Total Synthesis

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Light-Mediated Total Synthesis of 17-Deoxyprovidencin**

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Abstract: *An asymmetric synthesis of the diterpenoid 17-deoxyprovidencin is described. Key steps include an aldol addition, a base-catalyzed Wipf-type furan formation, a Z-selective ring-closing metathesis for macrocyclization, a photochemical E/Z isomerization to a highly strained and conformationally restricted ring system, and the stereoselective formation of two epoxides on the ring.*

The class of furanocembranoids offers a diverse range of structurally and biologically interesting natural compounds.[1] In 2003, a highly oxygenated furanobutenolide-based cembrane named providencin (**1**) was isolated from the Caribbean sea plume *Pseudopterogorgia kallos* (Bielschowsky, 1918) by the Rodriguez group.[2] The biosynthesis of **1** is unknown, even though bipinnatin J has been shown to be a plausible precursor.[1] In terms of its biological properties, **1** exhibits moderate activity against human breast cancer and lung and CNS cancer cell lines. The relative configuration was determined by single-crystal X-ray analysis, but the absolute configuration has remained unknown (Figure 1). Compared to other members of the furanocembranoid family, **1** contains two unusual structural features: a cyclobutanol moiety and a Δ-7,8 *trans* epoxide in the macrocyclic ring.[3] The crystal structure[2] of **1** reveals a perpendicular arrangement of butenolide and furan in the macrocycle; the high ring strain of this macrocycle makes it impossible to build a Dreiding model without breaking any bonds. Evidently, the ring strain is mainly due to the *trans* arrangement of the Δ-7,8 epoxide and the rigid angle of 144° between the C7 and C2 appendages around the furan ring.

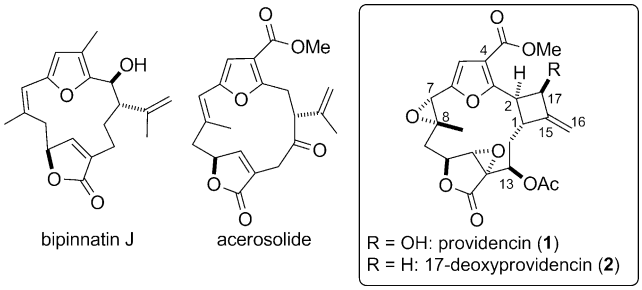

Figure 1. 17-Deoxyprovidencin, providencin, and two related furanocembranoids.

The complex and unusual molecular architecture renders **1** an attractive and yet elusive synthetic target.[4,5] In particular, a recent report by White and Jana has disclosed significant headway, yet underlined the difficulties in closing the highly strained macrocyclic ring.[6]

Considering the biosynthesis of this compound from bipinnatin J, we suggest in contrast to previous assumptions[1,4c] that the cyclobutane ring is closed through a cationic cyclization of **I-1** to form **I-2** and **I-3** (Figure 2). *E*/*Z* Isomerization to **I-4**, as indicated by the formation of acerosolide (Figure 1), and further oxidations may lead to 17-deoxy derivative **2** as a direct precursor to **1**.

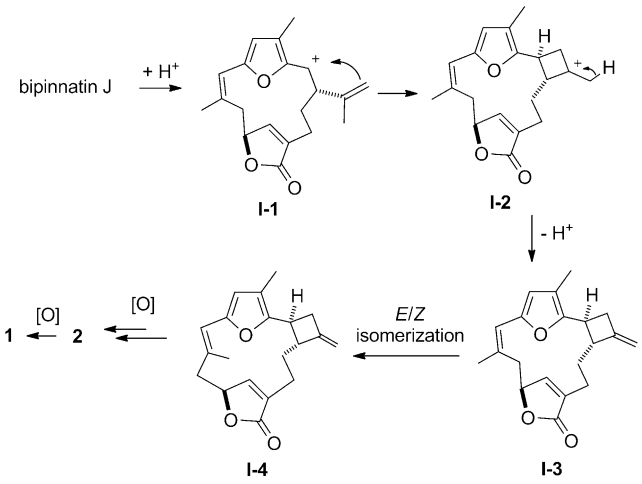

Figure 2. Hypothesis for the biosynthetic formation of **1**.

Herein, we report a synthesis of **2**. Our retrosynthetic plan (Figure 3) is based on precursor **3**, which should be accessible from **2** by formal removal of the epoxides and subsequent modifications on the cyclobutane moiety. Intermediate **3** should arise from the connection of the two main fragments **4** and **5** through an aldol addition[7] and ring-closing metathesis (RCM).[8] The olefin geometry was of minor concern, as we hoped to achieve *Z*/*E* double-bond interconversion by standard methods.

The preparation of **4** started from the known non-racemic compound **6**,[5] which was converted into diol **7** by ozonolysis and reduction (Scheme 1). The differentiation of the primary

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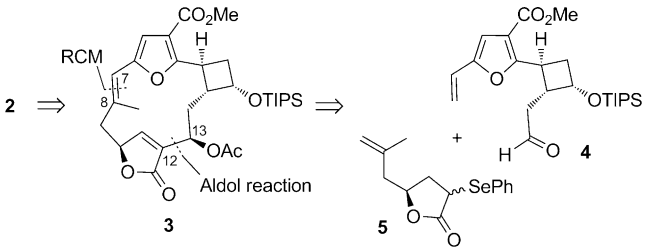
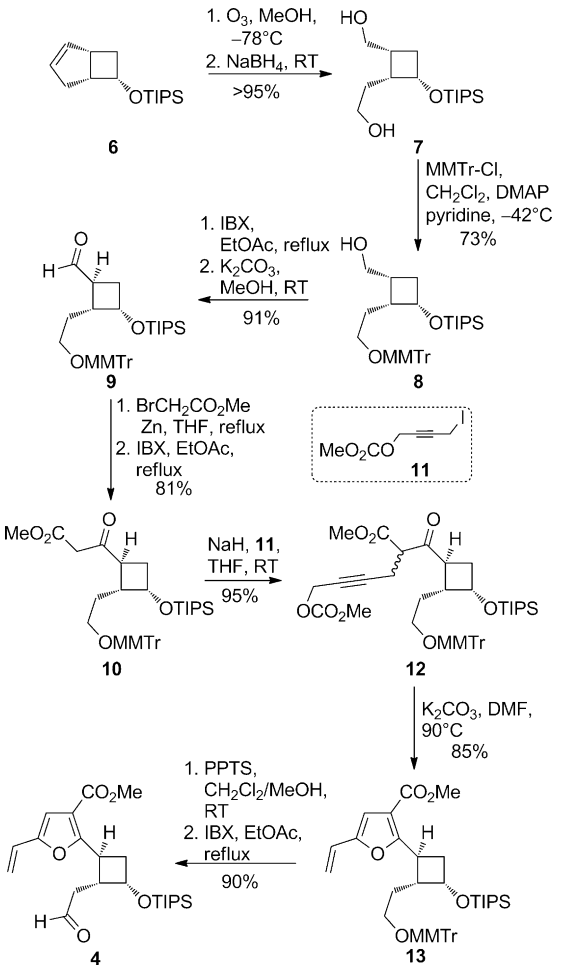


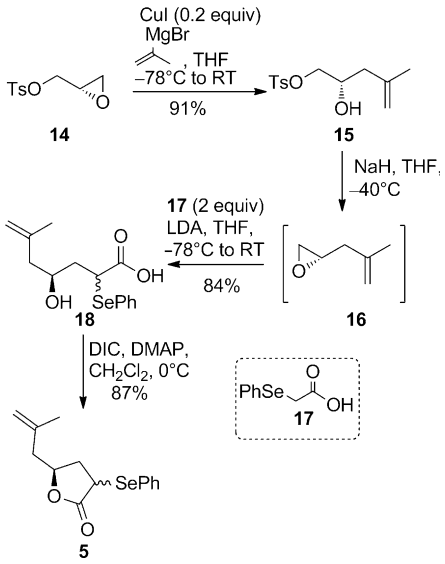
Figure 3. Retrosynthetic analysis of **2**.



Scheme 1. Preparation of fragment **4**. IBX = 2-iodoxybenzoic acid, MMTrCl = tris(4-methoxyphenyl)methylchloride, PPTS = pyridinium *p*-toluenesulfonate, TIPS = triisopropylsilyl.

OH groups was achieved by selective monotritylation of the less hindered position to give intermediate **8**. Oxidation led to the corresponding aldehyde, which underwent base-catalyzed in situ isomerization to *trans* diastereomer **9**. A Reformatsky reaction with bromoacatete followed by oxidation furnished ketoester **10** in excellent overall yield. Alkylation of **10** with propargyl iodide **11** led to **12**, which was cyclized to vinylfuran **13** under base catalysis.[9] Detritylation and oxidation with IBX gave aldehyde **4**.

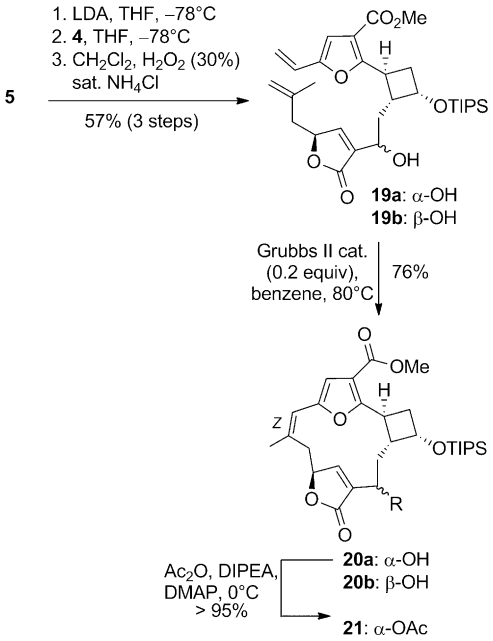
Selenolactone **5** was prepared from (*R*)-glycidyl tosylate (**14**) by cuprate addition to furnish alcohol **15**, which was converted into epoxide **16** with retention of the configuration



Scheme 2. Preparation of building block **5**. DIC = diisopropylcarbodiimide, DMAP = 4-*N*,*N*-dimethylaminopyridine, LDA = lithium diisopropylamide.

(Scheme 2). In situ treatment with the dianion of phenylselenyl acetic acid (**17**) furnished seco acid **18**, which was cyclized to **5** under Steglich conditions.[10]

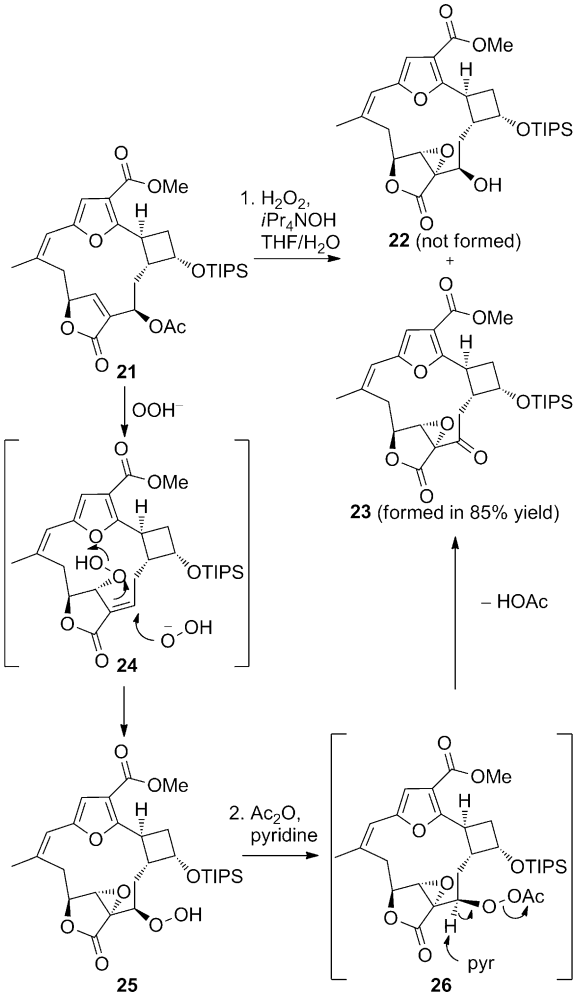
Deprotonation of **5** with LDA and addition of aldehyde **4** provided the aldol adduct as a mixture of four diastereomers. Oxidative elimination of selenide led to a mixture of the epimeric alcohols **19a/b**. For practical use, large-scale RCM[8] was performed with this mixture, which resulted in the formation of the *Z* olefins **20a/b** as a readily separable diastereomeric mixture in a 1.5:1 ratio. Acetylation of **20a** with acetic anhydride led to **21** (Scheme 3). Alternatively,



Scheme 3. Preparation of macrocycle **21**. DIPEA = diisopropylethylamine, Grubbs II cat. = [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium.

alcohols **19a** and **19b** were separated, and **19a** was cyclized to **20a**, whereas **19b** was converted directly into **21** through a Mitsunobu inversion[11] and subsequent RCM. All attempts to isomerize either the *Z* olefins **20a/b** or acetate **21** to their *E* isomers failed.[5a]

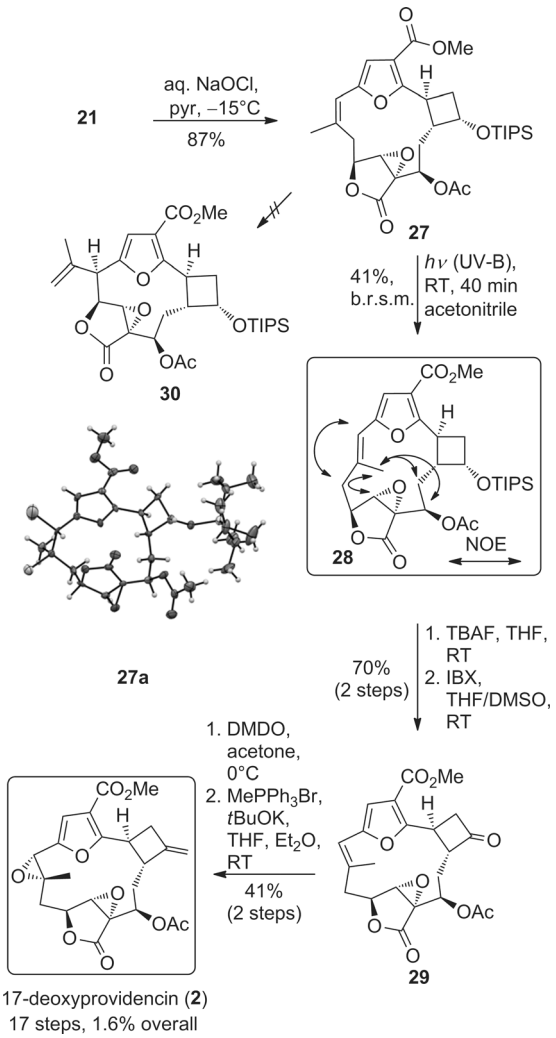
Therefore, we proceeded with the formation of the Δ-11,12 epoxide. Treatment of **20a** with hydrogen peroxide under basic conditions gave a diastereomerically pure compound, which we thought to be epoxy alcohol **22** (Scheme 4).



Scheme 4. Unexpected formation of ketone **23**.

Treatment with acetic anhydride, however, failed to produce the expected epoxy acetate and furnished ketone **23** instead, which was unambiguously characterized by ^1H and ^{13}C NMR spectroscopy. Presumably, 1,4-addition of a hydroperoxide anion to **21** had led to **24** through the elimination of acetate. A second 1,4-attack of the hydroperoxide anion generated epoxy hydroperoxide **25**, which was converted into acetate **26** when treated with acetic anhydride. Finally, elimination of acetic acid under the basic conditions furnished ketone **23**.

In contrast, when acetate **21** was subjected to the conditions developed by Node et al.,[12] epoxy acetate **27** was formed diastereoselectively (Scheme 5); this intermediated was characterized by single-crystal diffraction of the 7,8-



Scheme 5. Formation of epoxide **27**, photoinduced *Z*/*E* isomerization, and further elaboration to 17-deoxyprovidencin (**2**). b.r.s.m. = based on recovered starting material, DMDO = dimethyldioxirane, TBAF = tetrabutylammonium fluoride.

dichloride **27a**.[13a,b] Irradiation of **27** with UV-B light resulted in the desired *Z*/*E* isomerization[14] to olefin **28**. The use of Pyrex glass was crucial, because it cuts off UV wavelengths below 300 nm. The UV absorption maximum of **27** lies at 306 nm, whereas **28** absorbs below 300 nm and is thus not subjected to further photoreactions. With quartz glass, the irradiation produced unidentifiable product mixtures.

The ^1H NMR spectra of **27** and **28** were characteristically different. For **28**, typical line broadening indicated the formation of atropisomers at room temperature. Heating to 75 °C furnished sufficiently sharp signals, so that NOE measurements were feasible to provide evidence for the *E* configuration of the olefin.[13a] Interestingly, no photochemical 1,3-sigmatropic ring contraction (Rodriguez–Pattenden rearrangement)[15] to pseudopterane **30** was observed.

For the further elaboration of **28** towards **2**, the sequence of steps was carefully orchestrated. Thus, 16-ketone **29** was first generated by deprotection and oxidation. Now, it was possible to perform the stereoselective epoxidation of the Δ-7,8 olefin with DMDO.[16] Finally, the exocyclic double bond

at the C16 position was installed by Wittig methylenation. Using this sequence, 17-deoxyprovidencin (**2**) was obtained. A careful NOE analysis confirmed the correct configuration of the Δ-7,8 epoxide,[13a] which means that despite (or owing to) the restricted conformational flexibility of the macrocyclic periphery, the DMDO attack has occurred at the desired outside face of the olefin.

In conclusion, we have presented a synthesis of 17-deoxyprovidencin (**2**) in 17 steps along the longest linear sequence with an overall yield of 1.6%. Key steps include an aldol addition with subsequent oxidative elimination of selenide, a *Z*-selective RCM macrocyclization, a photo-induced *Z*/*E* isomerization to a highly strained conformationally restricted ring system, and a stereoselective epoxidation of the *E* olefin. To corroborate our biosynthetic hypothesis, various allylic oxidations[17] at the C17 position, including enzymatic hydroxylations,[18] remain to be performed.

Experimental Section

Synthesis of the *E*-configured pentacycle **28**: The *Z*-configured macrocycle **27** (233 mg, 396 mmol, 1.00 equiv) was dissolved in anhydrous degassed acetonitrile (75 mL, 190 mL mmol^{-1}) and filled in Pyrex tubes ($d = 1$ cm). The solution was further degassed, sealed with a septum and parafilm, and irradiated with UV-B light for 2 × 40 min without further heating (monitored by TLC, cooling). After the second irradiation, the solvent was removed under reduced pressure, and the crude product was subjected to column chromatography (hexanes/ethyl acetate 5:1 to 3:1) to yield 31% of the desired *E*-configured macrocycle **28** along with 34% of starting material. R_f (hexanes/ethylacetate = 3:1, CAM): **27**: 0.38 shiny lilac 256 nm, stains. **28**: 0.26 extinct. 256 nm, stains. ^{1}H NMR (600 MHz, [D$_8$]-toluene, 348.1 K): $\delta = 6.42$ (d, $J = 1.3$ Hz, 1H); 5.84 (s, 1H); 5.41 (d, $J = 10.3$ Hz, 1H); 4.40 (dd, $J = 5.4$, 5.4 Hz, 1H); 4.06 (dd, $J = 4.0$, 2.5 Hz, 1H); 3.88 (q, $J = 9.2$ Hz, 1H); 3.52 (m, 2H); 3.49 (s, 3H); 2.99 (m, 1H); 2.48 (dd, $J = 12.3$, 8.6 Hz, 1H); 2.28 (dd, $J = 13.9$, 3.9 Hz, 1H); 2.16 (m, 3H); 1.73 (s, 3H); 1.60 (s, 3H); 1.08 ppm (m, 21H). HRMS (ESI): *m*/*z* calcd for $C_{31}H_{44}O_8Si$ $[M]^+$: 588.2755; found: 588.2748.

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