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Transannular Diels-Alder Model Studies on the Total Synthesis of Chatancin. The Furanophane Approach. Part 2 [1]: Macrocyclization and Diels-Alder Reaction.

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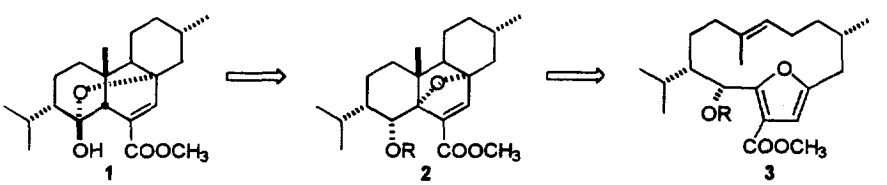
Abstract

Title investigation of three generations of model substrates targeting chatancin is presented. An unfunctionalized furan affords a reversible transannular Diels-Alder reaction producing only the two TAC-frameworks where the expected one is the kinetic product. A furan 3-COOMe functionalization allows the selective formation of the expected isomer which is still favored even in the presence of a quasi-axial isopropyl group on the furanophane.

Keywords: Furans; Diels-Alder reactions; Macrocycles; Transannular reactions.

In the previous letter of this issue [1], we have outlined our synthetic strategy for the total synthesis of chatancin **1** [2,3]. It involves a hydride shift mediated oxygen transposition on the transannular Diels-Alder (TADA) product **2** of the *quasi*-furanocembrane **3** (**scheme 1**). We have also described there the synthesis of three generations of acyclic precursors **4-6** prepared for the model studies of the above TADA reaction. Now, in this letter, we report on the macrocyclization



Scheme 1

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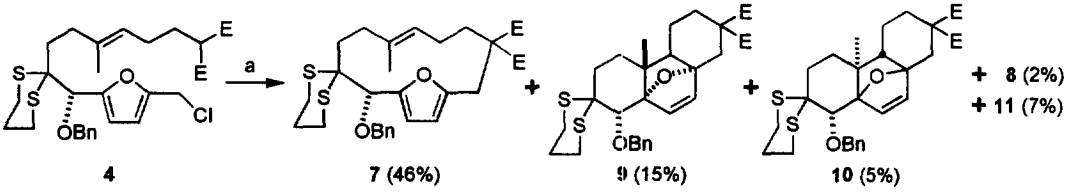
and the subsequent TADA model studies of these precursors as an extension of our fundamental research on TADA reaction [4] to furanophanes.

In the recorded two examples of furan TADA reactions, the results are opposite, reporting either a quantitative formation of a [5.6.5] tricycle [5] or a complete cycloreversion of a [7.6.7] tricycle formed under forcing conditions at high pressure [6]. Thus, in the first generation, its relevance to form the expected [6.6.6] tricycle was to be verified [7-9]. Due to the formation of a 2,5-furanophane with a *trans*-dienophile, a difficult macrocyclization was anticipated. Indeed, a complex mixture was obtained in every experiment. However, under high dilution conditions (c_{final}=2 mM) with a syringe-pump addition (17 h) of chloride **4** to a 10-fold excess of Cs_2CO_3 in refluxing acetonitrile, an acceptable yield of furanophane **7** was achieved, though the mixture was still contaminated with traces of dimeric macrocycle **8**. TADA products **9** and **10** as well as the corresponding *cis*-isomer of **7**, i.e., *cis*-macrocycle **11** [10,11] were also produced (**scheme 2**).



Scheme 2: a) Cs_2CO_3, MeCN reflux (see text).

Table 1: TADA reaction of **7** → **9** + **10**.

	Conditions	yield	9 / 10
1	PhMe, 190°C, 4.5 H	76% (86%)[a, b]	1 : 2
2	MeCN, 80°C, 7 days	92%	3 : 1
3	PhMe, 20°C, 18 kbar, 24 H	46% (95%)[a]	10 : 1

[a] % in parenthesis represent yields based on conversion.
[b] 2% of **11** was also formed.

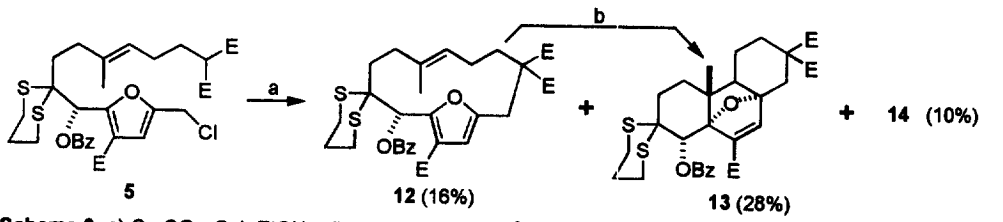
Table 2: Thermolysis of **9** and **10**.

	Substrate	Conditions	7 / 11 / 9 / 10
1	9	PhMe, 80°C, 24H	0 : 0 : 100 : 0
2	10	PhMe, 80°C, 24H	0 : 0 : 0 : 100
3	9	PhMe, 190°C, 4H	15 : 3 : 24 : 58
4	10	PhMe, 190°C, 4H	15 : 2 : 27 : 56

Nevertheless, the presence of compounds **9** and **10** predicted their ready access in the ensuing TADA study depicted in **table 1** showing three representative experiments. Accordingly, of the four hypothetical TADA products [12], only the two TAC-skeletons are formed and their ratio is much dependent on the activating temperature. To attempt the reversibility of TADA, **9** and **10** were also subjected to thermolysis. At 80°C, they are stable, however, at 190°C, they give an almost identical mixture of macrocycles **7** and **11** as well as TADA products **9** and **10** (**table 2**) to suggest a reversible TADA reaction where **9** is a kinetic and **10** is a thermodynamic product.

The lost aromaticity of the furan ring may be effectively compensated by the formation of a conjugated system in the following TADA reaction. This was tested in the next generation where the ester group of the target was already present on the substrate. Here the macrocyclization was

even more difficult despite 10 eq. of CsI and Cs_2CO_3 and a higher dilution (c_{final}=1 mM) with a 15 hour syringe pump addition of chloride **5** to refluxing propionitrile. It afforded a mixture of **12** and **13** but a considerable amount of dimeric macrocycle **14** was still formed (**Scheme 3**) [7-9].



Scheme 3: a) Cs_2CO_3, CsI, EtCN reflux (see text). b) 80°C, MeCN, 61 h, (100%).

However, the subsequent TADA reaction verified our expectations: isolated furanophane **12** quantitatively produced tetracycle **13** having the expected framework. Thus, the 3-furyl COOMe-group, beside reserving the TAC-selectivity, not only stabilized the TADA product but its steric hindrance prevented the formation of the *anti*-TAC isomer deriving from rotamer **B** [12] having a *quasi*-axial OBz. This high stereocontrol is clearly a result of the neighboring OR_1-functionality.

In the third generation, the limitation of this influence was examined with the selected target **1** in mind. Since, in this case, the symmetric dithiane [13] was replaced by a *quasi*-axial isopropyl group, its too early introduction might be inconvenient. Here, in the macrocyclization a 62% yield of furanophane **15** was achieved from chloride **6** with its 14 hour syringe pump addition (c_{final}=1 mM) to 10 eq. of Cs_2CO_3 and CsI in refluxing propionitrile (**scheme 4**) [7-9]. In **15**, the bulky silyl group prevented the TADA reaction even at 250°C. However, after deprotection, alcohol **16** was readily thermolysed to a mixture of TAC-products **17** and **18**, ratio of which was greatly depended on the solvent applied (**table 3**). Although a number of accounts discuss the solvent dependence of furan Diels-Alder reactions [14], we believe that here a protic solvent simply breaks an internal H-bond between the hydroxy and carbomethoxy functionalities which locks the

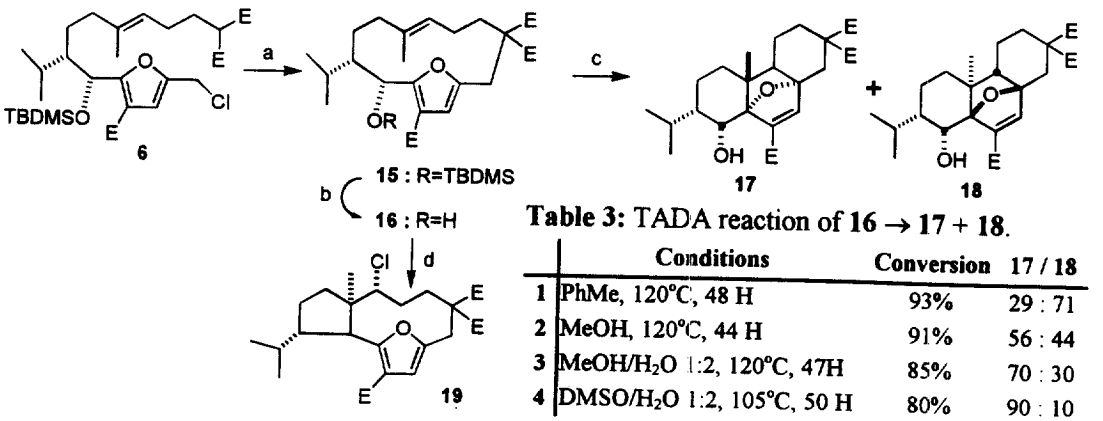


Table 3: TADA reaction of **16** → **17** + **18**.

	Conditions	Conversion	17 / 18
1	PhMe, 120°C, 48 H	93%	29 : 71
2	MeOH, 120°C, 44 H	91%	56 : 44
3	MeOH/H_2O 1:2, 120°C, 47H	85%	70 : 30
4	DMSO/H_2O 1:2, 105°C, 50 H	80%	90 : 10

Scheme 4: a) see text. b) TBAF, 1 eq. AcOH, CH_2Cl_2, (81%). c) see **Table 3**. d) $MeAlCl_2$, CH_2Cl_2, 0°C, 100%.

system in the otherwise minor **B** conformation [12].

In an attempt to induce Lewis-acid catalyzed TADA reaction on furanophane **16** [15] and a subsequent oxygen transposition, a quantitative formation of tricycle **19** was observed [9,16].

In summary, the furanophane TADA reaction has been proved successful to generate the expected tetracycles which demonstrates the power of this strategy. Since tetracycle **2** is closely related to **17**, it is apparently accessible from furanophane **3**. Now we are working on a straightforward asymmetric approach to attain this compound.

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References and notes:

[1] For Part 1, see preceding communication: Toró A, Wang Y, Deslongchamps P. Tetrahedron Letters 1999;40:2765-2768.
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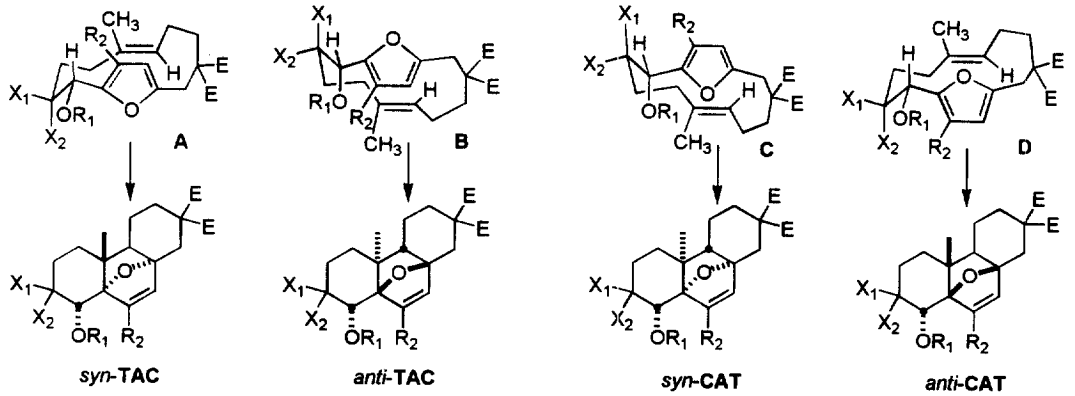
[7] For abbreviations see Part 1: ref.1, note 7.
[8] Depicted structures represent only relative stereochemistry.
[9] All the compounds reported herein are in full agreement with their ^1H and ^{13}C NMR, IR as well as mass spectra. Structure 7, **10**, **11**, **13**, **17**, **18** and **19** were also verified by X-ray crystallography (deposited to Cambridge Crystallographic Data Center).
[10] Applying radical scavenger did not prevent isomerization. In an attempt to induce TADA on **7** in CH_2Cl_2 with aminium radical cation $(4\text{-Br-Ph})_3N^{\cdot+}$ $SbCl_6^-$ (Bauld N. Tetrahedron 1989;45:5307-5363) at 0°C, a quantitative isomerization to **11** was observed.
[11] **11** resisted thermic TADA reaction: it was intact after a week at 80°C and it underwent only slow decomposition at 190°C.
[12] The conformers and the four theoretical products they may produce are as follows. (Only the α-OR_1 diastereoisomers (note 7) are depicted and syn-anti symbols denote the relative stereochemistry of the bridge and the adjacent oxygen functionality.)



[13] A geminal dialkyl- dialkoxy- or dithioalkyl-group is considered advantageous in the intramolecular Diels-Alder reactions, for further information see: Parrill AL, Dolata DP. Tetrahedron Letters 1994;35:7319-7322 and references cited therein.
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[15] Yu S, Beese G, Keay BA. J. Chem. Soc., Perkin Trans. 1, 1992;2729-2731.
[16] So far, we could not induce the oxygen transposition on **17**: with Lewis acid treatment only slow decomposition was observed.