Pergamon

Tetrahedron Letters, Vol. 38, No. 23, pp. 4017-4020, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00823-X

An Efficient Route to Functionalized Dienes for Decalin Synthesis

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Abstract. Reaction of the trimethylsilyl (TMS) enol ethers **6** derived from the conjugate addition of organocopper reagents to 3,4-dimethylcyclopentenone with dimethyl dioxirane (DMDO) leads to α-hydroxy ketones **7** with predominantly the *syn*-methyl orientation. Exposure of these systems to methanolic lead tetraacetate ($Pb(OAc)_4$) delivers aldehydic esters **8** which are homologated to the desired *E*-dienes **9** using Yamamoto's allylic phosphine oxide reagent. © 1997 Elsevier Science Ltd.

A variety of biologically active natural products contain the decalin ring system as a core structural unit; the clerodanes, arenols, chlorotricholides, and compactins are typical examples. The clerodanes and arenols have either a *cis*- or *trans*-fused decalin ring with a characteristic 9-alkyl-8,9-dimethyl substitution pattern.[1] A common approach to the *trans*-decalin systems uses annulation chemistry followed by the introduction of the quaternary stereocenter through a multi-step sequence. This has afforded several syntheses of complex examples,[2] but they are largely inadequate as a means of accessing the *cis*-fused systems. Recent efforts utilizing the intramolecular Mukaiyama cyclization[3] or the Diels-Alder reaction[4] have produced the *cis*-fused systems; however, lengthy routes were still required to install the B-ring stereocenters.

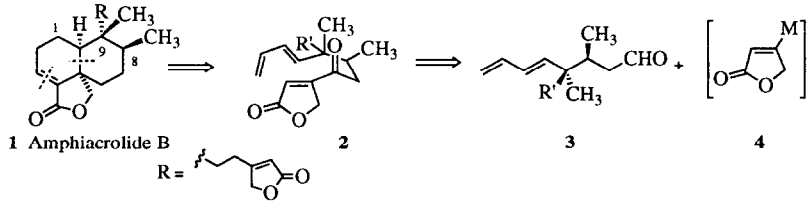


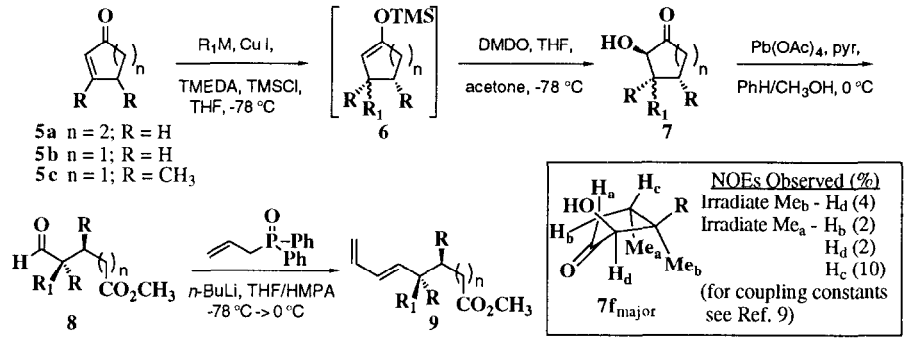
Figure 1

An attractive route to *cis*-decalin natural products, e.g., amphiacrolide B **1**,[5] would use an intramolecular cycloaddition of a functionalized substrate that contains the C8 and C9 stereocenters as directing elements for the Diels-Alder process. This strategy would require a general, stereocontrolled synthesis of functionalized dienes **3** (Fig. 1) that not only has good control in the formation of the C9 center but also provides access to either the

syn- or *anti-* methyl orientation. Herein we report an efficient process for the construction of such functionalized dienes.

The oxidative cleavage of silyl enol ethers obtained by a stereoselective, conjugate addition of a copper species to a substituted cyclic enone provides the desired substitution in the tether and allows differentiation of the two chain ends; an aldehyde for homologation into the diene, and an ester as a handle for the subsequent attachment of the dieneophile (Scheme 1). The addition and trimethylsilyl chloride (TMSCl) trapping was accomplished using a modification of Johnson's procedure.[6] We found that alkyl copper reagents gave excellent yields with simple cycloalkenones, but dialkyl cuprates were necessary for the addition to 3,4-dimethylcyclopentenone[7] (Table I, entries d-g). The best results were obtained when a THF solution of the enone was added to a cuprate/TMSCl mixture at -78 °C followed by the addition of *N,N*-tetramethylethylenediamine (TMEDA). The TMEDA should be added only after the starting enone has been consumed (as noted by TLC) because its addition to the cuprate mixture prior to the addition of the enone led to sluggish reactions due to precipitation of the organometallic reagent. Hexamethylphosphoramide (HMPA) was a necessary additive for the phenyl cuprate addition to **5c**, however no TMEDA was required for silyl enol ether formation.[8] Dilution of these reaction mixtures with pentane and removal of the copper salts by filtration through a Celite pad facilitated the Johnson workup.

Scheme 1



The stereoselectivity of these additions could be determined from the ratio of the vinylic enol ether resonances (δ = 4.30-4.80 ppm) in the ^{1}H NMR spectra of the crude reaction mixtures. The best stereocontrol was obtained using higher order cuprates which may be due to the homogeneity of the reactions relative to their alkyl copper counterparts. An NOE difference study on the major diastereomer from the addition of divinyl cuprate to **5c** confirmed that addition had occurred *anti-* to the γ-methyl substituent.[9]

The silyl enol ethers were routinely oxidized to the α-hydroxy ketone by treatment with dimethyldioxirane (DMDO, THF, -78 °C),[10] a method that provided **7** directly.[11] This procedure was preferred over the Rubottom conditions (RCO_3H)[12] because DMDO oxidation of the enol ether was fast and excellent chemoselectivity for the silyl enol ether was obtained (entries c and f). Ketone products from competitive hydrolysis of the silyl enol ether were also not observed. The stereospecificity of the hydroxylation was

excellent except for the phenyl case (entry g) where it was presumed that the steric bulk of the phenyl moiety eroded the selectivity.

Table 1. Formation of α-hydroxy ketones **7** and homologation to the dienes **9.**

Entry	n	R	R_1M	**6** (*syn/anti*)	**7** (%)	*syn:anti*	**8** (%)	**9** (%)
a	2	H	$PhCH_2MgCl$	-	92	-	87	86
b	1	H	$(CH_3)_2CuLi$	-	92	-	74	87
c	1	H	$(CH_2{=}CH)_2CuLi$	-	90	-	ref. 13	63*
d	1	CH_3	$(CH_3)_2CuLi$	-	79	-	90	74
e	1	CH_3	$PhCH_2MgCl$	(2.4:1)	75	(2.4:1)	92	77
f	1	CH_3	$(CH_2{=}CH)_2CuLi$	(6:1)	87	(6:1)	98	70
g	1	CH_3	Ph_2CuLi	(>20:1)	-	(2:1)	46*	77

* - Yield for two steps.

Conversion of **7** into the corresponding diene required oxidative cleavage of the C1-C2 bond and homologation of the derived aldehyde. The aldehydic esters **8** were generated using methanolic $Pb(OAc)_4$ in the presence of a pyridine buffer. The neopentyl products (**8d-g**) were prone to auto-oxidation but rapid chromatography through a short SiO_2 plug and their use within 24 h gave reproducible results. Several methods were surveyed for the homologation into the requisite diene. The Wittig reagent from allyl triphenylphosphonium bromide (*n*-BuLi, PhH) provided a moderate yield of the diene (39%) as a mixture of *Z/E* isomers, while the Julia-Lythgoe sulfone protocol[14] or a sequential Wittig homologation process (stabilized ylide, reduction, oxidation, methylene Wittig) were capricious and lengthy. The reductive elimination of the diastereomeric β-acetoxysulfones led mainly to vinyl sulfone products, and the more vigorous conditions required for the reaction of a stabilized ylide with neopentyl substrates ($PhCH_3$, Δ) led to extensive decomposition products. A convenient reagent that offered good nucleophilicity and ease of handling was the lithium anion of Yamamoto's allyl diphenyl phosphine oxide[15] which smoothly provided the diene in a single transformation with excellent stereocontrol (>95:5 *E/Z*).

A stereoselective synthesis of functionalized dienes has been described that is suitable for clerodane and arenol synthesis; the ester moiety is readily transformed into an aldehyde, iodide, or a Weinreb amide for coupling purposes. The *syn*-methyl orientation can be obtained with a high degree of stereoselectivity while the *anti*-congener would be accessible from the unsymmetrically substituted enone. The application of the intramolecular Diels-Alder cycloaddition for decalin synthesis is currently underway and the results will be reported in due course.

Acknowledgement: Financial support by the National Institutes of Health (Grant # 1-R15-CA70990-01) is gratefully acknowledged.

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9) For use of NOE in five-membered ring assignments, see: Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157-173. ^{1}H NMR for $\mathbf{7f}_{major}$ ($CDCl_3$) δ 5.80 (dd, J = 17.6, 11.1 Hz, 1H), 5.18 (d, J = 11.1 Hz, 1H), 5.14 (d, J =17.6 Hz, 1H), 3.96 (dd, J = 3.9, 1.8 Hz, 1H, H_d), 2.60 (dd, J = 19.6, 9.1 Hz, 1H, H_a), 2.39 (qd, J = 7.4, 3.7 Hz, 1H, H_c) 2.30 (d, J = 4.0 Hz, 1H, D_2O exchanges), 2.06 (ddd, J = 19.6, 3.7, 1.8 Hz, 1H, H_b), 1.22 (s, 3H, Me_b), 1.13 (d, J = 7.3 Hz, 3H, Me_a) ppm.

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13) Aldehyde **8c** rapidly isomerizes to the conjugated enal so the cleavage reaction was performed without pyridine and the crude product used in the homologation reaction. As chromatography (SiO_2) also caused rapid isomerization, the material was characterized as the enal. Methyl 4-formyl-4Z-hex-enoate: IR ν 2847, 2718, 1738, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.37 (s, 1H), 6.66 (q, J = 7.0 H, 1H), 3.66 (s, 3H), 2.59 (t, J = 7.5 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.03 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 194.7, 173.3, 151.2, 142.6, 51.6, 32.2, 19.3, 14.8 ppm.

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(*Received in USA* 2 *April* 1997; *accepted* 23 *April* 1997)