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

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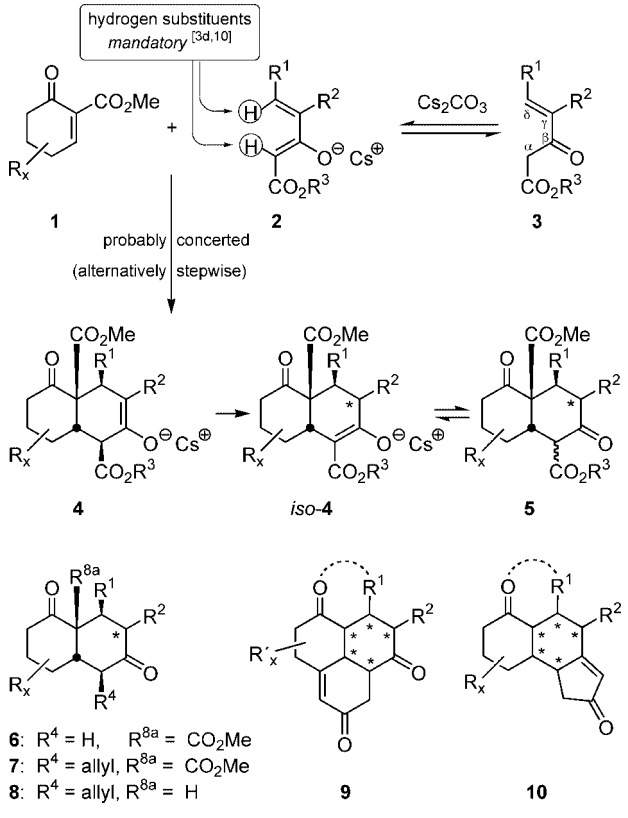
A conceptionally novel 1,3-asymmetric induction has been established. It controls the relative and absolute configuration of up to 5 stereocenters. They emerge from the anionic Diels–Alder reactions ("Deslongchamps annulations") between oxocyclohexenecarboxylates **25**, **29** and dienolates **26**, **30**. The latter contain a γ-lactone. A $Ph_3Si–CH_2$ substituent therein controls the asymmetry of C–C bond formation with *ds* ≈ 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** → **6** created up to four new stereocenters which matches the "stereogenecity" of Diels–Alder reactions.



Scheme 1. Deslongchamps annulations past (→ **5**, **6**) and present (→ **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.

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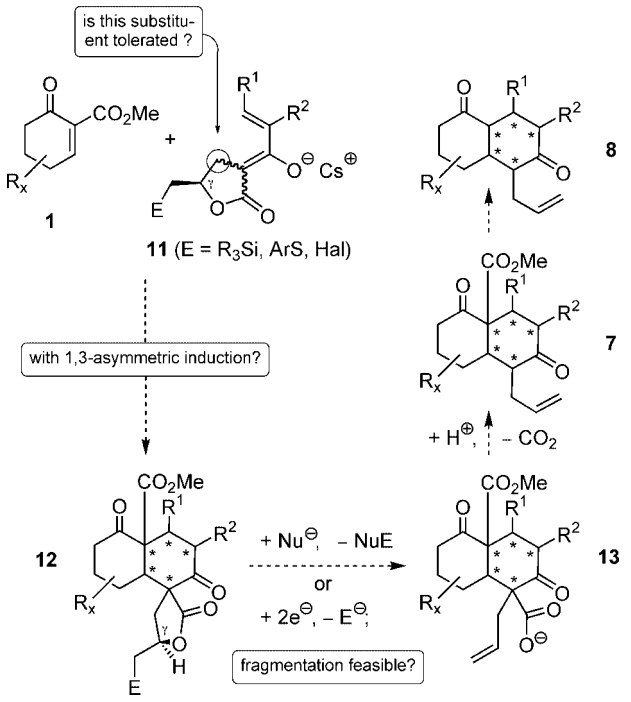
Recently, we showed that dioxodecalindicarboxylates **5** (with CO_2R^3 = CO_2allyl) give dioxodecalinmonocarboxylates **7**[10] by Tsuji's Pd-catalyzed decarboxylation/allylation.[11] They and the readily derived decalindiones **8**[10] display five new stereocenters. By this token their syntheses surpass the "stereogenecity" 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 moiety allowed to control the absolute configuration of the annulation products. Both features are important steps towards developing type-**8** decalindiones into precursors of tricyclic or tetracyclic structures **9** and **10**.[12]

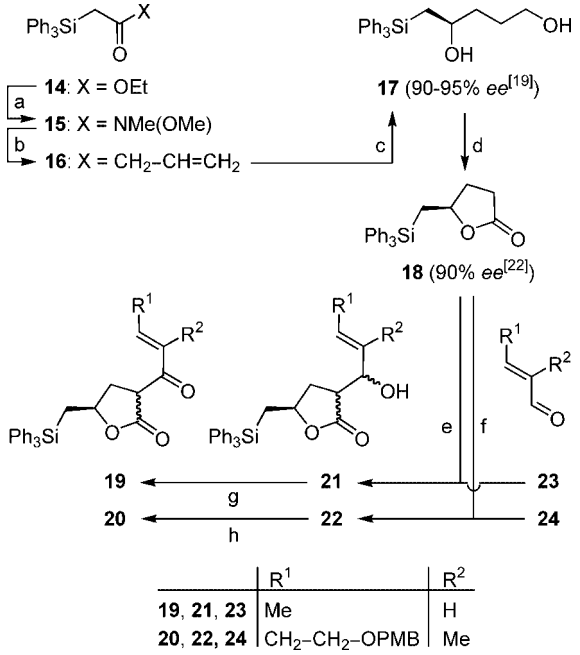
Results and Discussion

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** → **13** → **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 E = R_3Si) or a reductive (for E = ArS, Hal) elimination (**12** → **13**) followed by protonation and in-situ decarboxylation (**13** → **7**). We were particularly attracted by the possibility of a fluoride-mediated elimination **12** → **13**.[29] This was because of the prospect of cleaving simultaneously the acyclic ester moiety of intermediate **12** – provided the latter would be CO_2–CH_2–CH_2–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.)/$PhI(OAc)_2$ (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) HNMe(OMe)·HCl (1.5 equiv.), *i*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*), $PhI(OAc)_2$ (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 spirolactones. The major product possesses stereostructure **27** as revealed by X-ray structural analysis (Figure 1). If the minor spirolactone is *epi*-**27** as we believe,[27] **27** *and epi*-**27** would be derived from the same dienolate stereoisomer **26** [with a (*Z*)-configured $C^{\alpha}=C^{1'}$ 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 C^{γ}–CH_2SiPh_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** (→ *epi*-**27**). At present, we have no clue as to what the reason for this behavior is.

The major part of spirolactone **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 $^4J_{7eq,5}$ = 1.2 Hz in **28** and its absence ($^4J_{7eq,5} \approx 0$ Hz) in *epi*-**28** imply a W-conformation for substructure H–C^5–C^6–C^7–H^{eq} in **28** and a different array of the same substructure in *epi*-**28**. This means that the C^5–H bond of **28** is equatorial and the C^5–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 spirolactones **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-

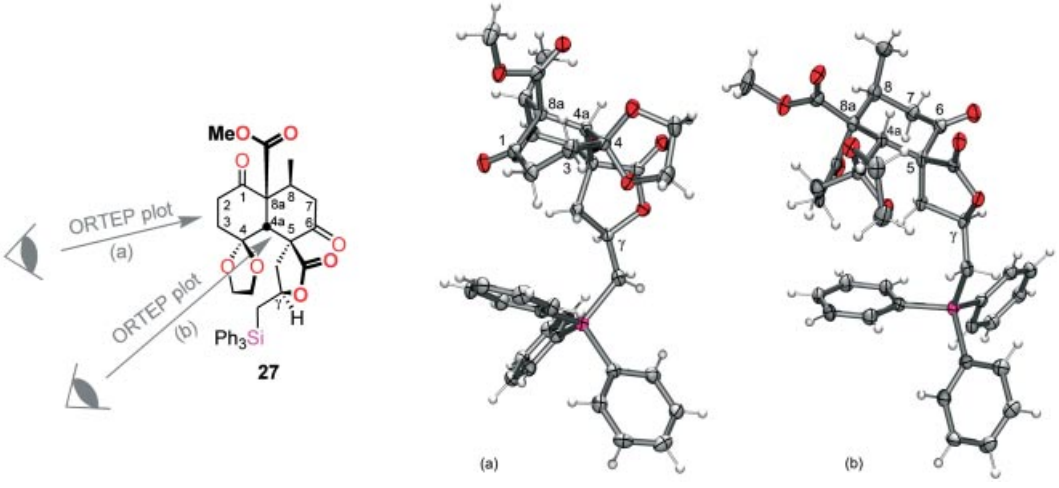
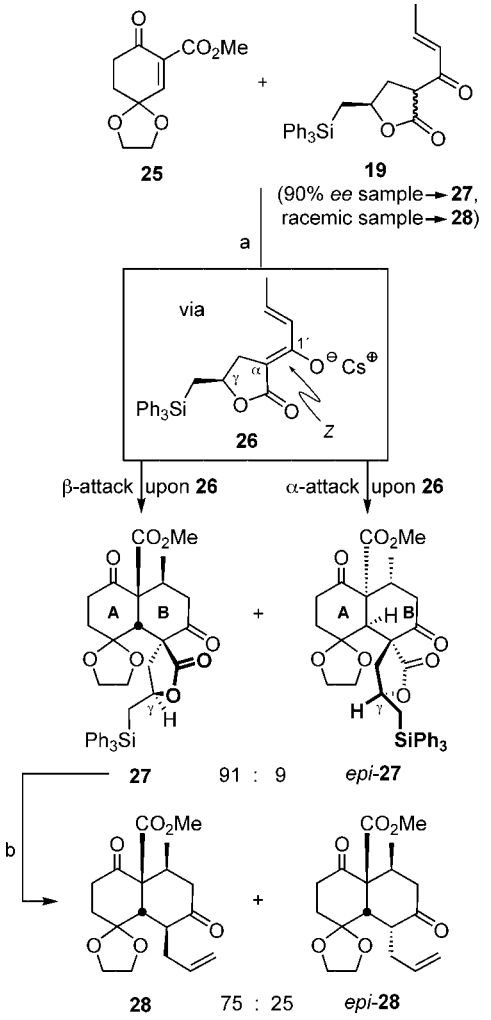


Figure 1. ORTEP plots of the crystal structure of decalindione **27**.[23] Projection (a) shows relative configuration at C-4a vs. C-8a and a front-view of a twist-boat conformation of cyclohexanone C-1/C-2/C-3/C-4/C-4a/C-8a (the oxygen atom attached to C-6 is hardly visible). Projection (b) shows relative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

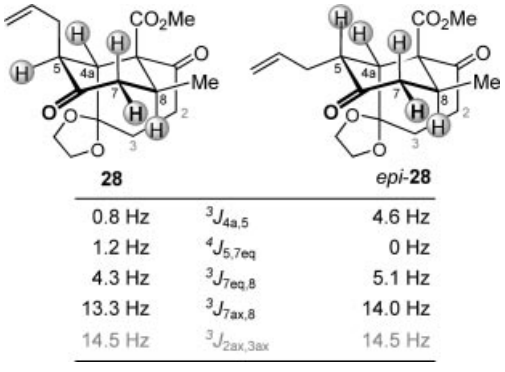
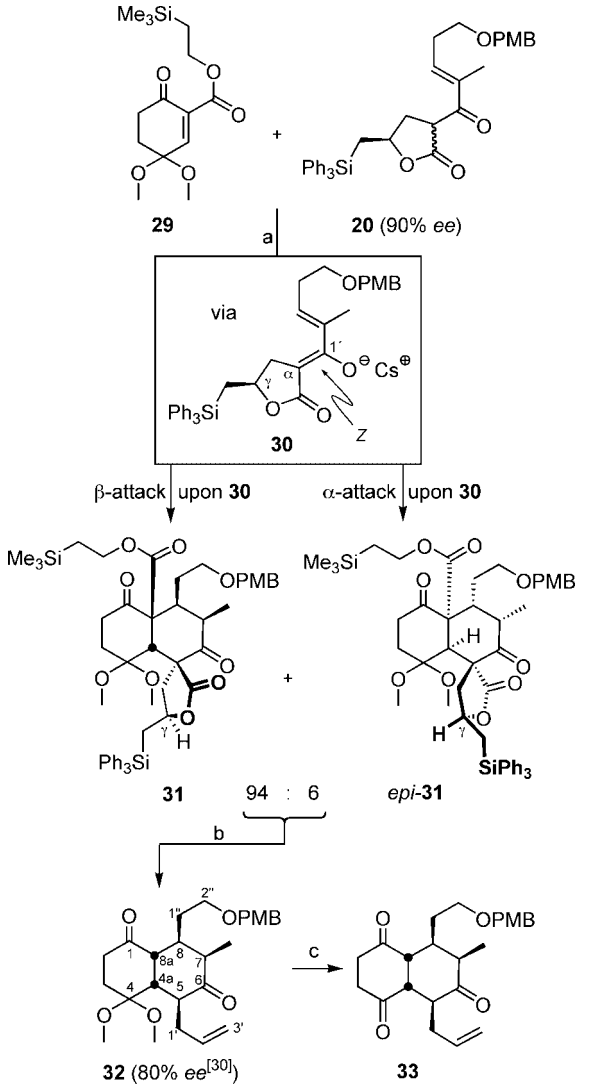


Figure 2. ^{1}H NMR coupling constants (500 MHz in $CDCl_3$) proving the relative configurations of decalindiones **28** and *epi*-**28**.

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*TsOH·H_2O (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

This work was generously supported by the Fonds der Chemischen Industrie through a Kekulé fellowship for T. T. We are indebted to Dr. Manfred Keller for contributing the X-ray structural analyses and detailed NMR studies.

[1] a) L. Chen, P. Deslongchamps, *Can. J. Chem.* **2005**, *83*, 728–740; b) Erratum: L. Chen, P. Deslongchamps, *Can. J. Chem.* **2005**, *83*, 2144.

[2] a) I. N. Nazarov, S. I. Zavyalov, *Zh. Obshch. Khim.* **1953**, *23*, 1703; b) I. N. Nazarov, S. I. Zavyalov, *Chem. Abstr.* **1954**, *48*, 13667h.

[3] Deslongchamps annulations with CO_2tBu-containing Nazarov reagents: a) J.-F. Lavallée, P. Deslongchamps, *Tetrahedron Lett.* **1988**, *29*, 5117–5118; b) J.-F. Lavallée, P. Deslongchamps, *Tetrahedron Lett.* **1988**, *29*, 6033–6036; c) R. Ruel, P. Deslongchamps, *Tetrahedron Lett.* **1990**, *31*, 3961–3964; d) R. Ruel, K. T. Hogan, P. Deslongchamps, *Synlett* **1990**, 516–518; e) J.-F. Lavallée, C. Spino, R. Ruel, K. T. Hogan, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1406–1426; f) R. Ruel, P. Deslongchamps, *Can. J. Chem.* **1992**, *70*, 1939–1949; g) D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669–5672; h) B. Guay, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 6140–6148.

[4] Deslongchamps annulations with CO_2Allyl-containing Nazarov reagents: a) O. Lepage, C. Stone, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 1091–1094; b) Z. Yang, D. Shannon, V. Truong, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 4693–4696; c) O. Lepage, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 2183–2186; d) A. Rouillard, M.-A. Bonin, P. Deslongchamps, *Helv. Chim. Acta* **2003**, *86*, 3730–3739; e) ref.[3h]; f) S. Trudeau, P. Deslongchamps, *J. Org. Chem.* **2004**, *69*, 832–838; g) ref.[1]

[5] Deslongchamps annulation with an SO_2Ph-containing Nazarov reagent: ref.[3e]

[6] Deslongchamps annulations with SOPh-containing Nazarov reagents: a) ref.[3e]; b) ref.[3h]

[7] *exo* with respect to the oxo group and *endo* with respect to the ester group of dienophiles **1**. This equals the simple diastereoselectivity of $SnCl_4$-catalyzed Diels–Alder reactions between neutral dienes and oxocyclohexenecarboxylates: a) H.-J. Liu, T. K. Ngooi, *Can. J. Chem.* **1984**, *62*, 2676–2681; b) H.-J. Liu, T. K. Ngooi, E. N. C. Browne, *Can. J. Chem.* **1988**, *66*, 3143–3152.

[8] Diastereoselectivity in Deslongchamps annulations induced by chiral oxocyclohexenecarboxylates: a) ref.[3c]; b) ref.[3e]; c) ref.[3f]; d) ref.[4f]; e) ref.[1]

[9] Diastereoselectivity in Deslongchamps annulations induced by chiral dienolates: a) ref.[4a]; b) ref.[4c]; c) ref.[4d]

[10] T. Tricotet, R. Brückner, *Tetrahedron Lett.* **2006**, *47*, 8499–8502.

[11] a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199–3202; b) J. Tsuji, T. Yamada, I. Minami, M. Yuhara, M. Nisar, I. Shimizu, *J. Org. Chem.* **1987**, *52*, 2988–2995.

[12] In order to attain tetracycles **9** or **10** from **7** via **8**, substituent R^1 must be functionalized in anticipation of the second ring-closure. Implementing such an option we chose $R^1 = CH_2$–CH_2–OPMB in our study (PMB = *p*-methoxybenzyl).

[13] T. Tricotet, Dissertation, University of Freiburg, **2006**.

[14] Representative examples for the selective functionalization of lithium enolates of γ-chiral γ-lactones by electrophiles ("$E^{\oplus}$") from the unhindered side: a) $E^{\oplus}$ = proton source: S. Takano, W. Uchida, S. Hatakeyama, K. Ogasawara, *Chem. Lett.* **1982**, 733–736; b) $E^{\oplus}$ = RX: K. Tomioka, H. Mizuguchi, K. Koga, *Chem. Pharm. Bull.* **1982**, *30*, 4304–4313 and references cited therein; c) $E^{\oplus}$ = RX, RCHO: C. Anceau, G. Dauphin, G. Coudert, G. Guillaumet, *Bull. Soc. Chim. Fr.* **1994**, *131*, 291–303; d) $E^{\oplus} = MoO_5$·pyridine·HMPA: S. Hanessian, S. P. Sahoo, P. J. Murray, *Tetrahedron Lett.* **1985**, *26*, 5631–5634; e) $E^{\oplus} = Ph_2S_2$:L. J. Wilson, D. C. Liotta, *J. Org. Chem.* **1992**, *57*, 1948–1950; f) $E^{\oplus} = Ts_2NF$: J. J. McAtee, R. F. Schinazi, D. C. Liotta, *J. Org. Chem.* **1998**, *63*, 2161–2167.The same asymmetric induction is encountered in the hydrogenation of α-(arylmethylene)-γ-valerolactones (ref.[14b]).

[15] We prepared ester **14** from ethyl diazoacetate, Ph_3SiH, and either $Rh_2(OAc)_4$ as described by V. Bagheri, M. P. Doyle, J. Taunton, E. E. Claxton, *J. Org. Chem.* **1988**, *53*, 6158–6160 or $Cu(OTf)_2$ as described by O. Audrey, Y. Landais, D. Planchenault, V. Weber, *Tetrahedron* **1995**, *51*, 12083–12096.

[16] All new compounds gave satisfactory ^1H and ^{13}C NMR spectra and either correct combustion analyses (except oxo ester **29**, which was used without purification, and β-hydroxylactones **21** and **22**, which were oxidized without characterization) or correct HRMS data (**19**, **20**).

[17] Method: G. A. Molander, K. L. Bobitt, *J. Org. Chem.* **1994**, *59*, 2676–2678.

[18] Prepared from (–)-α-pinene as described by H. C. Brown, N. N. Joshi, *J. Org. Chem.* **1988**, *53*, 4059–4062.

[19] The *ee* of diol **17** was determined by HPLC {Chiralpak AD column, *n*-heptane/*i*PrOH 90:10, 0.8 mL/min, 23 °C, UV detection 223 nm; t_R[(*S*) enantiomer] = 14.9 min, t_R[(*R*) enantiomer] = 19.7 min}, the result varying (90–95%) with the (+)-$(IPC)_2$-BH sample used.

[20] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.

[21] T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, C. J. Forsyth, *Tetrahedron Lett.* **2003**, *44*, 57–59.

[22] The *ee* of lactone **18** was determined by HPLC {Chiralpak AD column, *n*-heptane/*i*PrOH 97:3, 0.8 mL/min, 23 °C, UV detection 223 nm; t_R[(*S*) enantiomer] = 13.1 min, t_R[(*R*) enantiomer] = 14.4 min}.

[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.

[24] α,β-Unsaturated aldehyde **24** was prepared from *p*-anisaldehyde and propane-1,3-diol in 3 known steps (F. M. Cordero, F. Pisaneschi, M. Gensini, A. Goti, A. Branchi, *Eur. J. Org. Chem.* **2002**, 1941–1951) followed by a Wittig reaction with Ph_3P=C(Me)–CH=O (prepared by the procedure of R. H. Schlessinger, M. A. Poss, S. Richardson, P. Lin, *Tetrahedron Lett.* **1985**, *26*, 2391–2394).

[25] The ^1H NMR spectrum (500 MHz, $CDCl_3$) of Nazarov reagent **19** showed a 33:30:37 mixture of 2 diastereomeric ketones and

an enol, respectively, the spectrum of Nazarov reagent **20** a quite differently composed 52:45:3 mixture.

[26] Oxocyclohexenecarboxylate **25** was prepared from 4,4-(ethylenedioxy)cyclohexanone in 3 steps as described by D. Liotta, C. Barnum, G. Zima, C. Bayer, H. S. Kezar III, *J. Org. Chem.* **1981**, *46*, 2920–2923.

[27] This assignment accomodates the following observations: a) the ^{1}H NMR subspectra of the A-ring/B-ring moieties of compounds *epi*-**27** and **27** are nearly identical; b) the proton at C^γ of the lactone moiety is deshielded in the major ($\delta_{\mathbf{27}}$ = 4.91 ppm) compared to the minor isomer ($\delta_{epi\text{-}\mathbf{27}}$ = 4.57 ppm); this appears to reflect the proximity between the γ-H and the B-ring carbonyl group in isomer **27**.

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[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 solvolyzing $SOCl_2$ 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 $HC(OMe)_3$/*p*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 $ClBu_2SnOSnBu_2OH$ (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] (4a*S*,5*S*,7*R*,8*S*,8a*R*)-5-Allyl-4,4-dimethoxy-3,4,4a,7,8,8a-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. ^{1}H NMR (500.0 MHz, $CDCl_3$): δ = 0.97 (d, $J_{7\text{-}CH3,7}$ = 6.6 Hz, 7-CH_3), 1.03 (m_c, 1′′-H^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′′-H^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, 4a-H, 2-H_2, 1′-H^A), 2.66 (m_c, 1′-H^B), 2.76 (m_c, 8-H), 2.87 (dq, $J_{7,7\text{-}CH3} = J_{7,8}$ = 6.4 Hz, 7-H), 2.98 (dd, $J_{8a,8}$ = 4.7 Hz, $J_{8a,4a}$ = 1.9 Hz, 8a-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′′-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′-H^E), 4.96 (m_c, 3′-H^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′-H), 6.85 (m_c, 2 × H_{meta}), 7.20 (m_c, 2 × H_{ortho}).

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