

Deslongchamps Annulations with
Benzoquinone Monoketals

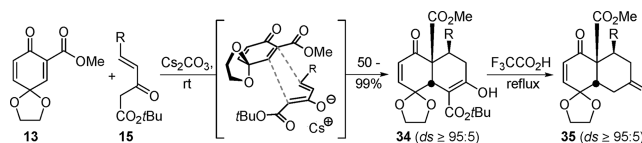
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ABSTRACT



The so-called Deslongchamps annulation of deprotonated γ,δ -unsaturated β -ketoesters 15 to 2-(alkoxycarbonyl)cyclohex-2-en-1-ones or similarly activated cyclohex-2-en-1-ones offers a versatile access to various kinds of decalindiones. The scope of Deslongchamps annulations was extended by establishing acceptor-substituted benzoquinone monoketals such as 13 as viable substrates. They gave octalindiones such as 35 with diastereoselectivities $\geq 95:5$.

Decalins are a structural motif from a large number of natural products.¹ The most famous decalins are the steroid hormones.² Tetracycline antibiotics³ are *cis*-octalins, and there is a strong demand for new variants.⁴ Mevastatin, or compactin, is a hexalin, which lowered cholesterol production in man in an unprecedented way.⁵ Its pharmacophore initiated the development of the statin family⁶ of blockbuster drugs in the pharmaceutical industry. Azadirachtin is a crop-protecting *cis*-decalin with a

THF bridge; it was an exceptionally tough synthetic target.⁷

Reflecting this significance, decalin syntheses abound.^{8,9} Preferred approaches are by Diels–Alder reactions¹⁰ or Robinson annulations.¹¹ The Hajos–Parrish–Wiechert–Eder–Sauer variant¹² provides enantiomerically pure octalindiones that include the Wieland–Miescher ketone,¹³ a key intermediate en route to synthetic steroids. Tandem cyclizations are particularly suited for making decalins and cyclohex-annulated or (oligocyclohex)-annulated decalins.

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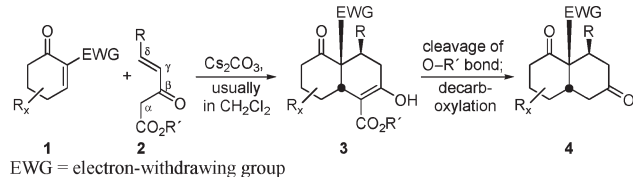
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Originally cationic approaches predominated,¹⁴ but now radical-induced¹⁵ or radical-cation-induced¹⁶ (poly)cyclizations exist as well.

Scheme 1. Deslongchamps Annulation of Nazarov Reagents **2** to Electron-Deficient Cyclohexenones **1**^a

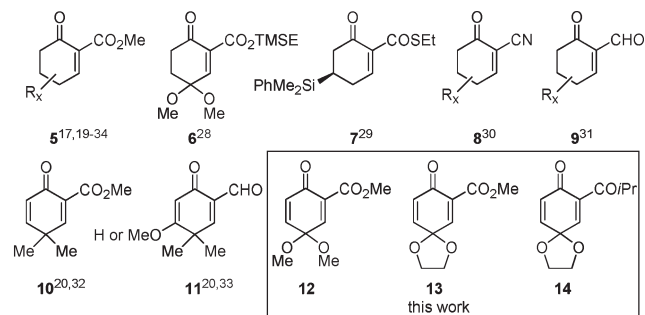


^a Usually a defunctionalization of **3**→**4** follows.

Deslongchamps and Lavallée contributed a decalin synthesis,¹⁷ referred to as the “Deslongchamps annulation”. It fuses the cesium enolate of a “Nazarov reagent” **2** (i.e., a γ,δ -unsaturated β -ketoester¹⁸) to an ester- or a similarly substituted cyclohexenone **1** (Scheme 1).^{19–34} Such annulations³⁵ give decalindiones with *cis*-fused rings at both the initial (**3**) and the de(alkoxycarbonylated) stage (**4**). A variety of structural changes in the cyclohexenone (Scheme 2) and in the Nazarov reagent are tolerated (Scheme 3); cesium enolates of the γ,δ -unsaturated

β -ketosulfoxides **19**^{32,34} and of the analogous β -ketosulfone **20**³² react like Nazarov reagents (Scheme 3).

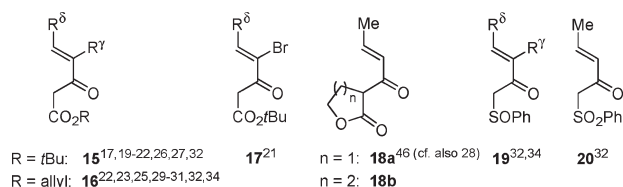
Scheme 2. Scope of Deslongchamps Annulations with Respect to Cyclohexenones or Cyclohexadienones



TMSE = 2-(trimethylsilyl)ethyl

Deslongchamps products **3** and **4** contain four and three functional groups, respectively. These functional groups increase in number when cyclohexa-2,5-dien-1-ones **10**^{20,32} or **11**^{20,33} rather than cyclohex-2-en-1-ones (**5–9**) are incorporated. We describe the first Deslongchamps annulations of benzoquinone monoketals, namely compounds **12–14**. They deliver the most densely functionalized Deslongchamps products to date.

Scheme 3. Scope of Deslongchamps Annulations with Respect to the Nazarov or Related Reagent (**18b**: This Work)



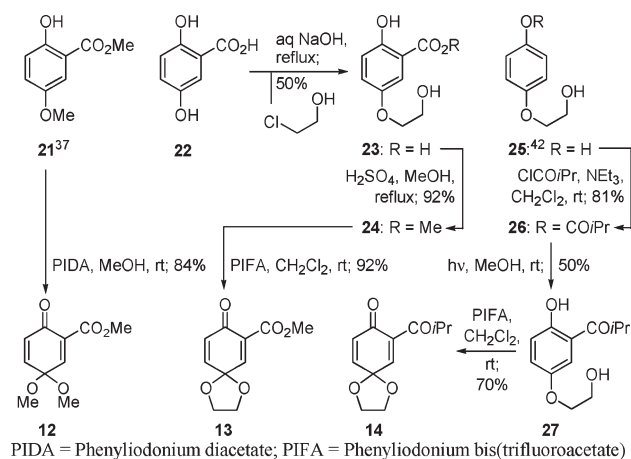
Benzoquinone monoketal **12** was obtained like its analogue containing C(OEt)₂³⁶ instead of C(OMe)₂, by oxidizing a solution of ester **21**³⁷ in methanol with PhI(OAc)₂³⁸ (Scheme 4). Quinone spiroketal **13** resulted from the commercially available acid **22** after a regioselective etherification with chloroethanol and esterification with H₂SO₄ and methanol. The resulting ester **24**³⁹ decomposed when exposed to PhI(OAc)₂ but gave 93% **13** when oxidized with PhI(O₂CCF₃)₂.⁴⁰ While ester-substituted benzoquinone

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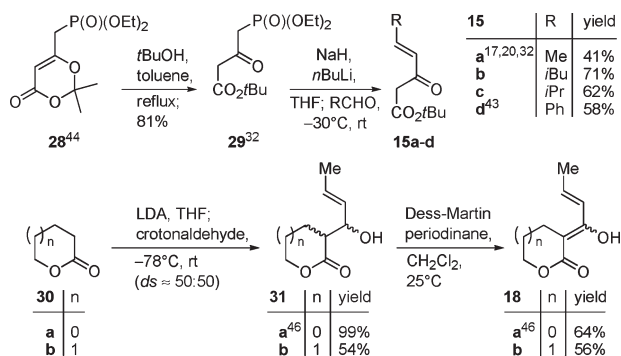
monoketals were described earlier,^{36,41} the ketone-substituted monoketal **14** is the first of its kind. It was prepared from phenol **25**⁴² via isobutyrate **26**. A photo-Fries rearrangement ($\lambda = 254$ nm) provided ketone **27**, which was oxidized with $\text{PhI}(\text{O}_2\text{CF}_3)_2$.⁴⁰

Scheme 4. Synthesis of Benzoquinone Monoketals **12–14**



Nazarov reagents **15a**^{17,20,32} and **15d**⁴³ and analogs **15b** and **15c** were synthesized *trans*-selectively by Horner–Wadsworth–Emmons reactions of an appropriate aldehyde with the dianion of phosphonoketoester **29**³² (Scheme 5). We found it advantageous to access **29** by fragmenting the phosphonodioxinone **28**⁴⁴ in *tert*-butanol/toluene at reflux (i.e., differently than described²⁷).⁴⁵ Nazarov reagents **18a**⁴⁶ and **18b** emerged from aldol addition/oxidation⁴⁷ sequences engaging γ -butyrolactone (**30a**) and δ -valerolactone (**30b**), respectively, with crotonaldehyde.

Scheme 5. Synthesis of Nazarov Reagents **15a–15d** and **18a–18b**^a



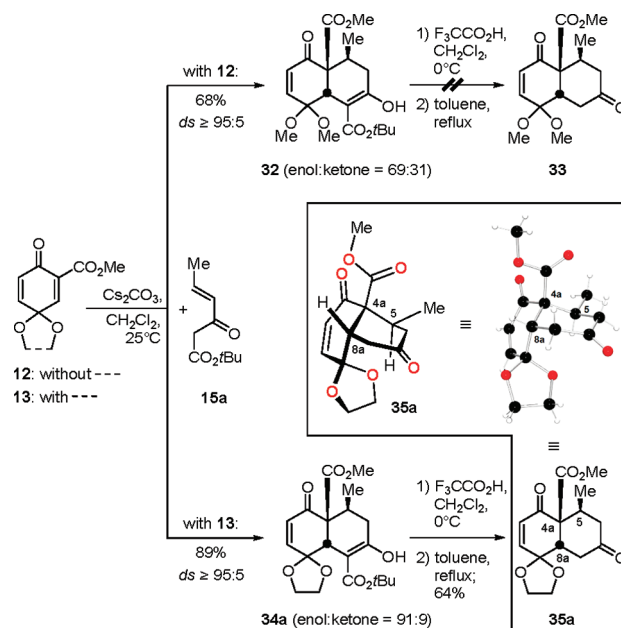
^a Keto/enol ratios in CDCl_3 solution (400 MHz, ^1H NMR spectra): for **15a**, 60:40; for **15b**, 73:27; for **15c**, 69:31; for **15d**, 57:43; for **18a** 17:83; for **18b**, 6:94.

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A suspension of benzoquinone monoketal **12**, Nazarov reagent **15a**, and Cs_2CO_3 in CH_2Cl_2 underwent a Deslongchamps annulation at room temp within 21 h (Scheme 6). It afforded 68% of the octalindione **32** as a single stereoisomer.⁴⁸ Benzoquinone monoketal **13** and the same Nazarov reagent required 3 h to form 89% of the octalindione **34a** with the same amount of diastereocontrol.^{48,49} The increases in reactivity and yield suggest that

Scheme 6. Deslongchamps Annulations I to Benzoquinone Monoketals Plus Subsequent De(*tert*-butoxy)carbonylations



the dioxolane ring exerts less steric hindrance in **13** than the $\text{C}(\text{OMe})_2$ moiety in **12**. Another beneficial dioxolane effect was that octalindione **34a**, in contrast to **32**, was cleanly de-*tert*-butylated at 0 $^\circ\text{C}$ by $\text{CF}_3\text{CO}_2\text{H}$ (25% solution in CH_2Cl_2). Decarboxylation of the resulting β -ketoacid in refluxing toluene provided octalindione **35a** in 64% yield.

(43) Compound **15d** was obtained differently by Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, 2757–2760.

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(45) We developed this access because the condensation between the bis(enolate) of *tert*-butyl acetoacetate and diethyl chlorophosphonate³² provided **29** in unsatisfactory yields and with inseparable contaminants.

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(48) This was concluded from the virtual absence of extraresonances in the respective ^1H (400 MHz, CDCl_3) and ^{13}C NMR spectra (100 MHz, CDCl_3). We assume that such spectra should have revealed the presence of another diastereomer if the latter represented more than 5% of the material.

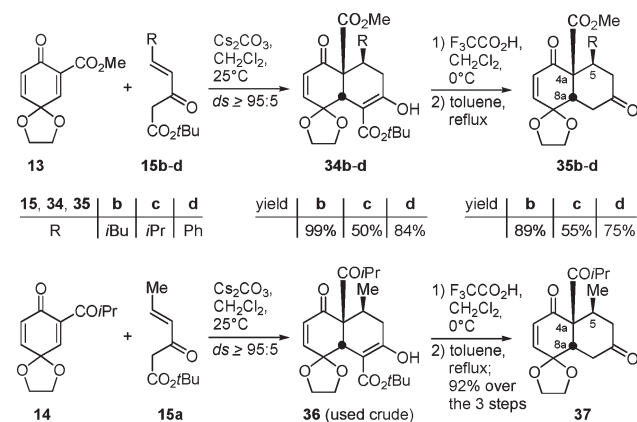
(49) When the Nazarov reagent **15a** was deprotonated by K_2CO_3 or *n*-BuLi in the presence of the benzoquinone monoketal **13** or before the latter was added, respectively, the Deslongchamps adduct **34a** did not form at all.

(50) CCDC 849007 (**35a**), 849008 (**38a**), and 849006 (**38b**) contain the crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via the link www.ccdc.cam.ac.uk/data_request/cif.

Its X-ray analysis⁵⁰ proved the *cis*-fusion of the rings and the *cis*-orientation of the substituents at C-4a and C-5. Both features are typical for Deslongchamps annulations.^{19–34}

The ester-substituted benzoquinone monoketal **13** accepted the somewhat bulkier Nazarov reagents **15b–d** almost as readily as **15a** and again with excellent diastereoselectivities (*ds* ≥ 95:5;⁴⁸ Scheme 7). Subsequent defunctionalizations by trifluoroacetylation/thermolysis were feasible, too. They delivered the octalindiones **35b–d** as single diastereomers. The relative configuration of the stereocenters of **35b–d** should be the same as that in the parent compound **35a**.⁵¹ The ketone-substituted benzoquinone monoketal **14** and the Nazarov reagent **15a** were processed similarly. This led to the ketone-substituted octalindione **37** selectively.⁴⁸ It, too, should be configured like analogue **35a**.⁵¹

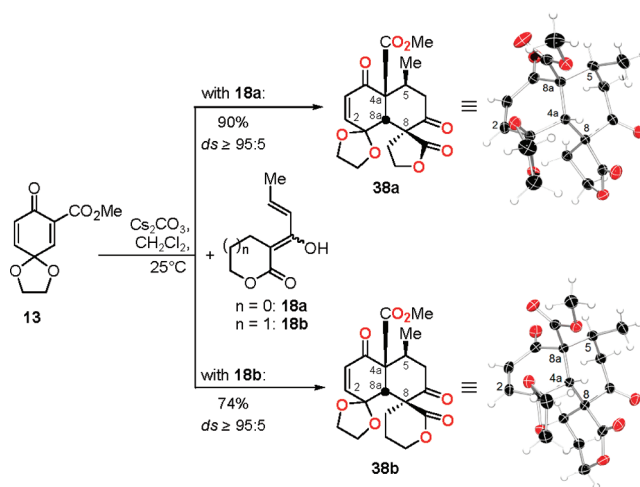
Scheme 7. Deslongchamps Annulations II to Benzoquinone Monoketals Plus Subsequent De(*tert*-butoxy)carbonylations



A while ago we established that lactone-containing Nazarov reagents undergo Deslongchamps annulations with type-5 cyclohexenones.^{28,46} We have found since that they also annulate to the benzoquinone monoketal **13** (Scheme 8). Nazarov reagent **18a** delivered 90% diastereomerically pure spiro- γ -lactone **38a**, and Nazarov reagent **18b**, 74% diastereomerically pure spiro- δ -lactone **38b**.⁴⁸ Both products were elucidated configurationally by X-ray crystallography.⁵⁰ It is noteworthy that the *cis*-orientation of their C-5—Me and C-8—C=O bonds would follow *with necessity* from the intermediacy of a cesium-chelating

(51) This conclusion is not only based on a plausible analogy but also on circumstantial ¹H NMR evidence. In CDCl₃ solutions 8a-H is significantly deshielded (**35a**: δ = 3.40 ppm; **35b**: δ = 3.43 ppm; **35c**: δ = 3.39 ppm; **35d**: δ = 4.05–4.10 ppm (includes deshielding effect of α -phenyl group); **37**: δ = 3.22 ppm) compared to 5-H (**35a**: δ = 2.79 ppm; **35b**: δ = 2.68 ppm; **35c**: δ = 2.58 ppm; **35d**: δ = 3.48 ppm (includes deshielding effect of α -phenyl group); **37**: δ = 2.56–2.68 ppm). This indicates that 8a-H is *cis*-oriented and 4-H *trans*-oriented relative to the ester substituent at C-4a.

Scheme 8. Deslongchamps Annulations III to Benzoquinone Monoketals



enolate, which would be (*Z*)-configured, *if* these annulations were 1-step reactions.³⁵

In summary we synthesized a number of acceptor-substituted benzoquinone monoketals (**12–14**). We found that they undergo Deslongchamps annulations with standard Nazarov reagents (**15a–d**) or their lactone-containing variants (**18a,b**). These annulations proceeded with a high degree of both simple and induced diastereoselectivity. The initially obtained octalindiones (**32, 34a–d, 36**) or their readily prepared de(*tert*-butoxy)carbonylation products (**35a–d, 37**) exhibit five to six functional groups. The lactone-based Nazarov reagents **18a,b** furnished the tricyclic annulation products **38a,b**, respectively. They feature six functional groups and a spirolactone moiety. Since diterpenoids with a spirolactone-substituted decalin scaffold are widespread⁵² and their syntheses are an area of current activity,⁵³ accessing such compounds by the strategy shown in Scheme 8 is an interesting perspective.

Acknowledgment. The authors thank Dr. Jens Geier and Dr. Manfred Keller (Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg) for the X-ray analyses.

Supporting Information Available. Experimental procedures, characterization data, copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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