Natural Products

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The Total Synthesis of Corallopyronin A and Myxopyronin B**

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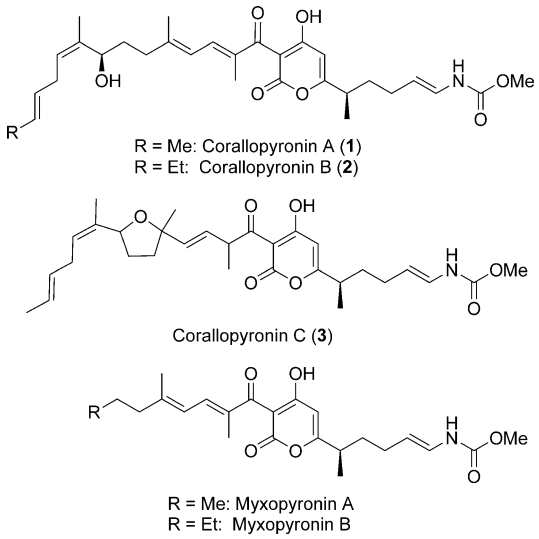
Dedicated to Professor Johann Mulzer on the occasion of his retirement

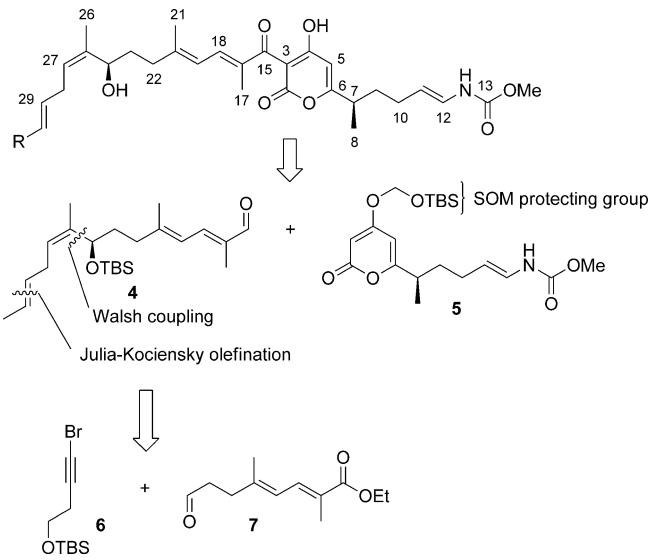
In 1984, Höfle and co-workers isolated three closely related corallopyronins (**1**, **2**, **3**) from the fermentation broth of *Corallococcus coralloides* (strain Cc c127, DSM 2550).[1] These natural products exhibit large regions of structural homology (C23–C14), both to one another as well as to the myxopyronins (Scheme 1). The 4-hydroxy-α-pyrone moiety is the central structural motif and has a side chain attached at C6. This chain contains one stereogenic center at C7 and an α,β-unsaturated methyl carbamate function. Since these natural products, as well as ripostatin,[2] were found to target the "switch region" within bacterial RNA polymerase (RNAP),[3] they became prominent leads for biomedical research.



Scheme 1. Structures of corallopyronin and myxopyronin.

Additional questions regarding the structure arose when the research group of König[4] reported their independent isolation of the corallopyronins, for which they reported NMR spectra that differed in parts from those reported by Höfle and co-workers (see the Supporting Information). So far, the research groups of Panek and Lira have put forward the only two reports on the racemic synthesis of myxopyronin.[5]

Our retrosynthetic analysis disconnects both natural products between the pyrone and the carbonyl group in the side chain (Scheme 2). Our initial plan was to introduce the unsaturated carbamate in the end game of the synthesis, but we realized that the carbamate group has the required stability to survive a multistep sequence.



Scheme 2. Retrosynthesis of corallopyronin.

In our synthesis, β-(−)-citronellene provides the stereogenic center at C7. The required functional groups were introduced by oxidation of the trisubstituted double bond, cleavage with periodate,[6] and transformation to the corresponding alcohol. Subsequent protecting group manipulations provided aldehyde **10**. A vinylogous Mukaiyama aldol reaction[7] followed by oxidation and a retro Diels–Alder reaction[8] generated pyrone **13** (Scheme 3).

An additional challenge was the choice of the appropriate protecting group for the hydroxy group on the pyrone ring. Standard silyl protecting groups, such as TBS, as well as acetal-containing groups, such as MOM or SEM, led to decomposition during isolation or on their removal. Finally, the *tert*-butyldimethylsilyloxymethyl group (SOM)[9] introduced by Benneche and co-workers proved ideal for our purposes. It combines the advantages of both the acetal-

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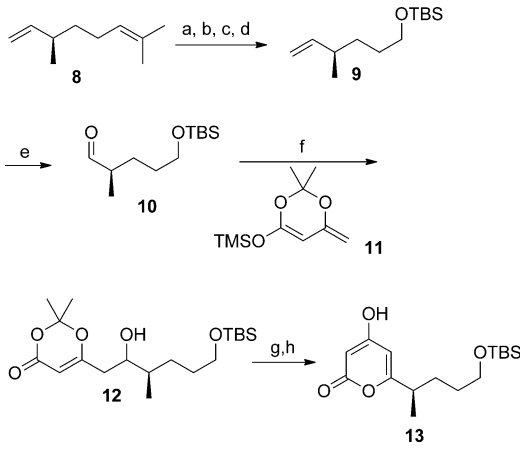
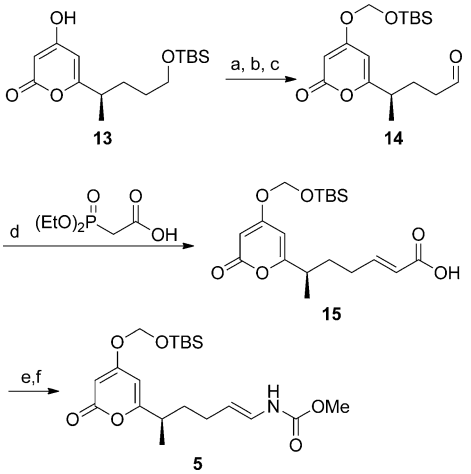


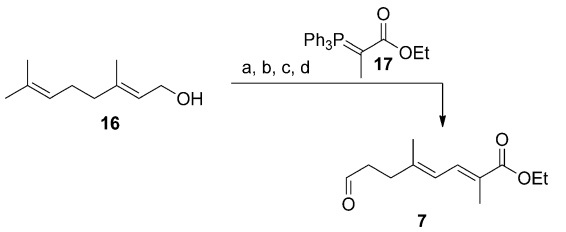
Scheme 3. Synthesis of pyrone **13**. a) *m*CPBA, NaOAc, CH_2Cl_2, −20 °C; b) H_5IO_6, Et_2O/THF; c) $NaBH_4$, Et_2O/THF, 75% over 3 steps; d) TBSCl, imd, THF, 95%; e) O_3, PPh_3, CH_2Cl_2/MeOH, 90%; f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 78%; g) DMP, CH_2Cl_2, 97%; h) toluene, reflux, 75%. *m*CPBA = 3-chloroperbenzoic acid, TBSCl = *tert*-butyldimethylsilyl chloride, imd = imidazole, DMP = Dess–Martin periodinane.

containing and the silyl protecting groups. Ultimately, we were able to selectively cleave the TBS group at the primary alcohol in the presence of the SOM group. The so-obtained alcohol was oxidized with IBX and transformed to unsaturated acid **15** through a Wittig–Horner reaction.[10] The Curtis rearrangement described by Panek and co-workers during their synthesis of myxopyronin was applied to generate the vinyl carbamate (Scheme 4).[4a]

Another challenge was the synthesis of the secondary alcohol next to the *Z*-configured double bond. We aimed to install this functional group by adding vinylzinc intermediate **21**, obtained from the preceding Walsh reaction, to aldehyde



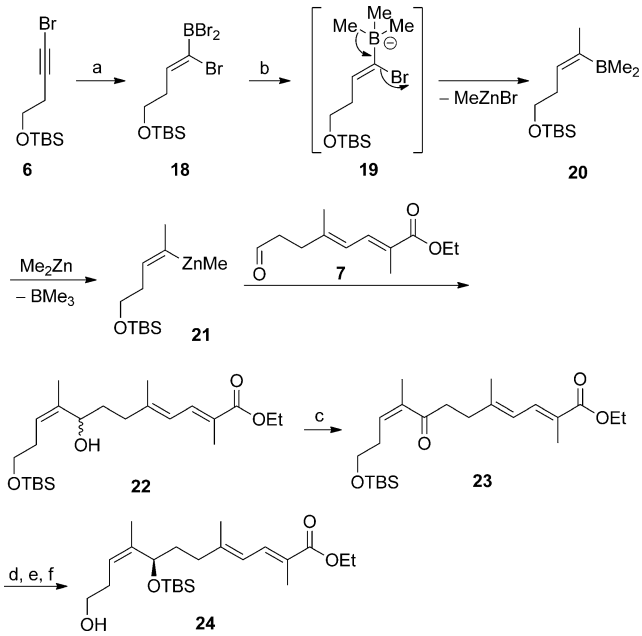
Scheme 4. Synthesis of vinyl carbamate **5**. a) $TBSOCH_2Cl$, DIPEA, CH_2Cl_2, 0 °C→RT, 37% + 23% TBS-deprotected product, (55% brsm); b) PPTS, THF/MeOH, 89%; c) IBX, DMSO, 79%; d) *n*BuLi, THF, −60 °C→RT; e) $ClCO_2Et$, DIPEA, NaN_3, acetone, H_2O, f) toluene, MeOH, reflux, 45% over 3 steps. DIPEA = *N*,*N*-diisopropylethylamine, PPTS = pyridinium *p*-toluenesulfonate, IBX = 2-iodoxybenzoic acid, DMSO = dimethyl sulfoxide, brsm = based on recovered starting material.



Scheme 5. Synthesis of aldehyde **7**. a) MnO_2, CH_2Cl_2, b) **17**, CH_2Cl_2, 88% over 2 steps, *E*/*Z* > 19:1; c) *m*CPBA, CH_2Cl_2, −20 °C→RT, 80%; d) H_5IO_6, THF, 0 °C→RT, 80%.

7. To prepare this aldehyde, geraniol was oxidized and subjected to olefination. A final epoxidation followed by cleavage with periodate provided the desired aldehyde (Scheme 5).

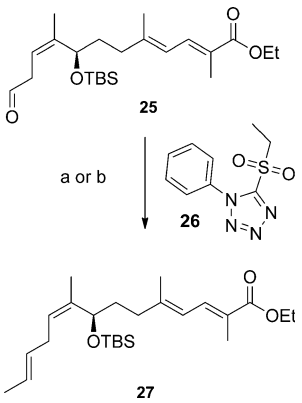
The pivotal Walsh reaction[11] takes advantage of intermediate **18**, which is derived from the hydroboration of bromoacetylene **6**. Addition of dimethylzinc leads to cross-coupling and simultaneous rearrangement to afford *Z*-vinylborane **20**. A subsequent transmetalation and reaction with aldehyde **7** generates ester **22** (Scheme 6). At this stage the secondary alcohol is established as a racemate. However, a sequence of oxidation and reduction with (−)-DIPCl provides the desired *R* enantiomer with useful selectivity (95% *ee*). Here it should be pointed out that comparable substrates with *E*-configured double bonds provide the opposite enantiomer.[12] Irrespective of the theory of the reaction, we were able to confirm the configuration by the



Scheme 6. Synthesis of the side chain through Walsh coupling. a) $BBr_2H{\cdot}SMe_2$, toluene, 70 °C; b) Me_2Zn, toluene, −78 °C→0 °C then aldehyde **7**, 56%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 80%; d) (−)-DIPCl, THF, −30 °C; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 76% over 2 steps; f) CSA, CH_2Cl_2/MeOH, 75%. DIPCl = diisopinocampheylchloroborane, CSA = camphorsulfonic acid.

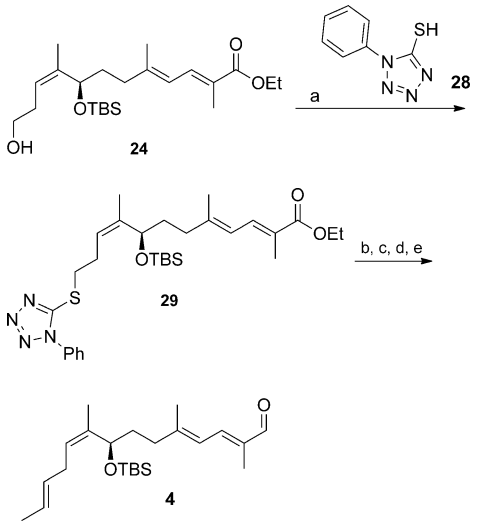
Mosher ester method. By using this route we generated compound **24** in nine steps starting from **16** (Scheme 6).

After the successful reduction with (−)-DIPCl, functional group manipulations afforded substrate **25** for the final olefination. Both the Takai–Utimoto and the Julia–Kociensky olefinations[13] provided the desired product, although in unsatisfactory yields (Scheme 7). Consequently we decided to exchange the functionalities in the two fragments.

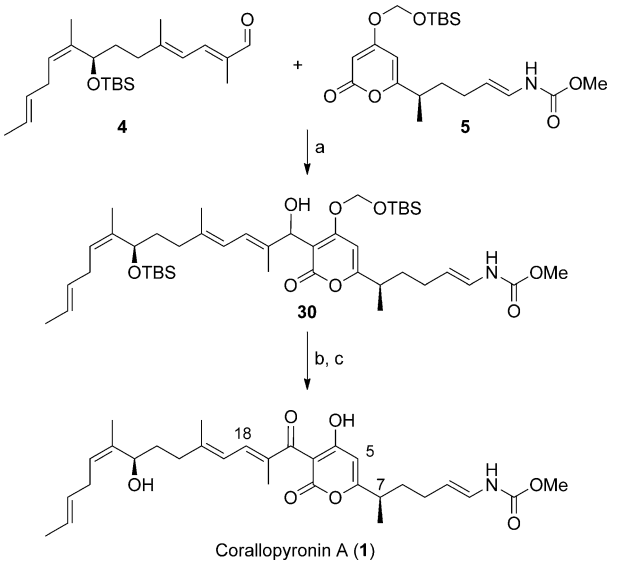


Scheme 7. a) $CrCl_2$, CH_3CHI_2, THF, 30–40%; b) KHMDS, **26**, DME, −60°C, 26%. KHMDS = potassium bis(trimethylsilyl)amide, DME = 1,2-dimethoxyethane.

The Mitsunobu reaction was utilized to introduce sulfide **28** in good yields, and **29** was oxidized to the corresponding sulfone. Deprotonation with KHMDS and reaction with acetaldehyde established the desired olefin.[14] The subsequent reduction/oxidation sequence completed the synthesis of fragment **4** (Scheme 8).



Scheme 8. Synthesis of **4**. a) PPh_3, DEAD, THF, 95%; b) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH, 76%; c) KHMDS, acetaldehyde, DME, 90% (*E*/*Z* = 6:1), d) DIBAl-H, CH_2Cl_2, −78°C; e) MnO_2, CH_2Cl_2, 79%. DIBAl-H = diisobutylaluminumhydride, DME = 1,2-dimethoxyethane, DEAD = diethyl azodicarboxylate.



Scheme 9. a) *n*BuLi, TMP, THF, −78°C→RT, 47% (54% brsm); b) MnO_2, CH_2Cl_2, 80%; c) TBAF, THF, 33%. TMP = 2,2,6,6-tetramethylpiperidine, TBAF = tetrabutylammoniumfluoride.

The first steps in the end game of the synthesis involved deprotonation of the pyrone with LiTMP and reaction with aldehyde **4**. The alcohol obtained was oxidized with MnO_2 and the protecting groups removed with TBAF (Scheme 9).

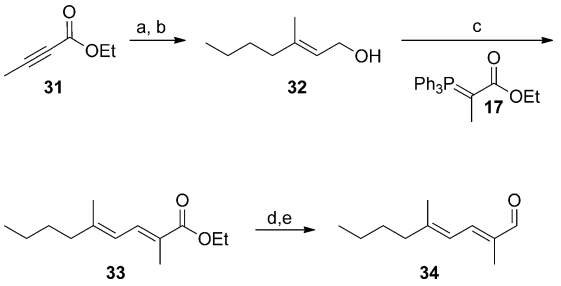
All the spectroscopic data were in good agreement with those obtained from the authentic sample. The difference in optical rotation (synthetic: −69.1, authentic: −95.8)[1] was attributed to the enantiomeric excess of the commercially available β-(−)-citronellene (56% *ee*). The two diastereomers were not visible as two separate sets of signals in the NMR spectra, an observation we had made before for other natural products that exhibit stereogenic centers in separate regions of the molecule.[15]

During the spectroscopic analysis we were able to reproduce the spectra reported by the research groups of both Höfle and König (see the Supporting Information). The spectrum obtained depended on the final deprotection conditions. Even though we are still not in a position to pinpoint the reasons for this observation, we have evidence that the coordination of different cations is likely the reason for the observed changes in the chemical shifts. Remarkably, extensive HPLC purification provided a third NMR spectrum that is different from the two others.

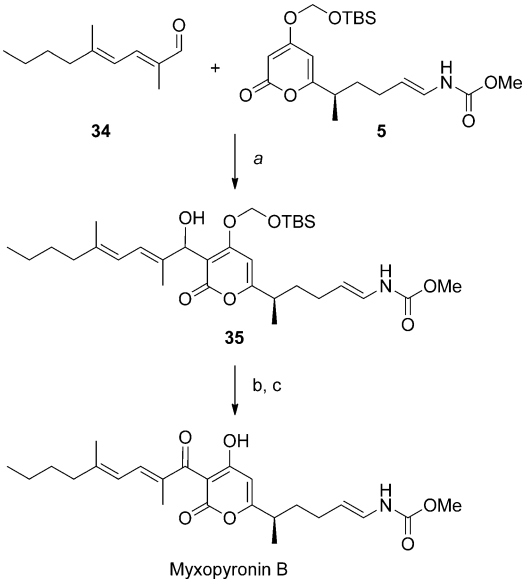
The synthesis established for corallopyronin, but using a different side chain, was also utilized for the synthesis of myxopyronin. The required side chain was obtained by 1,4-addition[16] to unsaturated ester **31**, followed by establishing the appropriate oxidation state for olefination with **17** (Scheme 10).

Coupling the side chain with SOM-protected pyrone **5** delivered, after oxidation and deprotection, the expected natural product (Scheme 11).

In conclusion, we were able to complete the synthesis of corallopyronin A and myxopyronin B and could demonstrate that vinyl carbamates are sufficiently stable to survive multistep syntheses. The underexploited SOM group was essential



Scheme 10. Synthesis of **34**. a) *n*BuLi, $BrCu(SMe_2)$, THF, −45 °C→ −78 °C; b) DIBAl-H, CH_2Cl_2, −78 °C→RT; c) MnO_2, CH_2Cl_2, 17, 58% over 3 steps; d) DIBAl-H, CH_2Cl_2, −78 °C; e) MnO_2, CH_2Cl_2, 78% over 2 steps.



Scheme 11. a) *n*BuLi, TMP, THF, −78 °C→RT, 53%; b) MnO_2, CH_2Cl_2, 80%; c) HF·pyridine, THF/pyridine, 45%. TMP = 2,2,6,6-tetramethylpiperidine.

to the success of these syntheses and proved to be an ideal protecting group for pyrones. Finally, the syntheses confirmed the structures proposed by the research groups of Höfle and König. The use of the established route for the synthesis of myxopyronin demonstrates the robustness of this sequence for the preparation of analogues, and opens the way for preparing different variants of this new antibiotic with optimized pharmaceutical properties starting form building block **5.**

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