An unprecedented stereoselective [2+2] cycloreversion of cyclobutanones[†]

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A one-pot metathetic ring opening of substituted bicyclo[3.2.0]heptenones to linear polyene ketones is described. The reaction proceeds with conservation of the endocyclic (Z)-double bond. *Exo*-substituted vinylcyclobutanones result in (4Z, 6E)-configured trienones, while *endo*-substituted phenyl derivatives generate (4Z, 6Z)-configured dienones.

Vinylcyclobutanones are versatile building blocks in preparative organic chemistry as they undergo a remarkable diversity of rearrangement reactions.¹ In particular, transformations of easily accessible addition products of cyclopentadiene and vinylketenes² have been thoroughly investigated over the past 30 years. For instance, Dreiding and Danheiser reported the thermal or acid-catalyzed Cope rearrangement of I to bicyclo-[4.2.1]nonenones II (Scheme 1).³ This reaction was often accompanied by [1,3]-rearrangements to cyclohexenones III, or, depending on the substitution pattern, by a [1,2]-migration to IV.⁴ Paquette *et al.* used I in an elegant one-pot alkenvlation/ oxy-Cope/methylation sequence for the synthesis of the structural core V of ophiobolins and other natural products.⁵ Finally, Danheiser et al. reported the oxyanion-accelerated [1,3]-rearrangement of *in situ* reduced I to cyclohexenols VI.⁶ Similar 2-carbon ring extensions were described by Cohen et al. who elaborated the method into a synthesis of (-)- β -selinene.^{7,8} Importantly, in all these rearrangements, the cyclopentene ring does not open.

Herein, we report a novel reaction of compounds I: the oxyanion-promoted [2+2]cycloreversion of cyclobutanones 1 triggered by an *in situ* alkylation with alkyl or aryllithium reagents in the presence of catalytic amounts of DMPU or



Scheme 1 Rearrangements of bicycloheptenones.

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Shanghai 201203, China. E-mail: andreas.goeke@givaudan.com † Electronic supplementary information (ESI) available: Experimental procedures, characterization of new compounds and spectra. See DOI: 10.1039/c0cc02694h **Table 1** Screening of reaction parameters for the cycloreversion of vinyl bicycloheptenones^a



Entry	Reagent	Additive (mol%)	Product (R)	Yield [%] ^c 85	
1	<i>n</i> -BuLi	_	3a , (<i>n</i> -Bu)		
2	n-BuLi	TMEDA (10)	2a, (n-Bu)	15	
3	n-BuLi	DMPU (5)	2a, (n-Bu)	79 $(68)^d$	
4	n-BuLi	HMPT (5)	2a, (n-Bu)	55	
5	n-BuLi	DMPU (300)	2a, (n-Bu)	45	
6	n-BuLi	HMPT (300)	2a, (n-Bu)	51	
7	n-BuLi	12-C-4 (10)	3a, (n-Bu)	89	
8^b	MeMgBr	TMEDÀ (10)	3b , (Me)	80	
9	KH^{d}	DMPU (5)	Decomp.		

^{*a*} The addition of *n*-BuLi (1.05 equiv.) to the bicyclic ketone **1a** was performed in THF at -78 °C, then added the catalyst and refluxed for 6 h. ^{*b*} The reaction was carried at 0 °C, then refluxed for 6 h. ^{*c*} Isolated yield after chromatography. ^{*d*} Alcohol **3a** was used as substrate.

HMPT as complexing agents to yield functionalized polyene ketones **2** with high chemo- as well as diastereoselectivity (Table 1). It is important to note that this metathetic cycloreversion is different from a formal retro-[2 + 2] cycloaddion to ketone **4**; such an oxyanion-promoted fragmentation had indeed been described by Snider.⁹ Polyenes of type **2** constitute an important substructure in pheromones,¹⁰ retinoids¹¹ and complex antibiotics.¹² For instance, (3E,5Z)-1,3,5-undecatriene **5** occurs in many natural essential oils, *e.g.* pineapple and galbanum.¹³ The (5Z)-double bond is important for its extremely low odor threshold and olfactory quality.



Recently, keto and hydroxy derivatives **6** were also claimed for its use in the flavor and fragrance industry. These compounds were prepared by Wittig reactions of α , β -unsaturated aldehydes.¹⁴ However, stabilized ylides usually do not react diastereoselectively and produce considerable amounts of *trans*-configured olefins that possess undesirable odor properties. Therefore, we decided to elaborate this cycloreversion reaction also with respect to a structure–odor correlation study of new undecatriene analogues.¹⁵ While the reaction of **1a**

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with *n*-BuLi in refluxing THF resulted in the formation of the trivial adduct **3a** (Table 1, entry 1), the cycloreversion of the intermediate lithium alkoxide only occurred in the presence of Li-chelating agents. Thus, using TMEDA as an additive led to trienone **2a** in a yield of 15% (Table 1, entry 2).

This initial result could be improved by using catalytic amounts of DMPU or HMPT with increased Li-binding affinities (Table 1, entries 3 and 4).¹⁶ The use of stoichiometric or higher concentrations of DMPU (Table 1, entry 3 vs. 5) did not further improve yields. Application of the crown ether 12-C-4 likewise failed to promote the ring opening (Table 1, entry 7). Furthermore, a magnesium alkoxide (Table 1, entry 8) generated from the reaction of MeMgBr to the convex face of **1a** also failed to undergo the cycloreversion. However, the stepwise protocol *via* compound **3a** resulted in a higher yield of ketone **2** (Table 1, entry 3) but an attempt of performing the same cycloreversion using KH in refluxing THF led to the decomposition of the starting material (Table 1, entry 9). Importantly, in all cases in which



Scheme 2 Thermal rearrangement of silylether 7.

 Table 2
 Ring opening of substituted bicycle[3.2.0]heptenones^a

the ring-opening occurred, the *cis*-configured double bond in **1a** retained its configuration in the (4Z, 6E)-configured trienone **2a**.

Since rate accelerations were achieved by the introduction of silyloxy groups into Cope systems,¹⁷ an attempt to also facilitate the cycloreversion started from silylether 7 which was subjected to thermal conditions up to 300 °C. However, only the Cope rearrangement product **8** was isolated after *in situ* hydrolysis (Scheme 2). Apparently, a more dissociated character of the intermediate metal alkoxide is necessary for the cycloreversion to proceed.

Following this surprising finding of the cycloreversion which contrasts Danheiser's earlier results of the 1,3-ring expansion sequence,⁶ we addressed questions regarding the scope of this new ring opening (Table 2). The substrates 1a-d and 9 were synthesized by $[\pi 2_s + \pi 2_a]$ cycloadditions of cyclopentadiene or 5,5-ethylenecyclopenta-1,3-diene with ketenes (prepared in situ via dehydrochlorination of the corresponding α,β -unsaturated acid chlorides using triethylamine).^{2b,4a} It is well known that compound 9 is formed with high endo-selectivity while vinyl-substituted cycloadducts 1 are generated with exo-preference.4b Upon addition of organolithium reagents to substrates 1 and 9 followed by heating of the resulting intermediates 11, these selectivities were translated into aryldienones 10 with exclusive (4Z, 6Z)-configuration (Table 2, entries 1–3) and into (4Z,6E)-configured trienones 2 with different substitution patterns (Table 2, entries 4-8).

 R^3 R^3 O R^4 R^4

		$R^{3} \xrightarrow{R^{4}} R^{2} \xrightarrow{R^{4}} R^{3} \xrightarrow{R^{4}} R^{3$						
Entry	Bicyclus (polyene)	$\frac{11}{R^1} = \frac{1}{R^1}$	$\frac{12}{R^2}$	R ³	13 R ¹		Yield $(\%)^{b} (6E:6Z)^{c}$	
1	9	Ph	Me	Н	<i>n</i> -Bu	2	77	
	(10a)	N		**			(<2:98)	
2	9 (10b)	Ph	Me	Н	s-Bu	I	(< 2.98)	
3	9	Ph	Me	Н	Ph	6	51	
	(10c)						(<2:98)	
4	1a (2b)	Me	vinyl	Н	s-Bu	2	71	
5	(20) 1a	Me	vinvl	Н	Me	1	(>98:2) 46	
0	(2c)	1,10	,			•	(>98:2)	
6	1b	Me	propenyl	Н	<i>n</i> -Bu	12	31	
7	(2d)	N		d	P	4	(8:2)	
1	lc	Me	vinyl	u	<i>n</i> -Bu	4	60°	
8	(2e) 1a	Me	vinvl	н	Ph	6	(8.2)	
0	(2f)	WIC	viiiyi	11	1 11	0	$(9:1^{f})$	
	· · ·							

R⁴Li, THF

^{*a*} The addition of R⁴Li (1.05 equiv.) to the bicyclic ketone **1** or **9** in the presence of DMPU (0.05 equiv.) was performed in THF at -78 °C, then refluxed for the time indicated. ^{*b*} Isolated yield after chromatography. ^{*c*} E/Z ratio determined by NMR. ^{*d*} R³–R³ = CH₂–CH₂. ^{*e*} Isolated yield after distillation. ^{*f*} E/Z ratio determined by GC-MS.

Although the outcome of these cycloreversions is in accordance with an allowed retro- $[\sigma_2_s + \sigma_2_a]$ ring opening, the reaction seems to rather involve a stepwise mechanism *via* intermediate Li-complexes 12.⁷ Its formation corresponds to a reversed allyl (benzyl) lithium addition¹⁸ of initially formed compounds 11. Such retro-allyl lithium additions were found to be about ten times faster than the reversal of the corresponding magnesium alkoxides.^{18a} This also explains why Grignard addition products of 1 did not at all undergo the ring-opening under standard reaction conditions (Table 1, entry 8).

The subsequent cleavage of the cyclopentenyl ring in 12 to enolate 13, however, has to be explained by the increased electrophilic potential of lithium¹⁹ (*vs.* K and Mg); although species 12 must be regarded as a canonical structure of a delocalized contact ion pair of allyl/benzyl anions, a tighter geometrical stabilization of the involved intermediates in comparison with those that involve K as the counterion are obvious—independent from the catalytic activity of DMPU. Intermediate 12 is expected to be highly reactive and short lived; it rapidly fragments into more stable Li-enolates 13, before the dynamic properties²⁰ of the allyl anion result in a loss of stereochemistry.

This assumption of a reactive and short-lived allyl lithium species is also fuelled by the conversion of less substituted *endo*-1d (Scheme 3). The reaction takes exclusively the route of the 1,3-shift (α -attack *via* 12'b) leading to the tertiary bicyclic alcohol 14. The bond order and electron density of this less substituted derivative is diminished at the γ -position²⁰ rendering a less reactive species which undergoes isomerization as well as rotation around the pentanoyl group.

In comparison to the formation of compounds 10 from *endo*-9, a strikingly different result was observed in the transformation of vinyl-substituted cyclobutanone *endo*-1a to (E,E,Z)-configured trienone 16 as described in Scheme 4. The diastereoselective shift of the triene unit into the β -position of the carbonyl group can be explained by a [1,7]-H-shift in postulated intermediate 15.²¹ The neighboring enolate



Scheme 3 Cycloreversion of endo-1d.



Scheme 4 Ring-opening of endo-1a followed by a 1,7-H-shift.

may cause a carbanion-acceleration of this hydrogen shift.²² For geometrical reasons, this formal [1,7]-H-shift cannot occur in the (6E)-configured intermediate enolate **13** (Table 2).

In conclusion, we have uncovered a novel metathetic cycloreversion of 7-vinyl and aryl bicyclo[3.2.0]hept-2-en-6-ones giving rise to linear polyene ketones with high selectivity. This ring opening offers a fascinating two-step route to olfactory useful compounds from easily available starting materials.

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