Synthetic Methods

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Tandem Cross-Dimerisation/Oxonia-Cope Reaction of Carbonyl Compounds to Homoallylic Esters and Lactones**

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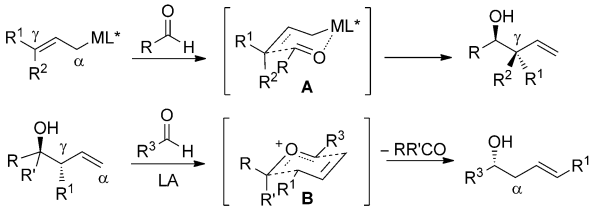
Dedicated to Professor Georg Fráter

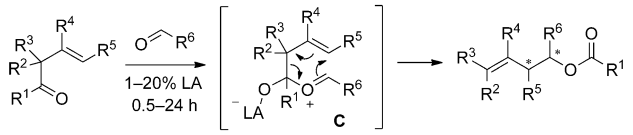
Homoallylic subunits constitute ubiquitous structural motifs in organic chemistry, and their stereoselective introduction is of fundamental academic and industrial importance. In addition to carbonyl ene reactions,[1] allylations of carbonyl compounds with allylic organometal species represent the main route to these subunits.[2] The reactivity of diverse reagents can be tuned to effect high levels of diastereo- and enantioselectivity, which usually originates from the chairlike 6-membered-ring transition state **A** (Scheme 1).[2b] A characteristic feature of this approach is the reaction with allylic



Scheme 1. Allylation of aldehydes and allyl transfer to α adducts. L = ligand, LA = Lewis acid, M = metal.

inversion of allyl metal species to form γ products. Changing this regioselectivity toward the homoallylic α adducts represents a significant challenge.[3] The Lewis acid catalyzed allyl transfer of secondary and tertiary alcohols to carbonyl compounds[4] is an established method and has been used successfully in natural product synthesis.[5] This reaction proceeds with inversion of configuration at the hydroxy group via an oxonia-Cope transition state **B** (Scheme 1); one equivalent of a carbonyl compound is sacrificed, thus assuring an irreversible course of the rearrangement.

Herein, we describe a stereoselective and conceptually new allylation method of broad scope (Scheme 2). The allyl

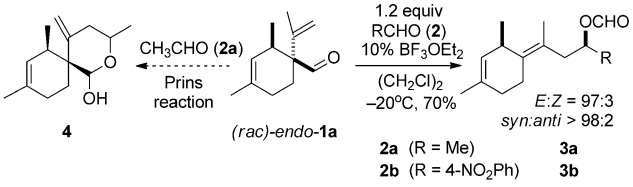


Scheme 2. Tandem cross-dimerisation/oxonia-Cope sequence of two different aldehydes.

unit is not delivered by an organometallic reagent to generate a homoallylic alcoholate, but through a cross-disproportionation of a β,γ-unsaturated carbonyl compound with another aldehyde to result in a homoallylic ester. Unlike in the crossed-Tishchenko reaction,[6] this disproportionation of two different aldehydes is not the result of a hydride transfer, instead it is brought about by an oxonia-Cope rearrangement to form homoallylic esters and lactones.

During investigation of this unique stereoselective transformation, the concept was further developed into a general, convergent, and atom-economical $[n+4]$ ring enlargement to homoallylic macrolides with 9- to 16-membered rings. With regard to the latent functionality embedded in the homoallyl substructure, this novel macrolactonization illustrates a powerful synthetic strategy toward a large variety of important bioactive macrolides.[7] In addition to presenting the scope of this tandem cross-dimerization/oxonia-Cope sequence, we also elucidate its mechanistic and stereochemical principles.

The transformation was discovered during an attempt to synthesize compound **4** as a derivative of oxaspiro odorants that have interesting cassis/grapefruit-like odors (Scheme 3).[8] However, instead of undergoing the expected



Scheme 3. 2-Oxonia-Cope rearrangement of **1a** versus expected Prins reaction.

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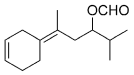
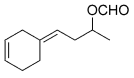
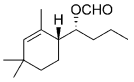
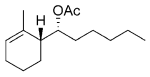
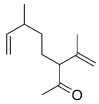
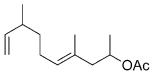
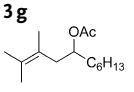
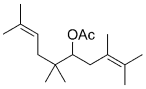
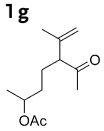
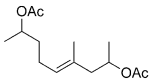
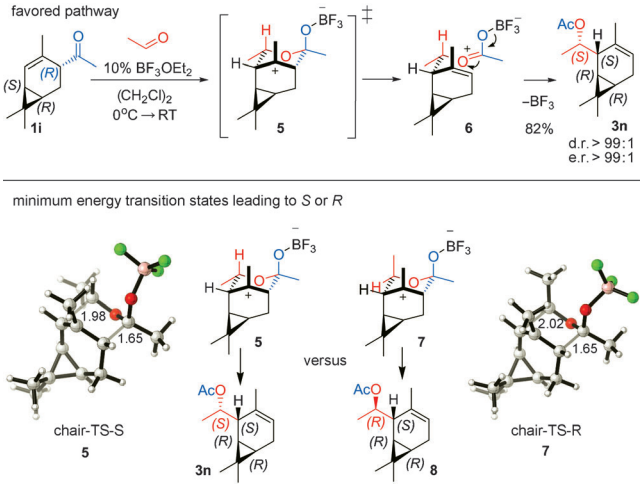
Prins cyclization in the presence of acetaldehyde (**2a**) to hemiacetal **4**, β,γ-unsaturated aldehyde **1a** was smoothly converted into homoallylic ester **3a** in good yield.[9,10] This rearrangement is remarkable from two perspectives: the transformation is clean, and the formation of homo- or cross-aldol products was not observed. The reaction obviously involves an intermolecular disproportionation of the different carbonyl groups to form a homoallylic ester, and the high *E*/*Z* and *syn*/*anti* selectivities of the product clearly indicate a well-organized transition state (TS). In addition, the transformation is significantly accelerated by a wide variety of Lewis and Brønsted acid catalysts (examples are listed in the Supporting Information); the conversion of **1a** with acetaldehyde to product **3a** was not observed under thermal conditions at temperatures of $<350\,^{\circ}C$. Thus, this reaction could be described as an oxy-oxonia-Cope rearrangement.

The broad scope of the rearrangement is shown in Table 1. The β,γ-unsaturated substrates were prepared by Diels–Alder reactions[8] or by Friedel–Crafts acylations of olefins.[11] Other options to access such deconjugated β,γ-unsaturated carbonyl compounds are, for example, hydroacylation reactions of dienes[12] or carbonyl ene reactions followed by oxidation.[1] Several conclusions can be drawn from the results that are summarized in Table 1. Substitution at the vinyl group results in a smooth outcome of the reaction, thus indicating that stabilization of the positive charge at this position in the intermediate is important. For example, compound **3d** was obtained with lower yield than product **3c** (Table 1, entries 1 and 2). Diverse structures are accepted by the transformation and steric bulk around the carbonyl group of compound **1** is generally tolerated. For example, α-cyclocitral **1d** is diastereoselectively converted to **3e** in high yield; isomerisation of the double bond of α-cyclocitral to obtain conjugated β-cyclocitral was not observed under the acidic reaction conditions (Table 1, entry 3; see also entries 4, 5, and 8). A variety of functional groups, such as esters (Table 1, entry 8) or additional double bonds (entries 1, 2, 5, and 7), in compounds **1** and **2** are also permitted in this reaction. Excellent diastereoselectivities can be achieved when the double bond at the β,γ position in compounds **1** is part of a ring system (Table 1, entries 3 and 4), an observation that led us to analyze the essential question regarding the extent of chirality transfer in this rearrangement (Scheme 4). For this purpose, we chose to examine the conversion of compound (1R,3R,6S)-(+)-**1i**, which was obtained from readily available Δ-3-carene with known absolute configuration,[11] with acetaldehyde **2a**. The reaction proceeded under complete transfer of stereochemical information to give ester **3n** (Scheme 4). The relative and absolute configurations of compound **3n** were determined by electronic circular dichroism (ECD) measurement and X-ray crystallographic analysis after transformation of **3n** into its 4-nitrobenzoic acid ester (Supporting Information). In parallel, we studied this transformation computationally,[13] applying B3LYP,[14] M062X,[15] and SCS-MP2[16] levels of theory. Chairlike TSs are generally preferred over boatlike TSs in [3,3]-sigmatropic shifts;[17] however, in cyclic systems, the preference for chairlike TSs may be smaller as a result of larger steric hindrance, which may even cause the chairlike TS to be disfavored.[18]

Table 1: Scope of the oxonia-Cope rearrangement.[a]

Entry	Substrate **1**	Aldehyde **2**	Product **3**	Yield [%][b] (*E*/*Z*) {*anti*/*syn*}
1	 **1b**	 **2c**	 **3c**	70 (56:44)
2	 **1c**	 **2a**	 **3d**	40 (57:43)
3	 **1d**	 **2d**	 **3e**[c]	90 {>99:1}
4	 **1e**	 **2e**	 **3f**[c]	75 {>99:1}
5	 **1f**	 **2a**	 **3g**	85[d] (75:25) {50:50}
6	 **1g**	 **2f**	 **3h**	91
7	 **1g**	 **2g**	 **3i**	51
8	 **1h**	 **2a**	 **3j**	94[d] (72:28) {50:50}

[a] Conditions: a solution of 1,2-dichloroethane (20 mL), aldehyde **1** (10 mmol), aldehyde **2** (12 mmol), and BF_3OEt_2 (1.0 mmol) was stirred under Ar for 2 h at 0 °C→RT. [b] Yields of isolated products after flash chromatography or Kugelrohr distillation. [c] Relative configuration shown. [d] $SnCl_4$ used instead of BF_3OEt_2.

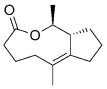
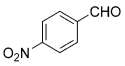
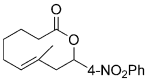
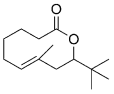
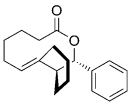
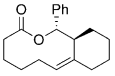
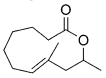
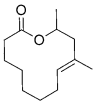
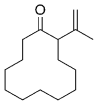
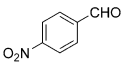
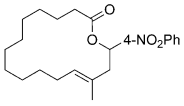


Scheme 4. Favored reaction pathway for the oxy-oxonia-Cope rearrangement and illustration of transition states.

Our calculations of the oxy-oxonia-Cope reaction of substrate **1i** to **3n** predict a chairlike TS (chair-TS-S, Scheme 4) to be favored (by $\Delta\Delta H^{\neq} = 7.6$ kcal mol^{-1} over the minimum-energy boatlike TS at B3LYP/6-31G(d)). The chairlike TS is asynchronous but concerted, and is formed with an activation barrier of $\Delta G^{\neq} = 25.5$ kcal mol^{-1} at SCS-MP2 (DCM)/6-31G(d)//B3LYP/6-31G(d) level relative to the aldehyde and the BF_3-complexed reactant **1i**.[19] The reaction path via chair-TS-S (**5**, see Scheme 4) gives rise to the experimentally observed *S* selectivity. The lowest energy pathway that leads to *R* configured product **8** would proceed via chair-TS-R (see Scheme 4 and also Scheme S5 in the Supporting Information for compilation of all possible TS conformers). Chair-TS-R is substantially higher in energy than chair-TS-S ($\Delta\Delta G^{\neq} = 3.5$ to 4.8 kcal mol^{-1}, depending on the level of theory applied, see Table 2), an observation that is in agreement with the high enantioselectivity observed experimentally. An exergonicity of $\Delta G_{rxn} = -7.9$ kcal mol^{-1} at M062X, but only $\Delta G_{rxn} = -1$ kcal mol^{-1} at SCS-MP2 level of theory was calculated, thus suggesting that the oxy-oxonia-Cope rearrangement might be reversible at higher temperatures,[20] although we did not see any indication of such reversibility at low temperature. Overall, the model predicts a concerted asynchronous reaction pathway for the oxy-oxonia-Cope rearrangement, but this may vary with the substitution pattern.

With these considerations in mind, we intended to further amplify the scope of this reaction through a novel and general macrolactonization method that involves linking R^1 together with R^2 or R^3 by a carbon chain of a given length (Scheme 2, Table 3). It should be noted that this sequence does not represent a macrolactonization, which proceeds primarily through an intramolecular ring closure via activated esters, in the classical sense.[7] The described macrolactonization is rather an $[n+4]$ ring enlargement of 2-vinyl-substituted cyclic ketones, and does not require application of high-dilution techniques. Lactones with 9- to 16-membered

Table 3: Oxonia-Cope $[n+4]$ ring enlargement to macrolides.

Entry	Substrate **10**	Aldehyde **2**	Lewis acid [20%]	*T* [°C]	Product **11**	Yield [%][b] (*E*/*Z*)[c]
1	 **10a**	 **2a**	$SnCl_4$	0	 **11a**	83 (<1:99)[d]
2	 **10b**	 **2a**	$SnCl_4$	0	 **11b**	35[f] (<1:99)
3	 **10c**	 **2b**	BF_3OEt_2	−20	 **11c**	97 (96:4)
4	 **10c**	 **2j**	BF_3OEt_2	−20	 **11d**	90 (82:18)
5	 **10d**	 **2a**	BF_3OEt_2	−20 −70[e]	 **11e**	93 (90:10)[d] 88[e] (85:15)[d,e]
6	 **10d**	 **2k**	BF_3OEt_2	−20	 **11f**	84 (86:14)[d]
7	 **10d**	 **2k**	BF_3OEt_2	0→RT	 **11g**	74 (15:85)[d]
8	 **10e**	 **2a**	BF_3OEt_2	0	 **11h**	72 (58:42)
9	 **10f**	 **2a**	$SnCl_4$	0	 **11i**	52 (62:38)
10	 **10g**	 **2b**	BF_3OEt_2	−20	 **11j**	94 (92:8)

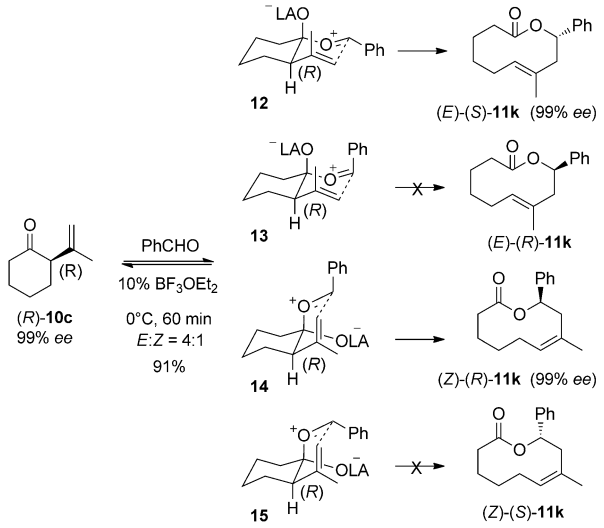
[a] Conditions: a solution of aldehyde **10** (10 mmol), aldehyde **2** (12 mmol), and BF_3OEt_2 or $SnCl_4$ (2.0 mmol) in CH_2Cl_2 (20 mL) was stirred under Ar at the indicated temperature for 6 h. [b] Yields of isolated products after flash chromatography or Kugelrohr distillation. [c] *E*/*Z* ratios were determined by GC and NMR analysis. [d] *syn*/*anti* < 1:99. [e] The reaction was carried out on a 100 g scale (see Experimental Section). [f] The yield was low because of double bond isomerization of **10b** into conjugation.

Table 2: Free energy difference (kcal mol^{-1}) between the lowest-energy chairlike transition states, which lead to the (*R*)-**8** or (*S*)-**3n**.

Method	$\Delta\Delta G^{\neq}$ [TS-*R* (**7**) − TS-*S* (**5**)]
SCS-MP2/6-31G(d)//B3LYP/6-31G(d)	4.8
M062X/6-31+G(d,p)	3.5
B3LYP/6-31G(d)	4.6

rings were prepared (Table 3); yields and selectivities of the lactone formation depend primarily on the ring size of the product and the reaction temperature. This behavior was expected, because the conformations of 6-membered-ring TSs can deviate very much from chairlike geometries with equatorial substituents, depending on the strain exerted by the annulated ring system. High *Z* selectivity was observed in lactones with 9-membered rings (Table 3, entries 1 and 2) even at 0 °C. In addition, the methyl group in bicyclic compound **11a** is exclusively in the anti-position. This excellent diastereoselectivity was also determined in higher homologues **11e–g**, irrespective of the double bond configuration in the product (Table 3, entries 5–7). The double bonds in lactones with larger ring sizes preferentially occupy *E* configurations, although the selectivity also depends on the reaction temperature. This influence is particularly obvious in the reaction of substrate **10d** with benzaldehyde: while *E* configuration prevails at −20 °C (Table 3, entry 6), it switches to *Z* selectivity at higher temperatures (entry 7). The sensitive influence of the reaction temperature on the configuration of the double bond is also evident from a reaction of compound **10d** with acetaldehyde on a large scale (100 g) and with a high concentration (2.5 M; Table 3, entry 5; see also Experimental Section). Although this reaction was carried out at −70 °C, the *E*/*Z* ratio of 85:15 was lower than that obtained in a reaction on a small scale and with a lower concentration (1 M; *E*/*Z* = 9:1 at −20 °C). This result can be explained by limited heat transfer occurring in the exothermal reaction at high concentration.

The stereochemistry was investigated in more detail in lactones with 10-membered rings (Scheme 5). Compound (*R*)-**10c** (99 % *ee*)[9] was reacted with acetaldehyde **2a** in the presence of 10 mol % BF_3OEt_2 to give a mixture of (*E*)-(*S*)-**11k** and (*Z*)-(*R*)-**11k** in a ratio of 4:1. The fact that the optical information was completely transferred, presumably via *trans*-decalin-like species **12**, to the major (*E*)-(*S*)-**11k** (99 % *ee*) isomer, excludes the occurrence of a *Z* oxocarbenium ion[21] **13**, which would have generated product (*E*)-(*R*)-**11k**. But the question remained how (*Z*)-(*R*)-**11k** arose. We can exclude the possibility of isomerization of both the substrate (*R*)-**10c** and the product (*E*)-(*S*)-**11k**, because neither of the compounds showed a sign of isomerization, when treated with BF_3OEt_2 or $SnCl_4$ under the reaction conditions and reaction time. Clearly, the *Z* configured isomer must come from the *cis*-decalin-like conformer **14**, which leads to the observed *R* configured isomer **11k** with opposite absolute configuration. Again, the occurrence of a *Z* oxocarbenium ion like species **15** can be excluded,[22] because it would have led to partial racemization through formation of isomer (*Z*)-(*S*)-**11k**. Expectedly, this experiment also confirms that the stereoselectivity of the oxonia-Cope reaction is mainly controlled by the population of different chairlike conformers at a given temperature, rather than by the configuration of intermediate oxocarbenium ions.



Scheme 5. Chirality transfer in the series of lactones with 10-membered rings.

We have described an unprecedented stereoselective allylation method, which does not include an allylic organometallic reagent, but a cross-dimerization of an β,γ-unsaturated carbonyl compound with another aldehyde to produce homoallylic esters through disproportionation of the carbonyl functionalities in an atom-economical way. The proposed irreversible and well-organized oxy-oxonia-Cope rearrangement enables high diastereoselectivities and transfer of chirality. The broad scope of the approach was further substantiated by the introduction of a novel $[n+4]$ ring enlargement toward macrolides with 9- to 16-membered rings.[23] The reactions are highly productive and work on multigram scale.

Experimental Section

A solution of BF_3OEt_2 (7.84 g, 0.055 mol) in 50 mL CH_2Cl_2 was added dropwise to a cooled (−78 °C) mixture of compound **10d** (107 g, 92 % purity, 0.55 mol) and acetaldehyde (**2a**, 29.2 g, 0.66 mol) in CH_2Cl_2 (200 mL) over a period of 60 min while the temperature was kept below −70 °C. The temperature was allowed to increase to −20 °C during 10 h. Saturated aqueous $NaHCO_3$ (50 mL) was added and the organic phase was separated. The aqueous layer was extracted once with CH_2Cl_2 (100 mL). The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ solution (100 mL), dried over $MgSO_4$ (10 g), and concentrated in vacuo to give a light-yellow oil, which was distilled through a short-path distillation head, thus affording lactone **11e** (109 g, 88 %) as a colorless oil. B.p. 105–110 °C (0.12 mbar). Mixture of *E*/*Z* isomers in a ratio of 85:15 (d.r. > 99:1).[9]

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