

Enantio- and Diastereomerically Pure Decalins by Deslongchamps-Type Annulation of Dienolates Containing a Chiral Lactone Substituent

Thomas Tricotet^[a] and Reinhard Brückner*^[a]

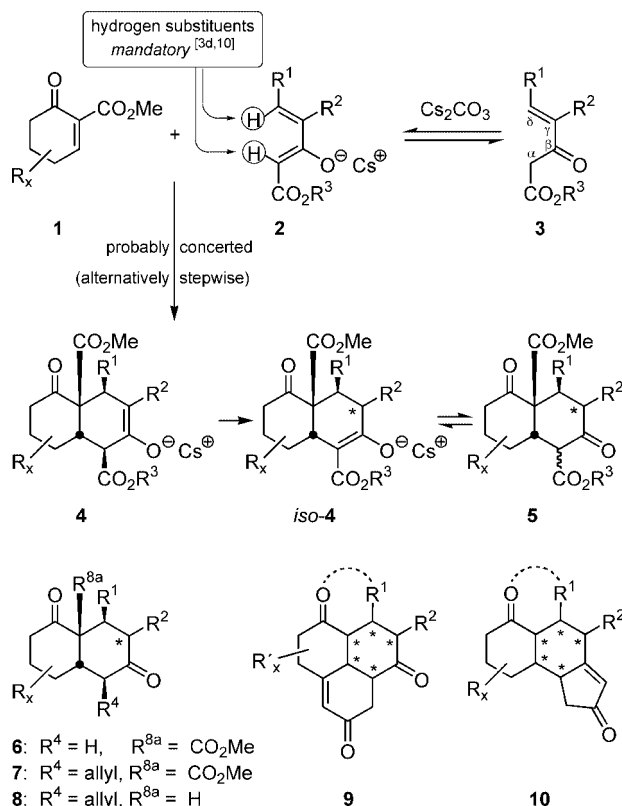
Keywords: 1,3-Asymmetric induction / Bicyclo[4.4.0]decane / De(alkoxycarbonylation) / Homoallyl anion equivalent / γ -Lactone fragmentation / Stereoselective synthesis / Tandem reaction

A conceptionally novel 1,3-asymmetric induction has been established. It controls the relative and absolute configuration of up to 5 stereocenters. They emerge from the anionic Diels–Alder reactions (“Deslongchamps annulations”) between oxocyclohexenecarboxylates **25**, **29** and dienolates **26**, **30**. The latter contain a γ -lactone. A $\text{Ph}_3\text{Si}-\text{CH}_2$ substituent therein controls the asymmetry of C–C bond formation with

$ds \approx 10:1$. Strangely, the preferred sense of attack of the dienophile is contrasteric. Cycloadduct **31** was processed by an unprecedented fluoride-induced ambient-temperature tandem fragmentation. It turned the lactone moiety into an allyl group and the β -oxo (trimethylsilyl)ethyl ester into a ketone. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

The stereocontrolled construction of decalins is required in many contexts. The dominating accesses are by Diels–Alder reactions – both inter- and intramolecular –, Robinson annulation – the most conspicuous variant of the latter being the Hajos–Parrish–Eder–Sauer–Wiechert reaction –, and cation- or radical-induced polyene cyclizations. Arguably, a runner-up strategy for establishing decalin scaffolds is the “anionic Diels–Alder reaction” developed by Deslongchamps et al. It is a cyclohexenone annulation highlighted in steroid synthesis repeatedly, the most recently accomplished target being ouabagenin.^[1] Usually, such “Deslongchamps annulations” consist of the addition of an ester-substituted dienolate **2** – generated from Cs_2CO_3 and a γ,δ -unsaturated β -oxo ester **3** or so-called Nazarov reagent^[2] – to an oxocyclohexenecarboxylate **1** (Scheme 1).^[3–6] These entities combine with the indicated simple diastereoselectivity^[7] and in pairs of properly designed reactants with good induced diastereoselectivities as well.^[8,9] Deslongchamps et al. obtained dioxodecalindicarboxylates **5** by such annulations and dioxodecalinmonocarboxylates **6** by the subsequent removal of the CO_2R^3 group. Such annulations **1** + **3** $\rightarrow$ **6** created up to four new stereocenters which matches the “stereogeneity” of Diels–Alder reactions.



Scheme 1. Deslongchamps annulations past ($\rightarrow$ **5**, **6**) and present ($\rightarrow$ **7**, **8**; ref.^[10] and this work). Polycyclic structures **9** and **10** to be derived from **8**. R_x stands for substituents introduced in the annulation step and R'_x for potentially modified substituents generated thereafter.

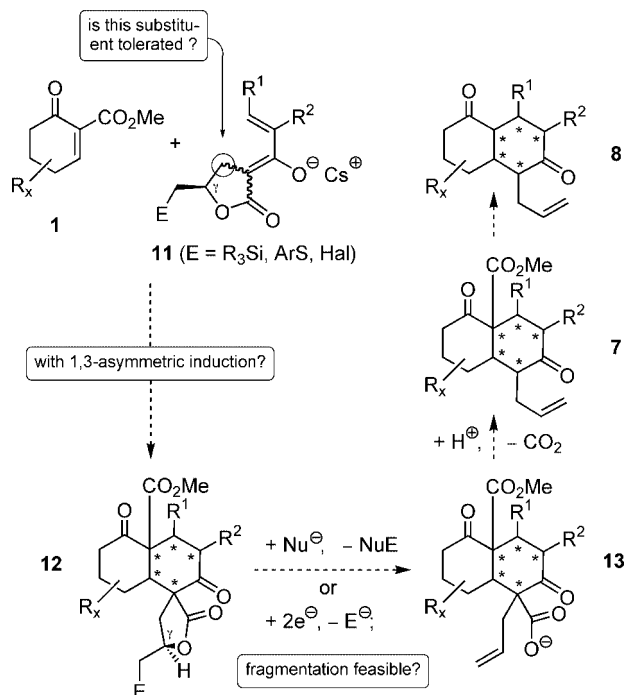
[a] Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität, Albertstr. 21, 79104 Freiburg, Germany
 Fax: +49-761-2036100
 E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de

Recently, we showed that dioxodecalindicarboxylates **5** (with $\text{CO}_2\text{R}^3 = \text{CO}_2\text{allyl}$) give dioxodecalinmonocarboxylates **7**^[10] by Tsuji's Pd-catalyzed decarboxylation/allylation.^[11] They and the readily derived decalindiones **8**^[10] display five new stereocenters. By this token their syntheses surpass the "stereogenicity" of a Diels–Alder reaction – a rare attribute in synthetic methodology! In the present study we were able to increase the hitherto unsatisfactory yields of **7** and thereby **8** two- to threefold. This was possible by incorporating lactone- rather than ester-substituted dienolates. At the same time a stereocenter in the lactone annulation products. Both features are important steps towards developing type-**8** decalindiones into precursors of tricyclic or tetracyclic structures **9** and **10**.^[12]

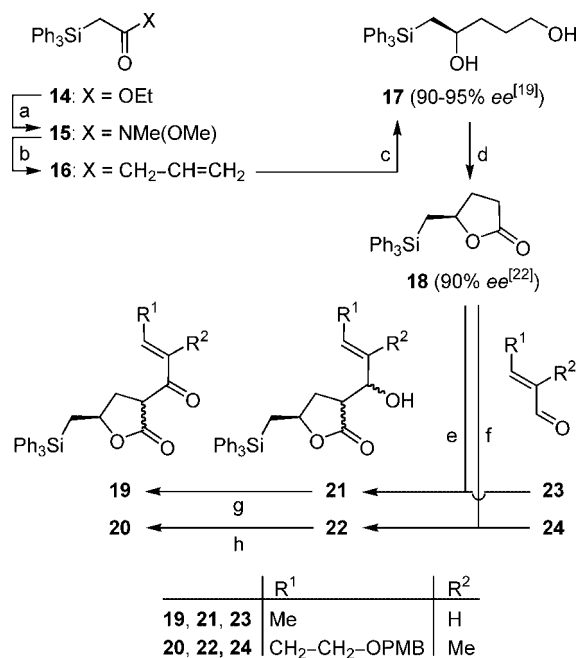
Results and Discussion

Our concept is shown in Scheme 2. It emerged from the finding^[13] that in Deslongchamps annulations γ -lactone-substituted dienolates tolerate a non-hydrogen substituent at one of the positions where ester-substituted dienolates **2** do not.^[10] Accordingly, we expected that dienolates **11** with a γ -chiral γ -lactone moiety would undergo Deslongchamps annulations, too. We hoped that the latter would proceed with considerable induced diastereoselectivity because of the ample precedence for such a selectivity in many other functionalizations of γ -chiral γ -lactone enolates.^[14] Finally, the partial sequence **12** $\rightarrow$ **13** $\rightarrow$ **7** of our strategy illustrates a previously unrecognized synthetic equivalence between appropriately substituted γ -lactones and a homoallyl group. This sequence was conceived of a nucleophilic (for $\text{E} = \text{R}_3\text{Si}$) or a reductive (for $\text{E} = \text{ArS}$, Hal) elimination (**12** $\rightarrow$ **13**) followed by protonation and in-situ decarboxylation (**13** $\rightarrow$ **7**). We were particularly attracted by the possibility of a fluoride-mediated elimination **12** $\rightarrow$ **13**.^[29] This was because of the prospect of cleaving simultaneously the acyclic ester moiety of intermediate **12** – provided the latter would be $\text{CO}_2\text{-CH}_2\text{-CH}_2\text{-SiR}_3$ and not, as shown in Scheme 2, CO_2Me .

Lactone-containing Nazarov reagents **19** and **20** were prepared starting from the readily available triphenylsilylated ethyl acetate **14**^[15] (Scheme 3). Hydroxylaminolysis gave Weinreb amide **15**.^[16] Then, allylmagnesium bromide was added, affording the unsaturated ketone **16** (83% overall yield for the 2 steps). We hydroborated its C=C bond intermolecularly and its C=O bond intramolecularly^[17] with Brown's (+)- Ipc_2BH .^[18] After treatment with NaOOH , this furnished 1,4-diol **17** in 75% yield and with an ee ,^[19] which varied somewhat (90–95%) from experiment to experiment. 1,3-Diols in which the 1-OH group is primary can be selectively oxidized with TEMPO (cat.)/ $\text{PhI}(\text{OAc})_2$ (stoichiom.) affording hydroxy aldehydes.^[20] Under identical conditions, 1,5-diols in which the 1-OH group is primary are oxidized via lactol intermediates giving δ -lactones.^[21] Analogously, we oxidized the primary OH group of a 90% ee specimen of 1,4-diol **17** selectively. This made



Scheme 2. Novel strategy for the asymmetric synthesis of type-**8** decalins and challenges faced in its realization.



Scheme 3. Synthesis of Nazarov reagents **19** and **20**. a) $\text{HNMe}(\text{OMe})\cdot\text{HCl}$ (1.5 equiv.), $i\text{PrMgCl}$ (3.0 equiv.), THF, -20°C , 15 min, **14**, -10°C , 10 min, 92%; b) AllylMgBr (1.5 equiv.), THF, -20°C , 15 min, -10°C , 15 min, 90%; c) (+)- Ipc_2BH (1.05 equiv.), THF, 0°C , 40 min, 4°C , 36 h, 0°C , NaOH (3 M), H_2O_2 (30%), room temp., 10 min, 73%; d) **17** (90% ee), $\text{PhI}(\text{OAc})_2$ (2.2 equiv.), TEMPO (10 mol-%), CH_2Cl_2 , room temp., 3 h, 84%; e) LDA (1.1 equiv.), THF, -78°C , 1 h, **23** (1.1 equiv.), 20 min, 77%; f) same as (e) but with **24**, 88%; g) PDC (2.5 equiv.), CH_2Cl_2 , room temp., 18 h, 60%; h) same as (g) but 3 d, 74%. PMB = *p*-methoxybenzyl; TEMPO = 2,2,6,6-tetramethylpiperidinoxyl.

γ -lactone **18** accessible in 84% yield and with unchanged *ee*.^[22] Since compound **18** crystallized nicely, we were able to determine its absolute configuration crystallographically.^[23] Our result was in accordance with the prediction from the literature.^[17] The lithium enolate of lactone **18** was 1,2-added to crotonaldehyde (**23**) as well as to the more highly substituted α,β -unsaturated aldehyde **24**.^[24] This led to hydroxyalkylated lactones **21** and **22**. Oxidation with PDC took the material on to Nazarov reagents **19** and **20**, respectively. Each of them consisted of two ketone epimers and the enol tautomer.^[25]

A 90% *ee* sample of Nazarov reagent **19** was annulated to oxocyclohexenecarboxylate **25**^[26] under standard Deslongchamps conditions,^[3,4] i.e., by exposure to a suspension of Cs_2CO_3 (0.5 equiv.) in dichloromethane at room temp. (Scheme 4). After 10 h and complete consumption – as judged by TLC – of both reactants, we obtained a 91:9 mixture of two spiro lactones. The major product possesses stereostructure **27** as revealed by X-ray structural analysis (Figure 1). If the minor spiro lactone is *epi-27* as we believe,^[27] **27** and *epi-27* would be derived from the same dienolate stereoisomer **26** [with a (*Z*)-configured $\text{C}^a=\text{C}^{1'}$ bond]. In addition, both **27** and *epi-27* would be formed with the usual simple diastereoselectivity (ketone *exo*, ester *endo*^[3,4]). The difference between annulation products **27** and *epi-27* would be the opposite orientation of the newly formed stereogenic bonds relative to the $\text{C}^\gamma\text{--CH}_2\text{SiPh}_3$ bond at the inducing stereocenter of the lactone. Unequivocally, the major annulation product **27** stems from an approach of cyclohexenecarboxylate **25** to dienolate **26** from the hindered β -face. This direction of the asymmetric induction is unprecedented in the chemistry of γ -chiral γ -lactone enolates.^[14] The expected combination of the reactants should have occurred on the unhindered α -face of dienolate **26** ($\rightarrow$ *epi-27*). At present, we have no clue as to what the reason for this behavior is.

The major part of spiro lactone **27** was separated from the minor isomer *epi-27* by flash chromatography on silica gel.^[28] Treatment of pure **27** with a solution of Bu_4NF in THF led to >63% of a separable (vide infra) 75:25 mixture of decalindione isomers **28** and *epi-28*. This transformation shows that a γ -[(triphenylsilyl)methyl]- γ -butyrolactone may be used as synthetic equivalent of a homoallyl group. The first step is analogous to the fluoride-induced β -elimination of γ -[(trimethylsilyl)methyl]- γ -butyrolactones delivering γ,δ -unsaturated carboxylic acids.^[29] Here, however, the reaction continues. This is because here the γ,δ -unsaturated carboxylic acid intermediate is a β -oxo acid, which decarboxylates and renders the ketone. The configuration of the newly formed, i.e., homoallylic stereocenter in decalindiones **28** and *epi-28* was deduced from the H,H coupling constants compiled in Figure 2. We observed *one trans*-diaxial H,H coupling per cyclohexanone ring, which means that each of them is a chair conformer and in that regard conformationally distinct from predecessor **27**. The occurrence of $^4J_{7\text{eq},5} = 1.2$ Hz in **28** and its absence ($^4J_{7\text{eq},5} \approx 0$ Hz) in *epi-28* imply a W-conformation for substructure $\text{H--C}^5\text{--C}^6\text{--C}^7\text{--H}^{\text{eq}}$ in **28** and a different array of the same substructure in *epi-28*. This means that the $\text{C}^5\text{--H}$ bond of **28** is equatorial and the $\text{C}^5\text{--allyl}$ bond accordingly axial, while the opposite is true for *epi-28*.

The Deslongchamps annulation of the cesium enolate of Nazarov reagent **20** to oxocyclohexenecarboxylate **29**^[31] proceeded similarly (Scheme 5) as the annulation of Scheme 4. The spiro lactones **31** and *epi-31* resulted as a 94:6 mixture (76% yield). Again, the underlying stereocontrol is due to a hitherto unprecedented 1,3-asymmetric induction^[14] by the chiral γ -lactone substituent of dienolate intermediate **30**; as in the example of Scheme 4, the favored sense of attack is contrasteric and presently inexplicable.

Isomers **31** and *epi-31* were chromatographically^[28] inseparable. Thus, their mixture was subjected to the Bu_4NF -

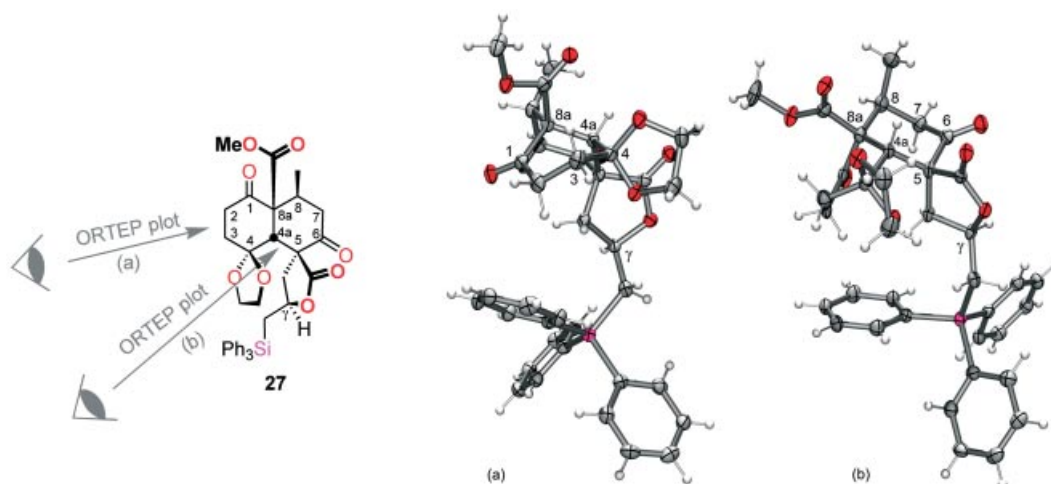
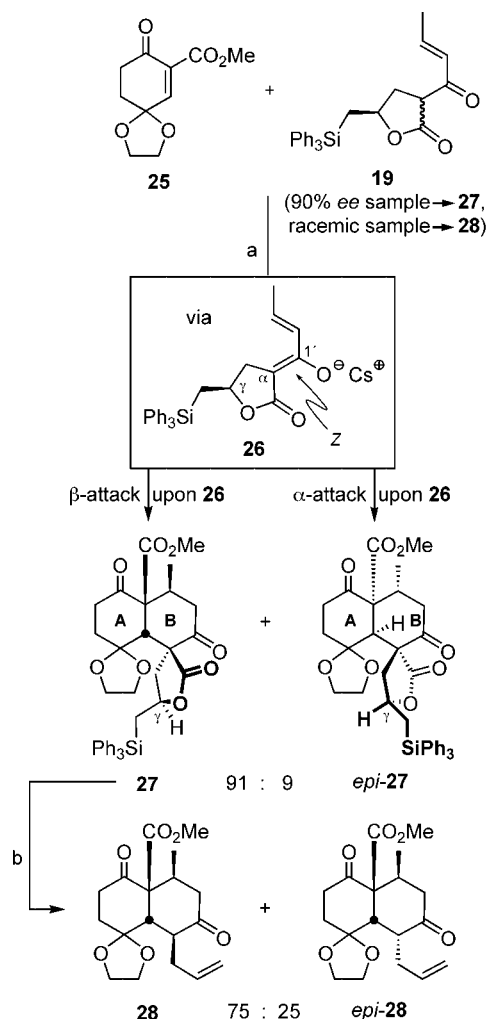


Figure 1. ORTEP plots of the crystal structure of decalindione **27**.^[23] Projection (a) shows relative configuration at C-4a vs. C-8a and a front-view of a twist-boat conformation of cyclohexanone C-1/C-2/C-3/C-4/C-4a/C-8a (the oxygen atom attached to C-6 is hardly visible). Projection (b) shows relative configurations at C-5 vs. C-4a vs. C-8a vs. C-8 vs. C-7 and represents a view upon a chair conformation of cyclohexanone C-4a/C-5/C-6/C-7/C-8/C-8a (the oxygen atom attached to C-1 and the α -oriented oxygen atom of the dioxolane ring are hardly visible).



Scheme 4. Deslongchamps annulation of lactone **19** to oxocyclohexenecarboxylate **25**. a) Cs_2CO_3 (0.5 equiv.), CH_2Cl_2 , room temp., 3 h (crude product: **27**/*epi*-**27** = 91:9), **27** (36%) + 75:25 mixture of **27**/*epi*-**27** (23%); b) Bu_4NF (2.2 equiv.), THF, room temp., 10 h (crude product: **28**/*epi*-**28** = 75:25), **28** (37%) + **28**/*epi*-**28** mixture (50:50; 20%) + *epi*-**28** (6%).

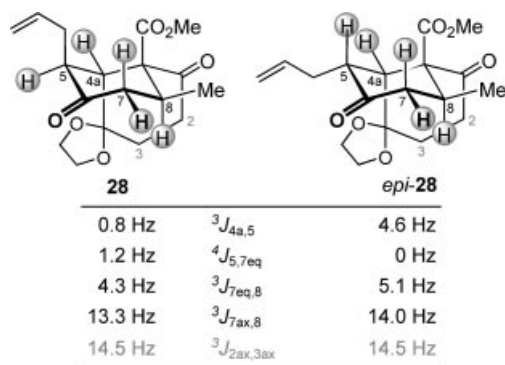
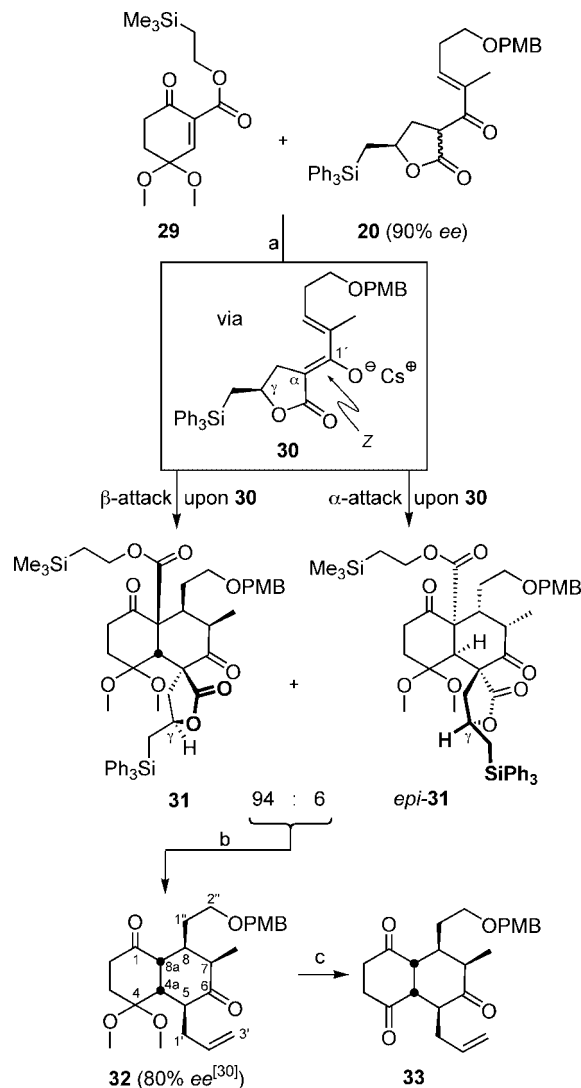


Figure 2. ^1H NMR coupling constants (500 MHz in CDCl_3) proving the relative configurations of decalindiones **28** and *epi*-**28**.

induced tandem elimination/decarboxylation reaction first described in the context of Scheme 4. The lactone moieties gave allyl groups thereby. Remarkably, there was an ac-



Scheme 5. Deslongchamps annulation of lactone **20** to oxocyclohexenecarboxylate **29**. a) Cs_2CO_3 (0.5 equiv.), CH_2Cl_2 , room temp., 10 h, 76% of an inseparable mixture of **31** and *epi*-**31**; b) Bu_4NF (3.0 equiv.), THF, room temp., 10 h, 64% (80% ee); c) $p\text{TsOH}\cdot\text{H}_2\text{O}$ (0.5 equiv.), acetone/ H_2O (2:1), room temp., 2 h, 88%.

companying tandem process, namely the cleavage/decarboxylation of the β -oxo (trimethylsilyl)ethyl ester unit. This reaction appears to be novel, too. It may become a room-temp. alternative and orthogonal supplement to the Pd-catalyzed cleavage/decarboxylation of β -oxo allyl esters.^[32] The result of this twin-tandem defunctionalization was a 64% yield of decalindione **32**.^[33] This compound possessed 80% ee.^[29] This value means – considering that the precursor Nazarov reagent **20** had 90% ee – that decalindione **32** was generated from *both* precursors **31** and *epi*-**31** in their mixing ratio of 94:6.

The acid-catalyzed cleavage of the dimethyl ketal moiety of decalindione **32** in wet acetone led to decalintrione **33** in the terminating step of Scheme 5. According to our analyses of the magnitudes of $J_{\text{ring-H,vicinal ring-H}}$ values and ROESY cross-peaks in the 500 MHz NMR spectra of deca-

lindione **32** and decalintrione **33**, the latter compounds conserve the *cis* junction of the underlying rings already present in spirolactones **31** and *epi*-**31**.

Conclusions

The present investigation establishes a conceptually novel 1,3-asymmetric induction as an efficient means for achieving stereocontrol in Deslongchamps annulations. The latter provided substituted decalindiones and -triones with up to five contiguous stereocenters. Functionalized side-chains were incorporated, which should allow further elaboration into tricyclic or tetracyclic ring systems like **9** and **10**. Last but not least, there are two worthwhile spin-off results, namely (1) the use of a silylated lactone enolate as a homoallyl anion equivalent and (2) the first observation of the dealkoxycarbonylation of a β -oxo (trimethylsilyl)ethyl ester by treatment with Bu_4NF at room temp.

Acknowledgments

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- [23] CCDC-627185 (for **18**) and -627186 (for **27**) contain the supplementary 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.
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- an enol, respectively, the spectrum of Nazarov reagent **20** a quite differently composed 52:45:3 mixture.
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- [29] a) G. Schmid, W. Hofheinz, *J. Am. Chem. Soc.* **1983**, *105*, 624–625; b) T. Mori, K. Suzuki, *Chem. Lett.* **1989**, 2165–2168.
- [30] The *ee* of decalindione **32** was determined by HPLC [Chiralpak AD column, *n*-heptane/*i*PrOH 95:5, 0.8 mL/min, 23 °C, UV detection 226 nm; t_{R} (minor enantiomer) = 17.4 min, t_{R} (major enantiomer) = 20.8 min].
- [31] Oxocyclohexenecarboxylate **29** was prepared in 5 steps: (1) addition (!) of 2 equiv. of MeOH to 3-(furan-2-yl)acrylic acid giving dimethyl 4-oxopimelate, yet not employing HCl gas as in the original report (W. Markwald, *Ber. Dtsch. Chem. Ges.* **1887**, 2811–2817) but solvolysing SOCl_2 as published for the otherwise analogous preparation of diethyl 4-oxopimelate (A. L. Gutman, K. Zuobi, T. Bravdo, *J. Org. Chem.* **1990**, *55*, 3546–3552); (2) ketal formation with $\text{HC(OMe)}_3/p\text{TsOH}$; (3) Dieckmann condensation as reported by J. A. Marshall, R. A. Ruden, *J. Org. Chem.* **1971**, *36*, 594–596; (4) transesterification with 2-(trimethylsilyl)ethanol catalyzed by $\text{ClBu}_2\text{SnOSnBu}_2\text{OH}$ (method: J. Otera, T. Yano, A. Kawabata, H. Nozaki, *Tetrahedron Lett.* **1986**, *27*, 2383–2386); (5) successive treatments with PhSeCl/pyridine and H_2O_2 as described in ref.^[4f] Because of the instability of oxocyclohexenecarboxylate **29** its phenyl selenide precursor was oxidized directly before use. This afforded **29** in 100% yield sufficiently pure.
- [32] T. Tricotet, R. Kramer, R. Brückner, unpublished results.
- [33] (4*a,S*,5*S*,7*R*,8*S*,8*a,R*)-5-Allyl-4,4-dimethoxy-3,4,4*a*,7,8,8*a*-hexahydro-8-{2-[(4-methoxybenzyl)oxy]ethyl}-7-methylnaphthalene-1,6(2*H*,5*H*)-dione (**32**): At 0 °C Cs_2CO_3 (180 mg, 0.55 mmol, 0.5 equiv.) was added to a stirred solution of Nazarov reagent **19** (656 mg, 1.11 mmol) in CH_2Cl_2 (10 mL). After 5 min, a solution of oxocyclohexenecarboxylate **29** (333 mg, 1.11 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added dropwise over a period of 1 min. A yellow heterogeneous mixture resulted, which was stirred at 0 °C for 1 h and at room temp. for 2 h and then filtered through a pad of silica gel. The pad was eluted first with CH_2Cl_2 , then with EtOAc. The late fractions were collected and the solvent was evaporated under reduced pressure. This provided a mixture of annulation products **31** and *epi-31* (750 mg, 76%). Without further purification, a portion of this mixture (154 mg, 173 μmol) was dissolved in THF (4 mL). Bu_4NF (1.0 M in THF, 518 μL , 518 μmol , 3.0 equiv.) was added dropwise while stirring at 0 °C during 2 min. The mixture was warmed to room temp. slowly (3 h), stirred for another 7 h, and poured into a mixture of water (20 mL) and brine (10 mL). Extraction with Et_2O (4×30 mL), drying of the combined extracts with Na_2SO_4 , evaporation of the solvent under reduced pressure, and flash chromatography on silica gel^[28] (cyclohexane/EtOAc, 5:1) furnished the title compound (49.0 mg, 64%) as a colorless oil. ^1H NMR (500.0 MHz, CDCl_3): δ = 0.97 (d, $J_{7\text{-CH}_3,7}$ = 6.6 Hz, 7- CH_3), 1.03 (m_{c} , $1''\text{-H}^{\text{A}}$), 1.72 (dddd, J_{gem} = 14.3 Hz, $J_{1''\text{-H(B)},2''\text{-H(A)}}$ = $J_{1''\text{-H(B)},2''\text{-H(B)}}$ = 7.1 Hz, $J_{1''\text{-H(B)},8}$ = 4.0 Hz, $1''\text{-H}^{\text{B}}$), 1.93 (m_{c} , 3- H^{ax}), 2.16 (m_{c} , 5-H), 2.22 (m_{c} , 3- H^{eq}), 2.44–2.54 (m, 4*a*-H, 2- H_2 , $1'\text{-H}^{\text{A}}$), 2.66 (m_{c} , $1'\text{-H}^{\text{B}}$), 2.76 (m_{c} , 8-H), 2.87 (dq, $J_{7,7\text{-CH}_3}$ = $J_{7,8}$ = 6.4 Hz, 7-H), 2.98 (dd, $J_{8\text{a},8}$ = 4.7 Hz, $J_{8\text{a},4\text{a}}$ = 1.9 Hz, 8*a*-H), 3.15 (s, 4-OMe), 3.17 (s, 4-OMe), AB signal (δ_{A} = 2.88, δ_{B} = 2.88, J_{AB} = 6.5 Hz, $2''\text{-H}_2$), 3.80 (s, OMe, PMB), AB signal (δ_{A} = 4.34, δ_{B} = 4.42, J_{AB} = 11.7 Hz, OCH_2Ar), 4.91 (m_{c} , $3'\text{-H}^{\text{E}}$), 4.96 (m_{c} , $3'\text{-H}^{\text{Z}}$), 5.72 (dddd, J_{trans} = 17.1 Hz, J_{cis} = 10.2, $J_{2',1'\text{-H(A)}}$ $\approx$ $J_{2',1'\text{-H(B)}}$ = 6.8 Hz, $2'\text{-H}$), 6.85 (m_{c} , $2 \times \text{H}_{\text{meta}}$), 7.20 (m_{c} , $2 \times \text{H}_{\text{ortho}}$).

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