Chiral [η^6-Arene – $Cr(CO)_3$] Complexes as Synthetic Building Blocks: A Short Enantioselective Total Synthesis of (+)-Ptilocaulin

Kurt Schellhaas, Hans-Günther Schmalz,* and Jan W. Bats

Abstract: An enantioselective total synthesis of the marine natural product (+)-ptilocaulin is described. The synthesis starts from [anisole – $Cr(CO)_3$], which is converted to [2-trimethylsilylanisole – $Cr(CO)_3$] ($\geq 99\%$ *ee*) by enantioselective deprotonation/silylation and recrystallization. After attachment of a 2-butenyl side-chain, nucleophile addition (2-lithio-1,3-dithiane) followed by treatment with chlorotrimethylsilane and hydrolysis leads to (5*S*,6*S*)-6-((*E*)-but-2-enyl)-5-[1,3]-dithian-2-yl-2-trimethylsilylcyclohex-2-enone with complete chirality transfer. This compound, which was characterized by X-ray crystallography, is transformed into (5ξ,6*S*,7a*S*)-5-butyl-6-methyl-1,2,5,6,7,7a-hexahydroinden-4-one, a ptilocaulin precursor known from the literature, by a 4-step sequence consisting of diastereoselective 1,4-addition, ultrasound-assisted desulfurization/hydrogenation (Raney Ni) and aldol cyclization. The target molecule was prepared in both racemic and optically active form. The X-ray crystal structure of *rac*-ptilocaulin nitrate shows flat ribbons of homochiral units (parallel double chains) connected by an interesting pattern of hydrogen bonds between the guanidinium and the nitrate ions. A different mode of hydrogen bonding resulting in the formation of helical monochains was found in the solid-state structure of (+)-ptilocaulin co-crystallized with about 29% of its C-3a epimer.

Keywords: arene complexes · chirality · chromium · natural products · ptilocaulins · total synthesis

Introduction

Among the various types of transition metal π-complexes, [η^6-arene – $Cr(CO)_3$] complexes possess a particularly broad potential for organic synthesis, and the chemistry of this class of compounds has been the subject of intense investigation for many years.[1–3] Besides some applications as catalysts for hydrogenation and isomerization reactions,[4] [arene – $Cr(CO)_3$] complexes have proven their value above all in stoichiometric transformations, the $Cr(CO)_3$ moiety serving as an activating and stereodirecting functionality. As complexes of unsymmetrically substituted (C_s symmetric) arene ligands are chiral,[5] absolute stereochemical information can be introduced into a synthetic course by employing chiral nonracemic complexes (of achiral ligands) as building blocks. Nevertheless, the number of practical applications of such planar chiral [arene – $Cr(CO)_3$] complexes in enantioselective total syntheses still remains rather small.[6,7]

In the course of our research program aimed at the synthesis of bioactive compounds by strategies centrally based on both the reactivity and the stereochemistry of [arene – $Cr(CO)_3$] complexes,[7] we selected (+)-ptilocaulin as a biologically relevant and structurally challenging target. This compound was first isolated in 1981 as its nitrate **1**, a highly antimicrobial and cytotoxic active metabolite from the Caribbean sponge *Ptilocaulis aff. P. spiculifer* (Lamarck, 1814) by Rinehart and coworkers.[8] The constitution and relative configuration of **1** was established by means of spectroscopic methods[8,9] and the absolute configuration was determined independently by Snider[10] and Roush[11] through stereorational total syntheses of *ent*-**1**. In addition, one total synthesis of the natural enantiomer **1**,[12] two total syntheses of *rac*-**1**[13,14] and a formal synthesis of **1**[15] have been reported. Recently, a number of new (oxidized) ptilocaulin relatives such as 8b-hydroxyptilocaulin (**2**)[16] and mirabilin D (**3**)[17] were isolated from antibacterial and antifungal extracts of other marine sponges. This demonstrates the biological importance of these marine alkaloids and their attractiveness as targets for chemical synthesis. In this paper, we describe a short and

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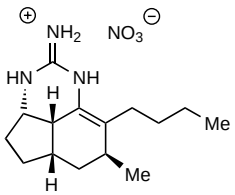

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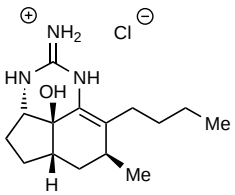

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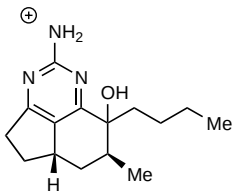

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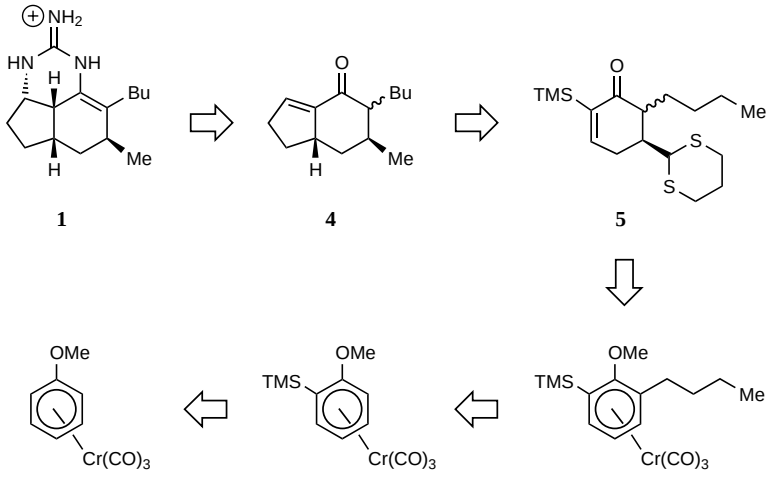
highly enantioselective total synthesis of (+)-ptilocaulin nitrate (**1**) which, as a key feature, is based on the utilization of chiral [arene – $Cr(CO)_3$] complexes.[18] In addition we disclose fascinating details of the crystal structures of *rac*-**1** and **1**, which have completely different hydrogen-bonding patterns.

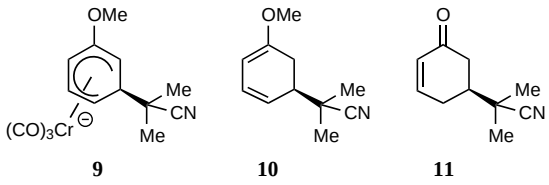
Results and Discussion

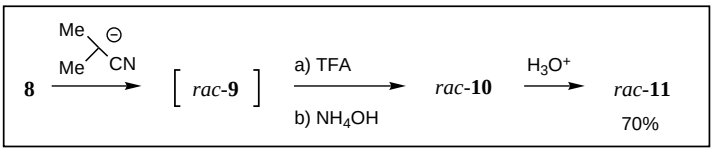
Strategic considerations: Our synthetic strategy is delineated in Scheme 1. Following the original disconnection of Snider,[10] we chose the enone **4** as pre-target molecule, as both diastereomers of this structure can be converted into ptilocaulin by condensation with guanidine.[10,12–14] As a precursor of **4** we proposed the cyclohexenone derivative **5**, which, in principle, should be convertible to **4** through a desulfurization/cyclopentene annulation sequence. As the key step of the synthesis, we envisioned the preparation of **5** from the chiral complex **6** by addition of a C_1 nucleophile (2-lithio-1,3-dithiane) followed by protonation and hydrolysis.[19] Complex **6** in turn could eventually be obtained by *ortho*-alkylation[20] of **7**, which represents the product of enantioselective deprotonation/silylation[21] of the prochiral [anisole – $Cr(CO)_3$] complex **8**.



Scheme 1. Concept of a synthesis of (+)-ptilocaulin (**1**) in retrosynthetic presentation.

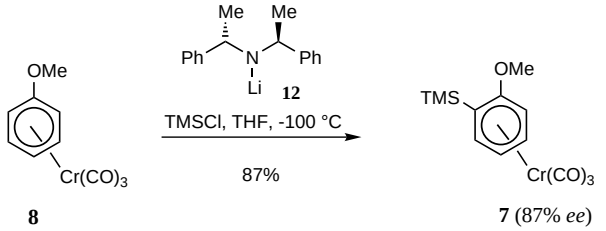
With some optimism, the crucial transformation (**6** → **5**) appeared feasible to us because of the analogy to the transformation shown in Scheme 2, which was described by Semmelhack et al. several years ago.[19,22] These authors discovered that the addition of 2-lithioisobutyronitrile to the [anisole – $Cr(CO)_3$] complex (**8**) gives rise to an anionic η^5 intermediate (*rac*-**9**), which on protonation and decomplexation leads to a dienol ether (*rac*-**10**) which is finally hydrolyzed to the enone *rac*-**11**.[22a] While the intramolecular version of this chemistry has proven useful for the synthesis of spirocyclic 5,5-disubstituted cyclohexenone derivatives,[23] almost no intermolecular applications of the Semmelhack cyclohexenone synthesis have yet appeared in the literature.[24] Due to the fact that the two *meta* positions of **8** are enantiotopic and are therefore attacked by the (achiral) nucleophile with equal probability, the product (*rac*-**11**) is formed as a racemic mixture. Recent reports have shown that **11** can be obtained enantioselectively (up to 56% *ee*) from $Cr(CO)_3$-complexed aryl ethers derived from chiral (nonracemic) alcohols.[25] As an important element of our strategy, however, we intended to employ a chiral (nonracemic) [anisole – $Cr(CO)_3$] derivative (such as **6**) as substrate for the enone formation. We had good reason to assume that the reaction would proceed with chirality transfer because the nucleophile should attack from the *exo* face (at the sterically less hindered position) of the arene ligand. For the projected synthesis of (+)-ptilocaulin it was therefore necessary to have access to the nonracemic chiral building block **7** with the correct absolute configuration.





Scheme 2. Cyclohexenone synthesis according to M. F. Semmelhack et al.[19,22]

Enantioselective preparation of the chiral building block 7: Following the general strategy outlined above (Scheme 1), we started with the anisole complex **8**,[26] which was prepared in almost quantitative yield from [$Cr(CO)_6$] by thermolysis in the presence of 5 equivalents of anisole. The enantioselective *ortho*-silylation was accomplished following the protocol of Simpkins[21a] with the chiral base **12**[27] in the presence of excess TMSCl in THF at $-78\,^{\circ}C$ (in situ quench conditions; Scheme 3). On a submmol scale, the product (**7**) was obtained in 95% yield and 88% *ee*. On a scale $\geq$2.5 mmol, however, it was necessary to run the reaction at even lower temperature ($-100\,^{\circ}C$) to obtain good results (typically 87% yield; 87% *ee*). The optical purity of **7** was routinely determined by HPLC, but it is



Scheme 3. Preparation of the optically active complex **7** by enantioselective deprotonation/silylation.

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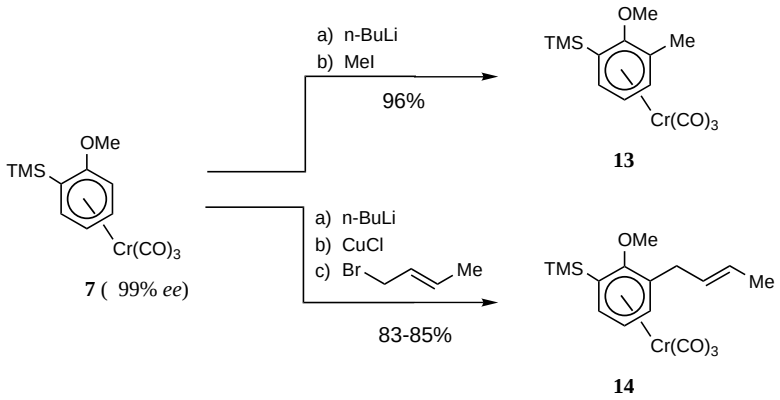
noteworthy that we were also able to separate the enantiomers by chiral GLC.[28] The absolute configuration of **7**, which was first established by Simpkins,[21a,21e] was confirmed by the conversion into (+)-ptilocaulin (see below). A single recrystallization of enantioenriched **7** from hexane afforded nearly enantiomerically pure material ($\geq 99\,\%$ *ee*) in 70 % yield. This material was utilized for the synthesis of (+)-ptilocaulin as described below. Nevertheless, the whole synthesis was first carried out with the racemic compounds in order to optimize the individual steps.

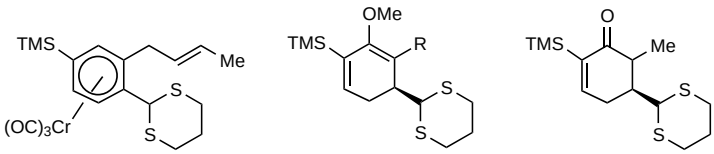
Attachment of the C_4 side-chain: While the *ortho*-methylation of **7** to afford **13** was easily accomplished (*n*-BuLi, MeI; Scheme 4), all our attempts to transform **7** into the projected butylated compound **6** by alkylation of the lithiated intermediate with butyl iodide failed. We therefore decided to follow Semmelhack's protocol,[29] which involves coupling of the corresponding organocopper species with crotyl bromide. This way, the 2-butenylated compound **14** was obtained in 83 % yield (Scheme 4). Since we did not succeed in achieving the catalytic hydrogenation of *rac*-**14** (→*rac*-**6**) we decided to proceed with the unsaturated compound and to remove the side-chain double bond at a later stage of the synthesis.



Scheme 4. Preparation of compounds **13** and **14**.

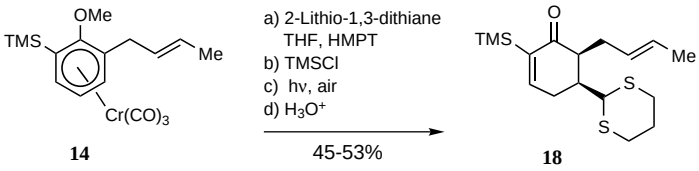
The key step—cyclohexenone formation: We then endeavored to perform the crucial conversion of complex *rac*-**14** into a cyclohexenone by addition of 2-lithio-1,3-dithiane[30] as a C_1 nucleophile followed by protonation with trifluoroacetic acid (TFA) under the reaction and workup conditions described by Semmelhack for the conversion of **8** to *rac*-**11**.[19] We were surprised to find that under these conditions not even a trace of the expected product(s) could be detected. Instead, the *tele*-substituted complex *rac*-**15** was isolated in good yield as the exclusive product, along with some recovered starting material. By varying the substrate, the nucleophile, and the reaction conditions we were able to show that (intermolecular) nucleophilic addition/protonation reactions of *ortho*-alkylated [anisole–$Cr(CO)_3$] derivatives *in general* furnish *tele*-substituted complexes.[18b,31]

Nevertheless, after considerable experimentation employing the model compound *rac*-**13**, we found that the *tele*-substitution can be suppressed by trapping the primary



nucleophile addition product with acid-free TMSCl in the presence of hexamethylphosphoric triamide (HMPA).[18a] After extractive workup and light-induced decomplexation,[32] a dienol ether of type **16** is formed as the dominant product,[33] which is finally converted to the desired enone by acidic hydrolysis (2 N HCl, THF, 80 °C). With this protocol, the conversion of *rac*-**13** to the enone *rac*-**17** proceeded in 63 % yield. Similarly, *rac*-**14** gave rise to the diastereomerically pure crystalline enone *rac*-**18** (53 %; Scheme 5). It must be emphasised that the *tele*-substituted products were formed only in trace amounts under these conditions. In contrast to our expectations,[18a] the *cis* configuration of *rac*-**18** was unambiguously established by X-ray crystallography (Figure 1).[34] Obviously, the *cis* isomer is formed in this case as the thermodynamically more stable diastereomer under the equilibrating conditions of the dienol ether hydrolysis.

In the optically active series, an experiment performed on a 2 g scale provided **18** in 45 % yield (Scheme 5). The enantiomeric purity ($\geq$ 99 % *ee*) of the product **18** was corroborated by means of HPLC,[18a,35] demonstrating that the predicted chirality transfer from the metal complex (planar chirality) to the permanent chirality β to the carbonyl function had occurred without racemization.



Scheme 5. The key reaction: preparation of **18** by nucleophile addition to **14**.

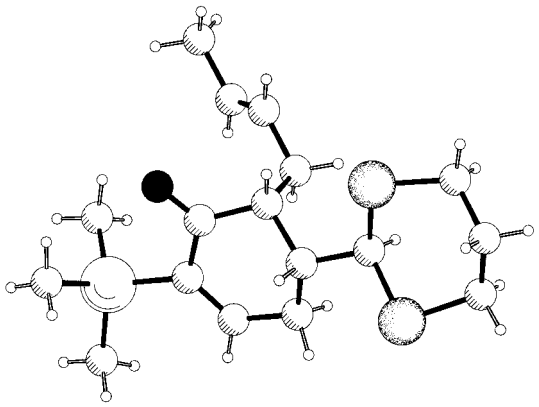
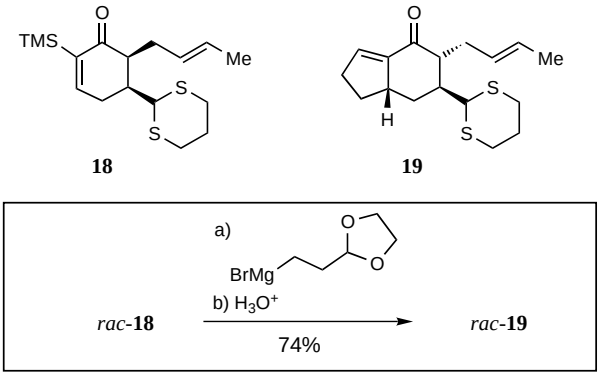


Figure 1. Structure of *rac*-**18** in the crystalline state (only *ent*-**18** is depicted).

Thus, the enantioselective synthesis of the highly functionalized ptilocaulin precursor **18** (which involves the dearomatization of an anisole derivative) was achieved in only four steps with ca. 25% overall yield starting from anisole.

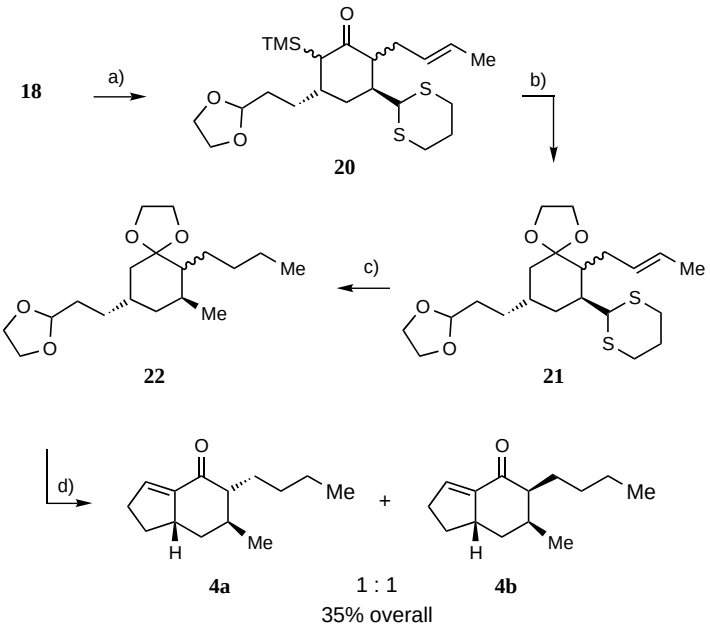
Preparation of hexahydroindenones: The next task in the projected synthesis (see Scheme 1) was the construction of the hydroindenone core. In analogy to the syntheses of Snider,[10] Asaoka,[12] and Cossy[15] we intended to accomplish this by conjugate addition of a C_3 nucleophile and subsequent aldol cyclization. Since compound **18** represents an α-silylated enone, we were confident that it would react directly with a nucleophile by conjugate addition.[36] Indeed, when *rac*-**18** was treated with an excess of the Grignard reagent prepared from 2-bromoethyl-1,3-dioxolane[37] followed by heating with aqueous hydrochloric acid, the cyclized product *rac*-**19** was isolated in good yield and high diastereomeric purity ($\geq 95\%$). Obviously, the Grignard reagent had added to *rac*-**18** in a highly regio- and diastereoselective manner (Scheme 6). The



Scheme 6. Preparation of *rac*-**19**.

relative configuration of *rac*-**19** was assigned based on the assumption that the approach of the nucleophile would occur from the less hindered π-face as is the case in other conjugate additions to 5-substituted cyclohexenones.[38] In addition, we expected a *trans* orientation of the two side-chains to be thermodynamically favored.

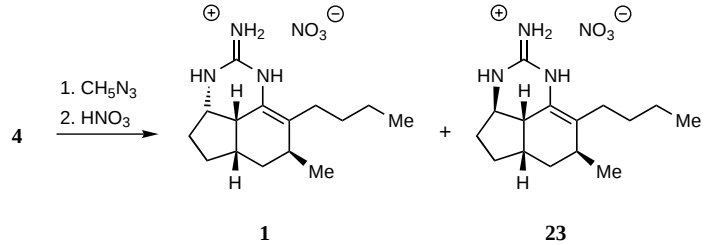
Treatment of *rac*-**19** with commercially available Raney nickel (W2 type) in ethanol did not result in the desired desulfurization. In contrast, when Raney nickel W4[39] was employed, the desulfurization was accompanied by over-reduction of the enone functionality. We therefore decided to perform the desulfurization at a later stage, that of **21**, after 1,4-addition and protection of the carbonyl function as an ethylene ketal. Best results were obtained when the desulfurization (with the concomitant hydrogenation of the side-chain double bond) was conducted under sonication in an ultrasound cleaning bath. The conversion of **18** to the hydroindenones **4** under the optimized conditions is shown in Scheme 7. It is noteworthy that intermediates **20**, **21**, and **22** (all isolated as mixtures of diastereomers) were not purified. At the end of this 4-step sequence, a mixture of **4a** and **4b** (1:1) was obtained in 35% overall yield after purification. The separation of these epimers was achieved by chromatography;



Scheme 7. Conversion of **18** into the pre-target compound **4**. a) Grignard reagent prepared from 2-bromoethyl-1,3-dioxolane (3 equiv), THF, $-70\,^{\circ}C \rightarrow$room temp.; b) 1,2-ethanediol, cat. *p*-TsOH, benzene, reflux ($-H_2O$), 24 h; c) Raney Ni (W4), 1 atm H_2, EtOH, ultrasound, room temp., 10 h, then reflux 3 d; d) 2 N HCl, THF, 80 °C, 3 h.

however, the mixture could be directly employed for the conversion to ptilocaulin. The high enantiomeric purity of our material was further corroborated by comparison of the molecular rotation of **4a** ($[\alpha]_D^{20} = -76^{\circ}$ in $CDCl_3$) with a literature value reported for an enantioenriched sample of **4a** (92% *ee*) ($[\alpha]_D = -65^{\circ}$ in $CHCl_3$).[15]

Preparation of ptilocaulin: Having synthesized the hydroindenones **4** (and also *rac*-**4**), the formal total synthesis of ptilocaulin was already achieved, because this compound has been converted to the target molecules before.[10,12–14] Nevertheless, we decided to complete the total synthesis with our own material. Following the protocol of Snider,[10] a solution of **4** in benzene was refluxed with guanidine under an atmosphere of argon and with removal of water. After protonation with dilute nitric acid, the reaction mixture yielded a crude product consisting mainly of ptilocaulin nitrate (**1**) and its C-3a-diastereomer **23**[40] in a ratio of ca. 4:1 (Scheme 8). In the racemic series, pure *rac*-**1** was obtained after chromatography and double recrystallization from ethanol/ether followed by recrystallization from methanol/chloroform. An X-ray crystal structure analysis[41] of *rac*-**1**



Scheme 8. Preparation of ptilocaulin (**1**) and its C-3a epimer (**23**).

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(Figure 2) confirmed the expected structure and revealed an interesting pattern of hydrogen bonding between the guanidinium and the nitrate ions (Figure 3).

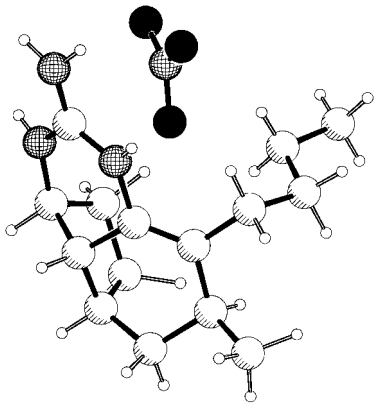

Figure 2. Structure of *rac*-**1** in the crystalline state.

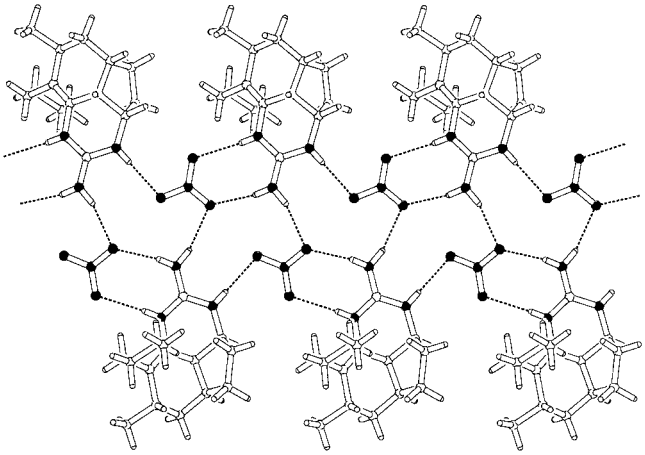

Figure 3. Ribbon of hydrogen bonds formed by *rac*-**1** in the crystalline state.

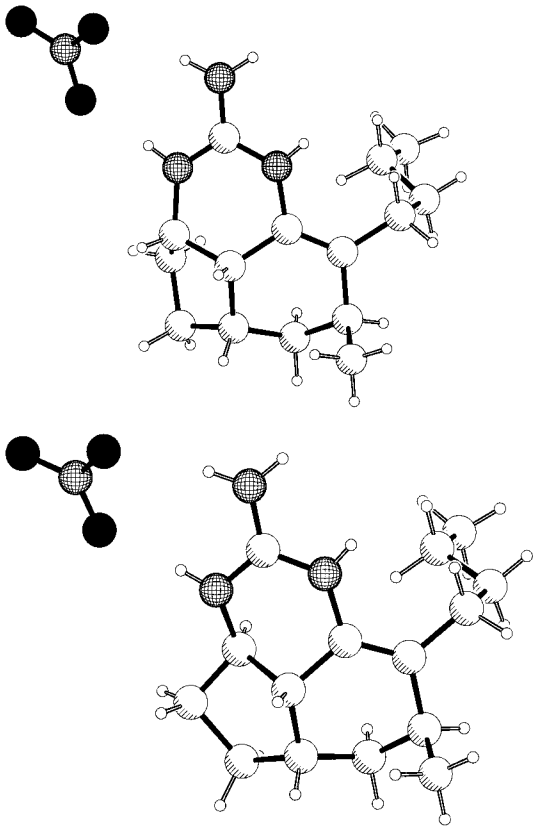

Figure 4. Structures of **1** (top) and **23** (bottom) in the crystalline state.

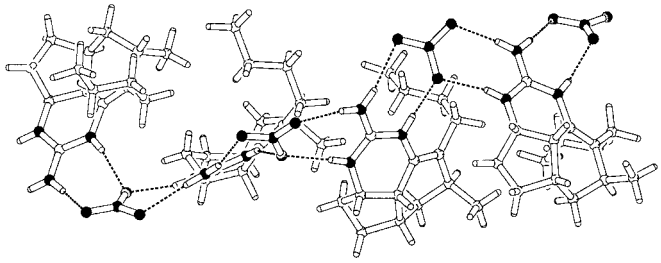

Figure 5. Helical chains formed by **1** (and **23**) in the crystalline state.

In the optically active case, however, the crystallization of the chromatographed mixture of **1** and **23** proved to be much more difficult. In this case, cocrystallization of **1** and **23** occurred. While we did finally succeed in obtaining an amorphous sample of almost pure (+)-ptilocaulin (**1**) from the mother liquor, clear single crystals formed only as a 2.4:1 mixture of **1** and **23**. A crystal structure analysis[42] allowed the separate structure determination of both components (Figure 4). Thus, for the first time the structure of the main side product, which is always formed along with **1** (or *rac*-**1**) on condensing the synthetic precursor with guanidine, was unambiguously assigned—in contrast to previous (tentative) assignments which could not be confirmed.[10–14] The crystal structure also shows the ion pair units arranged to helical chains. Obviously, compared with the crystal structure of racemic ptilocaulin nitrate, a different pattern of hydrogen bonds is involved (Figure 5). In addition, the conformation of the ptilocaulin molecule differs considerably from that found in the case of *rac*-**1**.

On the hydrogen bonding in the solid-state structures of ptilocaulin: In recent years, the question of how large supramolecular structures assemble from smaller building blocks by hydrogen bonding has become an important issue in organic chemistry and crystal engineering.[43] Therefore, the two completely different hydrogen-bond patterns found in the crystal structures of **1** and *rac*-**1** certainly deserve some special attention.

In the case of ptilocaulin nitrate, two double hydrogen-bonded ion pairs **A** and **B** (Figure 6) come into consideration as monomeric building blocks for supramolecular networks. Bearing in mind that N–H···O bonds generally prefer a colinear geometry and that the N–O···H angle tends to be around 120°, only a few types of dimers (such as **C** and **D** in Figure 6) can be constructed which are suited to further oligomerization into longer regular chains.

A closer look at the structure of *rac*-**1** (Figure 3) shows that each guanidinium group donates four hydrogen bonds to

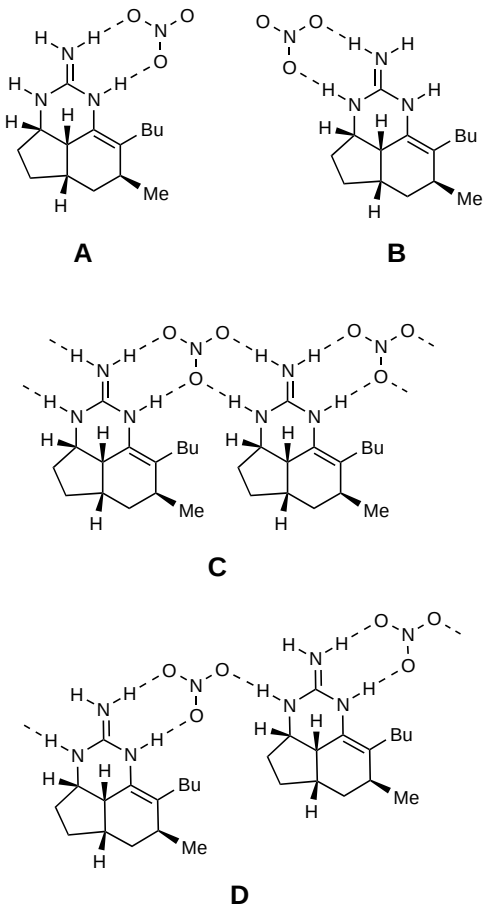

Figure 6. Possible monomeric (**A** and **B**) and (selected) dimeric ion pairs (**C** and **D**) of ptilocaulin nitrate.

three different nitrate ions. Actually, dimers of type **D** assemble to infinite parallel double chains as is apparent in Figure 7. The resulting flat ribbons run in the crystallographic *b* direction, which also corresponds to the needle direction of the crystal. Interestingly, each ribbon is constructed exclusively of homochiral units. Thus, both types of enantiomorphic ribbons contribute equally to the overall crystal structure of *rac*-**1**.

In contrast, a closer look at the solid-state structure of **1**/**23** = 2.4:1 (Figure 5) reveals the existence of infinite single chains (Figure 8), which formally result from polymerization of dimers of type **C**. These chains are twisted into helices (columns) in which the two diastereomeric monomers **1** and **23** contribute equally due to their very similar structures (Figure 4).

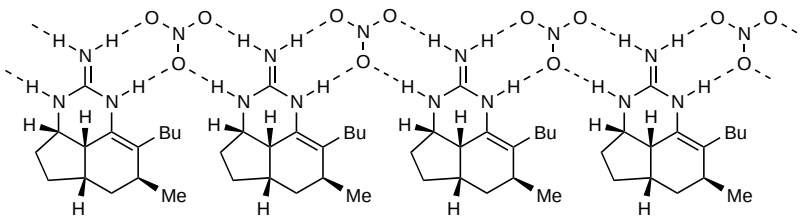

Figure 8. Idealized hydrogen-bond pattern (single chain) of **1** in the crystalline state.

We believe that the two very different crystal structures (based on the two very different hydrogen-bond patterns) of racemic and nonracemic ptilocaulin nitrate are an impressive example for the formation of completely different supramolecular networks from structurally closely related components. While we are not able to give an explanation for the observed phenomena, we consider guanidinium nitrate ion pairs as ideal building material for rational crystal engineering in the future.[44]

Conclusion

We have described a short and highly stereoselective total synthesis of (+)-ptilocaulin using a strategy which is centrally based on the specific reactivity and chirality of [arene–$Cr(CO)_3$] complexes. The synthesis starts from anisole and leads to the nonracemic target compound ($\geq 99\,\%$ *ee*) in only 9 steps with ca. 5 % overall yield. This demonstrates the power and competitiveness of the underlying strategy. Compared to previous syntheses of **1**[12,15] or *ent*-**1**,[10,11] which rely either on the use of chiral starting materials,[10,11] the resolution of a racemic intermediate,[12] or the employment of a covalently attached chiral auxiliary,[15] our synthesis is more efficient and differs insofar as it does employ a chirogenic step[45] (**8** → **7**) which is performed in an enantioselective manner.

This work represents the first intermolecular application of the Semmelhack cyclohexenone formation[22] in the context of a total synthesis of a natural product. We would like to emphasize that we would not have found the rather special conditions for this reaction without the evolutionary pressure we were exposed to as a result of our desire to reach the target molecule. Current efforts in our laboratory are now directed towards the further exploration of the scope and limitations of the general methodology of addition of carbon nucleophiles to *ortho*-substituted [anisole–$Cr(CO)_3$] derivatives.

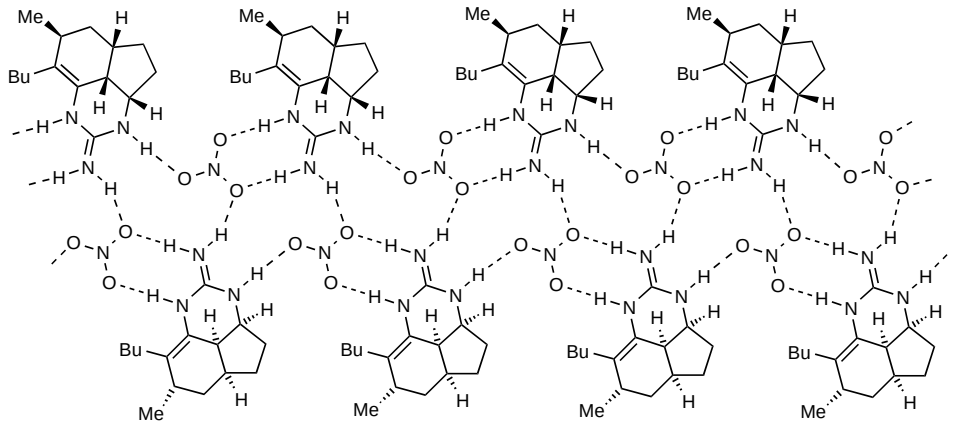

Figure 7. Idealized hydrogen-bond pattern (parallel double chain) formed by *rac*-**1** in the crystalline state.

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Experimental Section

All reactions involving [arene–$Cr(CO)_3$] complexes were carried out under an atmosphere of argon by standard Schlenk and needle/syringe techniques. Solvents were dried by standard methods. Anhydrous THF was freshly distilled from sodium/benzophenone in an argon atmosphere. Methyl *tert*-butyl ether is abbreviated as MTBE, diethyl ether as Et_2O, and di-*n*-butyl ether as *n*-Bu_2O. Melting points were measured with a Büchi 510 apparatus and are uncorrected. FT-IR spectra were recorded with a Nicolet Magna FT-IR spectrometer, usually with the ATR (attenuated total reflectance) technique; abbreviations are: s, strong; m, medium; w, weak, and br, broad. NMR spectra were recorded on a Bruker AM 270 or AM 400 spectrometer. NMR recordings were usually referenced to the $CHCl_3$ resonances ($\delta = 7.26$ and 77.0). ^{1}H NMR: splitting pattern abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; ψ, pseudo. ^{13}C NMR: multiplicities were determined by DEPT,[46] abbreviations are: q, CH_3; t, CH_2; d, CH; s, quaternary carbons. High resolution mass spectra (HRMS) were obtained with a Varian MAT 711 instrument (70 eV). Elemental analyses were performed on a Perkin–Elmer CHNO/S-Analyser 2400 II or a Heraeus CHN-Rapid instrument. Unless otherwise indicated, optical rotations were measured in $CHCl_3$ (freshly filtered through ICN Aluminia B) on a Perkin–Elmer 241 polarimeter at 20 °C. Analytical thin-layer chromatography (TLC) was performed with Merck Silica 60 F254 glass plates; the chromatograms were visualized under ultraviolet light and/or by staining with a cerium reagent (prepared by dissolving 2 g of phosphomolybdic acid, 1 g cerium(IV) sulfate and 10 mL conc. sulfuric acid in 90 mL H_2O) followed by heating. Flash chromatography[47] was performed on Merck Silica 60 (230–400 mesh). Radial chromatography was carried out on a Chromatotron (Harrison Research Model 7924 T) on glass plates coated with 1–4 mm layers of silica containing gypsum (Merck PF 60 F 254).

[η^6-Anisole–$Cr(CO)_3$] (**8**): A 250 mL Schlenk-type reaction vessel equipped with a magnetic stirring bar and a reflux condenser topped with a Hg bubbler was flushed with argon and charged with anisole (18.9 g, 175 mmol), $[Cr(CO)_6]$ (7.70 g, 35 mmol), *n*-Bu_2O (100 mL), *n*-heptane (50 mL), and THF (15 mL). The whole apparatus was repeatedly briefly evacuated and flushed with argon before the stirred mixture was refluxed for 3 days (145 °C oil-bath temperature). Subliming $[Cr(CO)_6]$ was occasionally flushed back into the solution by interruption of the cooling water flow. The reaction mixture was cooled and the solvents removed in vacuo. The crude product was dissolved in ethyl acetate and filtered through a pad of Celite. The solution was concentrated to a volume of 10 mL, and hexane (50 mL) was added. Crystallization at −18 °C for 3 days afforded 7.59 g (88 %) of **8** as clear yellow crystals. Two subsequent crystallizations of the concentrated mother liquors furnished an additional 0.79 g (10 %) of **8**, m.p. 84 °C (ref. [26]: m.p. 83–84 °C); FT-IR (KBR): 1961 (s), 1870 (s), 1532 (m), 1470 (m), 1254 (m), 632 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.71 (s, 3H), 4.88 (t, $J = 6.5$ Hz, 1H), 5.13 (d, $J = 7$ Hz, 2H), 5.55 (t, $J =$ 6.5 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 55.5$ (q), 78.1 (d), 85.6 (d), 95.1 (d), 143.3 (s), 233.1 (s); MS (EI, 70 eV): m/z (%) = 244 (20), 188 (8), 160 (56), 108 (9), 52 (100); anal. calcd for $C_{10}H_8O_4Cr$ (244.17): C 49.19, H 3.30; found: C 49.21, H 3.31.

[(1*R*)-(η^6-1-Methoxy-2-trimethylsilylbenzene)–$Cr(CO)_3$] (**7**): A stirred solution of *(S,S)*-di-(1-phenylethyl)amine (608 mg, 2.70 mmol) in THF (60 mL) was cooled to −70 °C, and a solution of *n*-butyllithium (1.6 M in hexane) was added dropwise.[48] After 45 min, the solution was cooled to −100 °C. Under vigorous stirring TMSCl (1.86 mL, 14.7 mmol) and a solution of **8** (600 mg, 2.46 mmol) in THF (5 mL) were injected consecutively and very rapidly. After 5 min the mixture was diluted with MTBE and washed with 2 N HCl (150 mL) (the hydrochloride of the chiral amine precipitates out of this aqueous layer upon standing!). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over K_2CO_3. After flash chromatography (hexane/ethyl acetate = 4:1) complex **7** (673 mg, 87 %) was obtained as a greenish-yellow powder with 87 ± 2 % *ee* (HPLC). A sample of **7** (82 % *ee*, 3.40 g; combined product of several experiments)[48] was recrystallized from hexane (250 mL) at 4 °C and later at −18 °C to afford **7** (2.38 g, 70 %) with ≥ 99 % *ee*: m.p. 108 °C; $[\alpha]_D^{20} =$ −236.8 ($c = 1.105$, $CHCl_3$); analyt. HPLC (Chiralcel OJ, hexane/2-propanol = 90:10; 0.8 mL min^{-1}): $t_1 = 13.0$, $t_2 = 16.9$ min; FT-IR (KBr): 3096 (w), 2985 (w), 2958 (w), 2901 (w), 1942 (s), 1885 (s), 1865 (s), 1842 (s), 1517 (m), 1458 (m), 1408 (m), 1262 (m), 844 (m), 666 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.31$ (s, 9H), 3.73 (s, 3H), 4.79 (t, $J = 6$ Hz, 1H), 4.97 (d, $J =$ 7 Hz, 1H), 5.57 (dd, $J_1 = 6$ Hz, $J_2 = 1.5$ Hz, 1H), 5.68 (ψ dt, $J_t = 6$ Hz, $J_d =$ 1.5 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = -0.7$ (q), 55.3 (q), 73.4 (d), 85.0 (d), 88.8 (s), 95.9 (d), 101.8 (d), 147.5 (s), 233.2 (s); MS (EI, 70 eV): m/z (%) = 316 (18), 260 (10), 232 (100), 201 (9), 187 (11), 180 (4), 135 (31), 52 (100); anal. calcd for $C_{13}H_{16}O_4Cr$: C 49.39, H 5.10; found: C 49.26, H 5.14.

[(1*R*)-η^6-1-((*E*)-But-2-enyl)-2-methoxy-3-trimethylsilylbenzene]–$Cr(CO)_3$] (**14**): Following the general procedure of Semmelhack,[29] a stirred solution of **7** (2.33 g, 7.365 mmol, ≥ 99 % *ee*) in THF (50 mL) was cooled to −60 °C and 5.06 mL (8.10 mmol) of a solution of *n*-butyllithium (1.6 M in hexane) was added dropwise. After 1 h at the same temperature, copper(I) chloride (0.80 g, 8.08 mmol) was added all at once. The solution turned greenish-black immediately and was stirred for 2 h while being warmed to a final temperature of −10 °C before it was recooled to −70 °C, treated with crotyl bromide (1.14 mL, 11.05 mmol), and allowed to warm to room temperature over a period of 3 h. The mixture was then diluted with MTBE (500 mL) and washed repeatedly with 2 N HCl (150 mL portions) until the aqueous layer no longer turned green. The organic layer was washed with brine and dried over K_2CO_3. The solvent was removed in vacuo and the crude, oily product was purified by flash chromatography (hexane/ethyl acetate = 10:1) to afford an oil, which was finally crystallized from hexane (20 mL) at −18 °C to afford **14** (2.25 g, 83 %) as orange-yellow crystals; m.p. 55–56 °C; $[\alpha]_D^{20} = 195$ ($c = 0.45$, $CHCl_3$); FT-IR (KBr): 2955 (w), 2923 (w), 2854 (w), 1960 (s), 1883 (s), 1342 (w), 1250 (m), 1000 (w), 841 (m), 670 (m), 632 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl3): $\delta = 0.36$ (s, 9H), 1,75 (dd, $J_1 = 6$ Hz, $J_2 = 1$ Hz, 3H), 3.19 (d, $J = 6$ Hz, 2H), 3.74 (s, 3H), 4.88 (t, $J =$ 6.5 Hz, 1H), 5.40 (dd, $J_1 = 6.5$ Hz, $J_2 = 1.5$ Hz, 1H), 5.50–5.67 (m, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 0.1$ (q), 17.9 (q), 32.1 (t), 62.8 (q), 87.8 (d), 92.6 (s), 97.2 (d), 99.6 (d), 103.9 (s), 127.8 (d), 129.1 (d), 146.6 (s), 233.6 (s); MS (EI, 70 eV): m/z (%) = 370 (16), 286 (100), 254 (16), 234 (10), 189 (14), 89 (20), 59 (22), 52 (50); anal. calcd for $C_{17}H_{22}O_4CrSi$: C 55.12, H 5.99; found: C 55.11, H 6.04.

(5*S*,6*S*)-6-((*E*)-But-2-enyl)-5-[1,3]-dithian-2-yl-2-trimethylsilylcyclohex-2-enone (**18**): A solution of *n*-butyllithium (1.6 M in hexane, 3.53 mL, 5.65 mmol) was added dropwise to a stirred solution of 1,3-dithiane (0.68 g, 5.65 mmol) in THF (13.5 mL) and HMPT (8.9 mL, 51 mmol) at −60 °C. Stirring was continued for 2 h while the reaction mixture was warmed to −40 °C. The yellow-brown solution was recooled to −60 °C and a solution of **14** (1.90 g, 5.14 mmol) of THF (16.5 mL) was added dropwise over a period of 10 min. The solution was allowed to warm to −20 °C over a period of 3 h before it was recooled to −78 °C and TMSCl (8.9 mL, 51 mmol, freshly distilled from quinoline) was injected. Stirring was continued overnight while the solution slowly warmed up to room temperature. The mixture was then partitioned between 2 N HCl (50 mL) and MTBE, the green aqueous layer was separated and another 250 mL portion of 2 N HCl was added. This two-phase system was exposed to sunlight until the organic layer turned completely colorless (fluffy precipitates were occasional removed from the organic layer by shaking). The two layers were separated and the organic layer was concentrated in vacuo. The residue (enol ether **16**, R = $CH_2CH{=}CHCH_3$)[49] was dissolved in THF (30 mL) before 2 N HCl (30 mL) was added and the stirred mixture heated to 80 °C for 2 h. The mixture was diluted with MTBE and the layers were separated. The organic layer was washed with saturated solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After concentration in vacuo 1.8 g of a crude, solid product was obtained, which was separated by flash chromatography (hexane/ethyl acetate = 10:1, 200 g SiO_2) to afford **18** (0.79 g, 45 %) as a white crystalline solid. M.p. 157 °C; $[\alpha]_D^{20} = 46$ ($c = 0.4$ in $CHCl_3$); TLC: hexane/ethyl acetate = 10:1 ($R_f = 0.31$); analyt. HPLC (hexane/2-propanol = 98:2, 0.6 mL min^{-1}, 350 nm): $t = 8.9$ min (> 99 % *ee*); FT-IR (KBr): 2951 (w), 2930 (w), 2897 (w), 2858 (w), 1660 (s), 1593 (w), 1426 (w), 1355 (w), 1245 (m), 966 (w), 839 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.10$ (s, 9H), 1.60 (d, $J = 4.5$ Hz, 3H), 2.03–2.19 (m, 2H), 2.22–2.34 (m, 2H), 2.51 (m, 1H), 2.69–2.89 (m, 6H), 4.05 (d, $J =$ 9 Hz, 1H), 5.27–5.40 (m, 2H), 6.99 (dd, $J_1 = 5$ Hz, $J_2 = 3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -1.5$ (s), 17.8 (q), 25.8 (t), 28.3 (t), 29.3 (t), 29.7 (t), 29.8 (t), 40.6 (d), 48.6 (d), 49.2 (d), 127.0 (d), 127.8 (d), 140.5 (s), 154.5 (d), 203.9 (s); MS (EI, 70 eV): m/z (%) = 340 (72), 325 (13), 302 (6), 283 (8), 265 (11), 221 (28), 179 (41), 172 (27), 119 (100), 106 (43), 75 (40), 73 (97); anal. calcd for $C_{17}H_{28}OS_2Si$: C 59.95, H 8.29; found: C 59.50, H 8.22.

(5*SR*,6ξ)-5-[1,3]-Dithian-2-yl-6-methyl-2-trimethylsilylcyclohex-2-enone (*rac*-**17**): Following the procedure described above for the preparation of **18**, 1.50 g (4.55 mmol) of *rac*-**13** were transformed to give 840 mg (2.80 mmol, 62%) of *rac*-**17** as a colorless solid. M.p. 98 °C (hexane); TLC: hexane/ethyl acetate = 10:1 (R_f = 0.3); FT-IR (KBr): $\tilde{\nu}$ = 2957 (m), 2917 (m), 2898 (m), 1652 (s), 1597 (w), 1343 (m), 1246 (m), 841 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 9H), 1.05 (d, J = 7 Hz, 3H), 1.89 (m, 1H), 2.09 (m, 1H), 2.26 (ddd, J_1 = 20 Hz, J_2 = 10 Hz, J_3 = 2 Hz, 1H), 2.45 (ψ sept., J = 4.5 Hz, 1H), 2.69–2.91 (m, 6H), 4.00 (d, J = 10 Hz, 1H), 7.06 (ψ dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = −0.7 (q), 10.3 (q), 25.9 (t), 28.3 (t), 29.7 (t), 29.8 (t), 41.1 (d), 42.9 (d), 49.3 (d), 140.2 (s), 155.5 (d), 205.1 (s); MS (EI, 70 eV): m/z (%) = 300 (21), 285 (13), 211 (7), 181 (57), 165 (39), 119 (83), 73 (100); HRMS found 300.10378 as calcd for $C_{14}H_{24}OS_2Si$; anal. calcd for $C_{14}H_{24}OS_2Si$: C 55.95, H 8.05; found: C 55.93, H 8.04.

(5*RS*,6*SR*,7a*SR*)-5-((*E*)-But-2-enyl)-6-[1,3]-dithan-2-yl-1,2,5,6,7,7a-hexahydroinden-4-one (*rac*-**19**): A 25 mL three-necked flask equipped with a magnetic stirring bar, a thermometer, and a septum was charged with magnesium (87 mg, 3.59 mmol) and THF (3 mL). After addition of a small crystal of iodine, a few drops of a solution of 2-bromoethyl-1,3-dioxolane (1 mL) in THF (4 mL) were added. The mixture was heated briefly until sudden decolorization occurred. The temperature was then kept between 20–25 °C by occasional cooling with a water bath while the rest of the solution was added dropwise under gentle stirring over a period of 20 min. The mixture was then stirred for 2 h at room temperature resulting in a dark grey solution, which was cooled to −70 °C. Then a solution of compound *rac*-**18**[50] (342 mg, 1.01 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to room temperature overnight (ca. 14 h). After addition of THF (5 mL) and 5% HCl (15 mL) the vigorously stirred solution was heated under reflux for 4 h. The mixture was then extracted several times with MTBE, and the combined organic layers were washed with saturated solutions of $NaHCO_3$ and NaCl and dried with K_2CO_3. The crude product was purified by flash chromatography (hexane/ethyl acetate = 4:1) to yield 231 mg (0.749 mmol, 74%) of the indanone *rac*-**19** as a brownish resin contaminated with ca. 5% of a by-product (diastereomer). TLC: hexane/ethyl acetate = 10:1 (R_f = 0.4); FT-IR (ATR): 2932 (m), 2856 (m), 1714 (w), 1679 (m), 1612 (w), 1422 (w), 1275 (w), 1037 (w), 967 (w), 909 (w), 842 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.44–1.62 (m, 2H), 1.64 (d, J = 5.5 Hz, 3H), 1.78–1.91 (m, 1H), 2.05–2.50 (m, 8H), 2.74–2.94 (m, 5H), 3.13 (m, 1H), 4.03 (d, J = 9.5 Hz, 1H), 5.27–5.38 (m, 1H), 5.41–5.55 (m, 1H), 6.65 (ψ d, J = 2 Hz, 1H); characteristic signals of the diastereomer: δ = 4.27 (d) and 6.60 (d); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 17.9 (q), 25.9 (t), 28.9 (t), 30.6 (t), 30.7 (t), 32.0 (t), 33.6 (t), 35.0 (t), 40.9 (d), 41.8 (d), 50.7 (d), 51.6 (d), 127.9 (d), 128.0 (d), 139.6 (d), 143.6 (s), 200.7 (s); MS (EI, 70 eV): m/z (%) = 308 (8), 281 (6), 251 (37), 233 (13), 201 (26), 189 (100), 172 (53), 145 (36), 119 (57), 107 (61), 95 (50), 41 (23); HRMS calcd for $C_{17}H_{24}OS_2$ 308.12686; found 308.1269.

(5ξ,6*S*,7a*S*)-5-Butyl-6-methyl-1,2,5,6,7,7a-hexahydroinden-4-one (**4**): A 100 mL three-necked flask equipped with a magnetic stirring bar, a thermometer, and a septum was charged with 170 mg (6.96 mmol) of magnesium, a small, brown turning of magnesium corroded by subliming iodine, and THF (7 mL). Under gentle stirring, 1 mL of a solution of 2-bromoethyl-1,3-dioxolane (0.835 mL, 6.96 mmol) in THF (7 mL) was added. The temperature was carefully kept between 20–25 °C by occasional cooling with a water bath while the rest of the solution was added dropwise. The mixture was stirred for 2 h at room temperature resulting in a dark grey solution, which was cooled to −70 °C. Then a solution of compound **18** (790 mg, 2.32 mmol) in THF (14 mL) was added dropwise. The mixture was allowed to warm steadily to room temp. overnight, diluted with MTBE, washed with saturated solutions of $NaHCO_3$ and NaCl and dried with K_2CO_3. Removal of the solvents in vacuo afforded 1.28 g of a crude product as a greenish-yellow oil that consisted predominantly of compound **20**, as determined by GC-MS analysis. Selected data for **20**: FT-IR (ATR): 2946 (m), 2889 (m), 1669 (s), 1422 (w), 1250 (m), 1142 (s), 1036 (m), 966 (m), 948 (m), 841 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.69–2.99 (m, 4H), 3.75–3.87 (m, 2H), 3.89–4.00 (m, 3H), 4.77–4.89 (m, 1H), 5.27–5.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −1.3 (q), 17.9 (q), 34.4 (d), 37.4 (d), 49.2 (d), 50.0 (d), 51.2 (d), 64.76 (t), 64.83 (t), 104.1 (d), 104.4 (d), 126.6 (d), 128.3 (d), 211.8 (s); MS (EI, 70 eV): m/z (%) = 442 (6), 341 (7), 323 (19), 179 (14), 153 (12), 121 (24), 119 (95), 99 (22), 73 (100); HRMS calcd for $C_{22}H_{38}O_3S_2Si$ 442.20317; found 442.2032.

This crude product (**20**) was dissolved in benzene (60 mL); 1,2-ethanediol (2 mL) and a catalytic amount of *p*-toluenesulfonic acid were added. The mixture was refluxed for 24 h under azeotropic removal of water (by means of a small pressure-equalizing addition funnel (25 mL) filled with molecular sieves (4 Å), which was placed between the reaction flask and the condenser). After cooling, the mixture was diluted with MTBE, washed with satd. solutions of $NaHCO_3$ and NaCl and dried over K_2CO_3. The solvents were removed to afford 1.18 g of a brown oil consisting predominantly of compound **21**. Selected data for **21**: FT-IR (ATR): 2927 (s), 2891 (s), 2855 (m), 1731 (w), 1456 (m), 1247 (m), 1141 (s), 1036 (s), 969 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.8–4.1 (m, 20H), 4.57 (d, J = 11 Hz, 1H), 4.85 (m, 2H), 5.29–5.69 (m, 4H); MS (EI, 70 eV): m/z (%) = 414 (14), 370 (4), 352 (3), 295 (7), 258 (10), 233 (7), 199 (32), 145 (14), 119 (94), 99 (46), 81 (21), 73 (100), 55 (37); HRMS calcd for $C_{21}H_{34}O_4S_2$ 414.1899; found 414.1887.

The crude product (**21**) was dissolved in absolute ethanol (80 mL) and treated with approx. 10 g of freshly prepared Raney Nickel W4. Under an atmosphere of hydrogen the mixture was first treated with ultrasound (cleaning bath) for 10 h and then refluxed for 3 days. The mixture was filtered through a plug of Celite and concentrated in vacuo to afford 0.85 g of a colorless, partially solidifying oil: GC-MS analysis showed three isomers (one predominant) of compound **22** (m/z = 313); FT-IR (ATR): 2952 (m), 2926 (m), 2872 (m), 1733 (w), 1456 (w), 1377 (w), 1128 (m), 1063 (m), 972 (w), 947 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.9 (br, 6H), 1.07 (d, 3H), 1.20 (d), 3.76–4.02 (m, 16H), 4.84 (m, 2H); MS (EI, 70 eV): m/z (%) = 313 (7), 211 (58), 199 (16), 169 (40), 129 (21), 127 (31), 113 (17), 99 (100), 73 (66), 55 (34); HRMS calcd for $C_{18}H_{33}O_4$ [M+H^+] 313.2379; found 313.2358.

This material (**22**) was dissolved in THF (30 mL) and treated with 30 mL of 2 N HCl. The stirred mixture was heated to reflux for 3 h. It was then diluted with Et_2O, the layers were separated and the organic layer washed with sat. solutions of $NaHCO_3$ and NaCl and dried over Na_2SO_4. After removal of the solvents in vacuo the crude product was purified by radial chromatography (pentane/Et_2O = 10:1) affording 165 mg (0.81 mmol, 35%, from **18**) of a 1:1 mixture of the epimeric indenones **4a** and **4b** (contaminated with max. 7% of an undesired epimer) as a colorless, volatile oil. This mixture was employed for the synthesis of **1** (see below). For analytical purposes an aliquot was separated by means of careful radial chromatography (pentane/Et_2O = 10:1) to provide a pure sample of **4a** and a sample of **4b** that was still slightly contaminated with some **4a** and the third diastereomer. The characteristic data of **4a** and **4b** given below are in good general agreement with those described by Snider[10b] and Cossy et al.[15] Data for **4a**: TLC: pentane/Et_2O = 10:1 (R_f = 0.29); $[\alpha]_D^{20}$ = −75.9 (c = 0.81 in $CDCl_3$, >99% *ee*), ref. [15]: $[\alpha]_D^{20}$ = −65 (c = 1.6 in $CHCl_3$, 92% *ee*); FT-IR (ATR): 2955 (m), 2929 (m), 2871 (w), 2859 (w), 1682 (s), 1616 (m), 1460 (w), 1263 (m), 1243 (w), 979 (w), 914 (w); ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.30 (m, 4H), 1.40–1.66 (m, 4H), 1.76 (m, 1H), 2.10 (m, 2H), 2.23–2.54 (m, 3H), 3.07 (m, 1H), 6.54 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (q), 20.2 (q), 22.6 (t), 29.6 (t), 32.0 (t, 2C), 33.4 (t), 33.7 (t), 34.0 (d), 40.8 (d), 55.8 (d), 137.9 (d), 144.1 (s), 204.0 (s); MS (EI, 70 eV): m/z (%) = 206 (1), 191 (3), 163 (5), 150 (80), 135 (100), 121 (14), 107 (7), 93 (11), 79 (16), 67 (14), 55 (10); HRMS calcd for $C_{14}H_{22}O$ 206.1671; found 206.1664; Data for **4b**: TLC: pentane/Et_2O = 10:1 (R_f = 0.34); FT-IR (ATR): 2955 (m), 2930 (m), 2871 (m), 2858 (m), 1685 (s), 1619 (m), 1456 (m), 1382 (w), 1233 (w), 1183 (w), 1161 (w), 972 (w), 921 (w), 837 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 6H), 1.22–1.40 (m, 6H), 1.48–1.63 (m, 2H), 1.84–1.96 (m, 1H), 2.02 (m, 1H), 2.22–2.48 (m, 4H), 3.08 (m, 1H), 6.42 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (q), 14.2 (q), 22.8 (t), 25.7 (t), 29.7 (t), 32.1 (t), 33.5 (d), 33.8 (t), 39.3 (t), 41.6 (d), 54.6 (d), 135.8 (d), 145.5 (s), 202.5 (s); MS (EI, 70 eV): identical to **4a**; HRMS calcd for $C_{14}H_{22}O$ 206.1671; found 206.1682.

(+)-Ptilocaulin (**1**): A 1 M solution of guanidine was prepared by adding 6.105 g (50 mmol) of guanidine nitrate and 2.806 g (50 mmol) KOH to anhydrous methanol (50 mL) under argon. The solution was stirred for 1 h. An aliquot of 790 μL (0.79 mmol) of this solution was transferred to a two-necked flask equipped with a magnetic stirring bar and a Dean–Stark trap (with a Hg bubbler on top of the reflux condenser). The methanol was

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removed in vacuo and the apparatus was thoroughly flushed with argon. Then a solution of the epimeric indenones **4** (105 mg, 0.509 mmol) in dry benzene (40 mL) was added by syringe. The mixture was refluxed for 23 h while the color turned to intense yellow and a white, fluffy precipitate was formed. The mixture was cooled under argon and 4 mL of 1% nitric acid was injected. The reaction mixture was diluted with $CHCl_3$, and the aqueous layer was separated and extracted three times with $CHCl_3$. The combined organic layers were concentrated in vacuo to afford 180 mg of a dark brown oil, which was chromatographed on silica gel ($CHCl_3$/methanol = 85:15) to afford 86 mg (0.277 mmol, 54%) of a white, foamy solid that consisted of a 4:1 diastereomeric mixture containing (+)-ptilocaulin nitrate (**1**) as the major and **23** as the minor component. This material was recrystallized twice from ethanol/Et_2O and once from $CHCl_3$/methanol at $-18\,^\circ C$ to afford some shiny colorless crystals which were subjected to X-ray crystallographic investigation.[42] An amorphous solid material which also separated from the mother liquors was (+)-ptilocaulin (**1**) of 90–95% purity as estimated by ^1H NMR. TLC: $CHCl_3$/methanol = 85:15 ($R_f = 0.33$); m.p. 183–184 °C, ref. [16]: 183–185 °C, ref. [11a]: 183–184 °C; $[\alpha]_D^{20} = 99.0$ ($c = 0.195$ in MeOH), ref. [16]: $[\alpha]_D^{20} = 110$ ($c = 0.44$ in MeOH), ref. [11a]: $[\alpha]_D^{20} = 74.4$ (99.5% MeOH), ref. [11a]: $[\alpha]_D^{20} = -73.9$ ($c = 0.31$ in 99.9% MeOH, for *ent*-**1**); FT-IR (KBr): 3371 (brs), 3217 (brs), 3086 (brs), 2941 (s), 2871 (s), 2857 (s), 1691 (s), 1677 (s), 1665 (s), 1618 (s), 1584 (m), 1411 (s), 1384 (s), 1372 (s), 1309 (s), 1280 (m), 1040 (m), 825 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7$ Hz, 3H), 1.05 (d, $J = 7$ Hz, 3H), 1.21–1.74 (m, 8H), 1.95–2.11 (m, 2H), 2.29–2.45 (m, 3H), 2.49 (ψt, 1H), 3.77 (m, 1H), 7.47 (brs, 2H), 8.35 (brd, 1H), 8.89 (brs, 1H); these data are in good accordance to those given in the literature;[8,16] for a full assignment of all signals, see ref. [16]; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 14.0 (q), 19.5 (q), 22.4 (t), 24.6 (t), 26.7 (t), 27.6 (d), 29.5 (t), 32.2 (t), 33.9 (t), 36.5 (d), 53.2 (d), 121.0 (s), 127.0 (s), 151.7 (s); MS (EI, 70 eV): *m/z* (%) = 247 (35), 232 (85), 218 (18), 204 (100), 190 (41), 174 (9), 148 (8), 69 (19), 55 (14), 43 (13); HRMS calcd for $C_{15}H_{25}N_3$ 247.2048; found 247.2041.

The NMR analysis of the clear crystals used for the X-ray crystallographic investigation showed a 2.4:1 mixture of **1** and its diastereomer **23**.[51] From the spectra of this mixture the following characteristic data for **23** were obtained: ^1H NMR (600 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 7.1$ Hz, 3H), 1.12 (dt, $J_1 = 13$ Hz, $J_2 = 5$ Hz, 1H), 1.86 (ψ pent, $J = 7$ Hz, 1H), 2.55 (m, 1H), 3.13 (dt, $J_1 = 11.6$ Hz, $J_2 = 5.3$ Hz, 1H), 7.6 (br, 2H), 8.65 (brs, 1H), 9.04 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 14.1$, 18.8, 22.5, 27.1, 33.2, 35.4, 42.2, 55.2, 122.5, 125.6, 154.0.

(±)-Ptilocaulin (*rac*-**1**): Exactly as described above for the preparation of **1**, a sample of *rac*-**4** was treated with guanidine to give *rac*-**1**. In contrast to the optically active series, crystallization of the chromatographed product mixture provided a very pure sample of *rac*-**1** from which one crystal was taken for the X-ray crystallographic investigation.[41] M.p. 164 °C ($CHCl_3$/MeOH), ref. [10b]: 165–166.5 °C, ref. [13b]: 151–152 °C.

X-ray crystal structure analyses:[34,41,42] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100528. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: Int. code + 44 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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