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SYNTHESIS OF BRIDGED [4.3.3]OXAPROPELLANES BY ANGULAR CONDENSATION OF ETHYL TRICYCLODECADIENONE 2-CARBOXYLATE AND THEIR THERMAL CONVERSION INTO LACTONE ANNELATED CYCLOPENTENONES

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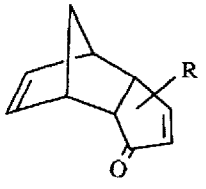
*Abstract: Condensation of tricyclodecadienone ester **2** with aldehydes and ketones leads to oxapropellanes **6** in good yields. With benzaldehyde, this reaction appears to be stereospecific. The lactones **6** undergo a rapid stereo- and regiospecific nucleophilic 1,4-addition to give **9** and **10**. Flash vacuum thermolysis of the latter compounds leads to lactone annelated cyclopentenones **11** in excellent yields.*

The tricyclo[5.2.1.$0^{2,6}$]decadienone system **1** has a great potential as synthetic equivalent of cyclopentadienone. Stereocontrolled conjugate addition to the cyclopentenone moiety together with appropriate functional group transformations followed by a thermal [4+2] cycloreversion, using the Flash Vacuum Thermolysis technique, allows the stereo- and enantioselective synthesis of a variety of cyclopentenoids in excellent chemical and optical yields[1,2]. Recently, we showed that angular alkylation of the readily accessible tricyclic ester **2** can be accomplished by deprotonation with LDA followed by electrophilic substitution with an alkyl halide to give the alkyl enones **3** in high yields[3].



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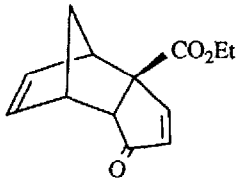

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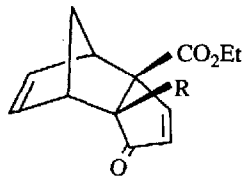

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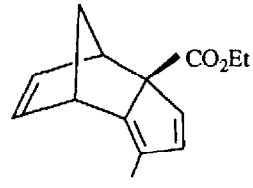

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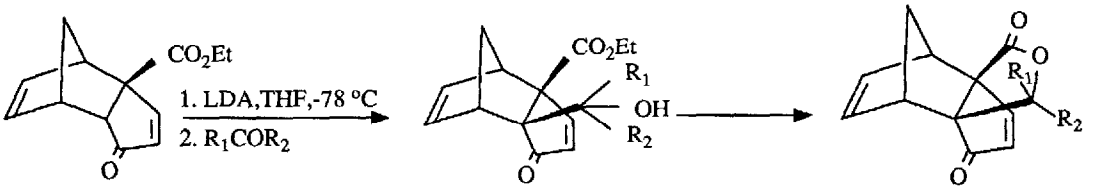
The efficient formation of *anti*-Bredt enolate **4** from **2** led us to investigate the use of this enolate in angular condensation reactions. In this communication, we report on the facile synthesis of a new type of [4.3.3]oxapropellanes and their use as synthons for lactone annelated cyclopentenoids.

Angular deprotonation of ester **2** with LDA and subsequent treatment with formaldehyde led to a mixture of carbinol **5a** and lactone **6a** in moderate yield (20-50%)(Scheme I). Lactonization of **5a** was readily accomplished by stirring with *p*-toluenesulfonic acid in CH_2Cl_2 at room temperature. With propionaldehyde, benzaldehyde and acetone no such carbinols were observed, the corresponding lactones **6b,c** and **d** were obtained as the only products (yields: 82, 69 and 72%, respectively). In view of the relief of steric congestion spontaneous

lactonization is apparently a favourable reaction. The structures of the lactones **6**, which are [4.3.3]propellanes containing an extra methylene bridge, were readily deduced from the NMR-spectral data. In the case of **6b** an

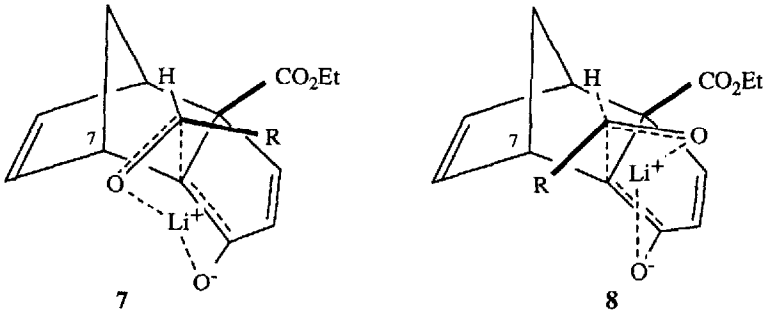
Scheme I



2 **5** **6**

a R_1=H, R_2=H
b R_1=H, R_2=Et
c R_1=H, R_2=Ph
d R_1=Me, R_2=Me

epimeric mixture was obtained with a diastereomeric ratio of 1:1. In contrast, the reaction with benzaldehyde had resulted in a single product[4], the exact structure of which was elucidated by means of an X-ray diffraction analysis[5]. It was found that the phenyl substituent is positioned *anti* to the methylene bridge of the norbornene moiety. The observed *exo*-enolate π-facial selectivity is clearly due to severe steric blocking of the *endo*-face by the C_8-C_9 olefinic bridge. Assuming that chelation of the Li-cation with both the enolate and the incoming carbonyl compound is a prerequisite[6], and that steric interaction with the methylene bridge is minimized, two conceivable diastereomeric transition states can be envisaged for the *exo*-approach of the aldehyde to the enolate **4**, *viz.* one having a six-membered chair-like transition state as shown in **7** and one proceeding through a boat-like transition state as depicted in **8**. In the case of benzaldehyde the experimental result can only be



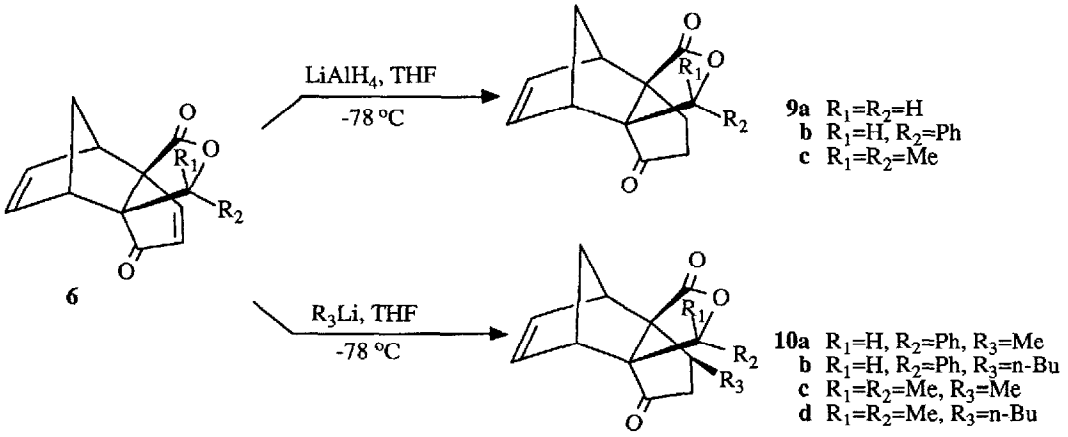
7 **8**

rationalized by adopting transition state **8**. Apparently, conceivable steric interaction of the phenyl ring and the C_7 bridgehead hydrogen, and the less favourable six-membered boat conformation as present in **8**, are outweighted by the stereoelectronic repulsion of the phenyl group and the dienolate system as experienced in transition state **7**[7].

Relevant for our strategy of using tricyclo[5.2.1.$0^{2,6}$]decadienone and its congeners as synthetic equivalents of cyclopentadienone, is modification of the enone moiety in the propellanes **6** just prepared. Selective conjugate 1,4-hydride addition was observed when the compounds **6a,c,d** were treated with $LiAlH_4$ in THF at -78 °C for just a few minutes. No 1,2-reduction products were found at all, the reduced ketones **9** (Scheme II)

were obtained in good yields (60-100%). Although low temperatures favour kinetic 1,4- over 1,2-hydride addition[9], the observed high regioselectivity is probably promoted by a considerable shielding of the enone carbonyl function by the $C(R_1R_2)$ group of the lactone[10].

Scheme II



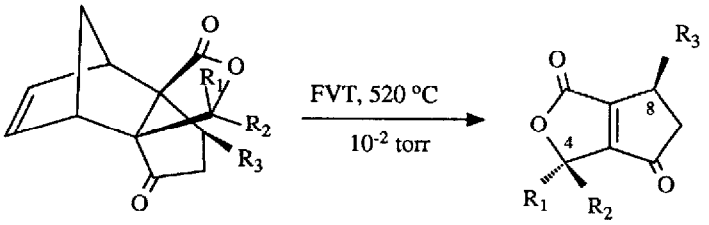
It is well known that alkyllithium compounds have a strong preference for 1,2-addition to enones[11]. In the case of substrates **6c,d** both MeLi and n-BuLi added regio- and stereospecifically in the 1,4-fashion to give products **10**. This result clearly confirms the complete shielding of the ketone function in **6c,d** for nucleophilic addition from the *endo*- as well as from the *exo*-face even for such reactive species like MeLi.

It is interesting to note that the enone moiety in **6** is considerably more reactive towards hydride reduction and alkyllithium addition than that in ester **2** despite its seemingly decreased accessibility. This observation may point to an anchimeric assistance of the lactone function in the complexation of the alkyllithium and bringing it in the necessary proximity of the β-C-atom of the enone moiety. Such a complexation will also play a role in the stereochemical course of the 1,4-addition and promote addition *syn* to the lactone ring as has been observed. The *syn* stereochemistry of the MeLi addition product **10a** was confirmed by an X-ray analysis[12].

The propellanes **9** and **10** were subjected to flash vacuum thermolysis in order to accomplish a thermal cycloreversion reaction (Scheme III). At 520 °C/10^{-2} torr, the substrates **9** and **10** gave the desired annelated cyclopentenones **11** in excellent yields (≥90%). The structures of the products were unequivocally deduced from ^{1}HNMR and ^{13}CNMR spectral data. In the case of substrates **10a** and **10b**, the relative stereochemistry of the phenyl group at C_4 and alkyl group at C_8 in **11b** (R_3=Me, n-Bu) is retained. The observed stereochemical integrity of this route to lactone annelated cyclopentenoids **11b** led us to extend this approach to their enantioselective synthesis. Starting from the readily available, optically pure ester **2** ($[\alpha]_D$=105.6°, MeOH)[2], we recently prepared optically active **11b** (R_3=H; $[\alpha]_D$= -19°, $CHCl_3$) in both high chemical (74%) and optical (ee >95%) overall yield.

In conclusion, angular condensation of tricyclic enone ester **2** with a variety aldehydes and ketones constitutes a valuable method for the synthesis of a variety of methano bridged oxapropellanes **6**, both racemic and optically active. Further elaboration of these unusual compounds leads to lactone annelated cyclopentenones

Scheme III



9,10

11a R_1=R_2=H, R_3=Me
b R_1=H, R_2=Ph, R_3=H, Me, n-Bu
c R_1=R_2=Me, R_3=H, Me, n-Bu

11, which offer good prospects as synthons for biologically interesting cyclopentenoids such as sarkomycins and methylenomycins[13].

References and Notes

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3. A.J.H. Klunder, J.H.M. Lange and B. Zwanenburg, Tetrahedron Letters **1987**, 3027.
4. We recently found that increasing the bulkiness of the aliphatic aldehydes dramatically enhances the stereoselectivity of their angular condensation with **2**, *e.g.* both with n-heptanal and pivaldehyde the formation of the propellanes is also completely stereoselective.
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7. It may be suggested that the observed preference for transition state **8** is also partly due to some stabilization of **8** by HOMO/LUMO interaction between the carbonyl function of the aldehyde and the electron rich dienic system of **4**. A similar explanation has been given by Mulzer *et.al*[8] for the deviating stereochemical results in the addition of metalated carboxylic acids to aldehydes.
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9. T. Cohen, W.D. Abraham and M. Myers, J. Amer. Chem. Soc., **109**, 7923 (1987).
10. Under the same conditions, ester **2** afforded a mixture of the 1,4- and 1,2-reduction products.
11. T. Eicher, 'The Chemistry of Carbonyl Compounds', 624-631, 662-678; Ed. S.Patai, Interscience Publishers, N.Y. (1966)
12. P.T. Beurskens, H. Behm, F.G. Moers, Crystallography Laboratory, University of Nijmegen (1987).
13. We just completed the synthesis of sarkomycin using tetracyclic lactone **6a** as the starting synthon. This synthesis will be published in a forthcoming paper.

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