The Spongistatins: Architecturally Complex Natural Products—Part Two: Synthesis of the C(29–51) Subunit, Fragment Assembly, and Final Elaboration to (+)-Spongistatin 2**

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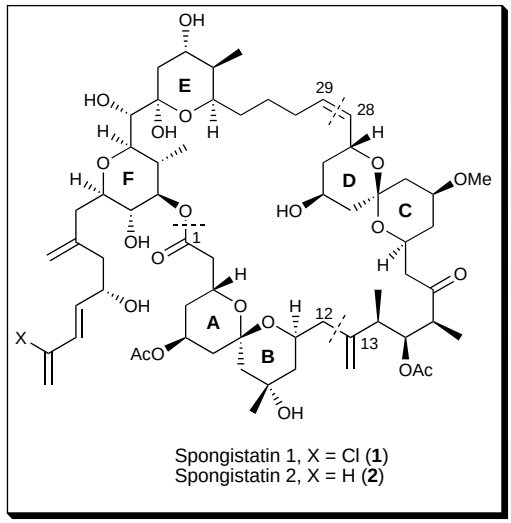
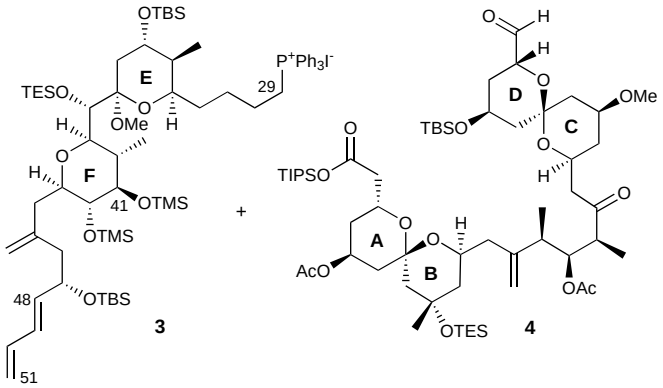
The spongistatins comprise an architecturally unique family of macrolides that have attracted wide interest in both the chemical and biomedical communities[1] as a consequence of their extraordinary cytotoxicity against several highly chemoresistant tumor cell lines. In the preceding communication[2] we described a formal total synthesis of (+)-spongistatin 1 (**1**), based on the epimerization of the CD spiroketal in an advanced ABCD fragment. We now report the synthesis of the C(29–51) subunit **3** (Scheme 1) incorporating both the E and F tetrahydropyran rings and the triene side chain, fragment assembly, and final elaboration to spongistatin 2 (**2**). Central to this achievement was the stereocontrolled epimerization of 23-*epi*-spongistatin 2 to **2**.

Synthetic analysis of the EF fragment **3** led to the side chain fragment **5** and bis(tetrahydropyran) **6** (Scheme 2). Further disconnections of **6** suggested the union of aldehyde **7** with dithiane **8**, prepared respectively from Brown crotylboration[3] products **9** and **10**. The synthesis of (+)-**7** employing a Sharpless asymmetric epoxidation,[4] the construction of (−)-**8** utilizing our IBr modification[5] of the Bartlett iodocarbonate cyclization,[6] and their union to give (+)-**11** (Scheme 3) were disclosed in an earlier communication.[7]

Elaboration of the E-ring pyran entailed acidic hydrolysis of the acetonide groups in (+)-**11** (Scheme 3), followed by removal of the dithiane (buffered mercury perchlorate/MeOH) with concomitant cyclization to the methyl ketal, and masking the primary hydroxyl group as a pivaloate (PivCl, pyr., stoichiometric DMAP) to furnish methyl ketal (+)-**12**[8] (45%, three steps). Protection of the least hindered-secondary hydroxyl group at C(35) as a TBS ether, removal of the two benzyl groups (hydrogenolysis), and reprotection of both the newly liberated primary hydroxyl group as a BPS





Scheme 1. Retrosynthetic analysis of spongistatin 2.

ether and the three secondary hydroxyl groups as TES ethers[9] then afforded (+)-**13** (70%, four steps). Reductive removal of the pivaloate (DIBAL) afforded the primary hydroxyl (81%). The use of a strongly coordinating solvent (namely, THF) was vital for a clean transformation; non-coordinating solvents led to competitive formation of the E-ring glycan, presumably through coordination of the methylketal to the electrophilic aluminum reagent. The resulting primary hydroxyl group was then converted into iodide (+)-**6** in excellent yield (95%).

Our point of departure for the side chain was sulfone (−)-**14**, previously prepared in connection with the synthesis of spongistatin analogues (Scheme 4).[10] Removal of the PMB ether and Dess–Martin oxidation[11] furnished the corresponding aldehyde which was subjected to Wittig olefination ($Ph_3P{=}CHCO_2Et$). Reduction of the ester, benzylation of the resulting alcohol, and coupling with iodide (+)-**6** then provided **15** as an inconsequential mixture of C(45) epimers in excellent yield (80%), with the balance of the material recovered being the product of elimination of the iodide. In contrast to the high yield observed in an earlier model system,[10] Julia methylenation[12] of **15** furnished (+)-**16** in only 25% yield (50% based on recovered starting material). Reductive removal of the benzyl ether (LiDBB) to unmask the primary hydroxyl group, followed by Dess–Martin

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[**] Financial support was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-70329, a NIH Post-doctoral Fellowship to C.S.B., a Japan Society for Promotion of Science Fellowship to N.M., and a Royal Society Fulbright Fellowship to V.A.D. We also thank the Daiichi Pharmaceutical Co., Ltd, and the Tanabe Seiyaku Co., Ltd for financial support. Finally we thank Dr George T. Furst, Dr. Patrick J. Carroll, and Dr. Rakesh Kohli of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra, respectively.

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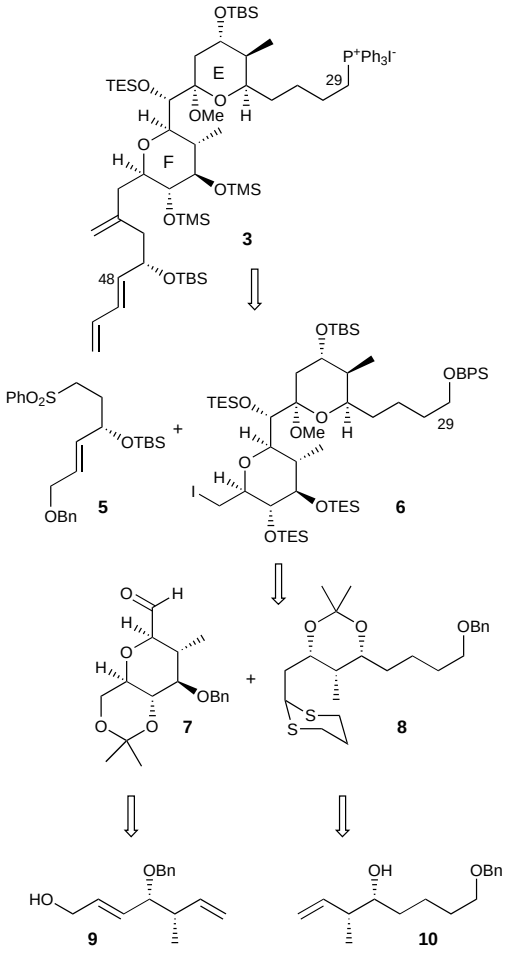
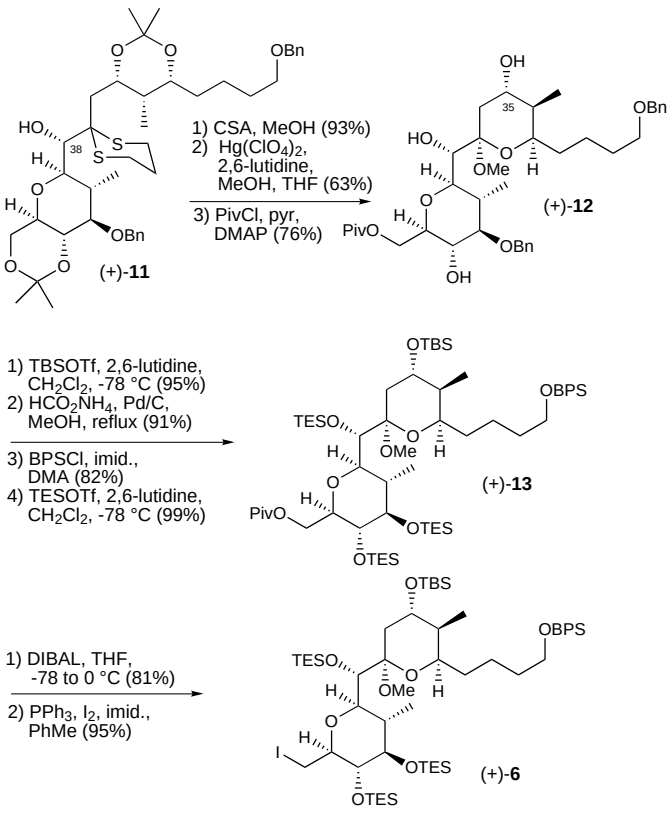
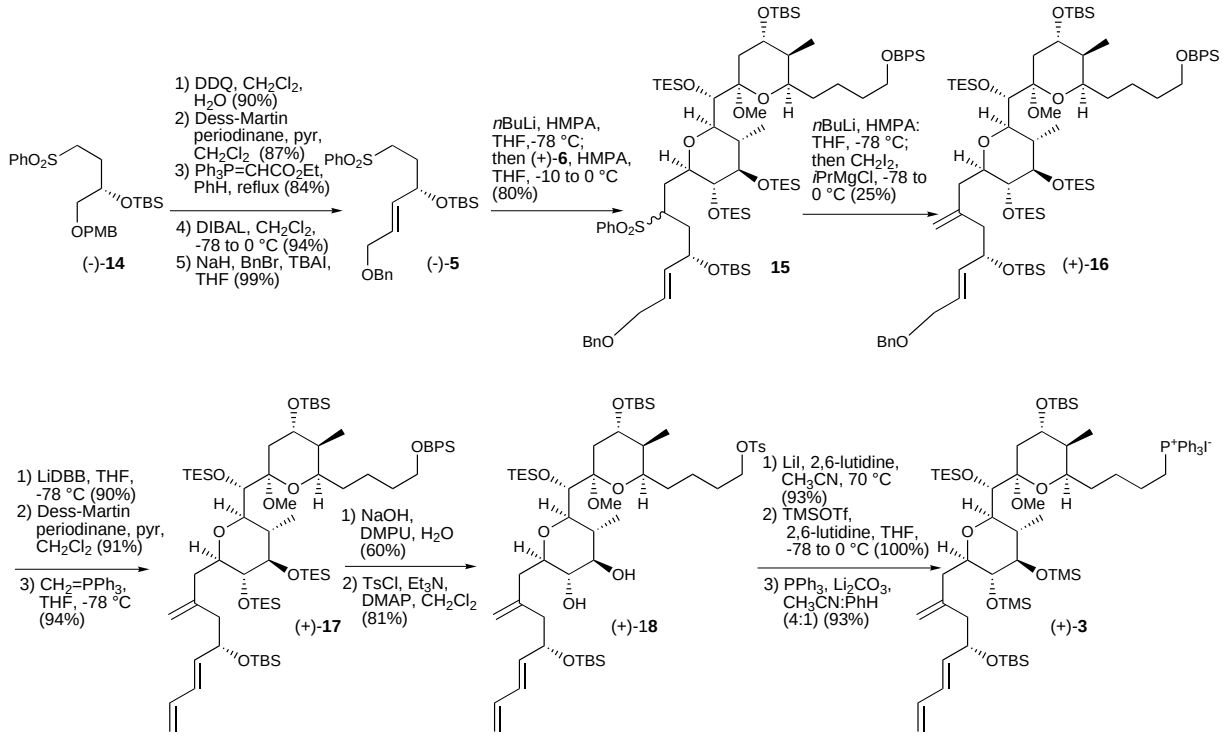


Scheme 2. Retrosynthetic analysis of the EF subunit **3** (see ref. [18] for abbreviations).



Scheme 3. Synthesis of EF iodide (+)-**6** (see ref. [18] for abbreviations).

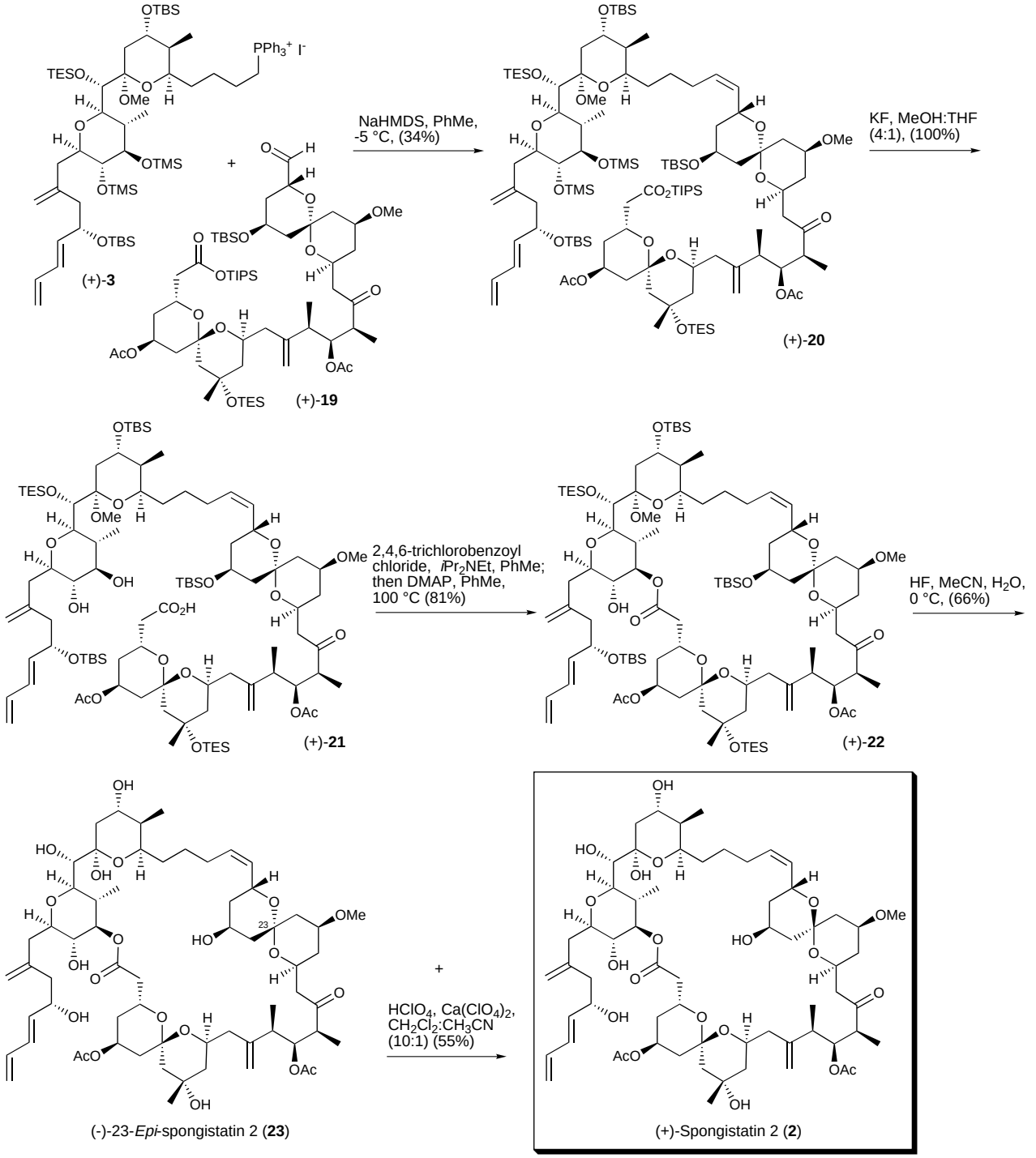
oxidation and olefination with $CH_2{=}PPh_3$ then led to (+)-**17**. At this point, removal of the BPS and the two sterically unencumbered TES groups (NaOH, DMPU/H_2O), followed by selective tosylation of the resultant primary hydroxyl group



Scheme 4. Synthesis of EF subunit (+)-**3** (see ref. [18] for abbreviations).

furnished (+)-**18**. Conversion to the iodide (LiI), reprotection of the two secondary hydroxyl groups (TMSOTf), and formation of the phosphonium salt (PPh_3) completed the assembly of the EF Wittig salt (+)-**3**.

Fragment assembly entailed Wittig coupling[13] of (+)-**3** with advanced aldehyde (+)-**19** possessing the *epi*-spiroketal configuration described in the preceding communication: (+)-**20** was obtained in 34% yield (Scheme 5). Selective removal of the TMS and TIPS groups (KF/methanol) then afforded seco-acid (+)-**21**. Regioselective macrolactonization[14] (Yamaguchi protocol)[15] afforded only (+)-**22**, the desired 42-membered macrocycle. While Evans et al. had previously reported the successful regioselective macrocyclization of a spongistatin seco-acid, it is intriguing to note that the 23-*epi*-seco acid also displays the same ring size preference. Global deprotection ($HF/CH_3CN/H_2O$)[14a] then furnished both (+)-spongistatin 2 (**2**) and the C(23) epimer (**23**) in 60–66% yield, with the unnatural congener predominating (3:1).[16] Acid-mediated epimerization of **23** in the presence of Ca^{2+} ions led to a mixture of (+)-spongistatin 2 (**2**) and (−)-*epi*-spongistatin 2 (**23**) in a ratio of 3.9–2.3:1 (ca. 55%), along with some degradation products. The synthetic (+)-spongis-



Scheme 5. Completion of the total synthesis of spongistatin 2 (+)-**2** and *epi*-spongistatin (−)-**23** (see ref. [18] for abbreviations).

  0044-8249/01/11301-0204 $ 17.50+.50/0 *Angew. Chem.* **2001**, *113*, Nr. 1

tatin 2 (**2**) was identical in all respects (500 MHz ^{1}H NMR, LR-MS, HR-MS, $[\alpha]_D^{25}$, TLC (3 solvent systems), and HPLC) with an authentic sample kindly provided by Professor Evans.[17]

In summary, the total synthesis of (+)-spongistatin 2 (**2**) has been achieved. Highlights of the synthesis include the stereocontrolled synthesis of the E and F bis(tetrahydropyran) subunit, Wittig coupling with an advanced ABCD fragment, and acid-mediated epimerization in the presence of a Ca^{2+} ion of (−)-*epi*-spongistatin (**23**) to (+)-spongistatin 2 (**2**).

Received: October 12, 2000 [Z15948]

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[8] Satisfactory spectroscopic data (^{1}H and ^{13}C NMR, LR-MS, HR-MS, $[\alpha]_D^{25}$, and IR) were obtained for all new compounds.

[9] When a TBS group was used to protect the C(38) hydroxyl group, it could not be removed in the final step of the synthesis.

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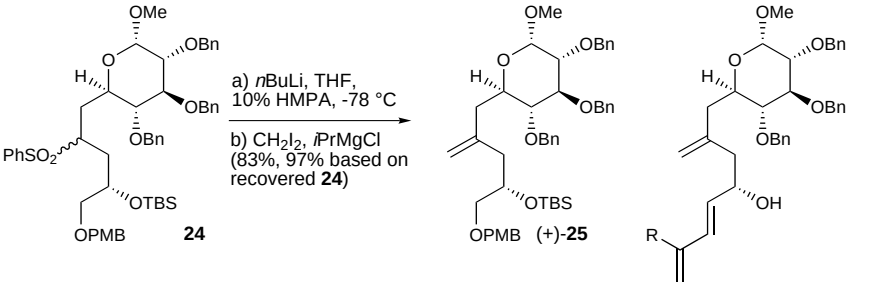

(+)-**26a**, R = H, GI_{50} 0.25 μg mL^{-1}, Pancreas-a BXPC-3
(+)-**26b**, R = Cl, GI_{50} 3.2 μg mL^{-1}, Pancreas-a BXPC-3

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[17] We thank Professor Evans for supplying an authentic sample of (+)-spongistatin 2 (**2**).

[18] Abbreviations used: Ac = acetyl; Bn = benzyl; TES = triethylsilyl; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; BPS = *tert*-butylbiphenylsilyl; CSA = 10-camphorsulfonic acid; LiDBB = di-*tert*-butylbiphenyllithium; Piv, pivaloyl = 2,2-dimethylpropanoyl; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBAI = tetrabutylammonium iodide; Tf = triflate = trifluoromethanesulfonyl; imid. = imidazole; DMA = *N*,*N*-dimethylacetamide; DIBAL = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Ts = tosyl; pyr = pyridine; HMPA = hexamethylphosphoramide; THF = tetrahydrofuran; HR-MS = high-resolution mass spectrometry; LR-MS = low-resolution mass spectrometry; TLC = thin-layer chromatography; HPLC = high-performance liquid chromatography.

A Chemical Model of Homeostasis**

Helmut H. Zepik, Eveline Blöchliger, and Pier Luigi Luisi*

The experimental realization of self-replication systems[1–3] has permitted the representation of one of the key mechanisms of life in simple chemical terms. The chemical rendering of other main cellular mechanisms remains, however, elusive. One of these is homeostasis. There are different forms of homeostasis, and in quite general terms one may envisage that the chemical rendering of such a cellular feature might be constituted by a spherical bilayer structure which hosts chemical reactions and which is self-maintaining, because these reactions regenerate all components of the system that disappear in the reactions. One simple possible working unit of this kind, based on the structure of liposomes and on the notion of chemical autopoiesis,[4–7] was proposed a few years ago[8] and is shown in Figure 1a.

This represents a spherical system with a semipermeable boundary formed by one single component S, into which the reagent

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[**] We would like to thank Dr. Sabrina Dallavalle, who under the direction of Prof. Stefano Colonna at the University of Milano carried out the first attempts to realize an autopoietic system, and F. Mayer for his help with gas chromatography analysis.