Macrolide Synthesis

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Concise Synthesis of a Pateamine A Analogue with In Vivo Anticancer Activity Based on an Iron-Catalyzed Pyrone Ring Opening/Cross-Coupling

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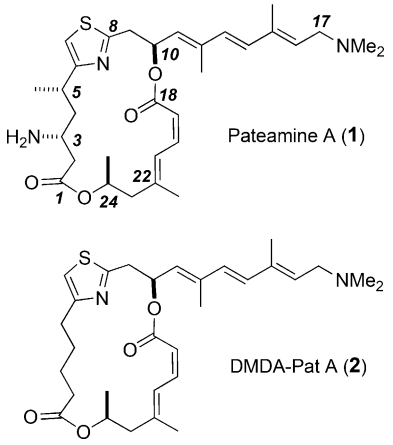
Abstract: *The marine macrolide pateamine A and its non-natural sibling DMDA-Pat A are potent translation inhibitors targeting the eukaryotic initiation factor 4A (eIF4A), an enzyme with RNA helicase activity. Although essential for every living cell, this protein target seems "drugable" since DMDA-Pat A has previously been shown to exhibit remarkable in vivo activity against two different melanoma mouse models. The novel entry into this promising compound presented herein is shorter and significantly more productive than the literature route. Key to success was the masking of the signature Z,E-configured dienoate subunit of DMDA-Pat A in the form of a 2-pyrone ring, which was best crafted by a gold-catalyzed cyclization. While the robustness of the heterocycle facilitated the entire assembly stage, the highly isomerization-prone seco-Z,E-dienoic acid could be unlocked in due time for macrolactonization by an unconventional iron-catalyzed ring opening/cross coupling. Moreover, the crystal structure analysis of an advanced intermediate gave first insights into the conformation of the macrodilactone framework of the pateamine family, which is thought to be critical for eliciting the desired biological response.*

The faithful conversion of genetic information into polypeptide products is vital for every living cell. Therefore it seems plausible that the sophisticated machinery accountable for this essential biological function does not represent a privileged drug target because the therapeutic window in response to its blocking is supposed to be narrow. A growing body of evidence, however, advocates for a more impartial assessment. As a matter of fact, several small molecules capable of obstructing protein biosynthesis were found to display promising antitumor activity alone or in combination with other anticancer agents. One of them is homoharringtonine (Omacetaxine mepesuccinate), which has been approved for the treatment of chronic myeloid leukemia resistant to tyrosin kinase inhibitors.[1] This particular natural product acts as a translation-initiation inhibitor primarily targeting the ribosome.[2] In fact, the translation stage is a conceivable candidate for chemotherapeutic intervention, not least because it is frequently affected by oncogenes and tumor suppressors.[3] Up-regulated translation, however, arguably renders transformed cells vulnerable, not least because several proteins relevant for tumor progression are short-lived and need to be constantly resynthesized.[3,4]

Pateamine A (**1**) is another translation inhibitor that shows considerable promise. The remarkable activity, selectivity and pro-apoptotic properties of this macrolide derived from a New Zealand sponge of the *Mycale* genus had already been recognized by the isolation team.[5,6] While other early work had suggested a potential use as an immunosuppressive agent,[7,8] the research activity was refocused once it became clear that **1** primarily targets the eukaryotic initiation factor 4A (eIF4A).[9,10] This enzyme with RNA helicase as well as ATPase activity is critically involved in the process of recruiting mRNA to the ribosome and is hence a key player in controlling the translation step of protein biosynthesis.[11,12]



A conceptually important step for the further development of this lead compound was taken when Romo and co-workers recognized that the molecular structure of **1** is comprised of two separate domains:[8] Whereas the "north-eastern" part, rigidified by multiple unsaturations, is crucial for protein binding, the "western" C1–C5 region basically entertains scaffolding duties in that it helps define the crucial—but still unknown—conformation of the macrocycle. In accord with this notion, the elimination-prone amine at C3 as well as the methyl group at C5 could be excised without loss of activity. The simplified analogue DMDA-Pat A (**2**) is in fact basically equipotent to **1**, and all available data suggest that it exerts its biological functions by the exact same mode of action as the parent natural product.[8,13]

Compound **2** shows impressive cytotoxicity against a panel of 32 human cancer cell lines in vitro with IC_{50} values mostly in the single-digit nanomolar range.[14] It retains

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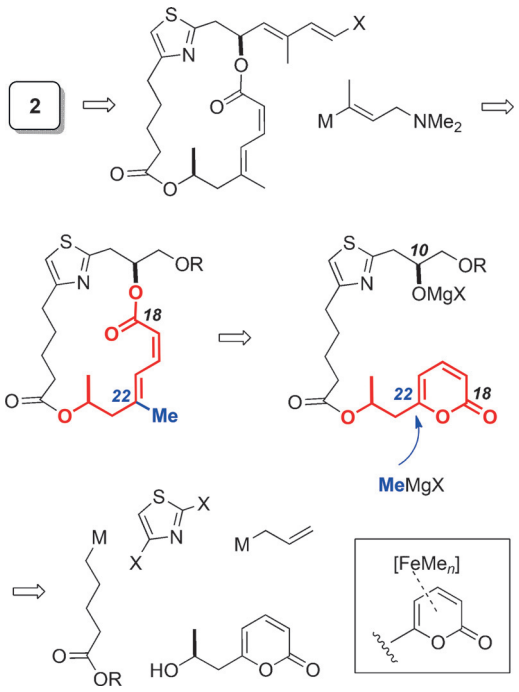
full potency against a paclitaxel-resistant uterine sarcoma cell line, which suggests that **2** is not subject to P-glycoprotein mediated drug efflux. Equally encouraging is the fact that **2** showed hardly any toxicity for quiescent human fibroblasts, thus promising a workable therapeutic window.[14] This aspect, however, needs more scrutiny as the in vitro effects on cell proliferation lack reversibility, which might indicate that the dienoate unit in **2** acts as a Michael acceptor for pertinent biological nucleophiles.[10]

The available in vivo data are even more encouraging as they hold the promise of differential activity. Specifically, **2** proved highly effective in two different melanoma xenograft models (LOX, MDA-MB-435), leading to significant regression in tumor size and weight, whereas it showed no significant effect in pancreatic or colon cancer mouse models.[14] It is not clear at this point why the compound is rather indiscriminative amongst different cancer cell lines in vitro but surprisingly selective in vivo. This prolife might mirror the massive overexpression of eIF4A by several types of melanoma.[10b] Furthermore, it has been suggested that secondary effects such as the activation of stress granules or independent surveillance mechanisms amplify the impact of **2** in a cell-line dependent manner.[15,16] This open question notwithstanding, a recent in vivo study provides additional impetus. Thus, it was shown that low doses of the parent compound **1** block the onset of cachexia in an ardenocarcinoma mouse model.[17] Cachexia is a serious and often lethal multi-factorial muscle wasting syndrome leading to massive loss of body weight, which affects many cancer or immunocompromised patients and for which no effective treatment is currently available.

Despite the already substantial body of work on **1** and **2**, many relevant aspects of their chemistry and biology still need to be addressed at a next stage of development. To this end, it is mandatory to have a reliable supply chain in place. Even aquaculture of the producing sponge was considered in the past;[18] given the size of the targets, however, chemical synthesis is deemed competitive and should excel when it comes to making further analogues for testing.[19] Critical for success is an efficient way of crafting the non-thermodynamic and highly isomerization-prone *Z,E*-configured dienoate entity. The available information suggests that changes to the stereostructure of this motif or its formal replacement by an enyne unit abrogate potency.[13] Outlined below is a novel solution for this formidable problem, which takes strategic advantage of an iron-catalyzed ring-opening/cross-coupling reaction that allows the overall synthesis of **2** to be streamlined.

DMDA-PatA (**2**) was retrosynthetically dismantled as shown in Scheme 1. While the attachment of the side chain follows the literature precedent,[7,8,19] the envisaged assembly of the macrocyclic framework is fundamentally different. In the conceived approach, the labile *Z,E*-dienoate is encoded as a 2-pyrone ring and unveiled only immediately prior to macrocyclization via an iron-catalyzed reaction that introduces the methyl substituent branching off C22.[20,21] In this formal ring-opening/cross-coupling step, which likely starts by recognition of the diene subunit of the pyrone by the (loaded) iron catalyst (see the Insert in Scheme 1),[20,22] the lactone

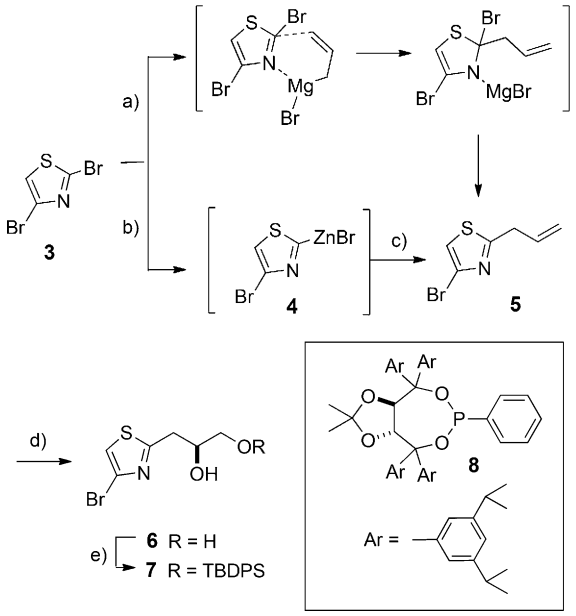


Scheme 1. Retrosynthetic analysis of DMDA-Pat A (**2**).

gains the role of a leaving group that is extruded by the incoming methyl group but retained in the product. As this non-orthodox transformation was previously shown to proceed under mild conditions,[20] the risk for double-bond isomerization was deemed low. However, the iron-catalyzed process has to outperform a potentially competing uncatalyzed attack of MeMgX onto the ester present in the substrate and must not be disrupted by the heteroatom donor sites of the thiazole ring; ideally, it would work with a free −OH at C10 in place to afford the *seco*-acid for macrolactonization right away.

If successful, this tactics might actually pay further dividends: the "internal protection" of the sensitive dienoate in form of a stable heterocyclic ring almost certainly facilitates the preparation of the building block as well as the assembly phase; as a result, the overall synthesis should gain robustness, convergence and flexibility. Moreover, the use of nucleophiles other than MeMgX in the iron-catalyzed step allows, a priori, deep-seated structural point mutations to be instigated at a key positon of the macrocyclic frame that is difficult to address otherwise. Therefore the envisaged blueprint could be serviceable once the project transitions from the stage of target-oriented to diversity-oriented synthesis.[23,24]

Dibromothiazole **3** served as convenient point of departure, which was selectively mono-allylated on treatment with allylmagnesium bromide by what is mechanistically believed to be a formal [3,3] sigmatropic rearrangement followed by elimination (Scheme 2);[25] although practical, the yield of **5** was moderate and somewhat variable. More concise results were obtained upon treatment of **3** with Zn/LiCl and quenching of the resulting functionalized organozinc species **4** with allyl bromide in the presence of catalytic CuCN;[26] this method worked particularly well on larger scale. Not unex-



Scheme 2. a) Allylmagnesium bromide, Et_2O, −30 °C, 50–68 %; b) Zn, LiCl, THF; c) allyl bromide, CuCN (5 mol %), THF, 0 °C, 89 %; d) (i) $B_2(pin)_2$, $Pt(dba)_3$ (2.4 mol %), **8** (2.8 mol %), THF, 60 °C; (ii) aq. H_2O_2, NaOH, 91 % (91 % *ee*); e) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C→RT, quant.; dba = dibenzylidene-acetone; DMAP = 4-dimethylaminopyridine; TBDPS = *tert*-butyldiphenylsilyl.

pectedly, attempted asymmetric dihydroxylation of the terminal olefin in **5** proved unsatisfactory, even though several ligands were surveyed ($ee \leq 65\,\%$).[27] This problem was conveniently solved by a two-step/one-pot procedure comprising a platinum-catalyzed enantioselective diboration controlled by the TADDOL-derived phosphonite ligand **8**, followed by oxidation of the vicinal boronate species primarily formed.[28] This method furnished excellent results in terms of selectivity and yield, and also scaled well; to the best of our knowledge, it is the first application to a heterocyclic substrate featuring possible coordination sites for the platinum catalyst. Selective protection of the primary alcohol in **6** thus formed gave building block **7** as necessary for the synthesis of DMDA-Pat A (**2**).

The crucial pyrone fragment was also readily prepared (Scheme 3). To this end, commercial (*S*)-**9** was opened with lithium acetylide and the resulting product **10** immediately engaged in a Sonogashira coupling with iodide **12** derived from propiolate **11** in one step. A loading of 1 mol % of [(XPhos)AuNTf$_2$] sufficed to convert the resulting product **13** into the corresponding pyrone **14**.[29,30] The reaction was exquisitely selective for the desired 6-*endo*-dig cyclization and proceeded without any noticeable interference of the unprotected −OH group; alternative protocols from the literature[31] were not nearly as effective and selective as this powerful π-acid catalyzed methodology.[32]

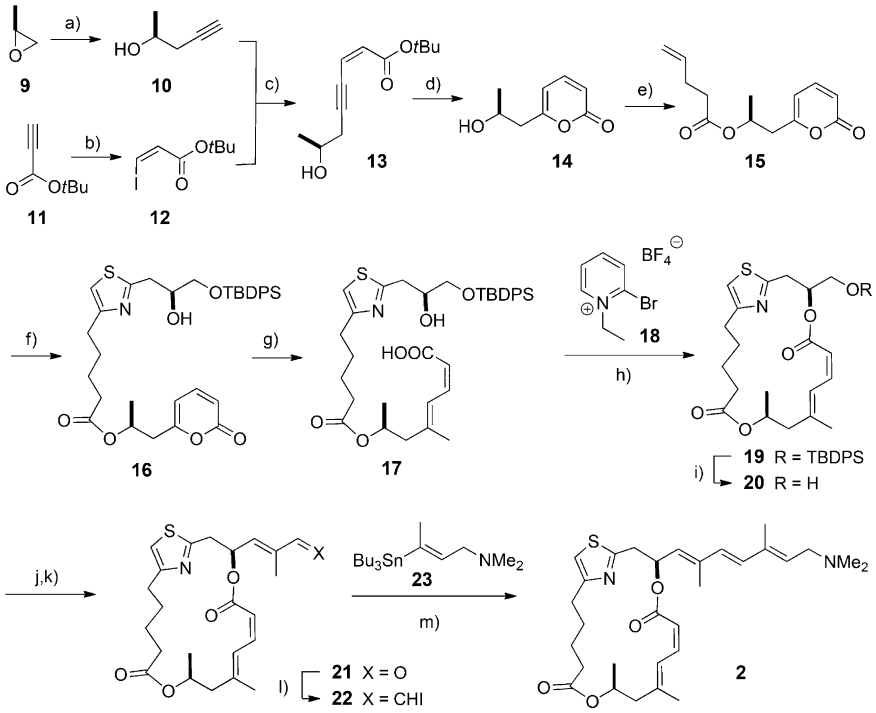
Esterification of **14** with 4-pentenoic acid followed by hydroboration of **15** gave an adequate nucleophilic partner for an alkyl-Suzuki coupling[33] with the bromothiazole fragment **7**. The use of $Pd(OAc)_2$ in combination with RuPhos[34] furnished a remarkably active catalyst that allowed product **16** to be obtained in well reproducible 82 % on a 1.4 g scale (single largest batch).[35]

With appreciable amounts of **16** in hand, the stage was set for the key ring-opening/cross-coupling reaction. Because of the presence of the free −OH group, an extra equivalent of MeMgBr had to be used; in practice, however, excess Grignard reagent was necessary for good conversion. Largely for the low solubility of the resulting magnesium alkoxide, the original solvent system (Et_2O/toluene)[20] was replaced by Et_2O/cyclopentyl methyl ether. Under these conditions, the iron-catalyzed reaction proceeded cleanly at −30 °C to give the desired *Z,E*-configured dienoic acid **17** in good yield and favorable isomeric purity (75 % (84 % brsm), ≥18:1) when the reaction was stopped after 3.5 h; no competing attack of the Grignard reagent onto the ester or lactone groups in **16** was noticed, and the compatibility of the iron catalyst with the sulfur and nitrogen donor sites is rewarding. A practical complication, however, arose from the fact that small amounts of unreacted starting material remained at this point which proved difficult to separate; actually, analytically pure samples of **17** could only be obtained by preparative TLC, which is obviously impractical on scale.

Because longer reaction times necessary for full conversion resulted in stereochemical erosion, the crude material of the iron-catalyzed pyrone ring opening reaction was directly subjected to macrolactonization under modified Mukaiyama conditions.[36] Specifically, the use of **18** as the activating agent, which is escorted by a non-nucleophilic counterion, furnished the macrocycle in isomerically pure form, whereas more conventional macrolactonization protocols resulted in massive isomerization.[37] At this stage, product **19** could be purified by flash chromatography and unreacted pyrone **16** be recovered. Although performed only with 250 mg batches, this protocol proved practical and well reproducible, and nothing augurs against applications on significantly larger scale.

From this point onward, the completion of the synthesis of DMDA-Pat A (**2**) followed the known route,[8,13] but not without notable improvements. Specifically, the oxidation of the primary alcohol **20** formed on deprotection of **19** with buffered TBAF proved delicate. In our hands, reproducible results were obtained when the reaction was performed under Parikh–Doering conditions[38] and telescoped with the Wittig olefination, as the intermediate aldehyde is rather sensitive and epimerization-prone. Single crystals of the resulting product **21** suitable for X-ray diffraction could be grown, which revealed, for the first time, the conformation of the pateamine macrocycle that is supposedly critical for eliciting the biological response (Figure 1). The large ring adopts an unusual triangular shape; the thiazole ring as well as the *Z,E*-configured dienoate lie perpenticular to its plane, thus forming a conspicuous "wall" each,[39] which is heightened by the methyl residue at C22 introduced via the iron chemistry. The two carbonyl groups are axially disposed but oriented to the opposite sides of the macrocycle as to minimize the overall dipole. As expected, the side chain is attached in an equatorial orientation.

Next, aldehyde **21** was subjected to a Takai olefination which gave alkenyl iodide **22** in high yield and appreciable



Scheme 3. a) HC≡CLi·eda, DMSO, 0 °C→RT; b) NaI, HOAc, 70 °C, 81 %; c) $Pd(PPh_3)_4$ (5 mol %), CuI (5 mol %), Et_3N, 30 °C, 93 %; d) [(XPhos)AuNTf$_2$] (1 mol %), $MeNO_2$/HOAc (4:1), 89 %; e) 4-pentenoic acid, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene, 0 °C→RT, 97 %; f) (i) 9-H-9-BBN, THF, 0 °C → RT; (ii) **7**, $Pd(OAc)_2$ (5 mol %), RuPhos (10 mol %), K_3PO_4, THF, 50 °C, 82 %; g) MeMgBr, $Fe(acac)_3$ (30 mol %), Et_2O/CPME, −30 °C; h) **18**, $NaHCO_3$, CH_2Cl_2, 64 % (brsm, over two steps); i) TBAF, HOAc, THF, quant.; j) SO_3·pyridine, DMSO, *i*Pr_2NEt, CH_2Cl_2, −20 °C; k) Ph_3PC-(Me)CHO, toluene, 80 °C, 86 % (over two steps); l) CHI_3, $CrCl_2$, THF, 0 °C, 91 % (ratio *E* to sum of other isomers = 94:6); m) $Pd(PPh_3)_4$ (10 mol %), CuTC, [Ph_2PO_2][NBu_4], DMF, 83 %; 9-BBN = 9-borabicyclononane; brsm = based on recovered starting material; CPME = cyclopentyl methyl ether; CuTC = copper thiophene-2-carboxylate; eda = ethylenediamine; TBAF = tetra-*n*-butylammonium fluoride; Tf = trifluoromethanesulfonate.

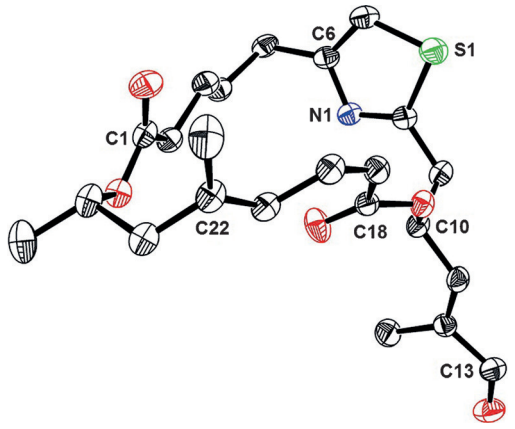


Figure 1. Structure of compound **21** in the solid state; pateamine numbering scheme.

isomeric purity.[40,41] This mixture was used in the final step, as only the *E*-isomer would participate in the cross coupling with the known stannane **23**.[19] It is of note that analogous Stille reactions had partly met with surprisingly low yields in previous work on the pateamines.[7,8,19] Gratifyingly though, application of a procedure developed in this laboratory for sensitive cases proved reliable and efficient, furnishing DMDA-Pat A (**2**) in 83 % yield.[42,43] The spectroscopic data of our samples compared favorably to those reported in the literature (see the Supporting Information).

The route outlined above opens access to the antiproliferative and pro-apoptotic macrolide DMDA-Pat A (**2**), a promising anticancer agent with proven in vivo activity and a possible lead in the quest for medication for the currently untreatable muscle wasting syndrome cachexia.[14,17] With only 12 steps in the longest linear sequence (19 steps total) and an overall yield of ≥18 %, it is distinguished by pleasing "economies"[44] and a multiplied material output as compared to the literature route (16 steps longest linear sequence, 36 steps total, ca. 3.8 % overall yield);[8] moreover, the sequence is robust and inherently flexible. This success hinges upon a panopticum of transition metal-catalyzed reactions used in concord: in addition to two different palladium-catalyzed cross coupling reactions, which are recurrent motifs in almost any contemporary synthesis project, it features the prowess of platinum-catalyzed asymmetric diboration/oxidation.[28] The key strategic element, however, is the orchestrated interplay of a gold-catalyzed pyrone formation[29,30] with an iron-catalyzed pyrone opening/cross coupling.[20] This maneuver showcases the use of a robust heterocyclic entity as surrogate of a fragile acyclic motif, and highlights an unorthodox and perhaps underutilized manifestation of cross coupling chemistry, where the new C–C bond is formed while the heterocycle is unwrapped and tethered new functionality unveiled.

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