Natural Product Synthesis

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Total Synthesis of Polyoxygenated Cembrenes**

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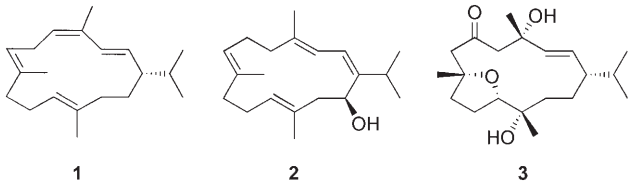
Dedicated to Professor Helmut Schwarz on the occasion of his 65th birthday

Numerous new biologically active and structurally interesting diterpenes containing a characteristic oxygenated 14-membered carbon ring system, which is derived formally from (+)-cembrene (**1**),[1] have been isolated from terrestrial and marine sources over the last few years (Scheme 1).[2] The

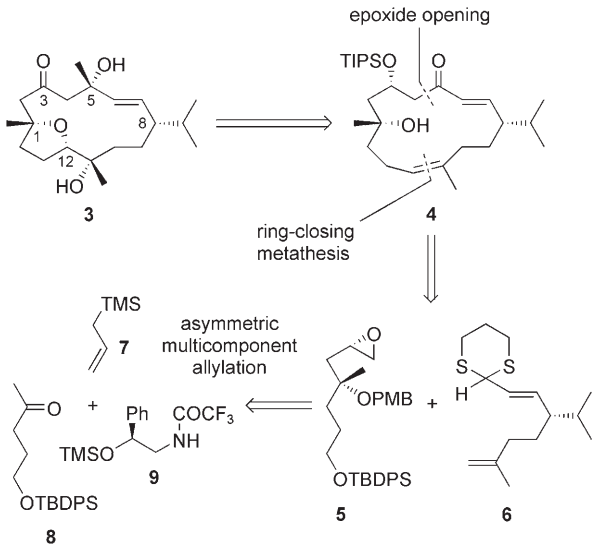


Scheme 1. (+)-Cembrene and oxygenated derivatives.

oxygenated cembrenes display amongst others anti-HIV activity, anti-inflammatory properties, and neuro- and cytotoxicity.[3] Sarcophytol A (**2**), isolated from soft coral, for example inhibits tumor growth and serves as the lead structure for the development of other pharmacologically active compounds.[4]

It is therefore essential for ongoing investigations that efficient strategies are developed for the synthesis of oxygenated, especially the more complex polyoxygenated, cembrenes,[5] which would allow general access to differently substituted compounds, and thereby make them available for testing. We describe here a stereoselective total synthetic access to the bicyclic polyoxygenated cembrene **3** with six stereogenic elements and four oxygen atoms. Compound **3** was structurally characterized as part of biosynthetic studies on polyoxygenated cembrenes occurring in Greek tobacco plants.[6] In addition an epimer of compound **3** was prepared.

Retrosynthetically, cembrene **3** may be broken down into the two almost equally sized building blocks **5** and **6** that can be coupled with one another by a nucleophilic epoxide opening (Scheme 2).[7] The tertiary alcohol function in **5** can



Scheme 2. Retrosynthetic analysis of compound **3**.

be constructed in a highly stereoselective domino multicomponent allylation[8] of the aliphatic ketone **8**, whereas the dithiane **6** is accessible by a modified Myers alkylation.[9] The 14-membered macrocycle is constructed by ring-closing metathesis.[10] The benzyl ether **10** with d.r. = 95:5 is obtained by allylation of the ketone **8** with the silyl ether **9**[8c] and allyl silane **7** under trifluoromethanesulfonic acid catalysis (Scheme 3). Reductive cleavage of the benzyl group with subsequent *p*-methoxybenzyl protection of the resulting tertiary alcohol and Sharpless dihydroxylation[11] afforded the diol **11** with d.r. = 91:9, which was transformed into the epoxide **5**.[12]

In the construction of the building block **6**, initially a diastereoselective α-alkylation of the pseudoephedrine amide **16** with the triflate **13** was carried out, followed by oxidation of the secondary alcohol function to give the ketoamide **17**, which could be enriched to d.r. = 99:1 by crystallization (Scheme 4).[9a] Triflate **13** was synthesized in quantitative yield from **12** by reaction with Tf_2O, and amide **16** was accessible from **14** in 94% yield by acylation with the acid chloride **15**. Reductive amide cleavage of **17** with LDA and a borane–ammonia complex,[9] and oxidation of the primary alcohol to the aldehyde with subsequent Wittig–Horner

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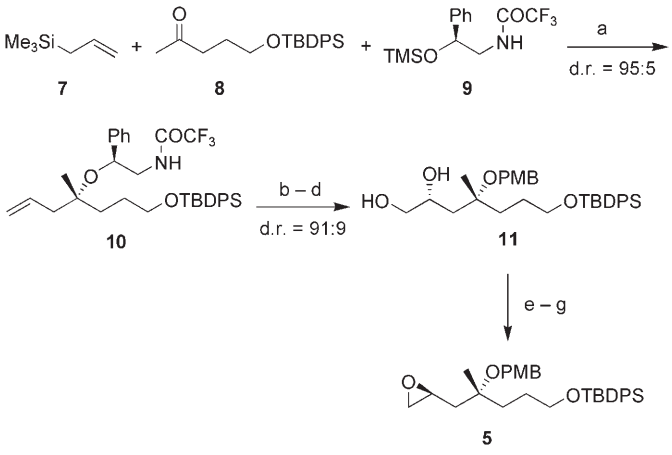
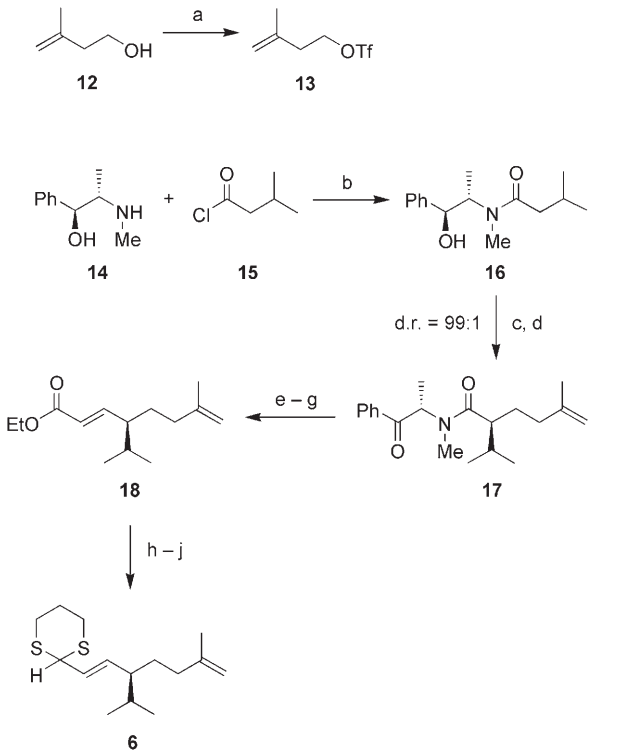


Scheme 3. a) 20 mol% TfOH, CH_2Cl_2, −196→−90°C; b) Li, DBBP, THF, −78→−45°C, 71% over 2 steps; c) PMBOC(=NH)CCl_3, 7 mol % La(OTf)$_3$, toluene, RT, 77%; d) 1 mol % $K_2OsO_2(OH)_4$, 5 mol% $(DHQD)_2Pyr$, $K_3[Fe(CN)_6]$, K_2CO_3, *t*BuOH/H_2O (1:1), 0°C; e) PivCl, pyridine, CH_2Cl_2, 0°C→RT, 64% over 2 steps; f) MsCl, NEt_3, cat. DMAP, CH_2Cl_2, RT, 83%; g) K_2CO_3, MeOH, RT, quant. DBBP = 4,4′-di-*tert*-butylbiphenyl, $(DHQD)_2Pyr$ = hydroquinidine-(2,5-diphenyl-4,6-pyrimidinediyl)diether, DMAP = 4-(dimethylamino)pyridine, Ms = methanesulfonyl, Piv = pivalyl, PMB = 4-methoxybenzyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.



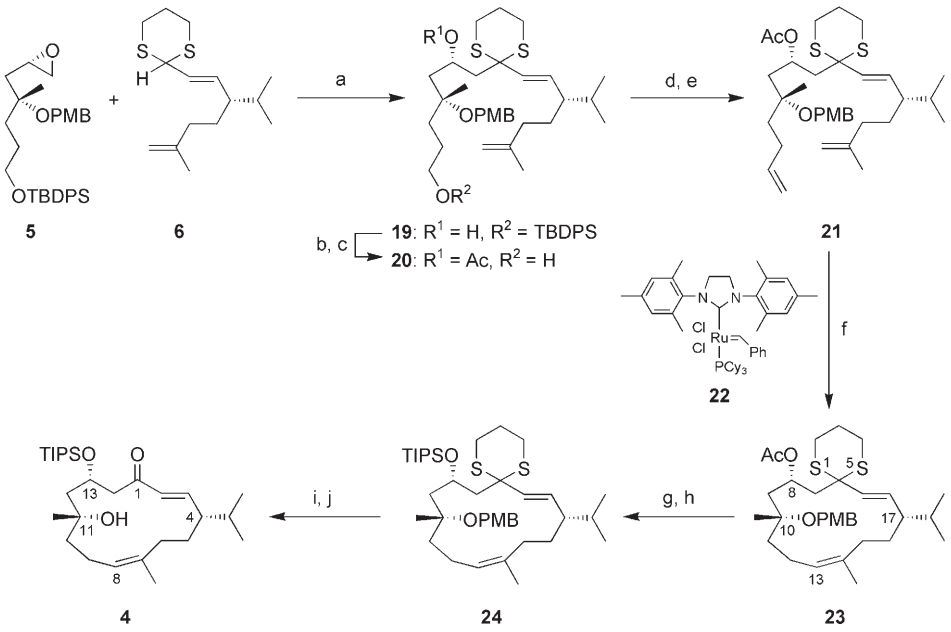
Scheme 4. a) Tf_2O, CH_2Cl_2, −78→0°C; b) NEt_3, THF, 0°C, 97%; c) LDA, LiCl, THF, −78°C→RT, then **13**, −78→−20°C, 83% over 2 steps; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then NEt_3, RT, 79%; e) $BH_3{\cdot}NH_3$, LDA, THF, 0°C→RT, 89%; f) IBX, DMSO, MS 4 Å, RT, quant.; g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C→RT, 89%; h) DIBAL-H, CH_2Cl_2, −78°C, quant.; i) MnO_2, CH_2Cl_2, RT; j) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, Et_2O, −40°C, 75% over 2 stages. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, LDA = lithium diisopropylamide, MS = molecular sieves.

olefination led to the α,β-unsaturated ester **18** in 79% yield over three steps. Compound **18** was reduced to the allyl alcohol with DIBAL-H, then oxidized to the α,β-unsaturated aldehyde with MnO_2, and subsequently converted into the dithiane **6** with propane-1,3-dithiol.

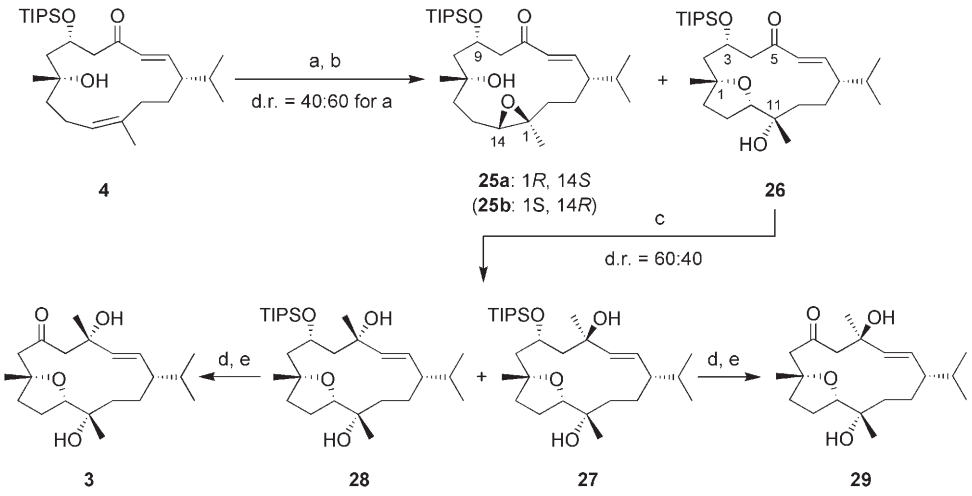
The secondary alcohol **19** was then obtained in 92% yield from the dithiane **6** and the epoxide **5** by nucleophilic epoxide opening[7] and was converted into the primary alcohol **20** by acetylation and cleavage of the silyl protecting group (Scheme 5). Compound **20** was oxidized to the corresponding aldehyde in 88% yield by using SO_3·pyridine under mild Parikh–Doering conditions[13] and subsequently converted directly to the triene **21** by a Wittig carbonyl olefination in 89% yield. Only decomposition occurred under Dess–Martin, Swern, and TPAP oxidation conditions, presumably owing to the sensitivity towards oxidation of the dithiane and *p*-methoxybenzyl ether groups in **20**. The ring-closing metathesis was carried out with the Grubbs catalyst **22**[14] (7 mol%) and provided the macrocycle **23** as a uniform *Z* diastereoisomer in an astonishingly good yield of 89%.

The orientation of the newly formed double bond and the relative configuration of the stereogenic centers in **23** were determined unambiguously by X-ray structure analysis.[15] The absolute configurations of the stereogenic centers in **23** were derived from the known configurations of **10** and **17**.[8,9a] Since the corresponding stereogenic centers in the product **23** have an *R* configuration at C-10 and an *S* configuration at C-17 as in **10** and **17**, respectively, it is also confirmed that no intermediate isomerization has occurred. The use of other catalysts for the metathesis, such as the Fürstner catalyst Neolyst M1,[16] afforded complex mixtures of dimers. Interestingly, the protective groups of the hydroxy groups at C-8 and C-10 have a large influence upon the metathesis. No ring-closure could be achieved by using a triisopropylsilyl group at C-8, which is presumably attributable to steric reasons.

For the diastereofacial introduction of the methyl groups at C-1 of ketone **4** it was necessary to carry out a reprotection of the macrocycle **23** by using the sterically demanding triisopropylsilyl protecting group at C-13. For this purpose the acetyl group was removed under basic conditions, and the resulting secondary alcohol was converted over two steps to **24** with triisopropylsilyl triflate in 80% yield. Subsequent oxidative cleavage of the *p*-methoxybenzyl ether with dichloro-5,6-dicyano-*p*-benzoquinone and of the dithiane with bis(trifluoroacetoxy)iodobenzene[17] led to the ketone **4** in 80% yield over two steps. Ketone **4** was epoxidized regioselectively with dimethyldioxirane[18] leading to the formation of two diastereoisomers **25a** and **25b** in a ratio of 40:60. Under acidic conditions, the main diastereoisomer **25b** underwent a nucleophilic intramolecular epoxide ring opening leading to **26**, which contains a tetrahydrofuran moiety (Scheme 6).[19]. A regioselective 1,2-addition of methyllithium to the carbonyl group in **26**, which however in spite of the sterically demanding triisopropylsilyl group at the neighboring position took place with only low diastereoselectivity, led to the diols **27** and **28** in a ratio of 40:60. As expected, the main product **28** was formed by an attack *anti* to the substituent at C-3.[20] Fortunately, it was possible to separate the two diastereoisomers **27** and **28**. The final steps in



Scheme 5. a) **6**, *n*BuLi, THF, HMPA, −78→−55 °C, then **5**, THF, −55 °C→RT, 92%; b) Ac_2O, pyridine, cat. DMAP, RT, quant.; c) TBAF·3 H_2O, THF, RT, quant.; d) SO_3·pyridine, NEt_3, DMSO, RT, 88%; e) KHMDS, Ph_3PMeBr, THF, −78 °C, then 0 °C, 89%; f) 7 mol % **22**, CH_2Cl_2, 40 °C, 89%; g) NaOMe, MeOH, Et_2O, 40 °C, 89%; h) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 90%; i) DDQ, CH_2Cl_2, buffer pH 7, 0 °C, 81%; j) $(CF_3CO_2)_2IPh$, MeOH/THF/H_2O (10:5:1), RT, 99%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, HMPA = hexamethylphosphoric triamide, KHMDS = potassium bis(trimethylsilyl)amide, TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.



Scheme 6. a) DMDO, acetone, CH_2Cl_2, −85 °C; b) 10 mol % CSA, CH_2Cl_2, −78→0 °C, 49% for **26** over 2 steps via **25b**, 40% for **25a**; c) MeLi, Et_2O, −110 °C→RT, 30% for **27**, 45% for **28**; d) TBAF·3 H_2O, THF, RT; e) 10 mol % TPAP, NMO, MS 4 Å, CH_2Cl_2, RT, 74% for **29** over 2 steps, 77% for **3** over 2 steps. DMDO = dimethyldioxirane, TPAP = tetra-*n*-butylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide.

the synthesis of the polyoxygenated cembrene **3** comprised cleavage of the TIPS group and oxidation of the resulting secondary alcohol to the ketone in 73% yield over two steps by using tetra-*n*-butylammonium perruthenate and *N*-methylmorpholine-*N*-oxide. The diastereoisomer **29** was obtained analogously from **27**.

Since NOE investigations on the molecules to determine the relative configuration of the newly formed stereogenic centers were generally poorly predictive, an X-ray structure analysis was carried out on the final product **3**.[21]. Compound **3** was synthesized in an overall yield of 2.7% over 24 steps; this corresponds to an average yield of 86% for each step. The analytical data of the synthetic material is identical to that for the polyoxygenated cembrene described by Wahlberg et al.[6,22]. In conclusion, by using ring-closing metathesis for the construction of the 14-membered carbon ring, a stereoselective Tietze allylation and a stereoselective Myers alkylation, we have developed a new and efficient route to complex polyoxygenated cembrenes, which offers a high degree of flexibility in respect of stereochemical variations and functionalization.

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[15] Single-crystal structure analysis of compound **23**: $C_{32}H_{48}O_4S_2$, monoclinic, space group $P2(1)$, $T = 133(2)$ K, $a = 11.0076(5)$, $b = 9.2718(3)$, $c = 30.9119(16)$ Å, $V = 3133.3(2)$ Å^3, $Z = 2$, $\rho = 1.189$ Mg m^{-3}, $R_1 = 0.0582$, $wR_2 = 0.0662$.[21]
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[21] Single-crystal structure analysis of compound **3**: $C_{20}H_{34}O_4$, monoclinic, space group $P2(1)$, $T = 133(2)$ K, $a = 6.3368(5)$, $b = 13.5693(10)$, $c = 11.4017(8)$ Å, $V = 971.21(13)$ Å^3, $Z = 2$, $\rho = 1.157$ Mg m^{-3}, $R_1 = 0.0589$, $wR_2 = 0.1008$. CCDC-676776 (**23**) and CCDC-676777 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..
[22] Rotation of the synthesized compound **3**: $[\alpha]_D^{20} = +39.4°$ ($c = 0.35$, chloroform); literature value: $[\alpha]_D^{20} = +38°$ ($c = 0.18$, chloroform).[6]

