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SYNTHESIS AND TRANSANNULAR DIELS-ALDER REACTION OF A *TRANS-CIS-CIS* 13-MEMBERED MACROCYCLIC TRIENONE[#]

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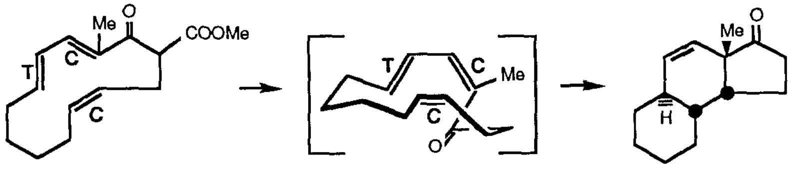
ABSTRACT: *Upon heating at 300°C, TCC trienone **14** gave tricyclic ketone **15**.*

Transannular Diels-Alder reaction on macrocycle is potentially a powerful new approach for the construction of polycyclic molecules. In the preceding communication,[1] we have reported our first study in this direction, *i.e.* the synthesis and Diels-Alder reactivity of a *cis-trans-trans* (CTT) 13-membered macrocyclic trienone. We wish now to report the synthesis and the transannular Diels-Alder reaction of *trans-cis-cis* (TCC) 13-membered macrocyclic trienone **14**.

Aldehyde-acetal **1** obtained from cyclohexene[2] was condensed with methyl bis(trifluoroethyl) phosphonoacetate following Still's procedure[3] to give a 5:1 mixture of *cis* and *trans* unsaturated esters which were separated by chromatography. The *cis* unsaturated ester **2**[4] was reduced, silylated[5] and hydrolyzed under acidic conditions to give aldehyde **5** which was treated with (formylmethylene) triphenylphosphorane[6] to give *trans* unsaturated aldehyde **6**. γ-Aldol condensation[7] of aldehyde **6** with the lithium dianion of methyl 3-oxo-pentanoate provided ß-ketoester alcohol **7** as a diastereoisomeric mixture which was converted into the THP-derivative **8**. Removal of the silyl protecting group gave allylic alcohols **9** which were converted into a diastereoisomeric mixture of allylic chlorides **10**.

Macrocyclization (NaI, K_2CO_3 in refluxing acetone, 72 h) of **10** provided *trans-cis* macrocycle **11** as a diastereoisomeric mixture in 74% yield. Methanolysis of **11** gave alcohols **12** which were converted into the diastereoisomeric acetates **13**. Treatment of **13** with 1,8-diazabicyclo[5.4.0]undec-7-ene in refluxing benzene provided the 13-membered macrocyclic trienone **14** in 50% yield after crystallization (m.p. 50-52°C). Its *trans-cis-cis* (TCC) configuration was assigned on the basis of its spectroscopic properties and those of its acyclic precursors.

On heating, macrocycle **14** at 300°C in toluene (sealed tube) for 1.25 h, transannular Diels-Alder reaction with concomitant decarbomethoxylation took place to produce tricyclic five-membered ketone **15** in high yield (85%, gc). The chemical structure of **15** was established spectroscopically and its relative stereochemistry was rigorously established by X-ray diffraction[11] analysis of its 2,4-dinitrophenylhydrazone derivative (m.p. 172-177° decomp.).

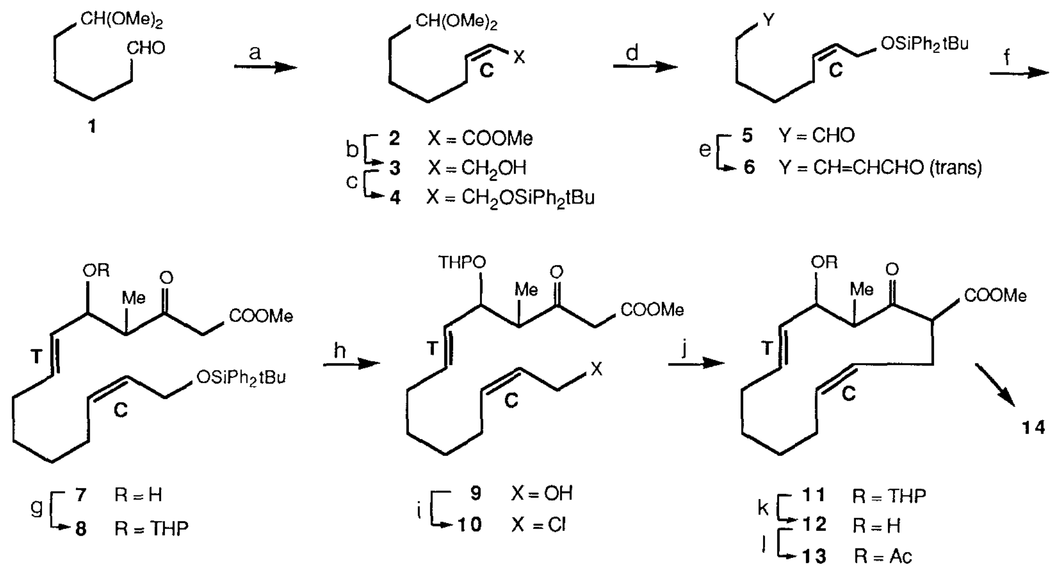


14 **14a** **15**

[#] This paper is dedicated to Professor Zdenek Valenta on the occasion of his 60th birthday.

Taking into account that the Diels-Alder reaction must take place via a boat like transition state producing an A,B,C tricycle in a conformation where ring B must be in a boat form, molecular models indicate that indeed TCC trienone **14** can only produce *trans-syn-cis* tricycle **15** via the Diels-Alder reaction of conformer **14a**.

In conclusion, this preliminary investigation demonstrates that transannular Diels-Alder reaction on a macrocyclic triene having a *trans-cis-cis* geometry is a high yield process which takes place with a complete stereochemical control to give a *trans-syn-cis* tricycle.[12]



(**a**) HMDSK, toluene, THF, $(CF_3CH_2O)_2POCH_2COOCH_3$, 0.5 h, -78°C, chromatography (*cis* ester = 79% and *trans* ester = 15%)[3] (**b**) Dibal-H, cyclohexane-CH_2Cl_2, 15 min , -78°C (72%) (**c**) Imidazole, *t*-$Bu(C_6H_5)_2SiCl$, DMF, 2 h, 0°C to r.t. (85%)[5] (**d**) HCl-5%, THF (1:1), 24 h, r.t. (88%) (**e**) $(C_6H_5)_3PCHCHO$, benzene-CH_2Cl_2 (7.5 : 3), reflux, 40 h (65%)[6] (**f**) NaH, methyl 3-oxo-pentanoate, THF, 30 min; *n*-BuLi, hexane, 30 min, -5°C; add **6** in THF, 5 min, -5°C, (72%)[7] (**g**) DHP, PPTS, CH_2Cl_2, 2 h, r.t. (88%)[8] (**h**) $(Bu)_4NF$, THF, 2 h, r.t. (88%)[9] (**i**) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0.5 h, 0°C; LiCl, HMPA, 1.5 h, r.t. (87%)[10] (**j**) K_2CO_3, NaI, acetone, reflux, 72 h (74%) (**k**) PPTS, CH_3OH-H_2O (9.5 : 0.5), reflux, 1.5 h (90%) (**l**) $(CH_3CO)_2O$, $(C_2H_5)_3N$, dimethylaminopyridine, CH_2Cl_2, 9 h, 0°C (93%) (**m**) DBU, benzene, reflux, 12 h (50% after crystallization).

References and Notes:

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