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Transannular Diels-Alder Model Studies on the Total Synthesis of Chatancin. The Furanophane Approach. Part 1: Assembly of the Acyclic Substrates.

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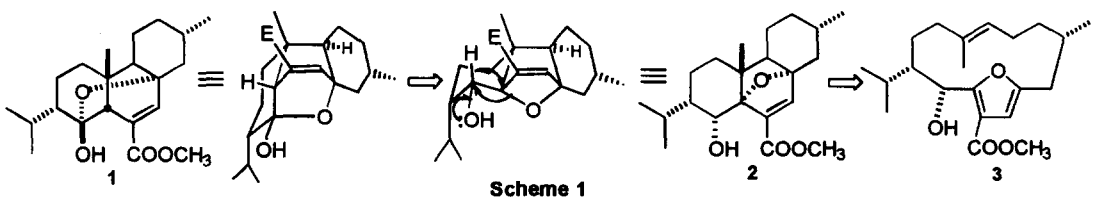
Abstract

Synthesis of three generations of model substrates with advancing similarity to chatancin are presented. In the first two generations, an Ireland-Claisen based six-step sequence supplied the *trans*-dienophile to be connected by dithiane chemistry to furfurals. In the third generation, a homogeraniol based dienophile aldehyde was coupled with a dilithiated 3-furoic acid. Subsequently, all three generations were concluded with similar functional group modifications as a preparation for a malonate-furyl chloride based macrocyclization.

Keywords: Dithianes; Furans; Lithiations; Macrocycles.

Intramolecular reactions are a well documented subdivision of furan Diels-Alder chemistry [1]. However, only two examples are reported where the dienophile is tethered to both sides of the furan to form a macrocycle and lock the system into an ideal conformation [2,3]. Recently, as a part of our ongoing research on transannular Diels-Alder (TADA) reactions [4], we had initiated a project involving furanophanes, macrocycles with a furan as a diene segment, towards the total



Scheme 1

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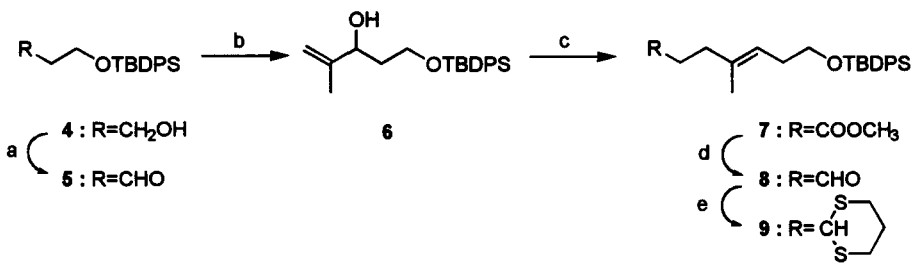
synthesis of chatancin (**1**), a PAF antagonist isolated from a soft coral Sarcophyton *sp.*[5]. Diterpene **1** is in principle available via a hydride shift mediated oxygen transposition on TADA product **2** deriving from furanophane **3** (**Scheme 1**). Since furanophane **3** has all the attributes of a furanocembranoid [6], this strategy may mimic the biogenesis of diterpene **1** [7].

In this two-part series, we wish to report on the evolution of three generations of model studies investigating the influence of advancing complexity of furanophane substrates on the TADA reaction. In Part 1, we describe the synthesis of these model substrates, while in Part 2 [8], the results of macrocyclizations and the TADA reactions are summarized [9,10].

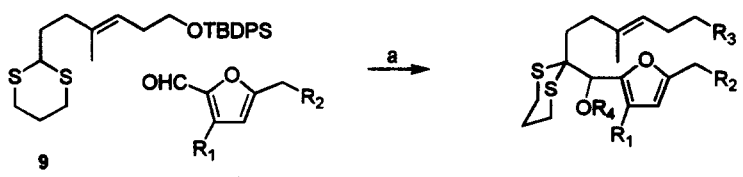
The assembly of the substrates followed the traditional highly convergent route developed in our laboratory [4]. For the first two generations, the requisite *trans*-dienophile was synthesized in six steps (**Scheme 2**). Thus, Swern oxidation [11] of monoprotected propanediol **4** [12] afforded



Scheme 2: (a) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C then Et_3N, 95%; (b) Isopropenyl-MgBr, Et_2O, 80%; (c) $CH_3CH(OCH_3)_3$, PrCOOH (cat.), 140°C, 80%; (d) DIBALH, CH_2Cl_2, 95%; (e) $CH_2(CH_2SH)_2$, BF_3Et_2O, CH_2Cl_2, 80%.

aldehyde **5**, a substrate for chain extension and selective double bond formation. Grignard reaction on **5** followed by Ireland-Claisen rearrangement [13] on allylic alcohol **6** gave ester **7** which was reduced to aldehyde **8** and transformed to dithiane **9**. This dienophile was then connected to furfural **10** or **11** [14] via dithiane chemistry [15]. The synthesis was concluded by certain functional group modifications as a preparation for the malonate based macrocyclization (**Scheme 3**). Thus, complete deprotonation of dithiane **9** was observed with 2 eq. of BuLi at 0°C to 23°C in 30 min and the anion was stable at -78°C. In the first generation, a good yield of coupling product **12** was obtained with furfural **10** within an hour at -78°C. Sequential protection to benzylether **13**, desilylation to alcohol **14**, its activation as mesylate **15** then a coupling with the connector [16] afforded malonate **16** without difficulty to fix this terminus for the macrocyclization. Cleavage of THP-ether to alcohol **17** and activation as chloride **18** [17] completed the other terminus [1].

Assembly of the second generation substrate resembled that of above with a difference of the application of the more practical MOM and Bz protections instead of THP and Bn, respectively. Although only 25% yield of coupling product **19** could be achieved even with 1.6 eq. of BuLi, 1.3 eq. of furfural **11** and 10 min reaction time as optimum condition, the rest of the synthesis was again without difficulty to afford furyl chloride **25** [18] in six steps from alcohol **19** [1].



10 : R_1=H, R_2=OTHP
11 : R_1=E, R_2=OMOM

	Gen.1	R_1	R_2	R_3	R_4
b	12	H	OTHP	OTBDPS	H
c	13	H	OTHP	OTBDPS	Bn
d	14	H	OTHP	OH	Bn
e	15	H	OTHP	OMs	Bn
f	16	H	OTHP	CHE_2	Bn
g	17	H	OH	CHE_2	Bn
	18	H	Cl	CHE_2	Bn

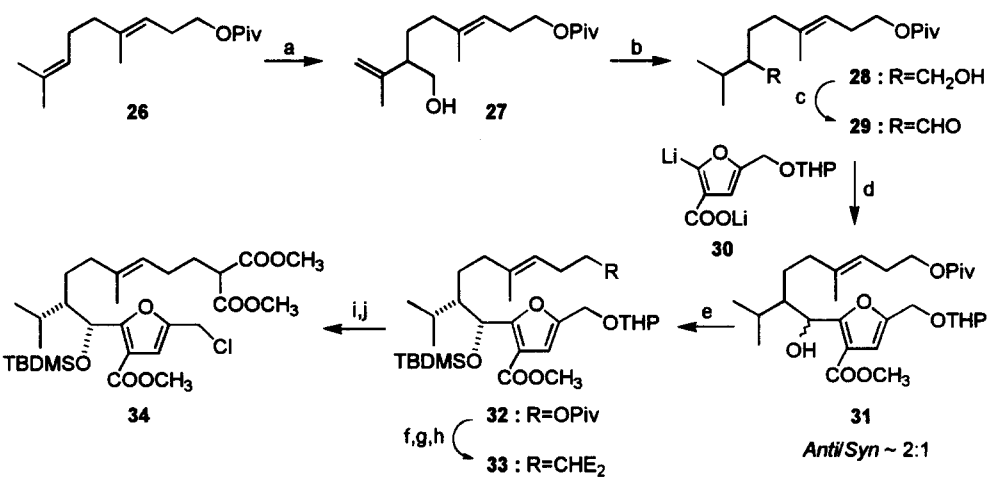
	Gen.2	R_1	R_2	R_3	R_4
b	19	E	OMOM	OTBDPS	H
c	20	E	OMOM	OTBDPS	Bz
d	21	E	OMOM	OH	Bz
e	22	E	OMOM	OMs	Bz
f	23	E	OMOM	CHE_2	Bz
g	24	E	OH	CHE_2	Bz
	25	E	Cl	CHE_2	Bz

Generation 1: (a) 2.0 eq. BuLi at 23°C then **10** at -78°C, THF, 80%; (b) NaH, BnBr, THF, 82%; (c) TBAF, THF, 93%; (d) Et_3N, MsCl, CH_2Cl_2; (e) $NaCHE_2$, KI, THF/DMF, 70°C, 88% over 2 steps; (f) PTSA, MeOH, 93% (g) MsCl, LiCl, DMF, 95%.

Generation 2: (a) 1.6 eq. BuLi at 23°C then **11** at -78°C, THF, 25%; (b) BzCl, Py, CH_2Cl_2, 92%; (c) TBAF, THF, 89%; (d) Et_3N, MsCl, CH_2Cl_2; (e) $NaCHE_2$, KI, THF/DMF 70°C, 98% over 2 steps; (f) HCl, MeOH, 83% (g) HCA, PPh_3, CH_2Cl_2, 93%.

Scheme 3

For the third generation, the dienophile was prepared from homogeranyl pivalate **26** [19] (**Scheme 4**). Thus selective Prins reaction [20] afforded homoallylic alcohol **27**. Regioselective



Generation 3: (a) $(CH_2O)_n$, Me_2AlCl, CH_2Cl_2, 90%; (b) H_2, $RhCl(PPh_3)_3$, PhH, 94%; (c) TPAP, NMO, CH_2Cl_2, 88%; (d) **30**, THF, then H^+ then CH_2N_2, 63%; (e) TBDMSOTf, lutidine, CH_2Cl_2, 92%; (f) MeO^-, MeOH; (g) MsCl, Py, CH_2Cl_2; (h) $NaCHE_2$, KI, THF/DMF, 70°C, 84% over 3 steps; (i) PTSA, MeOH; (j) HCA, PPh_3, CH_2Cl_2, 63% over 2 steps.

Scheme 4

hydrogenation [21] of the terminal double bond with Wilkinson catalyst gave alcohol **28** followed by an oxidation [22] to aldehyde **29** completed the dienophile. Its coupling [23] with dilithio 3-furoate **30** [24] and esterification with diazomethane furnished alcohol **31** in 63% yield with an *anti/syn* ratio of 2:1. Following a chromatographic separation, the *anti*-isomer was protected as silyl ether **32**. Conclusion of the synthesis paralleled that of the former model substrates after cleavage of the pivalate ester in **32**: connector coupling [16] afforded malonate **33** then transformation of THP-ether to furyl chloride [18] supplied the third model substrate **34** [10].

Having acquired three acyclic monosubstituted malonates with terminal furyl chlorides (**18**, **25** and **34**), now we are ready for macrocyclization and the TADA studies as described in the following communication [8].

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[9] ^{1}H and ^{13}C NMR, IR as well as mass spectra were in full agreement with the synthesized structures depicted.
[10] Abbreviations used in this communication: Bn: benzyl, BuLi: butyllithium, Bz: benzoate, DIBALH: diisobutylaluminumhydride, DMF: dimethylformamide, DMSO: dimethylsulfoxide, E: COOMe, HCA: hexachloroacetone, MOM: methoxymethyl, Ms: mesyl, NMO: N-methylmorpholine N-oxide, PAF: platelet activating factor, Piv: pivalate, Py: pyridine, PTSA: *para*-toluenesulfonic acid, TBAF: tetrabutylammonium fluoride, TBDMS: *tert*-butyldimethylsilyl, TBDPS: *tert*-butyldiphenylsilyl, Tf: triflate, THP: tetrahydropyranyl, TPAP: tetrapropylammonium perrhuthenate.
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