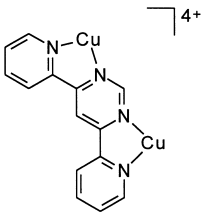
direct contribution of the structural metal M_s to Cu-mediated catalysis, and even hydrogen bonding of the phosphate oxygen atoms of a Cu-coordinated phosphate with axial M_s-H_2O, appear sterically impossible from a ball-and-stick model. Also, efficient cooperation of two metals across the bridging pyrimidine is ruled out by experiment: with the dicopper(II) complex of 4,6-di(2-pyridyl)pyrimidine, $[(dppm)Cu_2]^{4+}$, k_{obs} for HPNP cleavage is only $8\times10^{-6}\ s^{-1}$ (for conditions see caption from Figure 2).



$[(dppm)Cu_2]^{4+}$

Our system may be considered as a prototype of a synthetic allosteric catalyst having well defined catalytic and allosteric subunits, although it does not mimic the typical case of enzyme regulation in which a metal ion reversibly binds to the allosteric site as an external modifier. We see, however, certain parallels between our system and alkaline phosphatase enzymes in which the replacement of a structural Mg^{2+} ion by other divalent metal ions strongly influences the catalytic activity mediated by two functional Zn^{2+} ions.[2, 3] Another remarkable aspect is the possibility of fine-tuning the preorganization of the two functional metal ions M_f by variation of the structural metal M_s. This allows the systematic investigation of metal–metal cooperation in various reactions for a range of M_f-M_f separations and relative orientations of the M_f coordination polyhedra. Other approaches to this problem have been described but require laborious syntheses of a series of binucleating ligands with different spacers.[12]

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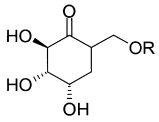
Hexacyclinic acid, a Polyketide from *Streptomyces* with a Novel Carbon Skeleton**

Regina Höfs, Martina Walker, and Axel Zeeck*

As shown in former investigations, *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013) only produces the carbasugars gabosine D (**1**) and E (**2**) when cultivated in Erlenmeyer flasks with a rolled oats medium.[1] Applying the OSMAC approach (OSMAC = one strain/many compounds)[2] in combination with the well established chemical screening method,[3] we intended to examine whether the production of new metabolites can be induced in this strain.



1: R = H
2: R = $COCH_3$

The OSMAC approach is based on the observation that individual strains are able to produce more metabolites than normally detected in a routine screening program. So it is easy to discover new natural products even when cultivating well-examined strains within the group of actinomycetes or fungi, with the aim being to induce or promote the biosynthesis of metabolites by variation of the cultivation parameters. According to this, one can discuss whether the detection of a new metabolite depends only on an increased production rate of a former, not previously provable, substance or if the natural product is formed for the first time. Within the OSMAC approach, the cultivation medium and culture vessel can be varied effectively, besides the temperature, aeration, pH value, and/or light intensity. C and N sources, as well as the addition of inorganic salts, enzyme inhibitors, or adsorbent materials, play an important role as part of the media. The intention of the OSMAC approach is the generation of

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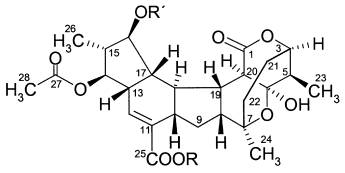
[**] We express our thanks to Hoechst AG (Frankfurt) for providing us with *Streptomyces cellulosae* (strain S1013) and Mr. M. Decke for excellent technical assistance. We wish to thank Prof. Dr. W. Beil for determining the cytotoxic activity. This work was supported by the Fonds der Chemischen Industrie.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3918-3258 $ 17.50+.50/0

variability concerning the metabolite formation and chemical diversity with regard to the carbon skeleton of the substances. Under varied conditions, some of our talented strains formed up to 50 secondary metabolites, whereby the number of new compounds was comparatively high.[2] The OSMAC approach proves to be very efficient while searching for new metabolites.[4] It is based on experience and finds its rationality in the fact that the genome of actinomycetes (approximately 8 Mb; 1 Mb = 10^6 bases), as well as that of talented fungi (approximately 30 Mb), is much larger than corresponds to the basic requirements of these organisms.[5] Thus, the silent biosynthetic genes, which can be activated, constitute the potential of this approach.

Following the OSMAC approach, our strain S 1013 has been cultivated in different culture vessels, using a rolled oats medium. In the culture filtrate extract from a 10 L fermentor we detected, by thin layer chromatography, an additional metabolite besides **1** and **2**. It gave an intensive blue color with anisaldehyde/H_2SO_4 as the staining reagent ($R_f = 0.30$, silica gel, chloroform/methanol 9/1), but its yield was not high enough for structure elucidation. Fermentation optimization by addition of different alkali halides resulted in strikingly increased yields (by a factor of 10–20) of this metabolite in the presence of 1 g L^{-1} of sodium bromide. This effect did not occur with lower or higher concentrations of the salt or by adding other salts. In different culture vessels the yield was up to 13 mg L^{-1}; with additional variation of the C source it rose to as much as 56 mg L^{-1}. Column chromatography on silica gel (chloroform/methanol 7/3 and 9/1) led to the isolation, in a reasonable quantity, of the new metabolite, which was named hexacyclinic acid after its structure, **3**.[6]



3: R = H, R′ = H
4: R = CH_3, R′ = H
5: R = CH_3, R′ = (*S*)-MTPA
6: R = CH_3, R′ = (*R*)-MTPA

Compound **3** crystallizes from methanol/water and is readily soluble in organic solvents. The direct chemical ionization (DCI) mass spectrum of **3** shows the molecular ion at *m*/*z* 508 $[M+NH_4]^+$. The molecular formula $C_{26}H_{34}O_9$ results from a high resolution (HR) EI mass spectrum (*m*/*z* 490). The ^{1}H NMR spectrum of **3** is characterized by a complex aliphatic region which can be differentiated with [D_5]pyridine to a large extend. The ^{13}C NMR spectrum exhibits 26 signals, two of them characterize a double bond and three can be attributed to carbonyl groups. The calculated double-bond equivalents derive from the molecular formula in combination with the ^{13}C NMR data and require cyclizations leading to a hexacyclic core structure of **3**. With the aid of several two-dimensional NMR spectra (COSY, HSQC, HMBC) the structures of two fragments could be established: the left five-membered ring with the acetoxy group and the right tricyclic ring system. The fragments could not be connected unequivocally because of overlapping proton signals in this section of the molecule and because of HMBC correlations whose $^nJ_{CH}$ character could not be clearly defined. Also, the use of calculation programs like COCON leads to more than one plausible proposal for the structure of **3**.[7] Finally, elucidation of the structure including the relative configuration was done by X-ray analysis of **3** (Figure 1).[8] NOESY NMR spectra, in connection with the other 2D NMR data, enabled the unambiguous assignment of all ^{1}H and ^{13}C NMR signals.

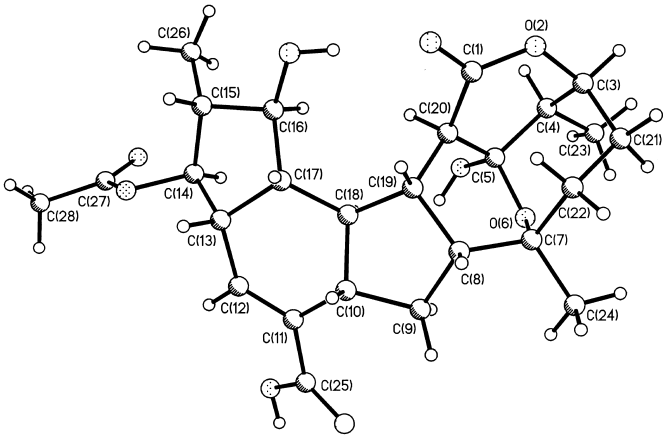


Figure 1. Crystal structure of hexacyclinic acid (**3**) with crystallographic numbering pattern. Only the relative configuration resulted from the X-ray analysis. The given absolute configuration was determined using Mosher's ester methodology.

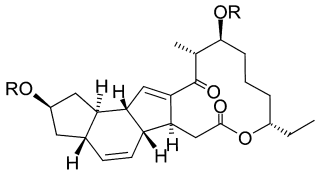
The absolute configuration of **3** was evaluated by performing the advanced Mosher's ester methodology. Therefore, we transformed the methyl ester of hexacyclinic acid **4**, which results from a methylation of **3** with diazomethane, into the diastereomeric Mosher's esters **5** and **6**.[9] Table 1 shows selected ^{1}H NMR data for **4**–**6**. From these data, the position of the Mosher's ester can be determined as C-16 and the absolute configuration of C-16 in **4** is derived as *S*, which results in the absolute configuration of **3** being: 3*S*, 4*R*, 5*R*, 7*S*, 8*R*, 10*S*, 13*R*, 14*R*, 15*R*, 16*S*, 17*R*, 18*S*, 19*S*, 20*R*.

Table 1. Selected ^{1}H NMR data (125.7 MHz, [D_5]pyridine) of **4** and the Mosher's esters **5** and **6**.

H Atom	**4**	**5**	**6**	$\delta(\mathbf{5}) - \delta(\mathbf{6})$
26-H_3	1.18	1.51	1.47	+0.04
15-H	2.36	2.55	2.39	+0.16
16-H	4.15	6.03	6.04	*S*[a]
17-H	2.49	2.61	2.73	−0.12
18-H	2.49	2.54	2.59	−0.05
19-H	3.21	3.12	3.20	−0.08

[a] Resulting chirality.

Compound **3** has a novel skeleton with a 5/6/5 ring system annelated to a bridged tricycle, which is characterized by a δ-lactone and a cyclic hemiketal. The left tricyclic section of **3** can be found similarly in the spinosynes **7**,[10] insecticidal metabolites from streptomycetes, and in ikaruguamycin.[11] In the given combination of structure elements, the hexacyclic skeleton of **3** with its 14 chiral



7 R = sugar units

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centers and different functionalities is not comparable with any known natural product.

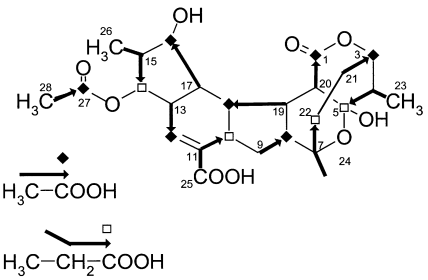
Compound **3** shows weak cytotoxicity for three tested cell lines (HM02, HEP G2, and MCF 7) with GI_{50} values up to 14.0 μmol L^{-1}. Further biological tests are in progress.

Polycyclic nonaromatic structures are characteristic for terpenoids but occur only rarely within actinomycetes. In order to get an idea of the biosynthesis of **3**, first feeding experiments were carried out. Feeding of [1-^{13}C]acetate to growing cultures of the strain resulted in signal enhancements of C-1, C-3, C-8, C-16, C-18, and C-27 (Table 2, Scheme 1). Values for specific incorporations of C-5 and C-12 are increased but not unambiguously. The lower incorporation in C-12 can be explained by the difficulty of detection of its comparatively broad ^{13}C NMR signal. Another feeding experiment with [1-^{13}C]propionate led to strong enrichments of C-5, C-10, C-14, and C-22 (Table 2, Scheme 1).

Table 2. ^{13}C NMR data (125.7 MHz, [D_5]pyridine) of hexacyclinic acid (**3**) and specific ^{13}C incorporation (relative to the natural intensity of the C-28 signal) after feeding experiments with [1-^{13}C]acetate (A) and [1-^{13}C]propionate (B).

	δ	A	B
C-1	177.0	2.1	0.3
C-3	78.9	3.3	0.3
C-4	45.0	−0.2	0.1
C-5	95.3	0.6	75.9
C-7	72.9	0.2	−0.1
C-8	46.1	3.1	0.2
C-9	31.9	−0.2	0.1
C-10	42.3	−0.4	54.5
C-11	136.4	−0.6	0.0
C-12	139.0	0.6	1.5
C-13	45.7	−0.2	−0.1
C-14	80.0	−0.2	37.6
C-15	47.8	−0.1	0.0
C-16	80.4	3.2	0.0
C-17	50.2	−0.3	0.0
C-18	53.2	1.7	−0.1
C-19	42.8	−0.2	0.4
C-20	48.3	−0.1	−0.3
C-21	23.6	−0.2	0.1
C-22	35.5	0.2	68.0
C-23	8.8	−0.1	0.2
C-24	27.2	−0.1	0.3
C-25	169.0	n.d.[a]	1.2
C-26	14.7	−0.1	0.2
C-27	170.8	5.9	0.0
C-28	20.9	0.0	0.0

[a] n.d. = not determined.



Scheme 1. Labeling pattern of hexacyclinic acid (**3**). Results of feeding experiments with [1-^{13}C]acetate and [1-^{13}C]propionate are shown, as well as the proposed direction of incorporation of the precursors.

These experiments reveal that hexacyclinic acid (**3**) is a polyketide built by seven acetate and four propionate units (Scheme 1). This however must be confirmed by further experiments, just like the determination of the starter unit. If one assumes only one polyketide chain, built by a modular type I polyketide synthase, multiple unusual cyclisation steps are necessary to generate **3**. We suppose an intramolecular Diels–Alder reaction, aldol reaction, lactonisation, and ketalisation which would provide all the functionalities needed in the intermediates. Further experiments to investigate the biosynthesis of hexacyclinic acid **3**, a novel type I polyketide, are in progress.

Experimental Section

Cultivation: Strain S 1013 was grown on agar slopes (10 g L^{-1} soluble starch, 2 g L^{-1} $(NH_4)_2SO_4$, 2 g L^{-1} $CaCO_3$, 1 g L^{-1} K_2HPO_4, 1 g L^{-1} NaCl, 1 g L^{-1} $MgSO_4$, 20 g L^{-1} agar, pH 7.0 prior to sterilization) at 28 °C until sporulation, and then stored at 4 °C. One eighth of these agar slopes was used to inoculate 100 mL of a soybean/mannitol medium (20 g L^{-1} D-mannitol, 20 g L^{-1} soybean meal (degreased), pH 7.2 prior to sterilization) in 300 mL Erlenmeyer flasks. These cultures were incubated on a rotary shaker (180 rpm) at 30 °C for 72 h. A 900 mL portion of this preculture was used to inoculate a 10 L fermentor (Braun, Biostat E, medium: 20 g L^{-1} rolled oats (cooked for 20 min and filtered), 1 g L^{-1} NaBr, 2.5 mL trace element solution (3 g L^{-1} $CaCl_2 \cdot 2H_2O$, 1 g L^{-1} Fe^{III}/citrate, 0.2 g L^{-1} $MnSO_4$, 0.1 g L^{-1} $ZnCl_2$, 0.025 g L^{-1} $CuSO_4 \cdot 5H_2O$, 0.03 g L^{-1} $Na_2B_4O_7 \cdot 10H_2O$, 0.004 g L^{-1} $CoCl_2$ 0.01 g L^{-1} $Na_2MoO_4 \cdot 2H_2O$), pH 7.0 prior to sterilization). The culture was incubated at 30 °C, 10 L min^{-1} aeration and harvested after 120 h.

Isolation of **3**: The culture broth was separated from the mycelium by centrifugation and the filtrate was concentrated by lyophilization. The crude residue was extracted with methanol and the combined organic layers were evaporated. The residue was purified twice by column chromatography on silica gel (first column: 4 × 27 cm, chloroform/methanol 7/3; second column: 2.5 × 32 cm, chloroform/methanol 9/1) to yield 130 mg of **3** as a solid.

Labeled precursors and feeding experiments: Sodium [1-^{13}C]acetate and sodium [1-^{13}C]propionate (each 99 % ^{13}C) were obtained from ISOTEC Inc. The main culture of the feeding experiments was carried out in ten 300 mL Erlenmeyer flasks, which contained 100 mL medium, at 30 °C and 180 rpm for 120 h. The cultures were inoculated with the described 72 h preculture. The precursors (1 g each) were added as sterile aqueous solutions, adjusted to pH 7.0, following the pulse feeding method in 1 mL portions at 80, 86, 94, 100, and 106 h after incubation. Isolation and purification followed the description above to yield 1.5 mg of **3** ([1-^{13}C]-acetate) or 56 mg of **3** ([1-^{13}C]propionate).

Hexacyclinic acid (**3**): $C_{26}H_{34}O_9$ (M_r = 490.55); m.p. 162 °C; $[\alpha]_D^{20} = +69°$ (c = 0.11 in MeOH); DCI-MS (200 eV): m/z: 508 ($[M+NH_4]^+$, 100 %); HR EI MS (70 eV): 490.2202, found as calculated for $C_{26}H_{34}O_9$; IR (KBr): $\tilde{\nu}_{max}$ = 3428, 2926, 1734, 1719, 1702, 1658, 1637, 1381, 1250, 1090, 1033 cm^{-1}; UV (MeOH): λ_{max} (ε) = 202 nm (11514); ^{1}H NMR (500 MHz, [D_5]pyridine): δ = 1.07 (s, 3H, 24-H_3), 1.14 (d, J = 6.9 Hz, 3H, 23-H_3), 1.19 (d, J = 6.5 Hz, 3H, 26-H_3), 1.55 (dm_c, J = 15.5 Hz, 1H, 22-H_a), 1.65 (m, 1H, 22-H_b), 1.72 (m, 1H, 21-H_a), 1.79 (ddd, J = 12.0, 12.0, 12.0 Hz, 1H, 9-H_a), 1.92 (m_c, 1H, 21-H_b), 2.05 (s, 3H, 28-H_3), 2.11 (ddd, J = 11.5, 11.5, 6.6 Hz, 1H, 8-H), 2.21 (m, 1H, 10-H), 2.26 (dq, J = 6.9, 3.5 Hz, 1H, 4-H), 2.36 (ddq, J = 10.0, 10.0, 6.5 Hz, 1H, 15-H), 2.55 (m, 2H, 18-H, 17-H), 2.79 (ddd, J = 11.5, 6.5, 6.5 Hz, 1H, 9-H_b), 3.11 (dddd, $J \approx 10, \approx 10, \approx 2, \approx 2$ Hz, 1H, 13-H), 3.22 (dd, J = 11.5, 10.5 Hz, 1H, 19-H), 3.95 (br.s, 1H, 20-H), 4.17 (dd, J = 10.0, 5.9 Hz, 1H, 16-H), 4.42 (ddd, J = 3.5, 3.5, 3.5 Hz, 1H, 3-H), 5.00 (dd, J = 10.0, 10.0 Hz, 1H, 14-H), 7.26 (dd, J = 2.5, 2.5 Hz, 1H, 12-H); ^{13}C NMR: see Table 2.

Data for compounds **4**–**6**: see the Supporting Information.

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[8] Crystal structure analysis of **3**: Stoe-Siemens-Huber four-circle diffractometer coupled to a Bruker CCD area detector, graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), ϕ and ω scans, empirical absorption correction with SADABS, structure solved with direct methods, refinement against F^2 by full-matrix least-squares methods with SHELXL-97, a riding model with idealized hydrogen geometry was employed, $C_{26}H_{34}O_9$, $0.5 \times 0.4 \times 0.1$ mm, orthorhombic, space group $P2_12_12_1$, $a = 12.371(3)$, $b = 13.559(3)$, $c = 30.004(6)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 5032.8(17)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.319$ g cm^{-3}, $\mu = 0.100$ mm^{-1}, $2\theta_{max} = 41.84$, $T = 133(2)$ K, 50542 reflections measured, 6207 unique, 5322 used for calculation, 674 refined parameters, $R1 = 0.0390$, $wR2 = 0.0751$, min./max. residual electron density 1.69/ – 1.79 e Å^3. 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-141597. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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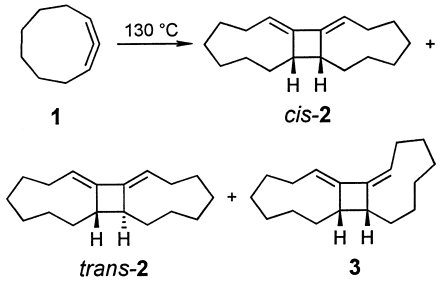
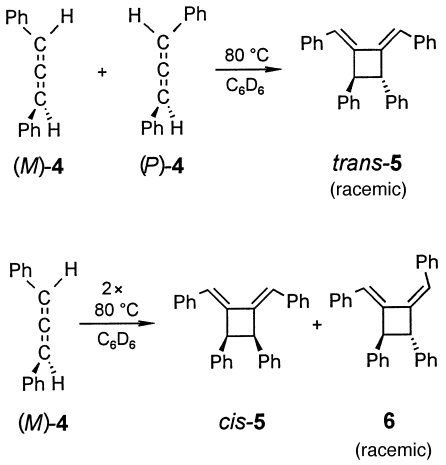
The Dimerization of Chiral Allenes: Pairs of Enantiomers and Pairs of Homomers Furnish Different Diastereomers**

Manfred Christl,* Stefan Groetsch, and Kurt Günther

At room temperature, cyclonona-1,2-diene (**1**) can be stored virtually unlimited. Proceeding at 130 °C, its dimerization furnishes the 1,2-bis(methylene)cyclobutane derivatives *cis*-**2**, *trans*-**2**, and **3** in the ratio of 5:10:1 in the case of the racemic mixture, whereas a nearly pure enantiomer affords almost only *cis*-**2**.[1] These findings suggest the interpretation that the combination of a pair of homomers in racemic **1** gives rise to *cis*-**2** and that of a pair of enantiomers provides preferentially *trans*-**2** and additionally **3**.



1,3-Diphenylallene (**4**) had been studied as a second example for the dimerization of chiral nonracemic allenes. By using a sample with an optical purity of 35 %, the optical rotation did decrease to zero, however, the ratio of products (*cis*-**5**, *trans*-**5**, and **6**) was unchanged compared to that from the dimerization of racemic **4**.[2] Assuming that the enantiomeric excess could have been too small for the observation of a deviation from the behavior of racemic **4**, we repeated the experiments. On heating in C_6D_6 at 80 °C for five days, racemic **4** was consumed to the extent of 93 % and yielded *cis*-**5**, *trans*-**5**, and **6** in the ratio of 44:28:28. The pure enantiomers of **4** were obtained by HPLC on Chiralcel OD[3] and dimerized to give predominantly *cis*-**5** and **6** and only a small proportion of *trans*-**5** (*cis*-**5**:*trans*-**5**:**6** = 46:4:50). Therefore, we conclude that in racemic **4** pairs of enantiomers prefer to form *trans*-**5**, while pairs of homomers produce mainly *cis*-**5** or **6**.



Recently, we reported on the dimerization of racemic 1-phenylcyclonona-1,2-diene (**7**) in $CDCl_3$, which occurs already at 20 °C with formation of *cis*- and *trans*-**8** in the ratio of about 1:2.[4] The reaction has now been conducted in C_6D_6 and the product ratio was found to be very close to 50:50. The pure enantiomers of **7** were obtained by HPLC of the racemic mixture on Chiralcel OD with hexane as eluant. Their dimerization in C_6D_6 (several weeks at 20 °C) gave *trans*-**8** with high preference (*cis*-**8**:*trans*-**8** = 8:92). These results

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