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Deslongchamps Annulations with Benzoquinone Monoketals

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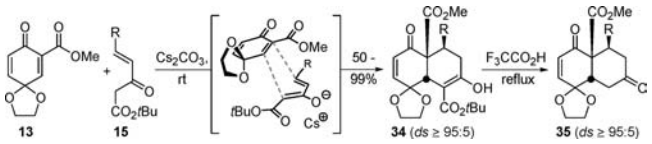
ABSTRACT



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 ≥ 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 antibiotics[3] 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 family[6] 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 reactions[10] or Robinson annulations.[11] The Hajos–Parrish–Wiechert–Eder–Sauer variant[12] 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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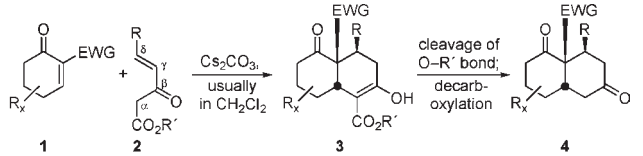
Originally cationic approaches predominated,[14] but now radical-induced[15] or radical-cation-induced[16] (poly)cyclizations exist as well.

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

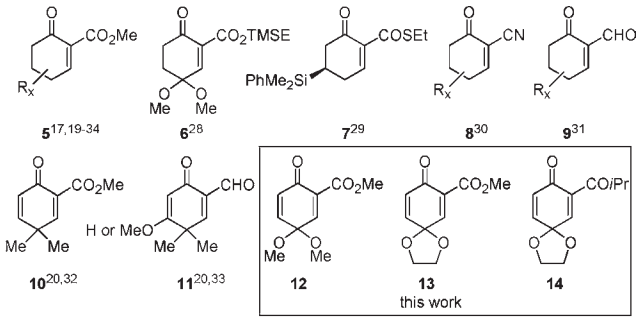


EWG = electron-withdrawing group

[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-ketoester[18]) to an ester- or a similarly substituted cyclohexenone **1** (Scheme 1).[19−34] Such annulations[35] 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).

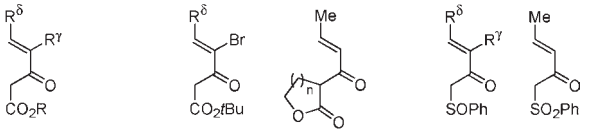
Scheme 2. Scope of Deslongchamps Annulations with Respect to Cyclohexenones or Cyclohexadienones



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)



R = *t*Bu: **15**[17,19-22,26,27,32] **17**[21] n = 1: **18a**[46] (cf. also 28) **19**[32,34] **20**[32]
R = allyl: **16**[22,23,25,29-31,32,34] n = 2: **18b**

Benzoquinone monoketal **12** was obtained like its analogue containing $C(OEt)_2$[36] instead of $C(OMe)_2$, by oxidizing a solution of ester **21**[37] in methanol with $PhI(OAc)_2$[38] (Scheme 4). Quinone spiroketal **13** resulted from the commercially available acid **22** after a regioselective etherification with chloroethanol and esterification with H_2SO_4 and methanol. The resulting ester **24**[39] decomposed when exposed to $PhI(OAc)_2$ but gave 93% **13** when oxidized with $PhI(O_2CCF_3)_2$.[40] While ester-substituted benzoquinone

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(22) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091–1094.
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(29) Trudeau, S.; Deslongchamps, P. *J. Org. Chem.* **2004**, *69*, 832–836.
(30) Caron, P.-Y.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 508–511.
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(37) Compound **21** was prepared from 5-methoxysalicylic acid: Chaudhury, D. N.; King, H. I.; Robertson, A. *J. Chem. Soc.* **1948**, 2220–2222.
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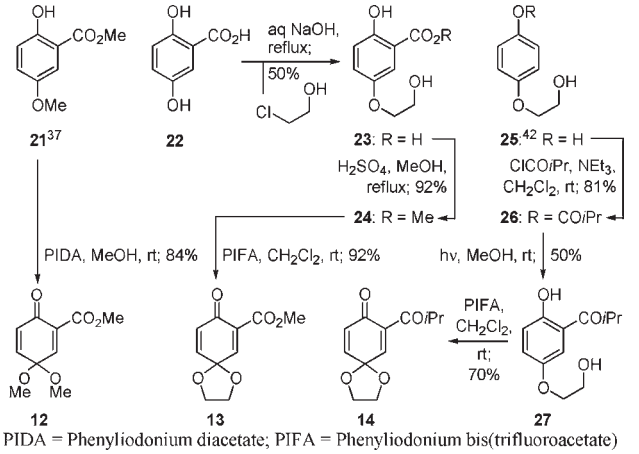
(40) First respective application of this reagentTamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927–3930.

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 (λ = 254 nm) provided ketone **27**, which was oxidized with $PhI(O_2CF_3)_2$.[40]

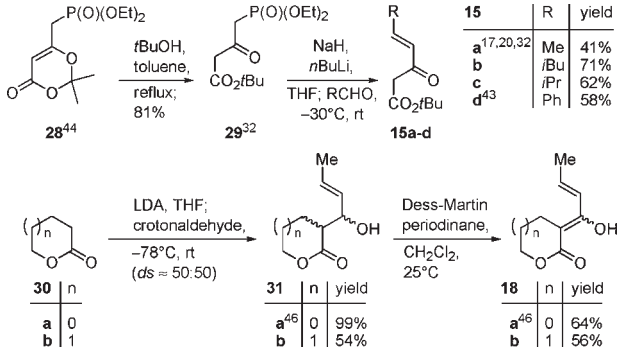
Scheme 4. Synthesis of Benzoquinone Monoketals **12**–**14**



PIDA = Phenyliodonium diacetate; PIFA = Phenyliodonium bis(trifluoroacetate)

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 described[27]).[45] Nazarov reagents **18a**[46] and **18b** emerged from aldol addition/oxidation[47] sequences engaging γ-butyrolactone (**30a**) and δ-valerolactone (**30b**), respectively, with crotonaldehyde.

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



15	R	yield
a[17,20,32]	Me	41%
b	*i*Bu	71%
c	*i*Pr	62%
d[43]	Ph	58%

30	n
a	0
b	1

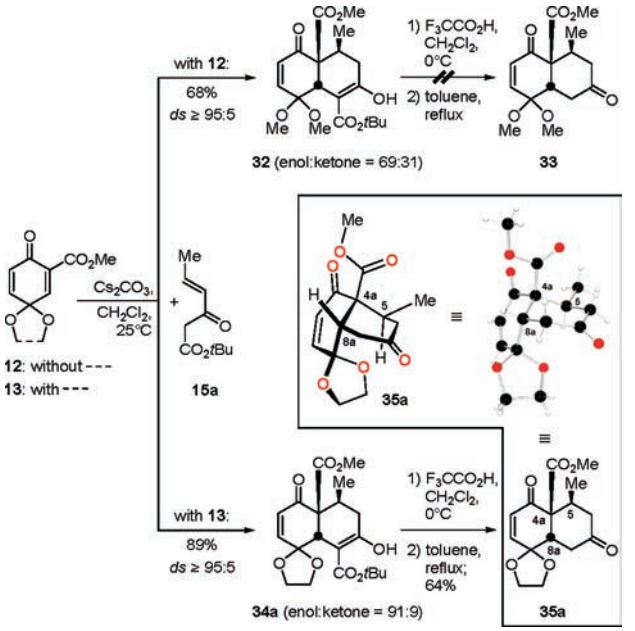
31	n	yield
a[46]	0	99%
b	1	54%

18	n	yield
a[46]	0	64%
b	1	56%

[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.

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 $C(OMe)_2$ moiety in **12**. Another beneficial dioxolane effect was that octalindione **34a**, in contrast to **32**, was cleanly de-*tert*-butylated at 0 °C by CF_3CO_2H (25% solution in CH_2Cl_2). Decarboxylation of the resulting β-ketoacid in refluxing toluene provided octalindione **35a** in 64% yield.

(41) Tsai, Y.-F.; Peddinti, R. K.; Liao, C.-C. *Chem. Commun.* **2000**, 475–476.

(42) Crombie, L.; Ryan, A. P.; Whiting, D. A.; Yeboah, S. O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2783–2786.

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

(44) Boeckman, R. K.; Thomas, A. J., Jr. *J. Org. Chem.* **1982**, *47*, 2823–2824.

(45) We developed this access because the condensation between the bis(enolate) of *tert*-butyl acetoacetate and diethyl chlorophosphonate[32] provided **29** in unsatisfactory yields and with inseparable contaminants.

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(47) Dess, A. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(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.

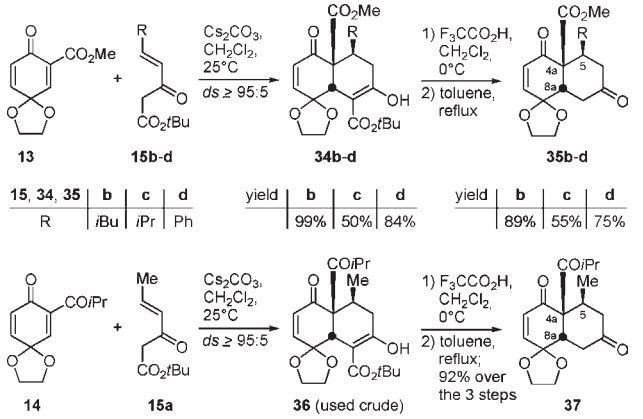
(49) When the Nazarov reagent **15a** was deprotonated by K_2CO_3 or *n*-BuLi in the presence of the benzoquinone monoketal **13** or before the latter was added, respectively, the Deslongchamps adduct **34a** did not form at all.

(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 analysis[50] 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]

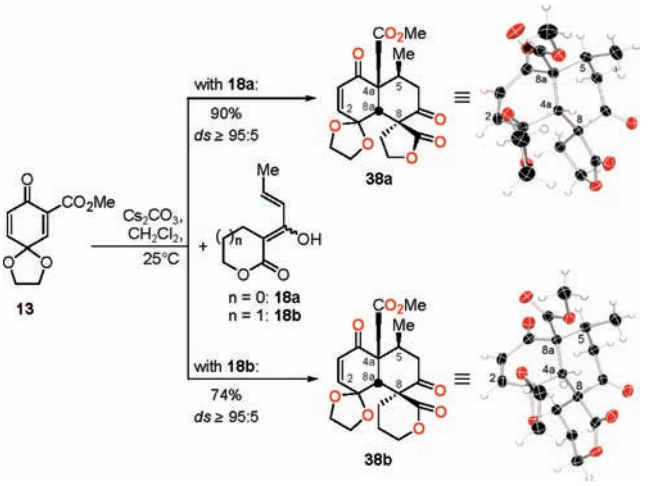
The ester-substituted benzoquinone monoketal **13** accepted the somewhat bulkier Nazarov reagents **15b**−**d** almost as readily as **15a** and again with excellent diastereoselectivities (ds ≥ 95:5;[48] Scheme 7). Subsequent defunctionalizations by trifluoroacetolysis/thermolysis were feasible, too. 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 enolate, which would be (*Z*)-configured, *if* these annulations were 1-step reactions.[35]

Scheme 8. Deslongchamps Annulations III to Benzoquinone Monoketals



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 diasteroselectivity. 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 widespread[52] 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.

(51) This conclusion is not only based on a plausible analogy but also on circumstantial ^{1}H NMR evidence. In $CDCl_3$ 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.

(52) Review: Bruno, M.; Piozzi, F.; Rosselli, S. *Nat. Prod. Rep.* **2002**, *19*, 357–378.

(53) Review: Bartoli, A.; Rodier, F.; Commeiras, L.; Parrain, J.-L.; Chouraqui, G. *Nat. Prod. Rep.* **2011**, *28*, 763–782.