Tetrahedron Letters,Vol.29,No.14,pp 1641-1644,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TRANSANNULAR DIELS-ALDER REACTION OF 14-MEMBERED MACROCYCLIC TRIENES. PART II: EXPERIMENTAL RESULTS AND SYNTHETIC POTENTIAL#

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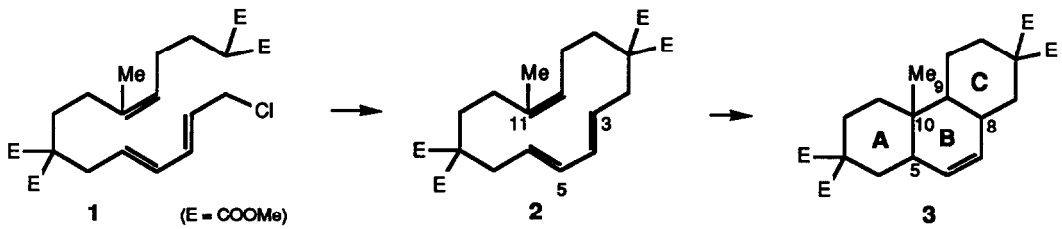
ABSTRACT: The synthesis and the transannular Diels-Alder reactivity of the 8 isomeric 14-membered macrocyclic trienes 2 are reported.

We reported in the preceding communication,[1] a theoretical analysis leading to predictions concerning the stereochemical outcome of the transannular Diels-Alder reactions on 14-membered macrocyclic trienes (**2** → **3**) as a function of the geometry of the olefins. These predictions were submitted to experimental verification and we wish to report this work.

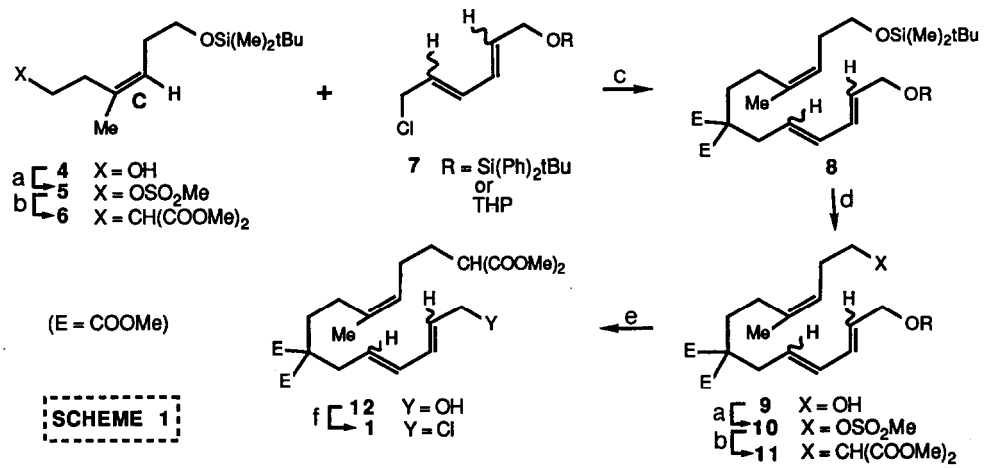


The macrocyclic trienes **2** were obtained by macrocyclization of acyclic trienes **1**. The four acyclic trienes **1** having a *cis* dienophile (*i.e.* TTC, TCC, CTC and CCC) were prepared starting from the four isomeric chlorodienes **7**[2] and the *cis* olefin **4**[2] as described in Scheme 1 which is self-explanatory.[3] The preparation of the four isomeric acyclic trienes **1** having a *trans* dienophile (*i.e.* TTT, TCT, CTT and CCT) was carried out by a modified version of the highly convergent and simple method described in Scheme 1, starting from *trans*-olefin ester **13**.[2] This is summarized in Scheme 2 which is also self-explanatory.

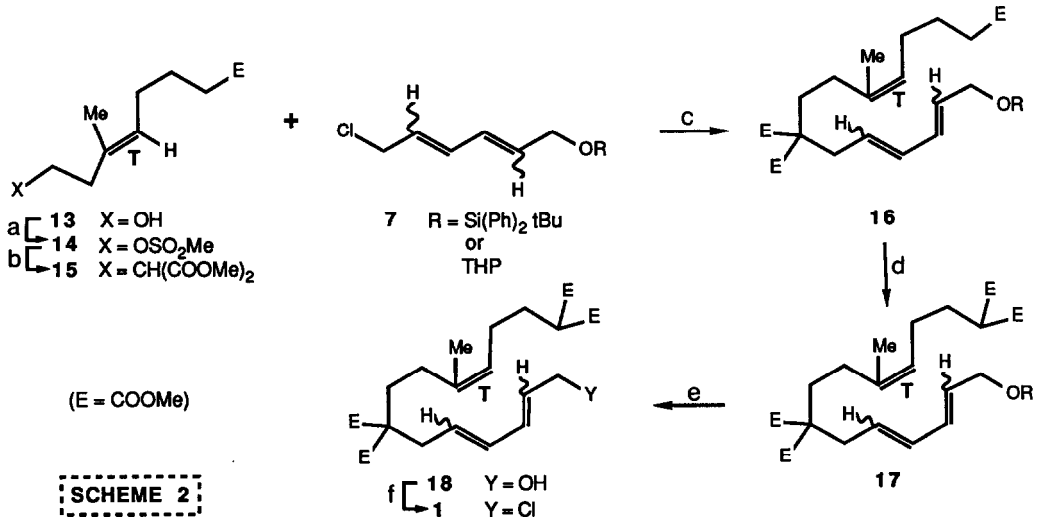
Macrocyclization[4] was carried out by slow addition of acyclic trienes **1** to a solution of cesium carbonate in THF-DMF (1:1) at ~80°C. The experimental results obtained for both, macrocyclizations and transannular Diels-Alder reactions are reported in the Table.

Five macrocyclizations (entries 1, 4-7) occurred in very good yield, two (entries 2, 8) in a moderate yield and only one (entry 3) with a relatively poor yield. In six cases (entries 1-2, 4-7), the macrocyclic triene was isolated and found to be crystalline. Interestingly, in the other two cases (TTT and TTC, entries 3 and 8), the expected macrocycles were not isolated because the transannular Diels-Alder reaction took place in the course of the macrocyclization, yielding directly the corresponding tricyclic products. The facile transannular Diels-Alder reaction in these two cases is explained by the fact that TTT and TTC trienes have each a TT diene which can easily take a cisoïd conformation, essentially devoid of steric interactions.

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



(a) $MeSO_2Cl$, $(C_2H_5)_3N$, CH_2Cl_2, 0°C (b) $CH_2(COOMe)_2$, NaH, KI, DMF-THF, ~10 h, 80°C (c) NaH, THF-DMF (1:1), 0°C to r.t. (d) *n*-Bu_4NF, THF[5] or PPTS, *i*-PrOH (e) PPTS, MeOH[6] or *n*-Bu_4NF, THF[5] (f) $MeSO_2Cl$, collidine, DMF, LiCl[7]



(a) $MeSO_2Cl$, $(C_2H_5)_3N$, CH_2Cl_2, 0°C (b) $CH_2(COOMe)_2$, NaH, KI, DMF-THF (1:1), ~10 h, 80°C (c) NaH, THF-DMF (1:1), 0°C to r.t. (d) LDA, $ClCO_2Me$, THF, -78°C (e) *n*-Bu_4NF, THF[5] or PPTS, MeOH[6] (f) $MeSO_2Cl$, collidine, DMF, LiCl[7]

The transannular Diels-Alder reactions of the macrocyclic trienes occurred between 80 and 365°C and were generally carried out in a sealed tube, neat or in toluene. This preliminary study indicates that the reactions proceed in high yield.

Theoretical predictions (*cf.* Table in reference 1) concerning the relative stereochemistry of the tricycles were confirmed experimentally in six series. As predicted, macrocyclic trienes CTT and TCT[8] (entries 1 and 2) gave the same tricycle (CAC). Also, triene TTT (entry 3) gave the expected mixture of the two stereoisomers TAC and CAT (ratio = 2:1) whereas trienes CTC and TCC (entries 5 and 6) gave tricycles CST and TSC respectively. As anticipated, triene CCT (entry 4) did not yield a Diels-

TABLE: MACROCYCLIZATION AND TRANSANNULAR DIELS-ALDER REACTION

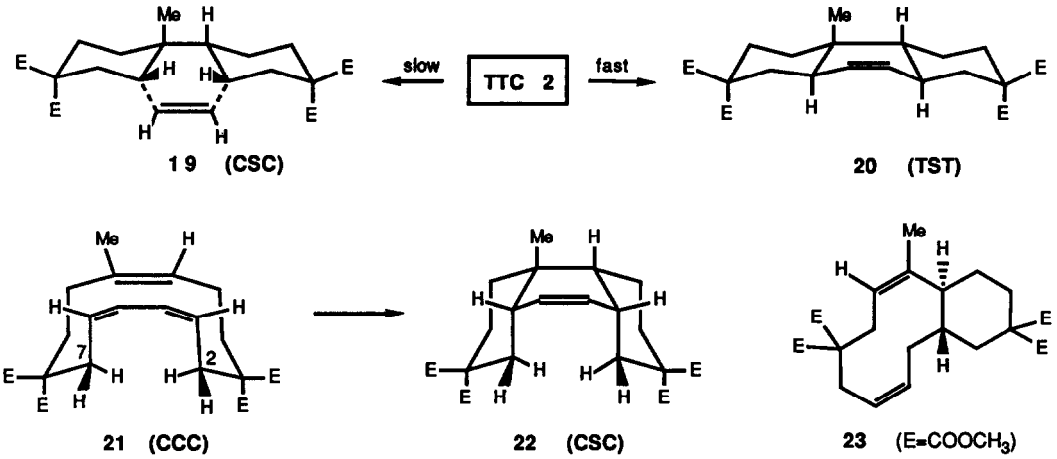
Entry	Triene 1 geometry	addition time → final conc.	Macrocycle 2 (yield)§	temp. time → solvent	Tricycle 3 stereochemistry(yield)£
1	CTT	5 h → $4x10^{-3}$ M	CTT (87%)	300°C, 2 h → toluene	CAC (91%)
2	TCT¶	17 h → $5x10^{-3}$ M	TCT (30%)	350°C, 1 h → toluene	CAC (38%) [8]
3	TTT	15 h → $2x10^{-3}$ M	TTT (not isolated)	80°C → DMF : THF	TAC + CAT (17%)¥
4	CCT	10 h → $1x10^{-3}$ M	CCT (66%)	300°C, 3 h → toluene	No D.A. Adduct
5	CTC	11 h → $5x10^{-3}$ M	CTC (81%)	300°C, 2.75 h → neat	CST (89%)
6	TCC	— → $5x10^{-3}$ M	TCC (88%)	300°C, 2 h → toluene	TSC¶ (100%)
7	CCC	14 h → $5x10^{-3}$ M	CCC (72%)	365°C, 30 min → toluene	CST + TSC (95%)¥
8	TTC	15 h → $5x10^{-3}$ M	TTC (not isolated)	80°C → DMF : THF	TST (53%)

§ Unoptimized yield.
£ Each tricyclic isomer has a distinct 250 MHz ^{1}H NMR spectrum.
¶ Structure has been confirmed by X-ray analysis.[9]
¥ Identified by VPC and ^{1}H NMR, not yet separated.

Alder product when heated at 300°C. Instead, it produced the isomeric compound **23** (resulting from a transannular ene reaction) as shown by X-ray analysis.[9]

We have made incorrect predictions in two cases (entries 7 and 8), but the results observed can be readily rationalized. We had predicted a mixture of diastereoisomers CSC and TST from macrocyclic triene TTC, but only one (assigned TST) was observed. Molecular models reveal that diastereoisomers CSC and TST should be formed in the chair-boat-chair conformations **19** and **20** respectively. It can be assumed that without the COOMe groups, the CSC and TST skeletons are of similar relative stability. However, in the CSC conformer **19**, the two axial COOMe groups have each a 1,3-diaxial steric interaction with the double bond. By comparison, the corresponding axial COOMe groups in the TST conformation **20** have each a much less severe 1,3-diaxial steric interaction (with a hydrogen atom). On that basis, the transition state leading to **20** is favored over that leading to **19**.

Contrary to our expectation, CCC macrocyclic triene gave a mixture of TSC and CST tricycles (ratio = 1:1) rather than the predicted CSC tricycle. The CCC macrocyclic triene must take conformation **21** with the diene in a cisoïd conformation in order to produce the CSC tricycle in conformation **22**. However, molecular models show that there must be a very severe steric repulsion between the C_2 and C_7 methylene groups in the planar cisoïd conformation, the resulting Diels-Alder reaction via **21** must consequently be a very high energy process. Indeed, this reaction was not



observed, and the results obtained suggest that the CCC macrocyclic triene underwent a thermal isomerization of the diene to give first a mixture of CTC and TCC macrocyclic trienes which yielded the observed mixture of CST and TSC tricycles.

In summary, we are reporting a general strategy for the synthesis of polycyclic compounds *via* the transannular Diels-Alder reaction on macrocyclic trienes. This strategy is simple and has a high degree of convergence, using four different prefabricated moieties, *i.e.*, the dienophile, the diene and the two connectors. In two operations, it produces 3 rings, 4 chiral centers (C_5, $C_{8\text{-}10}$) and leaves one functional group in each ring for further elaboration. The regioselectivity of the Diels-Alder reaction is automatically solved and the chemoselectivity is greatly enhanced. Indeed, the Diels-Alder reaction becomes an almost completely general reaction and there is an excellent control on the diastereoselectivity.

This new approach to synthesis has the potential of becoming a general method for the construction of polycyclic molecules of various stereochemistry. It is also possible to imagine various synthetic routes for a given natural product. For instance, a pentacyclic triterpene molecule can be synthesized *via* three different key tricycles (A.B.C, B.C.D or C.D.E) which in turn can be made from appropriate prefabricated dienes, dienophiles and connectors. This also suggests that a given tricycle can also be used to synthesize several natural products.[10,11,12]

REFERENCES AND NOTES

(1) S. Lamothe, A. Ndibwami, and P. Deslongchamps. *Tetrahedron Lett.* Preceding communication.
(2) The synthesis of the dienes (TT, TC, CT, and TT) and dienophiles (C and T) will be reported elsewhere.
(3) All spectra (250 MHz ^{1}H NMR, IR and MS) are in agreement with the assigned structures.
(4) D. Brillon and P. Deslongchamps. *Tetrahedron Lett.* **27**, 1131 (1986) and references quoted therein.
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(7) E.W. Collington and A.I. Meyers. *J. Org. Chem.* **36**, 3044 (1971).
(8) Macrocyclic triene TCT produced tricycle CAC plus two other compounds (ratio = 2:3:1) respectively. A rationalization for the formation of these unexpected compounds will be attempted when their structures will be elucidated.
(9) We are thankful to Dr James P. Springer (Merck, N.J.) for the X-ray analysis.
(10) T.K. Devon and A.I. Scott. "*Handbook of Naturally Occurring Compounds*", Vol.. II: Terpenes, Academic Press, New York, 1972.
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(12) Support by NSERCC (Canada) and FCAR (Québec) is gratefully acknowledged.

(Received in USA 9 September 1987)