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[4+2]-Annulations leading to configurationally homogeneous bicyclo[4.4.0]decanediones with five new stereocenters

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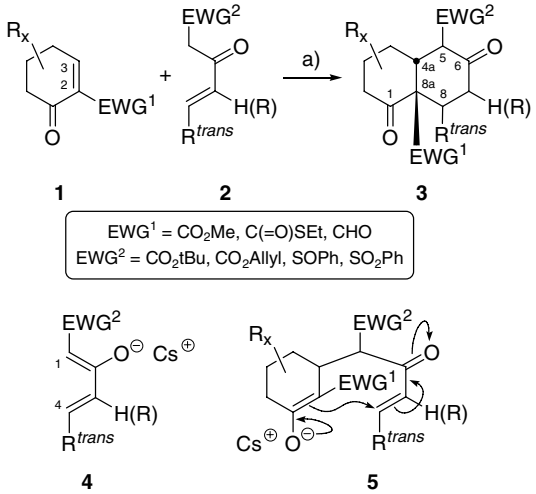
Dedicated to Professor Manfred Christl (Universität Würzburg) at the occasion of his 65th birthday

Abstract—Bicyclo[4.4.0]decanediones **16** and **21** were prepared in 3-step sequences and their congener **23** as well as bicyclo-[4.4.0]decanetrione **24** by subsequent modification. In step 1 the cesium enolate of γ,δ-unsaturated β-ketoester **13** was annulated to the ester-substituted cyclohexenones **6** (achiral; simple diastereoselectivity observed) and **18** (chiral; simple and induced diastereoselectivity observed). In step 2, Pd-catalyzed fragmentation provided bicyclo[4.4.0]decanediones **15** and **20**, respectively. De(methoxycarbonylation) of the latter in step 3 furnished compounds **16** and **21**.

The annulations of deprotonated γ,δ-unsaturated β-ketoesters **2** (or so-called 'Nazarov reagents'[1]) to 2-(alkoxycarbonyl)-2-cyclohexen-1-ones (**1**) or similarly activated cyclohexenones were discovered in 1988[2a] and widely explored by Deslongchamps et al. over the last two decades.[2b–n] They start with a Cs_2CO_3-mediated deprotonation of Nazarov reagent **2**, which gives dienolate **4** (Scheme 1). This species annulates to the ester-substituted cyclohexenone **1** by a concerted = Diels–Alder mechanism (believed to prevail in $CHCl_3$ or AcOEt[2d,3]) or two successive Michael additions, that is, via enolate **5** as an intermediate (suggested to be favored in CH_3CN or DMF[2d]). Perfect simple diastereoselectivity was observed in many of these 'Deslongchamps annulations' as well as the high levels of induced diastereoselectivity when chiral cyclohexenones[2c,e,f,m] or chiral bicyclic dienolates[2g,j,l] were employed. The initially obtained enolates of decalindiones **3** could be scavenged in situ by intramolecular aldol[2b,c] or 1,4-additions.[2l] Alternatively, decalindiones **3** were liberated from their substituent EWG^2 at C-5 by acidolysis (for $EWG^2 = CO_2t\text{-}Bu$[2a–f,h,k]), under palladium catalysis (for $EWG^2 = CO_2Allyl$[2g,i–n]), by reduction (for $EWG^2 = SO_2Ph$[2e,l]) or by a β-elimination (for $EWG^2 = SOPh$[2e,l]). In yet another variation, after decarboxylating bromine-containing derivatives of annulation products **3**, exposure to SmI_2 delivered an enolate, which could be engaged in intramolecular aldol additions.[2h]



Scheme 1. Reagents and conditions (Ref. 2a): (a) Cs_2CO_3 (0.4–2.0 equiv), $CHCl_3$ or AcOEt or THF, room temperature; → ⩾98:2 *cis*-orientation of C^8–R^{trans} versus C^{8a}–EWG^1 bond; same conditions in acetonitrile or DMF → 75:25 and 54:46 preference, respectively, for *cis*-orientation of C^8–R^{trans} versus C^{8a}–EWG^1 bond.

Being interested in highly substituted bicyclo-[4.4.0]decanediones ourselves, we extended the scope

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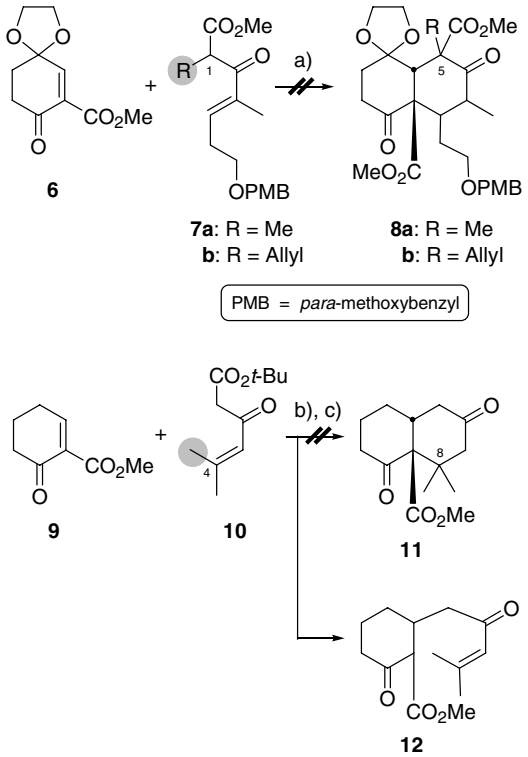
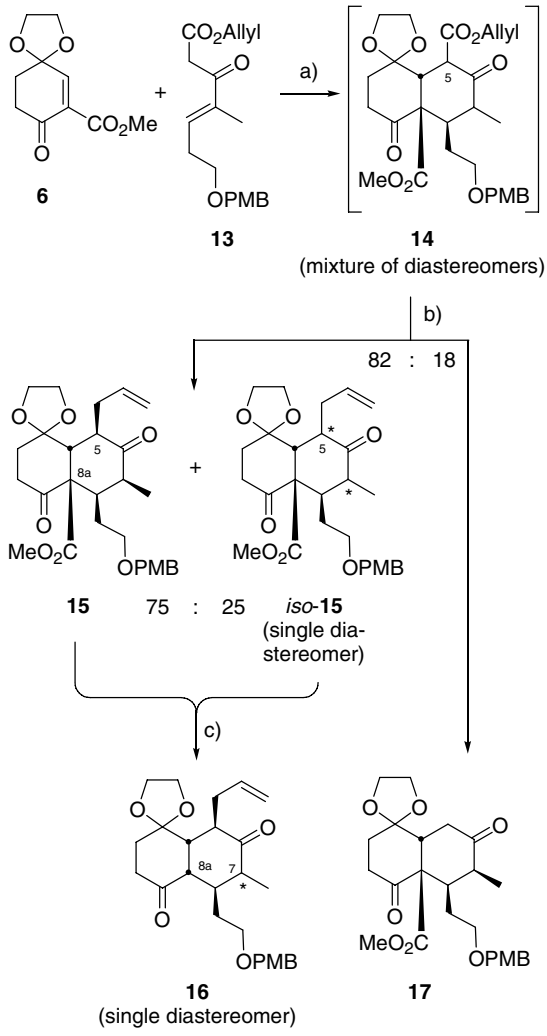
of Deslongchamps' annulation by modifying the emerging decalindiones **3** by introducing an allyl group at C-5 ($EWG^2 \rightarrow$ allyl) and by de(methoxycarbonylating) C-8a subsequently ($EWG^1 \rightarrow H$). To the best of our knowledge, these transformations are unrecorded.[2]

First, we attempted to install a methyl or an allyl group at C-5 of annulation products **8a** or **b** by annulating the α-methylated and α-allylated Nazarov reagents **7a** and **b**,[4] respectively, to the ester-substituted cyclohexenone **6**.[5] However, after 16 h the Nazarov reagents were re-isolated essentially unchanged by filtration through silica gel while none of the annulation products **8a**,**b** was found. This suggests that center C-1 of the dienolate intermediate is too sterically hindered through the extra substituent for becoming involved in Deslongchamps annulations at all. This is commemorative of the earlier observation[2d] that the 4,4-dimethylated Nazarov reagent **10** and cyclohexenone **9** do not react to give annulation product **11** but Michael adduct **12** (Scheme 2).

In response to these difficulties we introduced the allyl group at C-5 *after* the Deslongchamps annulation **6** + **13**[6] → **14**[7] (isolated in an 88% yield after filtration through silica gel) *in exchange* for a CO_2-allyl substituent located at C-5 as a placeholder (Scheme 3). This transformation was effected by one of the two procedures developed simultaneously by the Saegusa and



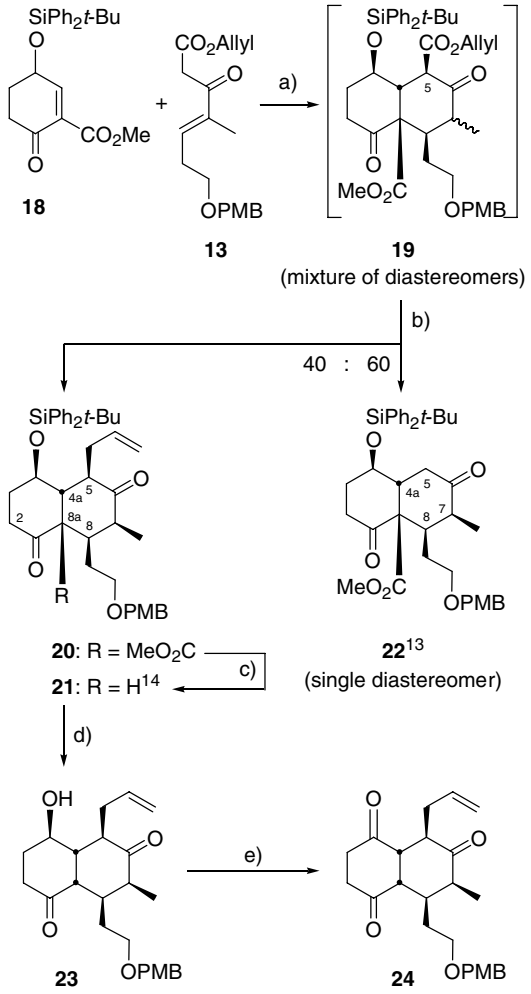
Scheme 2. Reagents and conditions: (a) Cs_2CO_3 (0.5 equiv), CH_2Cl_2, room temperature, 16 h; (b) Cs_2CO_3 (0.45 equiv), $CHCl_3$ or CH_3CN, room temperature, 3 h; (c) CF_3CO_2H, room temperature, 2 h; benzene, reflux, time not specified; 29% [step (b) in $CHCl_3$] or 57% [step (b) in CH_3CN] over the 2 steps (Ref. 2e).



Scheme 3. Reagents and conditions: (a) Cs_2CO_3 (2.2 equiv), CH_2Cl_2, room temperature, 3 h; 88%; (b) $Pd(OAc)_2$ (4 mol %), PPh_3 (16 mol %), THF, reflux, 2 h; 70% **15**:*iso*-**15** = 75:25 separated from 15% **17**; (c) LiCl (2.5 equiv), H_2O (1.2 equiv), DMF, 150 °C, 10 h; 35%.

Tsuji groups for converting allyl β-ketoesters into α-allylketones and CO_2,[8] that is, by exposure to in-situ reduced Pd(II) in THF under reflux.[8a] The diastereomeric 5-allylated products **15** and *iso*-**15** resulted as a 75:25-mixture in 70% yield.[9] The major constituent **15** could be separated by flash chromatography on silica gel.[10] In addition, we isolated 15% decalindione **17**. It was formed from some competing nonallylating de(allyloxycarbonylation) of annulation product **14**.

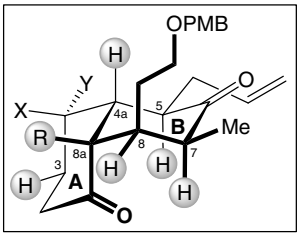
The 75:25-mixture of the 5-allylated decalindiones **15** and *iso*-**15** was de(methoxycarbonylated) under Krapcho conditions, that is, by heating in the presence of LiCl and water in DMF solution.[11] Another mixture resulted. After flash chromatography on silica gel[10] it provided the ester-free decalindione **16** in 35% yield as a single diastereomer of unknown configuration at C-7. It is noteworthy that the 8a-H bond in **16** has the same orientation as the 8a-CO_2Me bond in its precursors **15** and *iso*-**15**. In spite of its stereoselectivity, such a defunctionalization was never used by Deslongchamps et al.[2]



Scheme 4. Reagents and conditions: (a) Cs_2CO_3 (2.0 equiv), CH_2Cl_2, room temperature, 4 h; 95%; (b) $Pd(OAc)_2$ (2 mol %), PPh_3 (8 mol %), THF, reflux, 3 h; 22% **20**, 33% **22**; (c) LiCl (2.5 equiv), H_2O (1.2 equiv), DMF, 150 °C, 10 h; 64%; (d) Bu_4NF (2.2 equiv), THF, room temperature, 16 h; 56%; (e) Dess–Martin periodinane (4.0 equiv in two portions), CH_2Cl_2, room temperature, 2 h; 58%.

The sequence depicted in Scheme 3, which consists of the Deslongchamps annulation between Nazarov reagent **13** and the achiral cyclohexenone **6** and some follow-up chemistry, was equally applicable to the chiral cyclohexenone **18**[2h] as a starting material (Scheme 4). The annulation of dienolate-precursor **13** furnished decalinediones **19** as a mixture of diastereomers, yet with complete induced diastereoselectivity.[12] Filtration and submission to Tsuji's decarboxylative allylation protocol[8a] rendered bicyclic material. Flash chromatography on silica gel[10] allowed to separate 22% of allyl-containing decalindione **20** from 33% of its allyl-free analogue **22**.[13] The former was de(methoxycarbonylated) under the already mentioned Krapcho conditions. This led to yet another decalindione, namely compound **21** (64% yield), wherein again (cf. **15**/*iso*-**15** → **16**, Scheme 3) the configuration at the defunctionalized stereocenter is retained.[14] Desilylation by treatment with anhydrous $Bu_4N^{\oplus}F^{\ominus}$ in THF solution and oxidation with the Dess–Martin periodinane[15] provided decalintrione **24** with fully defined configurations at each of the five stereocenters.

Table 1. Stereochemically significant ^1H NMR coupling constants (Hz) of decalindiones **15**, **16**, **20**, and **23** (500 MHz in $CDCl_3$)



	15	**16**	**20**	**23**
R	MeO_2C	H	MeO_2C	H
X	O	O	*t*-$BuPh_2SiO$	HO
Y	O	O	H	H
$^4J_{3eq,4a}$	1.2	1.6	<1.0	[a]
$^3J_{5,4a}$	8.2	10.4	12.3	13.1
$^3J_{4a,8a}$	—	4.8	—	5.1
$^3J_{8a,8}$	—	4.2	—	<1.0
$^3J_{8,7}$	4.8	[b]	4.7	6.3

[a] In decalindione **23** $^4J_{3eq,4a}$ could not be determined because the resonances of 3-H_{eq} and 3-H_{ax} overlapped and the 4a-H multiplet was not well resolved.

[b] In decalindione **16**, $^3J_{8,7}$ could not be determined because the signals of 7-H and 8-H overlapped; accordingly, the configuration at C-7 remains unknown in this compound.

In the absence of X-ray structural analyses, stereostructures were attributed to the newly obtained decalindiones **15**–**16** and **20**–**24** based on the analysis of the $^1H,^1H$-coupling constants listed in Table 1. The occurrence of a 'W-coupling' between 3_{eq}-H and 4a-H shows that these protons are oriented equatorially in a chair conformer of the A-ring. The magnitude of the vicinal coupling between 4a-H and 5-H allows to deduce that those protons are oriented axially in a chair conformation of the B-ring. Both informations combined mean that there is a *cis*-junction between rings A and B. The magnitude of $J_{4a,8a}$ in compounds **16** and **23** is consistent with this inference. Vicinal 7-H,8-H-couplings ranging from 4.7 to 6.3 Hz are in accordance with those reported for [7,8]*cis*-disubstituted *cis*-fused decalindiones.[16] These conclusions were confirmed by ROESY experiments, which displayed crosspeaks between 4a-H and one of the diastereotopic protons of the 8-CH_2 group (for **20** and **24**) or between 5-H and 7-H (for decalintrione **24**).

The straightforward construction of *cis*-fused decalindiones exhibiting one per-substituted ring and containing 5 (**15**, **16**) or 6 (**20**, **21**, **23**) contiguous stereocenters reported in this study should prove applicable to the synthesis of polycyclic scaffolds. Studies aiming at an improved efficiency of introducing the allyl-substituent are in progress and will be reported in due course.

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11. Review: Krapcho, A. P. *Synthesis* **1982**, 805–822, and 893–914.
12. Dienophile **18** and dienolates are known to be subject to this kind of asymmetric induction, cf. Refs. 2g–j.
13. Alternatively, decalindione **22** was obtained *selectively* from allyl ester **19** by treatment with $Pd(PPh_3)_4$ (10 mol %) and morpholin (10 equiv) in THF at room temperature (70% yield). The stereostructure of compound **22** is in accordance with the ROESY-crosspeaks 4a-H/8-CH_2–CH_2OPMB (only low-field proton of the italicized group) and 5-H^{ax}/7-H.
14. The stereostructure of decalindione **21** was deduced from ROESY-crosspeaks 4a-H/8-CH_2–CH_2OPMB (only high-field proton of the italicized group) and 8a-H/2-H^{ax}. The orientation of the methyl group should be the same as in the follow-up products **23** and **24**.
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16. See Ref. 2e: 7β,8β-disubstituted *cis*-decalindiones exhibit $J_{7,8} = 5.0$ Hz, which is clearly different from $J_{7,8} > 11$ Hz in 7α,8β-disubstituted *cis*-decalindiones (where, in addition, a preference for the *inverted* chair conformation causes $J_{4a,5} = 5.0$ Hz).