Natural Product Synthesis

Enantioselective Total Synthesis of Cylindramide**

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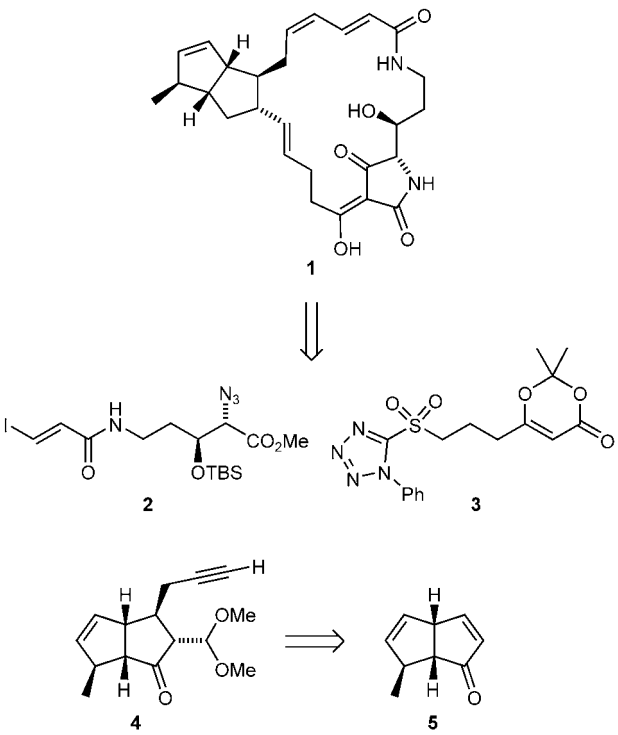
Dedicated to Professor Franz Effenberger on the occasion of his 75th birthday

Marine organisms produce a tremendous variety of bioactive secondary metabolites,[1] which are often used as lead structures in the development of novel pharmaceuticals. In 1993 Fusetani et al. isolated cylindramide (**1**) from the marine sponge *Halichondria cylindrata*, and it was found to exhibit pronounced cytotoxicity against B16 melanoma cells.[2] Cylindramide belongs to the class of complex tetramic acid lactams, which also includes structurally related compounds such as discodermide from the Caribbean marine sponge *Discodermia dissoluta*,[3] alteramide A from a bacterium *Alteromonas* sp. associated with the sponge *Halichondria okadai*,[4] aburatubolactam A isolated from a cultured broth of a *Streptomyces culture* stemming from a mollusk,[5] maltophilin produced by *Stenotrophomonas maltophilia*,[6] and geodin A magnesium salt, which was recently isolated from the Southern Australian marine sponge *Geodia*.[7] Besides the tetramic acid unit, a substituted bicyclo[3.3.0]octane skeleton is the characteristic feature of these macrocyclic compounds. However, to our knowledge, syntheses of this type of macrocycles have not yet been reported, with exception of one model study[8] and two total syntheses of the related ikarugamycin, in which the bicyclooctane moiety is replaced by a decahydroindacene framework.[9,10]

Our synthetic strategy was based on the retrosynthetic degradation of cylindramide (**1**) into the three fragments **2**–**4** (Scheme 1). The pentalene derivative **4** should be accessible from pentalenone **5** by a tandem process consisting of a Michael addition and an electrophilic trapping reaction. It should be possible to couple hydroxyornithine **2** and phenyltetrazolyl (PT) sulfone **3** to pentalene **4** by Sonogashira coupling and Julia–Kocienski olefination, respectively. After macrocyclization, the formation of the tetramic acid unit should conclude the synthesis.



Scheme 1. Retrosynthesis of cylindramide (**1**).

The generation of building block **2** (Scheme 2) started with a Wittig olefination of the Boc-protected β-aminoaldehyde **6**[11] to give derivative **7**, which was converted into alcohol **8** by Sharpless asymmetric dihydroxylation and subsequent regioselective nosylation.[12] A sequence of nucleophilic substitution with tetramethylguanidinium azide ($TMGN_3$),[13] protection of the OH function, and removal of the Boc protecting group afforded α-azidoester **9**. Following the method of Shioiri et al.,[14] we finally coupled derivative **9** with β-iodoacrylic acid **10** to give fragment **2** in 83% yield.

Sulfone **3** was prepared from precursor 2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (**11**)[15] (Scheme 3). Alkylation, ozonolysis, and reductive workup gave alcohol **13**. The phenyltetrazolthiol was introduced by a Mitsunobu reaction, and the resulting intermediate **14** oxidized to PT-sulfone **3** with H_2O_2 in the presence of a Mo catalyst.[16]

Enantiopure bicyclo[3.3.0]octanonacetal **15**, which is available in five steps by transannular Pd-catalyzed coupling of cycloocta-1,5-diene followed by enzymatic resolution,[17] served as the starting material for the pentalene unit. We employed the IBX method of Nicolaou et al.[18] to oxidize ketone **15** affording enone **16** in 63% yield (Scheme 4).

The 1,4-addition of Me_2CuLi to enone **16** and trapping with Comins reagent (**17**)[19] resulted, however, in a mixture of vinyl triflate **19** (47%) and ketone **18** (39%). Fortunately, the latter could be converted into the desired triflate **19** in 72%

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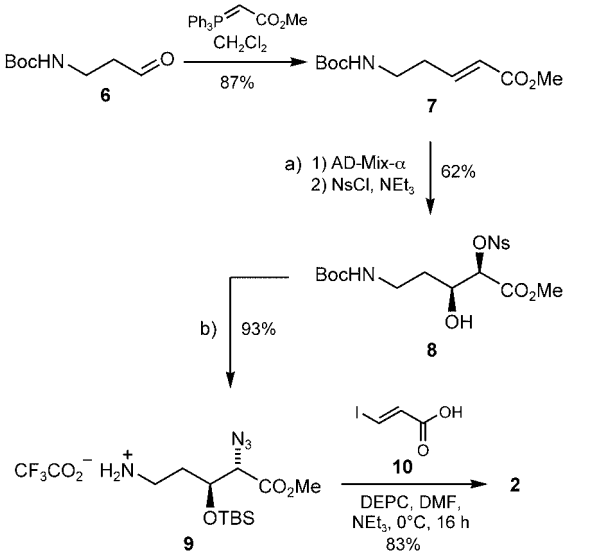
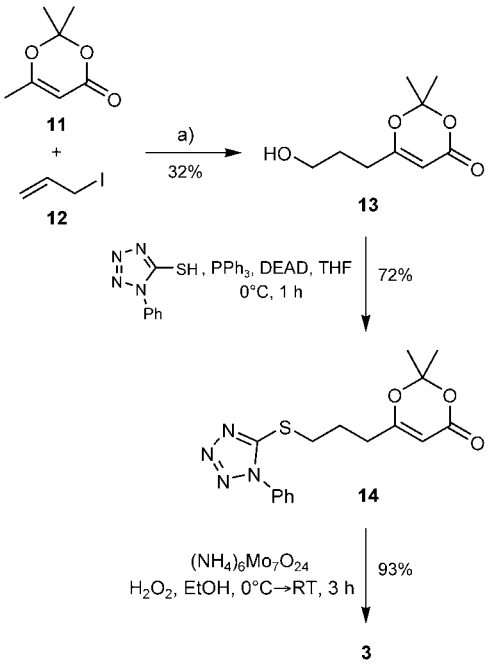
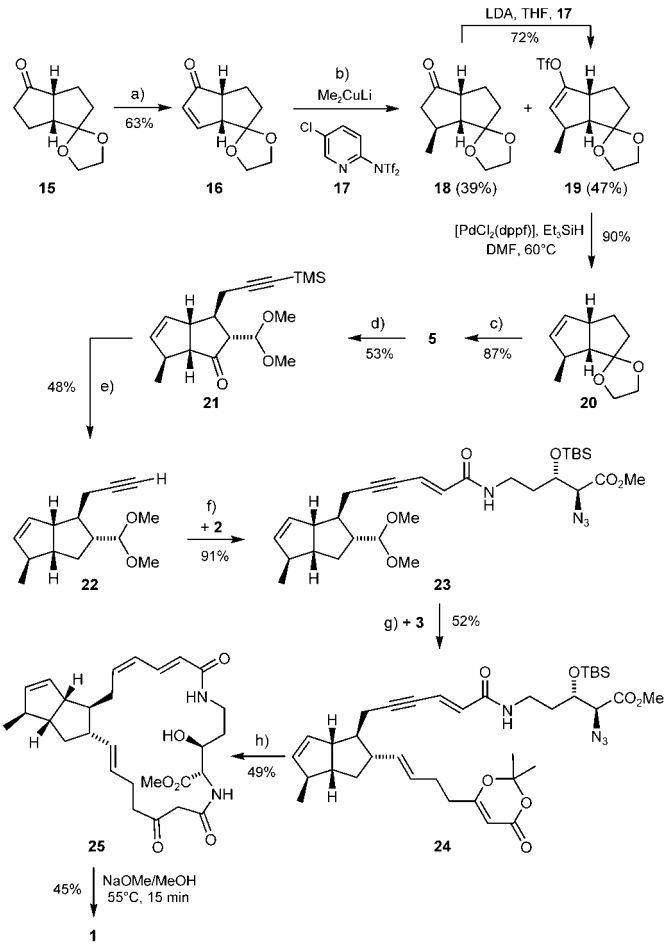


Scheme 2. Reagents and conditions: a) 1. AD-mix-α, *t*BuOH/H_2O, $MeSO_2NH_2$, 0 °C, 1 d, 95 %, 96 % *ee*, 2. NsCl (1 equiv), NEt_3, CH_2Cl_2, 0 °C, 12 h, 65 %; b) 1. tetramethylguanidinium azide ($TMGN_3$) (6 equiv), DMF, 50 °C, 15 h, 96 %, 85:15 d.r., 2. TBSCl, DMAP, DMF, 97 %, 3. TFA, CH_2Cl_2, 0 °C, 1 h, quant. Boc = *tert*-butoxycarbonyl, DEPC = diethyl cyanophosphonate, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, Ns = 4-nitrobenzenesulfonyl, TFA = trifluoroacetic acid, TBS = *tert*-butyldimethylsilyl.



Scheme 3. Reagents and conditions: a) 1. LDA, DMPU, THF, **11**, 0 °C, 1 h, **12**, −40 °C→RT, 16 h, 50 %; 2. O_3, $MeOH/CH_2Cl_2$/pyridine (3:3:1), −78 °C, then $NaBH_4$, 64 %. DEAD = diethylazodicarboxylate, DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea.



Scheme 4. Reagents and conditions: a) LDA, THF, TMSCl, −78 °C→0 °C, 4-methoxypyridin-*N*-oxide (MPO), IBX, DMSO, CH_2Cl_2, RT, 45 min, 63 %; b) Me_2CuLi, THF, **17**, −78 °C→0 °C; c) 1. PPTS, acetone, H_2O, reflux, quant., 2. LDA, THF, TMSCl, −78 °C→0 °C, then MPO, IBX, DMSO, CH_2Cl_2, RT, 30 min, 87 %; d) TMS-C≡CCH_3, *t*BuLi, TMEDA, THF, −40 °C, 1 h, CuI, TMSCl, THF, −78 °C, **5**, 2 h, then $BF_3{\cdot}OEt_2$, $HC(OMe)_3$, CH_2Cl_2, −20 °C, 1 h, 53 %; e) 1. $NaBH_4$, MeOH, 0 °C, 2. $(Im)_2CS$ (5 equiv), DMAP (5 equiv), DCE, reflux, 16 h, 3. Bu_3SnH, AIBN, toluene, 110 °C, 45 min, 57 % over 3 steps, 4. EtOH, H_2O, $AgNO_3$, 0 °C, 3 h, KCN, 30 min, 85 %; f) **2**, $[Pd(PPh_3)_4]$, CuI, NEt_3, THF, 91 %; g) 1. PPTS, acetone, H_2O, reflux, 2. **3** (3 equiv), NaHMDS, DME, −55 °C→RT, 52 %; h) 1. PPh_3, THF, H_2O, RT, 24 h, 2. toluene, 2.5×10^{-4} M, reflux, 10 h, 82 %, 3. H_2, $Pd/BaSO_4$, quinoline, EtOH, 66 % (referred to recovered starting material), 4. HF/MeCN, RT, 3 h, 91 %. AIBN = azobisisobutyronitrile, DCE = dichloroethane, DME = dimethoxyethane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, PPTS = pyridinium *p*-toluenesulfonate, NaHMDS = sodium hexamethyldisilazide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMS = trimethylsilyl.

yield by a second deprotonation with LDA and reaction with **17**. Pentalenacetal **20**, prepared from **19** in 90 % yield by Pd-catalyzed reduction using Et_3SiH,[20] was deprotected and transformed into the pentalenone **5** in 87 % yield. After reaction of **5** with TMS-protected propynyl cuprate[21] and subsequent addition of orthoformate and $BF_3{\cdot}OEt_2$, the pentalene derivative **21** was isolated in 53 % yield as a single diastereoisomer, as supported by NMR and GC data. Compound **21** was reduced with $NaBH_4$ to give a 1:1 mixture of diastereomeric alcohols. Despite the steric hindrance of the convex bicyclo[3.3.0]octane moiety, Barton deoxygenation followed by desilylation to **22** (48 % yield) was successful.

After all the required coupling components were available, we followed our strategy to create the macrocycle.

Sonogashira coupling[22] of pentalene **22** with iodoacrylate **2** provided the enyne **23** in 91% yield. The dimethyl acetal group was hydrolyzed to give the corresponding intermediate aldehyde, which was olefinated with sulfone **3** under Julia–Kocienski conditions[16] giving the *E*-alkene **24** (52%).[23] Cyclization to the macrolactam could be realized in 82% yield by Staudinger reduction of the azide function, subsequent dilution in toluene (2.5×10^{-4} M), and heating the dilute solution at reflux. The Lindlar reduction of the enyne moiety to yield the *Z*,*E*-diene turned out to be difficult. Only incomplete conversion resulted in 66% yield for the desired diene, whereas overreduction was observed at longer reaction times. Removal of the silyl protecting group afforded the macrocyclic β-hydroxy ester **25** in 91% yield. Brief heating of **25** with NaOMe in MeOH[24] finally gave the target macrolactam **1** with partial epimerization (3:1). The major diastereomer (2*S*,3*S*)-**1** could be isolated in pure form by reversed-phase chromatography, and the spectroscopic data of synthetic cylindramide (**1**, major diastereomer) are in accordance with those of the natural product.[25]

In summary, the described convergent route was used for the first total synthesis of the cytotoxic tetramic acid lactam **1** in 29 steps and in 1.0% overall yield, with a longest linear sequence of 18 steps. The synthetic strategy should allow access to the other interesting tetramic acid natural products mentioned in the introduction.

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