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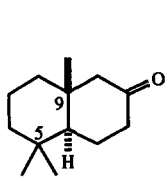
DIASTEREOCONTROLLED SYNTHESIS OF FUNCTIONALIZED *TRANS*-DECALINS *VIA* ELECTROCYCLIC REACTION OF TRIENOL ETHERS

Charles Fehr*, José Galindo and Olivier Guntern
Firmenich SA, Research Laboratories, CH-1211 Geneva 8

Summary: (*E*)-Trienol silyl ethers **10** and **11**, selectively prepared by *mono*-Grignard reaction on methyl β-cyclogeranate (**7**) or by deprotonation of enone **8** were transformed to *trans*-decalins **5** and **6** by a thermal electrocyclic reaction. The hitherto unknown enones **5** and **6** exhibit interesting organoleptic properties and show promise as versatile synthetic intermediates. The herein described transformation opens a new route for the direct construction of C(6)-functionalized drimanes such as cinnamodial (**3**) and forskolin (**4**).

A large number of naturally occurring 5,5,9-trimethyl-*trans*-decalins exhibiting diverse biological activities are known. As representative examples **1** [1-3] and **2** [1,4] (Ambrox®) constitute famous target molecules in perfumery, cinnamodial (**3**) [5,6] possesses insect antifeedant activity and triggers off peppery taste to the human tongue, whereas forskolin (**4**)[7] is known to activate ATP-AMP cyclase and shows very promising pharmacological activities [8].



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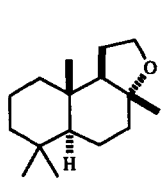

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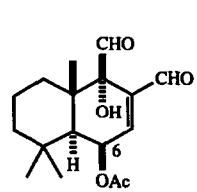

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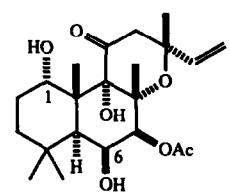

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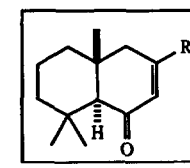
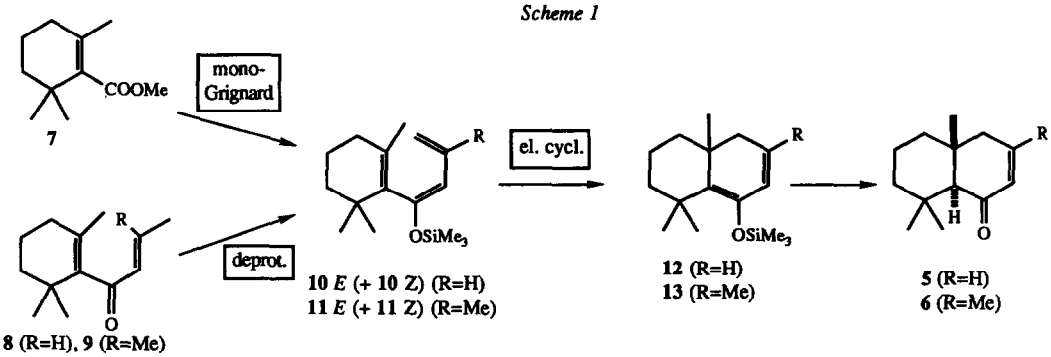


5 (R=H) **6** (R=Me)

The difficulty of introducing an oxygen at the sterically hindered C(6)-position in **3** and **4** has repeatedly been documented in the context of cinnamodial [6] and forskolin syntheses [9,10]. There is indeed a need for efficient synthetic methodologies allowing direct access to these systems.

As a solution to this problem, we herein describe a novel, direct and diastereocontrolled route to the hitherto unknown decalins **5** [11] and **6**. The strategy involves electrocyclic ring closure of a suitably substituted (*E*)-trienol ether (*cf.* **10** *E* and **11** *E*, *Scheme 1*) and opens a new route to the syntheses of **3** and **4**.

Scheme 1

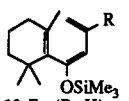


Recently, we published a procedure for converting non-enolizable or slowly enolizable carboxylic esters or amides into ketones, using RMgCl or RLi in combination with LDA [14,15]. This transformation proceeds *via* rapid deprotonation of the initially formed ketones by their *in situ* conversion into enolates. As an example, β-damascone (8) was obtained in 80% yield from methyl β-cyclogeranate (7) and [allyl MgCl, LDA] [14].

We recognized that, in the event of predominant formation of the *E*-enolate, a direct entry into *trans*-decalins could be envisaged *via* an electrocyclic reaction (*cf.* Scheme 1). Thus, ester **7** was treated with [allyl MgCl, LDA] (1.5 equiv.) in THF at 30° for 1 h, and the resultant enolate trapped with Me_3SiCl (3.0 equiv.) and NEt_3 (2.0 equiv.) at - 30°. After extractive work-up (sat. aq. $NaHCO_3$/ pet. ether, then sat. aq. NaCl) and distillation (60°/0.1 Torr), triene **10** was isolated in 80% yield as a 3:1 *E*/*Z* mixture (*cf. Table*):

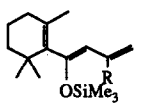
Table

sub- 1) reagent / THF
strate 2) Me_3SiCl / NEt_3



10 *E* (R=H)
11 *E* (R=Me)

\+

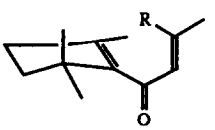


10 *Z* (R=H)
11 *Z* (R=Me)

					dist.	yield
7	[allyl MgCl, LDA]	3	:	1	80%	(R=H)
8	$LiN(SiMe_3)_2$	7	:	1	93%	(R=H)
8	$NaN(SiMe_3)_2$	11[16]	:	1	88%	(R=H)
8	$KN(SiMe_3)_2$	8	:	1	not isol.	(R=H)
7	[methallylMgCl, LDA]	2.2	:	1	55%[17]	(R=Me)
9	$NaN(SiMe_3)_2$	0	:	1	70%	(R=Me)

In addition, triene **10** *E* could also be prepared with excellent yields and high diastereoselectivity by deprotonation of **8** with Li-, Na- or K-bis(trimethyl silyl)amide (1.1 equiv.) in THF at -75°, followed by silylation (Me_3SiCl(1.2 equiv.)/NEt_3(1.0 equiv.); -75° to 0°, 2h)[16,18]. In an analogous manner, trienol silyl ether **11** *E*/*Z* was prepared from ester **7** by *mono*-Grignard reaction with [methallyl MgCl, LDA], followed by silylation. Deprotonation of the isolated ketone **9** with $NaN(SiMe_3)_2$ afforded **11** *Z* exclusively (*cf. Table*).

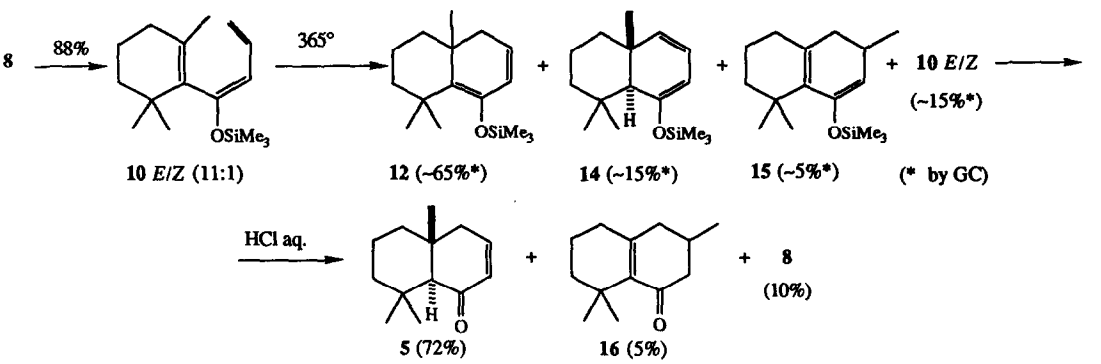
The preferential formation of **10** *E* by deprotonation of ketone **8** results from the s-*trans* conformation of the enone side chain. As this enone moiety is known to be twisted out of the cyclohexenyl π-system[19], the s-*trans* conformation (a) suffers no repulsive interactions [20]. Inversely, the additional Me-group in **9** favours a probably chelation controlled deprotonation *via* the s-*cis* conformer.



(a) R=H

Having developed an efficient method for the preparation of *E*-rich trienol ethers **10** and **11**, we could turn our attention to their electrocyclic ring closure. Pyrolysis of **10** *E*/*Z* (11:1) (0.5M in cyclohexane; 0.8ml/min; quartz tube (4m); 365°, N_2) afforded predominantly dienol ether **12** (~65%) and unreacted **10** *E*/*Z* (~1:9, ~15%). In addition, rearrangement products **14** (~15%) and **15**(~5%), were formed (*cf. Scheme* 2).

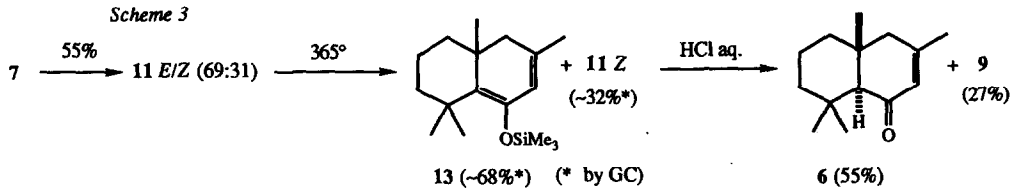
Scheme 2



After desilylation (aq. HCl/THF, 20°), isomerically pure *trans*-decalone **5** was obtained in 72% yield together with rearrangement product **16** (5%) and **8** (10%).

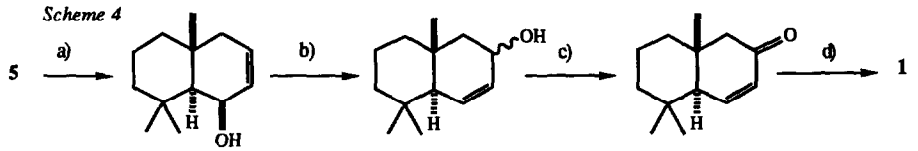
For the synthesis of decalone **6**, triene **11** *E/Z* (69:31) was pyrolyzed (as above) to afford **13**(~68%) and recovered **11** *Z* (~32%). Desilylation (aq. HCl/THF, 20°) afforded pure *trans*-**6** (55%) free of any rearrangement products and **9** (27%) (*cf. Scheme 3*).

Scheme 3



Decalones **5** and **6** which exhibit interesting olfactory properties [21], also represent valuable key intermediates for the elaboration of other *trans*-decalins. As an illustration, and for confirmation of the configurational assignment by ^{13}C-NMR [22], **5** was transformed into **1** [1-3] *via* enone transposition product **19** which was obtained for the first time stereoselectively[2](*cf. Scheme 4*). The herein described principle for the diastereoselective construction of suitably

Scheme 4



Reagents: a) $LiAlH_4$, Et_2O (72%) b) [H_2SO_4], dioxane, H_2O, 20°, 24 h c) MnO_2 (10 equiv.), CH_2Cl_2, 20° (60% from **17**) d) H_2, 5% Pd/C, EtOH (90%)

functionalized decalins **5** and **6** is versatile, and progress in the elaboration of more complex decalins by combination of appropriately substituted esters and Grignard reagents will be reported in due course.

We thank Dr. K.H. Shulte-Elte for helpful suggestions concerning the enone transposition **5** → **1** and Mr. W. Thommen for the NOE-experiments which allowed unambiguous assignment of all reported silyl ethers.

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16. As **8** contained 3% of *cis*-isomer (with *s-cis* conformation expected to be more stable), the diastereoselectivity of deprotonation of pure *trans*-**8** is expected to be even higher.
17. Isomeric (*E*)-1,1-dimethyl-3-methylene-2-(3-methyl-1-trimethylsilyloxy-3-butenylidene)cyclohexane.(~20%) was formed as a side product.
18. Deprotonation of **8** with LDA is less selective (→ **10** *E*/*Z*=2.7:1) and competing formation of a Michael adduct is observed. For Michael additions of LDA on enoates, see: Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1972**, 4249. Herrmann, L. J.; Kieczykowski, G. R.; Schlessinger, R. H. *ibid.* **1973**, 2433.
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