progress from compound **9** (Hal = Br) to phosphonium salts **8**. This reduces the overlap with Stoltz´ route to a single step, i. e., the brominating hydrolysis[9] **10**→**9**. It is akin to **16**→**15**.

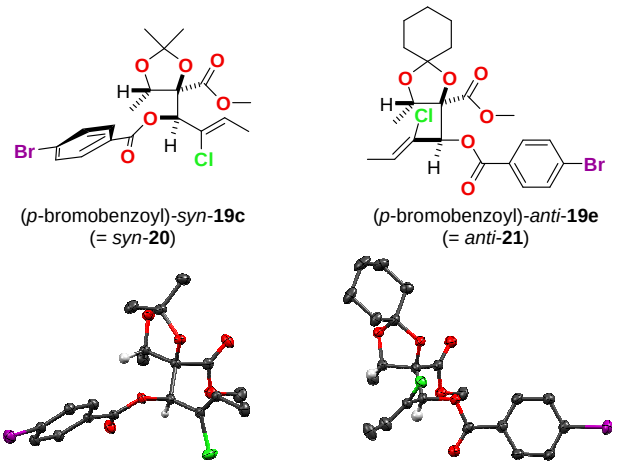
10. Related transformations are known.[10] Up to this point, our retrosynthetic simplification **7** ⇒ **8** ⇒ **9** ⇒ **10** parallels a 3-step route of Stoltz et al. to the cyclopentenone **13**[10b] (Scheme 1, at right). They treated the chloroolefin **16** with aqueous NaOBr in acetic acid, allowed the crude bromoketone **15** to react with PBu_3, and cyclized the resulting phosphonium salt **14** in situ by adding base. This gave rise to *their* cyclopentenone (**13**). We were not sure whether our envisaged sequence chloroolefin (**10**) → bromoketone (**9**) → phosphonium salt (**8**) → [ylide (in situ) →] cyclopentenone (symbolized by **7**) would proceed as smoothly, too. This is because in each step our reaction center would be more hindered than theirs – by an extra methyl group.[11]

Finishing the retrosynthetic analysis of Scheme 1, we realized that the chloroolefin **10** represents a protected β-hydroxyketone. It therefore looked accessible by an aldol addition.[12] The required aldehyde was (*Z*)-2-chlorobut-2-enal (**12**), a known compound.[13] Pertinent enolates should stem from dioxolane-4-esters of generic structure **11**.[14] For the present study we used those as racemic mixtures. Aldol additions of related dioxolane-4-esters to achiral electrophiles revealed a chance of steering their simple diastereoselectivity by moving from lithium enolate[15] to Mukaiyama-type aldol additions.[16] However, only very few of the reported reactions exhibited high simple and induced diastereoselectivities[17] simultaneously.[16]



Scheme 2. Aldol additions of esters **17a**-**e** via their lithium enolates (top and middle) or the derived silyl ketene acetals **18c**-**e** (bottom). a) LDA, THF, −78°C 15−60 min; **12**, −78°C, 3–4 h. b) LDA, THF, −78°C, 30 min; Me_3SiCl, −78°C → RT (within 4 h); product not purified. c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C → RT (within 5 h).

As explained above we needed to add an **11**-derived *C*-nucleophile to (*Z*)-2-chlorobut-2-enal (**12**[13]) with the highest possible simple and induced diastereoselectivity. **11**-based *C*-nucleophiles, which would react with the opposite simple diastereoselectivity should exhibit high induced diastereoselectivity, too. Scheme 2 shows how we accomplished both goals. We deprotonated the benzyl esters **17a** (acetonide-protected) and **b** (cyclohexylidene-protected), the corresponding methyl esters **17c** and **e**, and their analog **17d** (cyclopentylidene-protected) with LDA at −78°C in THF.[18] The resulting enolates were combined with (*Z*)-2-chlorobut-2-enal (**12**[13]). This delivered the aldols **19a**-

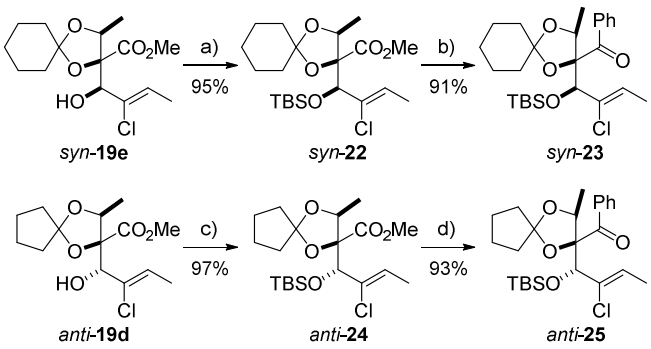


(*p*-bromobenzoyl)-*syn*-**19c** (= *syn*-**20**)

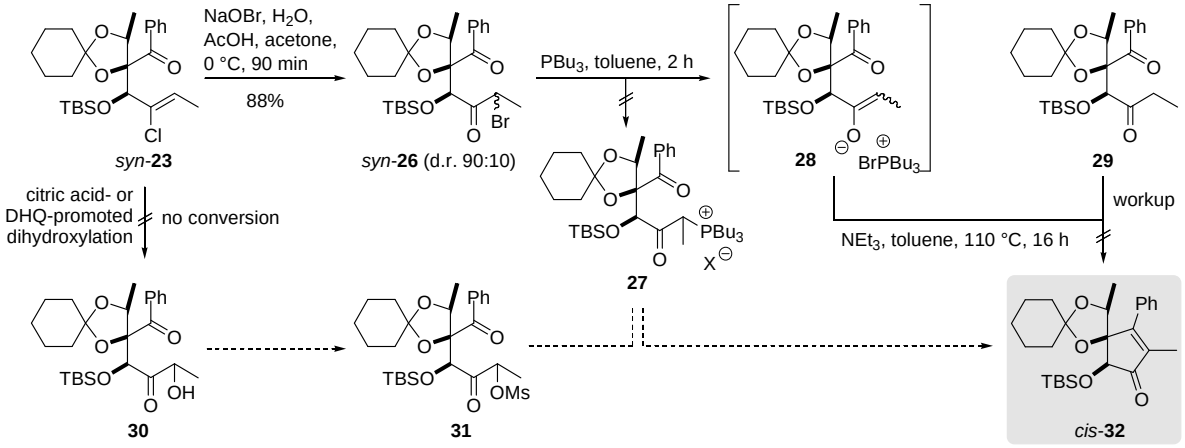
(*p*-bromobenzoyl)-*anti*-**19e** (= *anti*-**21**)

Figure 2. Crystal structures of esters *syn*-**20**[21] and *anti*-**21**[24] derived from the aldols *syn*-**19c** (yield: 72%) and *anti*-**19e** (yield: 78%), respectively, as configurational proofs. Ellipsoids shown at 50% probability; black: C, red: O, gray: H (omitted for clarity unless bound to a stereocenter), green: Cl, purple: Br.

e overwhelmingly ^{5,4}*trans*,$^{4,1'}$*syn*-configured.[19-22] Yields were lower starting from the benzyl (→ **19a**: 29%; **b**: 46%) than from the methyl esters (→ **19c**-**e**: 81-90%).[23] The *syn*-preference complies with precedence.[15] For obtaining the diastereomeric aldols *anti*-**19** we converted the methyl esters **17c**-**e** into the silyl ketene acetals **18c**-**e**. $BF_3{\cdot}OEt_2$ let them undergo Mukaiyama aldol additions to (*Z*)-2-chlorobut-2-enal (**12**[13]). In line with earlier observations[16] this occurred ^{5,4}*trans*- and $^{4,1'}$*anti*-selectively[19,20] and provided the aldols **19c**-**e** diastereopure.[24] All assignments were based on X-ray analyses (Figure 2) and NMR analogy.[21,24] We then silylated the OH group of the cyclohexylidene-protected aldol *syn*-**19e** and the cyclopentylidene-protected aldol *anti*-**19d** (Scheme 3). Next we elaborated the CO_2Me groups of the resulting ethers *syn*-**22** and *anti*-**24** into phenyl ketone. Surprisingly, the Weinreb amide derived from *syn*-**22** did not react with PhLi at −78°C or with PhMgBr at +60°C.[25] In contrast, PhLi reacted with the esters *syn*-**22** and *anti*-**24** already at −78°C. This gave the respective phenyl ketones *syn*-**23** and *anti*-**25** in 86% and 90% yield, respectively, over the 2 steps.[26] The corresponding tertiaryl alcohols were not observed.[27]

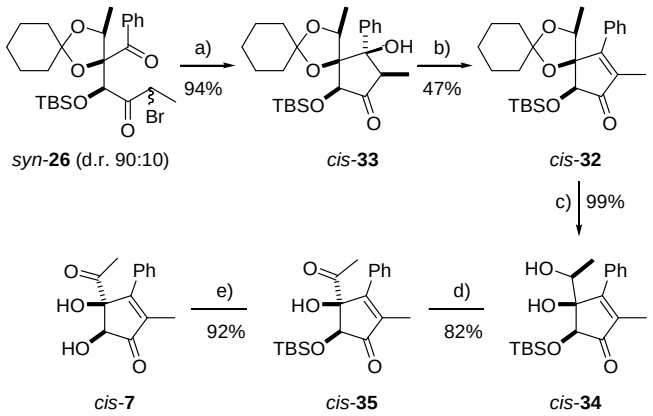


Scheme 3. Preparation of silyl-protected phenyl ketones. a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C → RT, 18 h; 95%. b) PhLi, THF, −78°C, 1 h; 91%. c) Same as (a); 97%. d) Same as (b); 93%.



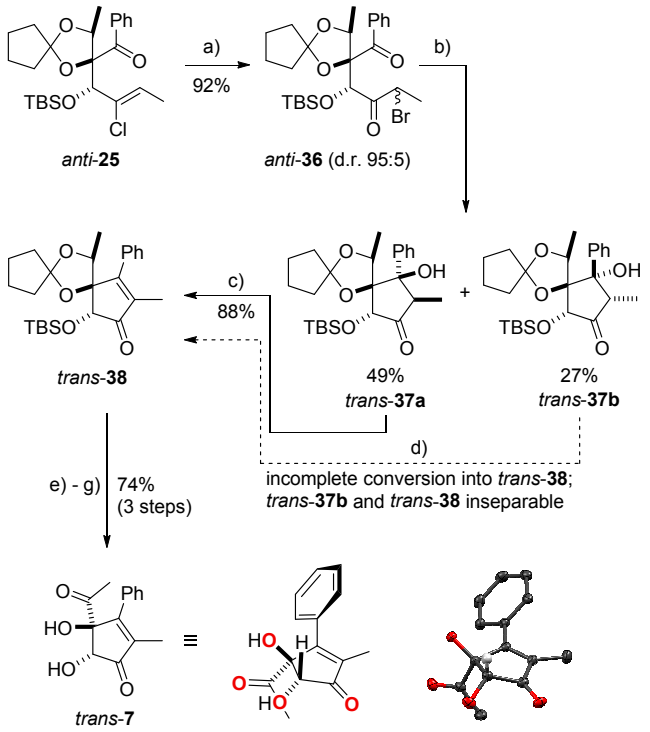
Scheme 4. Attempted conversions of the phenyl ketone *syn*-**23** into the cyclopentenenone *cis*-**32** via the bromoketone *syn*-**26** or the corresponding mesylate **31**.

The chloroolefin moiety of compound *syn*-**23** was hydrolyzed oxidatively with NaOBr in a mixture of aqueous acetone and AcOH (Scheme 4). The bromoketone *syn*-**26** was isolated as a 90:10 mixture of diastereomers (88% yield). It was treated with PBu_3 at room temp. for 2 h; we then added NEt_3 and heated at 110°C, establishing the conditions of Stoltz' conversion of the bromoketone **15** into the cyclopentenone **13**[10b] (Scheme 1). Unfortunately, the greater steric hindrance of bromoketone *syn*-**26** let PBu_3 attack at Br (→ phosphonium enolate **28**) rather than at C. This changed the chemoselectivity just like when moving from an Arbusov to a Perkow reaction. Protic workup gave the debromoketone **29** (68%). We hoped to circumvent this obstacle with the (mesyloxy)ketone **31** as a non-reducible alkylant. However, its putative precursor, the alcohol **30**, proved inaccessible by exposing the chloroolefin *syn*-**23** to several dihydroxylation cocktails.[28]



Scheme 5. Finishing our 2nd generation kodaistatin model *cis*-**7**. a) SmI_2, THF, −78°C → RT (within 2 h); 94%. b) Burgess reagent, toluene, 100°C, 12 h; 47% (74% accounting for 37% recovered *cis*-**33**). c) CF_3CO_2H, H_2O, CH_2Cl_2, RT, 1 h; 99%. d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C → −45°C (within 1 h); NEt_3, −45°C → RT (within 2 h); 82%. e) HCl, MeOH, RT, 18 h; 92%.

Scheme 5 shows that we got around that hurdle by engaging the bromoketone *syn*-**26** in an SmI_2-mediated cyclization.[29] It represents a Reformatsky reaction or the aldol addition of an Sm(III) enolate (if so, it is a far better nucleophile than the phosphonium enolate **28**; cf. Scheme 4).[30] The hydroxycyclopentanone *cis*-**33** resulted diastereopure[31] in 94% yield. It was dehydrated with the Burgess reagent[32] giving the cyclopentenone *cis*-**32** in 47% yield (after separation from 37% recovered starting material). Reaching the 1,2-diol *cis*-**7**, our first 2nd generation kodaistatin model, required 3 more steps: acetal cleavage to the diol *cis*-**34** (99%); Swern oxidation to the (*tert*-hydroxy)ketone *cis*-**35** (82%); desilylation (92%).



Scheme 6. Completion of the synthesis of our second kodaistatin model *trans*-**7** [crystal structure (ref.[35]) with ellipsoids at 50% probability; black: C, red: O, gray: H (omitted for clarity unless bound to a stereocenter)]. a) $Ca(OBr)_2$ in H_2O, AcOH, CH_3CN/CH_2Cl_2, 0°C, 6 h; 92%. b) SmI_2, THF, −78°C → −10°C (within 4 h); 49% *trans*-**37a** + 27% *trans*-**37b** (separable). c) Burgess reagent, toluene, 100°C, 17 h; 88% (97% accounting for 6% recovered *trans*-**37a**). d) Burgess reagent, toluene, 100°C, 18 h; 29% (inseparable from 58% unchanged *trans*-**37b**). e) CF_3CO_2H, H_2O, CH_2Cl_2, 0°C, 2 h; 89%. f) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C → −60°C (in 1 h); NEt_3, −78°C → RT (in 3 h); 95%. g) HCl, MeOH, RT, 3.5 d; 88%.

Our second 2nd generation kodaistatin model, the 1,2-diol *trans*-**7**, was synthesized from the aldol *anti*-**25** (Scheme 6) essentially like we had gained its isomer *cis*-**7** from the aldol *syn*-**23** (Scheme 4-5). One difference was that the brominating hydrolysis[9] of the chloroolefin *anti*-**25** required using $Ca(OBr)_2$, which was more reactive than NaOBr. The bromoketone *anti*-**36** resulted as a 95:5 mixture of diastereomers (92%). Its SmI_2-induced cyclization[29] was non-diastereoselective. The hydroxycyclopentanones *trans*-**37a**[33] and *trans*-**37b**[34] resulted in 49% and 27% yield, respectively, after separation by column chromatography. Treatment with Burgess' reagent[32] provided the cyclopentenone *trans*-**38**. It formed in 88% yield from *trans*-**37a** but was inseparably contaminated with unchanged substrate starting from *trans*-**37b**. Acetal cleavage, Swern oxidation, and desilylation completed the synthesis of *trans*-**7**.

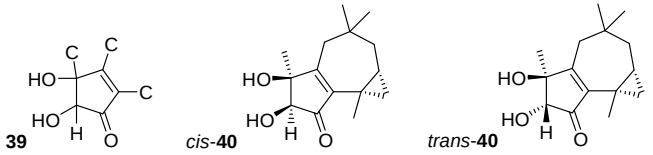


Figure 3. The uniquely substituted cyclopentenone core **39** targeted in this study.

The 3D structure of compound *trans*-**7** was ascertained by X-ray crystallography.[35] This and the similarity of the ^{13}C-NMR shifts of this compound and kodaistatin A (Table 1) support the correctness of the connectivity assigned[5] to the latter. This is reassuring considering the uniqueness of the dihydroxycyclopentenone motif **39** (Figure 3). In isolated rings it is non-existent except in compounds **1**-**4**, *cis*-**6**, *cis*- and *trans*-**7**); fused to an aliphatic ring it occurs only in compounds *cis*- and *trans*-**40**.[36]
Table 1 juxtaposes ^{13}C NMR shifts of the acetylcyclopentenone motifs of our 1st generation model *cis*-**6**,[6] 2nd generation models *cis*- and *trans*-**7**, and kodaistatin A (**1**). *Cis*-**6** having shown distinctive deviations,[6] it was no surprise retrieving them in compound *cis*-**7**, no matter the different side-chains. Still, this renewed negative evidence ("kodaistatin A should be configured **oppositely than *cis*-7**") fades besides the positive one: The ^{13}C NMR shift devations of our model *trans*-**7** vs. the natural product are as small as ≤2 ppm. This allows to deduce that kodaistatin A is configured **the same as *trans*-7**. The common origin of the kodaistatins A-D suggests they **share this *trans*-diol moiety**.
In conclusion, we synthesized a pair of *cis*,*trans*-isomeric models of the kodaistatin cyclopentenone core, beginning with diastereodivergent *and* highly stereocontrolled aldol additions. It is noteworthy that the inducing stereocenter was in a motif, which, overall, served as a latent acetyl group. Hence, this stereocenter was given up in the end. Our routes comprised 11 steps (→ *cis*-**7**, 28% total yield) and 12 steps (→ *trans*-**7**, 11% total yield), respectively. Stoltz´ chloroolefin → acylphosphorane → enone strategy was inapplicable to the spiroannulated precursors of our hindered targets. Accordingly, we developed a high-yielding bypass through a brominating hydrolysis,[9] an Sm(II)-induced cyclization, and a dehydration. It should provide other densely functionalized cyclopentenones,[37] too. ^{13}C NMR comparisons of *cis*- and *trans*-**7** with kodaistatin A (**1**) revealed that the latter is a *trans*-1,2-diol.

Acknowledgements

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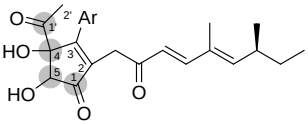
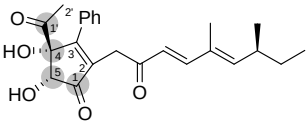
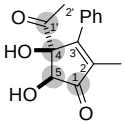
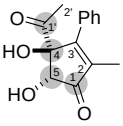
Keywords: aldol reaction • α-bromoketones • cyclopentenone • natural products • samarium enolate • structure elucidation

Table 1. ^{13}C NMR chemical shift comparisons (DMSO-d_6 solutions): kodaistatin A (**1**; 151 MHz),[5] model compounds *cis*-**6** (125.6 MHz; ref.[6]), *cis*-**7** (100.6 MHz; this study), and *trans*-**7** (100.6 MHz, this study). Structure-revealing shift differences Δδ (≡ $\delta_{in\ model} - \delta_{in\ 1}$) on grey background.

	 kodaistatin A (**1**[5])	 1st generation model (*cis*-**6**[6])		 *cis*-**7** (2nd generation models)		 *trans*-**7**	
C	δ/ppm	δ/ppm	Δδ/ppm	δ/ppm	Δδ/ppm	δ/ppm	Δδ/ppm
1	200.0	204.4	4.4	205.0	5.0	202.0	2.0
2	137.2	135.3	−1.9	136.4	−0.8	137.0	−0.2
3	161.6	165.3	3.7	162.7	1.1	160.5	−1.1
4	89.7	85.5	−4.2	85.1	−4.6	88.6	−1.1
5	84.5	75.5	−9.0	75.5	−9.0	82.9	−1.6
1'	207.7	210.9	3.2	211.3	3.6	207.8	0.1
2'	27.7	27.3	−0.4	27.1	−0. 6	26.9	−0.8

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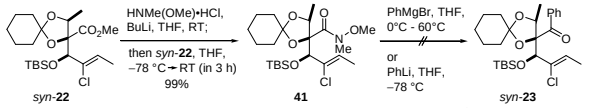
[7] Wedged bonds identify enantiomerically pure, straight bonds racemic compounds.
[8] a) B. M. Trost, D. P. Curran, *J. Am. Chem. Soc.* **1980**, *102*, 5699; b) C. Kuhn, J.-C. Florent, *Tetrahedron Letters* **1998**, *39*, 4247; c) T. Kanger, K. Raudla, R. Aav, A.-M. Müürisepp, T. Pehk, M. Lopp, *Synthesis* **2005**, 3147; e) T. Werner, M. Hoffmann, S. Deshmukh, *Eur. J. Org. Chem.* **2014**, 6630.
[9] The term "brominating hydrolysis" describes the overall change of substructure C(–Cl)C=C into substructure C(=O)C–C–Br. Formally (not mechanistically!), this transformation results from a hydrolysis C(–Cl)C=C → C(–OH)C=C, a tautomerization C(–OH)C=C → C(=O)C–C–H, and an α-bromination C(=O)C–C–H → C(=O)C–C–Br. Hence the designation.
[10] Selected precedents: a) C.-N. Hsiao, M. R. Leanna, L. Bhagavatula, E. de Lara, T. M. Zydowsky, B. W. Horrom, H. E. Morton, *Synthetic Comm.* **1990**, *20*, 3507: NBS, H_2O; b) R. A. Craig, J. L. Roizen, R. C. Smith, A. C. Jones, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5716: NaOBr, aq. AcOH; c) V. Pace, L. Castoldi, M. J. Hernáiz, A. R. Alcántara, W. Holzer, *Tetrahedron Lett.* **2013**, *54*, 4369: $Ca(OBr)_2$, aq. AcOH.
[11] As would turn out, our plan from Scheme 1 gave the α-bromoketone **9** alright but did not work out beyond (Scheme 4)
[12] Selected reviews: a) R. Mahrwald (Ed.), *Modern Methods in Stereoselective Aldol Reactions*, Wiley-VCH, Weinheim, New York, **2013**; b) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; *Angew. Chem.* **2013**, 9256; c) S. B. J. Kan, K. K. H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097; *Angew. Chem.* **2013**, 9267; d) J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109; *Angew. Chem.* **2013**, *125*, 9280.
[13] Prepared as described by L. Skattebøl, *J. Org. Chem.* **1966**, *31*, 1554.
[14] Exemplary preparation: Y. Yang, X. Fu, J. Chen, H. Zhai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9825; *Angew. Chem.* **2012**, *124*, 9963.
[15] Previous additions of Li enolates of type-**11** esters to achiral electrophiles: a) R. Naef, D. Seebach, *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 1030; *Angew. Chem.* **1981**, *93*, 1113; b) W. Ladner, *Chem. Ber*. **1983**, *116*, 3413; c) M. Pohmakotr, T. Junpirom, S. Popuang, P. Tuchinda, V. Reutrakul, *Tetrahedron Lett.* **2002**, *43*, 7385; c) M. S. M. Timmer, B. L. Stocker, P. H. Seeberger, *J. Org. Chem.* **2006**, *71*, 8294; d) E. Bette, A. Otto, T. Dräger, K. Merzweiler, N. Arnold, L. Wessjohann, B. Westermann, *Eur. J. Org. Chem.* **2015**, 2357; e) K. C. Nicolaou, Q. Cai, H. Sun, B. Qin, S. Zhu, *J. Am. Chem. Soc.* **2016**, *138*, 3118.
[16] Previous additions of silyl ketene acetals of type-**11** esters to achiral electrophiles: a) D. A. Evans, W. B. Trotter, J. C. Barrow, *Tetrahedron* **1997**, *53*, 8779; b) V. K. Aggarwal, S. J. Masters, H. Adams, S. E. Spey, G. R. Brown, A. J. Foubister, *J. Chem. Soc., Perkin Trans. 1* **1999**, 155; c) Y. Hayashi, M. Shoji, J. Yamaguchi, K. Sato, S. Yamaguchi, T. Mukaiyama, K. Sakai, Y. Asami, H. Kakeya, H. Osada, *J. Am. Chem. Soc.* **2002**, *124*, 12078.
[17] For an authoritative definition of these terms see Section 1.2.2.3 (pp. 53-55) of G. Helmchen *in* Houben-Weyl Methods of Organic Chemistry, Vol. E 21a (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart **1995**, pp. 1-74.
[18] Starting from crotonic acid or its methyl ester, we prepared the esters **17a**,**b** and **17c-e**, respectively, as detailed in the Supporting Information. Ester **17b** is new while **17a**,**c-e** were known: **a**: C. G. Boojamra, et al. (Gilead Sciences Inc.), US20110288053A1, **2011**; **c**: ref.[14]; **d**: W. R. Roush, R. A. Hartz, D. J. Gustin, *J. Am. Chem. Soc.* **1999**, *121*, 1990; **e**: J. H. Dodd, R. S. Garigipati, S. M. Weinreb, *J. Org. Chem.* **1982**, *47*, 4045.
[19] The stereodescriptor ^{5,4}*trans* refers to the orientation of the C^5–Me vs. C^4–$C^{1'}$ bond in the dioxolane ring of aldols **19a-e** {as imposed by induced diastereocontrol (cf. ref. [17])}. The stereodescriptor $^{4,1'}$*syn* – and $^{4,1'}$*anti* likewise – describes the orientation of the C^4–O vs. the $C^{1'}$–O bond {as imposed by simple diastereocontrol (cf. ref. [17])} if drawn as in Scheme 2 (cf. ref. [20]).
[20] An aldol addition subject to simple diastereocontrol creates two vicinal stereocenters. Their relative configurations were distinguished first as *erythro* and *threo* [a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920; b) W. A. Kleschick, C. T. Buse, C. H. Heathcock, , *J. Am. Chem. Soc.* **1977**, *99* 247; c) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127] and later as *syn* and *anti* [d) footnote 7 in S. Masamune, S. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557; *Angew. Chem.* **1980**, *92*, 573]. Our aldols **19** evade either nomenclature since a quaternary carbon separates the C–O from the C=O bond.
[21] Plausibly, the aldols *syn*-**19a**,**b** and **d**,**e** are configured like the aldol *syn*-**19c**, whose ^{5,4}*trans*,$^{4,1'}$*syn*-configuration was proved by an X-ray structural analysis of its bromobenzoate *syn*-**20** (Figure 2). The respective data are contained in CCDC 1508542 and available free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.
[22] The steric course of the underlying aldol addition is rationalized in the Supporting Information.
[23] Deprotonating the benzyl ester **17b** as before (LDA, THF, −78°C) but quenching it with aq. NH_4Cl 45 min later caused mainly decomposition.
[24] The aldol *anti*-**19c** should be identically configured as aldols *anti*-**19d** and **e**. The ^{5,4}*trans*,$^{4,1'}$*anti*-configuration of aldol *anti*-**19d** emerged from an X-ray structural analysis of the final product of the follow-up sequence *anti*-**19d** → *anti*-**24** → *anti*-**25** → *anti*-**36** → *trans*-**37a** → *trans*-**38** → *trans*-**7**. The ^{5,4}*trans*,$^{4,1'}$*anti*-configuration of aldol *anti*-**19e** was proved by X-raying its bromobenzoate *anti*-**21** (Figure 2). The crystallographic data are contained in CCDC 1508543 and available free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.
[25] Weinreb amide **41**, too poor an acylating agent for reacting with phenyl organometallics:



syn-**22** **41** *syn*-**23**

[26] Processing the CO_2Me-containing aldol adducts *anti*-**19c**,**e** of Scheme 2 analogously was less efficient – either until reaching the respective phenyl ketones or later on.
[27] This selectivity may have either of two reasons: (1) The ketones *syn*-**23** and *anti*-**25** are sterically too hindered for reacting with PhLi under the reaction

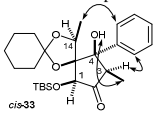
conditions. (2) The tetrahedral intermediate preceding the respective ketone is stabilized through chelation by the dioxolane ring until all PhLi is consumed. If the ketone forms after this point in time, it cannot encounter PhLi any more.

[28] In spite of that, a few chloroolefin → hydroxyketone conversions are known, e. g.: a) T. Satoh, K. Onda, K. Yamakawa, *J. Org. Chem.* **1991**, *56*, 4129; b) B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **2002**, *124*, 7376.

[29] Prior to our work SmI_2-induced inter- and intramolecular aldol additions of α-haloketones have been used by a) Z. Yang, D. Shannon, V.-L. Truong, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 4693; b) D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669; c) B. A. Sparling, R. M. Moslin, T. F. Jamison, *Org. Lett.* **2008**, *10*, 1291; d) E. J. Horn, J. S. Silverston, C. D. Vanderwal, *J. Org. Chem.* **2016**, *81*, 1819.

[30] A referee wondered whether a radical-mediated cyclization could represent yet another explanation. We do not think so because the bromoketone *syn*-**26** is reduced instantaneously when added, as a solution in THF, to 2.0 equiv. of SmI_2 at −78°C. As soon as the last drop was added, the reaction mixture turned from dark blue [Sm(II)] to yellow [Sm(III)]. Aqueous quenching of an aliquot of the reaction mixture a good hour later followed by TLC analysis indicated that the bromoketone had disappeared completely and the debrominated ketone **29** – plausibly formed from the Sm(III) enolate – and the aldol adduct *cis*-**33** were present instead. Thus (at least some) C–Br bond breakage occurs well ahead of C–C bond formation.

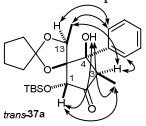
[31] The *cis*-orientation of the 3-Me, 4-OH, and 1-OTBS bond in compound *cis*-**33** follows from pertinent crosspeaks in the NOESY spectrum ($CDCl_3$):



cis-**33**

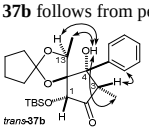
[32] a) Original report: G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744; summaries of applications: b) S. Santra, *Synlett* **2009**, 328, c) M. M. Heravi, T. Ahmadi, A. Fazeli, N. M. Kalkhorani, *Curr. Org. Synth.* **2015**, *12*, 328.

[33] The *cis*-orientation of the 3-Me, 4-OH, and 1-H bond in compound *trans*-**37a** follows from pertinent crosspeaks in the NOESY spectrum ($CDCl_3$):



trans-**37a**

[34] The *cis*-orientation of the 3-Me, 4-OH, and 1-OTBS bond in compound *trans*-**37b** follows from pertinent crosspeaks in the NOESY spectrum ($CDCl_3$):



trans-**37b**

[35] The crystallographic data of compound *trans*-**7** are contained in CCDC 1508544 and available free of charge from the *Cambridge Crystallographic Data Centre* via the link www.ccdc.cam.ac.uk/data_request/cif.

[36] G. B. Mitre, N. Kamiya, A. Bardón, Y. Asakawa, *J. Nat. Prod.* **2004**, *67*, 31-36).

[37] Reviews: a) S. P. Roche, D. J. Aitken, *Eur. J. Org. Chem.* **2010**, 5339; b) D. J. Aitken, H. Eijsberg, A. Frongi, J. Ollivier, P. P. Piras, *Synthesis* **2014**, *46*, 1; illustrative examples: c) ref.[15d]; d) Z. Zhou, D. D. Dixon, A. Jolit, M. A. Tius, *Chem. Eur. J.* **2016**, *22*, 15929.