Natural Product Synthesis

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Gephyronic Acid, a Missing Link between Polyketide Inhibitors of Eukaryotic Protein Synthesis (Part II): Total Synthesis of Gephyronic Acid**

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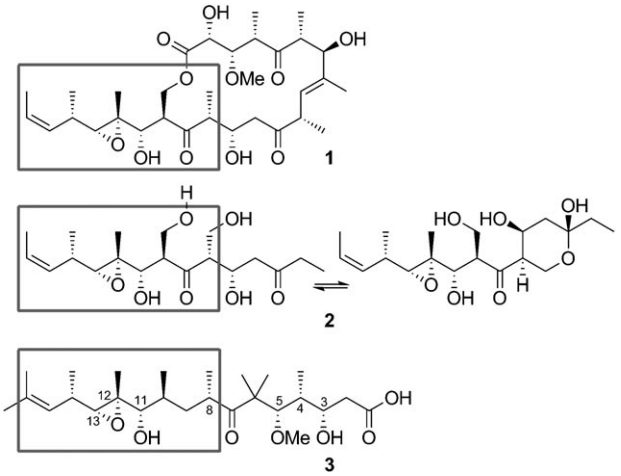
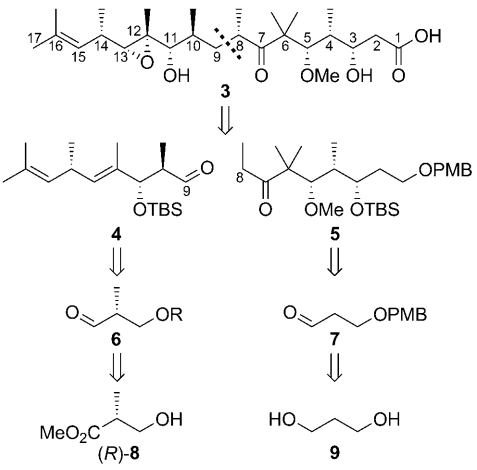
Dedicated to Professor Horst Kunz on the occasion of his 70th birthday

Marine invertebrates and microorganisms of marine and terrestrial origin are rich sources of biologically active secondary metabolites, which may be potent pharmaceutical lead compounds.[1] Among them are the structurally related polyketide natural products tedanolide (**1**), isolated from the Caribbean sponge *Tedania ignis*,[2] its truncated congeners myriaporone 3 and 4 (**2**) obtained from the Mediterranean false coral *Myriapora truncata*,[3] and gephyronic acid (**3**)[4] isolated from the myxobacterium *Archangium gephyra* strain Ar 3895; the latter is also a possible pharmacophoric link between structurally distinct classes of polyketides (Scheme 1).

Compounds **1**–**3** were found to be potent inhibitors of eukaryotic protein synthesis. On account of their pronounced cytotoxicities, synthetic approaches were elaborated,[5,6] culminating in the total synthesis of tedanolide (**1**)[7] and myriaporones (**2**).[8] The presence of a trisubstituted epoxide unit in gephyronic acid (**3**) was originally proposed in an article detailing the structural similarities between compounds **1**–**3** and pederin.[9] The lack of structural information regarding C8 and C3–C5 severely hampered further biological and synthetic studies, and thus, a detailed NMR study was initiated.[10] As the possible diastereomers of **3** were not unambiguously distinguishable from NMR data alone, analysis of synthetic fragments and ultimately total synthesis proved essential. Our retrosynthetic strategy was based on disconnection of gephyronic acid (**3**) into the fragments C9–C17 (**4**) and C1–C8 (**5**), which can be traced back to methyl (*R*)-3-hydroxy-2-methylpropionate ((*R*)-**8**) and 1,3-propanediol (**9**), respectively (Scheme 2).



Scheme 1. Polyketide natural products tedanolide (**1**), myriaporones 3 and 4 (**2**), and gephyronic acid (**3**; structure from NMR studies[9,10]).



Scheme 2. Retrosynthesis of gephyronic acid (**3**). PMB = *para*-methoxybenzyl.

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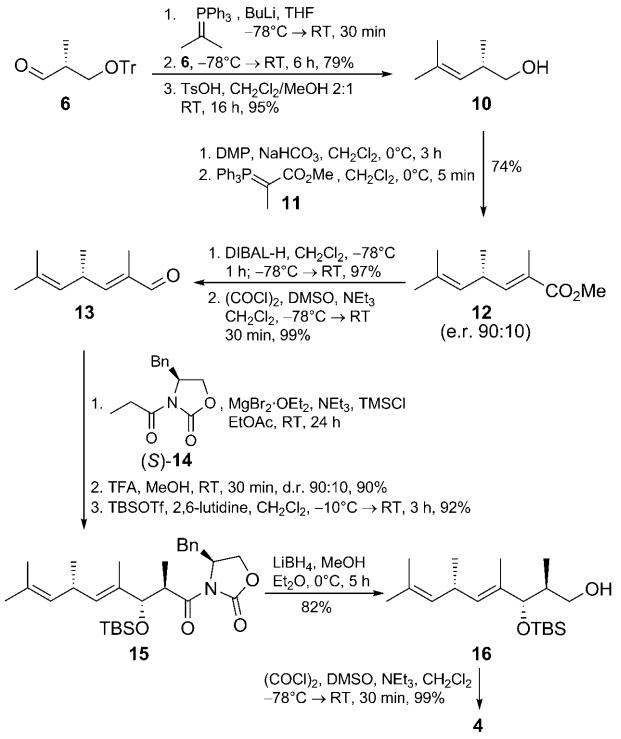
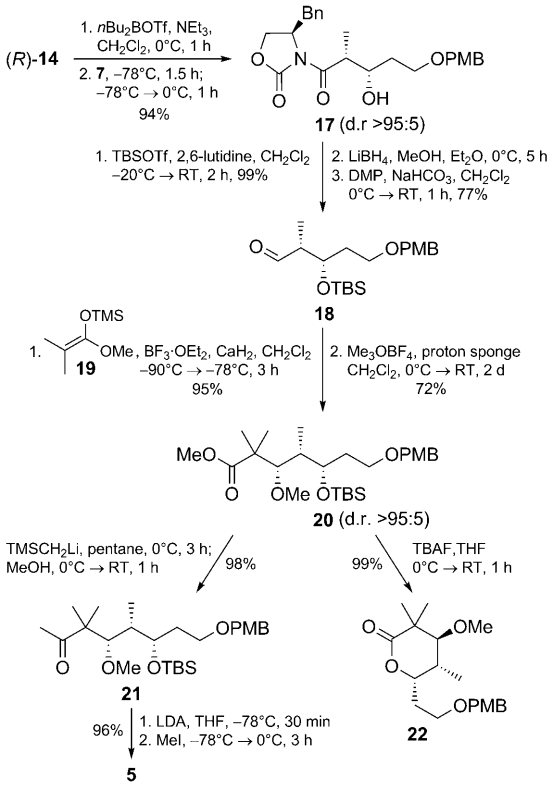
The synthesis of building block **4** started with a Wittig olefination of aldehyde **6**[11,12] and subsequent acidic deprotection[13] to give alcohol **10**. Oxidation with Dess–Martin periodinane followed by Wittig olefination with the stabilized ylide **11** afforded ester **12** (Scheme 3). Aldehyde **13**, which



Scheme 3. Synthesis of the C9–C17 fragment **4**. DMP = Dess–Martin periodinane, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, TFA = trifluoroacetic acid, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

was obtained after reduction with DIBAL-H[14] and Swern oxidation, was submitted to a $MgBr_2{\cdot}OEt_2$ catalyzed *anti*-aldol reaction[15,16] with oxazolidin-2-one **14** to provide the aldol product **15**. The major diastereomer could be separated chromatographically only after TBS protection of the secondary hydroxy substituent at C3. Removal of the Evans auxiliary from **15** with $LiBH_4$ in MeOH[17] and Swern oxidation of **16** accomplished the synthesis of fragment **4**.

We utilized Evans' aldol methodology[18] and treated (4*R*)-oxazolidinone **14** with propanal **7**[19–21] to give the *syn* aldol product **17** with high diastereoselectivity (d.r. > 95:5) (Scheme 4). Aldehyde **18** was accessible from **17** by a sequence of TBS protection, removal of the auxiliary, and Dess–Martin oxidation.[20] The $BF_3{\cdot}OEt_2$ mediated Mukaiyama aldol reaction[22] of **18** with silylketene acetal **19**[22b] occurred with excellent *syn* selectivity (Felkin–Anh control), and after O-methylation with Meerwein's salt and proton sponge,[23] the *syn*,*syn* methyl ester **20** was isolated as a single diastereomer (d.r. > 95:5). Treatment of **20** with $TMSCH_2Li$ and quenching with MeOH[24,25] gave methyl ketone **21**, which was methylated[24] to provide the target ethyl

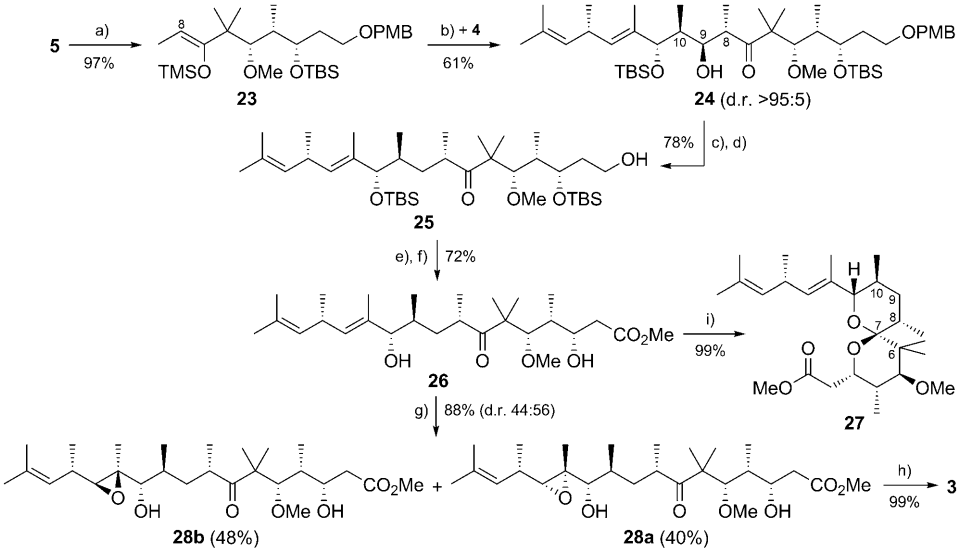


Scheme 4. Synthesis of the C1–C8 fragment **5**. LDA = lithium diisopropylamide, TBAF = *tert*-butylammonium fluoride.

ketone **5**. The *syn* stereochemistry in **20** was supported by NMR analysis of lactone **22** derived from **20** (Scheme 4).[26]

As the key step for coupling of the fragments **4** and **5**, a stereodifferentiating $BF_3{\cdot}OEt_2$ promoted Mukaiyama aldol reaction[27] was chosen (Scheme 5). Based on the facial selectivities of *anti* aldehyde **4** and the enolsilane of **5** we expected an *anti*-selective aldol formation.[22a,28,29] Indeed, enolsilane **23**, derived from **5** and fragment **4**, coupled to give the Felkin diastereomer **24** as the major product. Comparison of coupling constants ($J_{8\text{-H},9\text{-H}} = 9.8$ Hz, $J_{9\text{-H},10\text{-H}} = 1.4$ Hz) with those of structurally related compounds[27] revealed an *anti* configuration at C8–C9. Mild deoxygenation involving treatment with NaHMDS in CS_2 and MeI,[30] reduction of the xanthogenate with $Bu_3SnH{\cdot}Et_3B$,[31] and subsequent deprotection with DDQ[32] provided primary alcohol **25** in 78% yield over three steps. Successive Swern and Pinnick oxidation with $NaClO_2$ in the presence of 2-methyl-2-butene,[33] methylation of the resulting carboxylic acid with (trimethylsilyl) diazomethane,[34] and cleavage of the TBS protecting groups at C3 and C11 with $3\,HF{\cdot}NEt_3$[12] gave methyl ester **26**. The latter reaction required 7 days to yield **26** in 77% yield together with the ester singly deprotected at C3 in 21% yield. The coupling constants of the fully characterized spiro acetate **27** prepared from **26** confirmed the configuration at C8.

Unfortunately, with substrate **26**, epoxidation with *m*CPBA at −60 °C[8,12] after 2 days led to a mixture of oxidation products, and thus diol **26** was submitted to a Sharpless epoxidation.[35] However, with *S* configuration at C11, **26** is a typical mismatched case for classical Sharpless



Scheme 5. Completion of the synthesis of gephyronic acid (**3**). Reagents and conditions: a) 1. LDA (1.3 equiv), THF, −78 °C→−50 °C, 30 min, 2. HMPA (2.0 equiv), −78 °C, 30 min, 3. TMSOTf (2.0 equiv), −78 °C→RT, 5 h; b) **23** (3.0 equiv), $BF_3{\cdot}OEt_2$ (3.3 equiv), CaH_2 (1.0 equiv), +**4** (1.0 equiv), −100 °C→−78 °C, 3 h; c) 1. NaHMDS (1.4 equiv), CS_2, −78 °C, 1 h, then MeI (15.0 equiv), −78 °C→0 °C, 3 h, 99%, 2. Bu_3SnH (7.0 equiv), Et_3B (1.1 equiv), air, toluene, RT, 1 h, 86%; d) DDQ (1.3 equiv), CH_2Cl_2/pH 7 buffer 9:1, 0 °C→RT, 1 h, 93%; e) 1. $(COCl)_2$ (2.0 equiv), DMSO (3.0 equiv), NEt_3 (6.0 equiv), CH_2Cl_2, −78 °C→RT, 2. $NaClO_2$ (2.5 equiv), KH_2PO_4 (7.0 equiv), 2-methyl-2-butene (4.5 equiv), *t*BuOH/H_2O 3:1, RT, 1 h, 3. $TMSCHN_2$ (2.0 equiv), CH_2Cl_2/MeOH 4:1, RT, 1 h, 94%; f) 3 HF·NEt_3, NEt_3, MeCN, RT, 7 d, 77%; g) HOO*t*Bu (1.5 equiv), Ti(O*i*Pr)$_4$ (0.2 equiv), CH_2Cl_2, −20 °C, 14 h; h) 0.1 M KOH solution/MeOH 1:1, RT, 1.5 h; i) PPTS (20 mol%), MeOH, RT, 24 h. HMDS = bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, PPTS = pyridinium *p*-toluenesulfonate.

asymmetric epoxidation with D-(−)-diethyl tartrate; thus the reaction rate was so low that no conversion was observed. Upon reaction with *t*BuOOH and Ti(O*i*Pr)$_4$ in CH_2Cl_2 at −20 °C epoxides **28a**,**b** were obtained in 88% yield (d.r. 44:56). After chromatographic separation, **28a** (40% yield) was finally treated with KOH/MeOH (1:1)[36] to afford gephyronic acid (**3**) in 99% yield.

In conclusion, a 27 step (longest linear sequence 19 steps) convergent total synthesis of gephyronic acid **3** in 4.4% yield was realized. Comparison of the optical rotation in MeOH [natural product: $[\alpha]_D^{20} = +46.5\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.00$ in 100 mL), synthetic product: $[\alpha]_D^{20} = +45.7\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.42$ in 100 mL)] and spectroscopic data proved the identity with the natural product. The total synthesis has provided an alternative source of the natural product, enabling further biological investigations which are currently under way.

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