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[12] Compound **12** is formed as a mixture of two isomers that rapidly equilibrate under the reaction conditions. The *trans* isomer with methoxy groups in axial positions crystallizes preferentially from the reaction mixture and can be obtained pure in greater than 90% yield with only 10^{-4} mol% catalyst.
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[14] These catalysts are also able to catalyze the addition of water and carboxylic acids to alkynes. A preliminary report of this work appears in reference [7].
[15] Generated from [LAu(NO_3)] and ten equivalents of $BF_3 \cdot OEt_2$. The nitrates were synthesized from the known chlorides through metathesis with $AgNO_3$. For a typical procedure, see L. Malatesta, L. Naldini, G. Simonetta, F. Cariati, *Coord. Chem. Rev.* **1966**, *1*, 255.
[16] Nucleophilic carbenes such as 1,3,4-triphenyl-4,5-dihydro-1,2,4-triazol-(1*H*)-ylidene are also suitable ligands. We prepared the corresponding gold(I) chloride complex by treating the isolated carbene with dimethylsulfidegold(I) chloride. This carbenegold(I) complex proved to be 3.5 times more active than triphenylphosphanegold(I) chloride. Unfortunately we did not succeed in the preparation of either the carbenegold nitrate or the carbenegold methyl complexes.
[17] Amazingly, even HBF_4 is quickly hydrolyzed to trimethylborate under the reaction conditions.
[18] The same turnover rate ($700\ h^{-1}$) is observed when the catalyst is generated from the oxonium salt [$(Ph_3PAu)_3O^+BF_4^-$] and $BF_3 \cdot OEt_2$.
[19] All ab initio calculations were performed with the TURBOMOLE program package. For an overview of TURBOMOLE, see R. Ahlrichs, M. von Arnim in *Methods and Techniques in Computational Chemistry: METECC-95* (Eds.: E. Clementi, G. Corongiu) STEF, Cagliari, **1995**, P. 509–554. Geometries were calculated at the RI-DFT level (K. Eichkorn, O. Treutler, H. Ihm, M. Häser, R. Ahlrichs; *Chem. Phys. Lett.* **1995**, *242*, 652) with the Becke–Perdew functional and the TURBOMOLE SV(P) basis sets (K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theor. Chem. Acc.* **1997**, *97*, 119). For gold, the 60-mwb relativistic pseudopotential was utilized (D. Andrae, U. Haeussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123). Energies were calculated at the MP2 level with TZVP basis sets through the recently developed RI-MP2 implementation (F. Weigend, M. Häser, *Theor. Chem. Acc.* **1997**, *97*, 331).
[20] The peaks coalesce at $-40\,^\circ C$ to a single broad peak at $\delta = 32$. Above $-20\,^\circ C$ this peak becomes narrower, and at $0\,^\circ C$ only the sharp signal of [Ph_3PAuCl] remains at $\delta = 31$. The independently synthesized triphenylphosphanegold(I) methanesulfonate (from triphenylphosphanegold(I) iodide and silver methanesulfonate) shows a broadened peak at $\delta = 27$ (^{31}P NMR in CD_2Cl_2 at $-40\,^\circ C$).
[21] Coordination of methanol with **18** to form the T-shaped complex **19** disturbs the structure only slightly. The angle between phosphorus, gold, and the center of the triple bond changes from 179° in **18** to 175° in **19**. The Au–O bond in **19** is very long (3.7 Å compared to 2.1 Å for a Au–O single bond), and the P-Au-O angle is 83°.
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[23] The stereochemistry was determined by X-ray crystallography. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100957. 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).

Synthesis and Biological Activity of Sarcodictyins**

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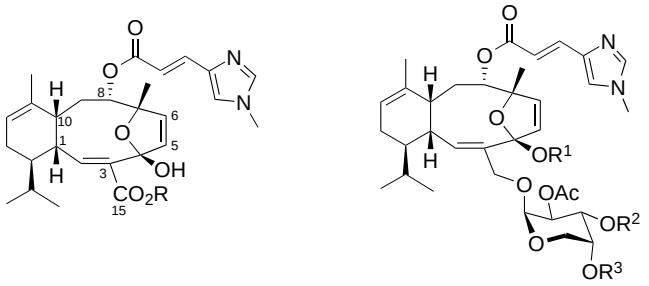
Isolated from certain species of soft corals, the sarcodictyins (**1**, **2**),[1, 2] eleutherobin (**3**),[3, 4] and the eleuthosides (**4**, **5**)[5] have become important synthetic targets because of their novel molecular architectures, biological activities, and medicinal potential (Figure 1). Of special interest is their taxol-like mechanism[6] of action, which involves tubulin polymeri-



1: R = Me
2: R = Et

3: R^1 = Me, R^2 = H, R^3 = H
4: R^1 = H, R^2 = Ac, R^3 = H
5: R^1 = H, R^2 = H, R^3 = Ac

Figure 1. Structures of sarcodictyins A (**1**) and B (**2**), eleutherobin (**3**), and eleuthosides A (**4**) and B (**5**).

zation and microtubule stabilization and results in tumor-cell death. The combination of the scarcity and the appealing biological activity of these materials prompted us to initiate a program directed at their chemical synthesis. We recently disclosed the first total syntheses of sarcodictyin A (**1**)[7] and eleutherobin (**3**).[8] Here we report the first synthesis of sarcodictyin B (**2**), the construction of a sarcodictyin library, and the tubulin-polymerization and cytotoxic properties of members of that library, including their action against a number of taxol-resistant tumor-cell lines.

To conveniently access a sarcodictyin library, an improved method for their construction was devised (Scheme 1), which

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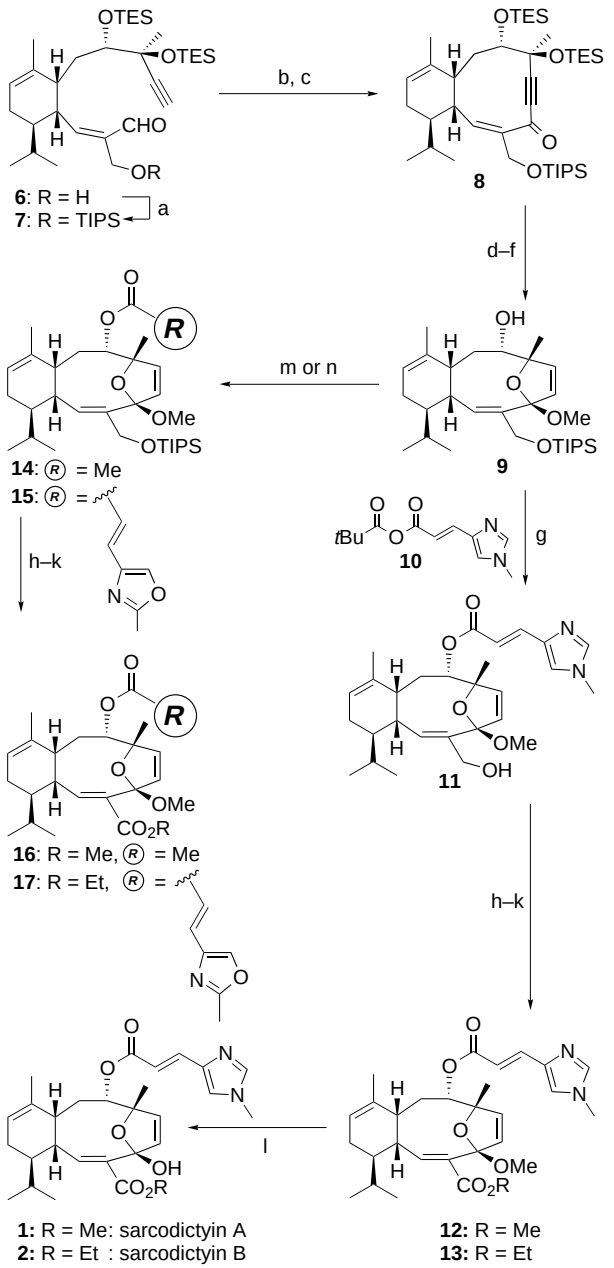
[**] This work was supported by The Skaggs Institute for Chemical Biology, the U.S. National Institutes of Health, Novartis, and the CaP CURE Foundation, and by fellowships from Novartis (D.V.), the Japanese Society for the Promotion of Science for Young Scientists (S.H.), and the U.S. Department of Defense (J.P.).

  1433-7851/98/3710-1418 $ 17.50+.50/0



Scheme 1. Syntheses of sarcodictyins A (**1**) and B (**2**) and various analogues. a) TIPSOTf (5.0 equiv), *i*Pr_2NEt (10 equiv), CH_2Cl_2, −78 °C, 1 h, 79 %; b) LiHMDS (2.0 equiv), THF, −20 °C, 20 min; c) Dess–Martin periodinane (2.0 equiv), pyridine (6.0 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, 0 °C, 1 h, 89 % over two steps; d) 3 HF · Et_3N (5.0 equiv), THF, 25 °C, 1.5 h, 78 %; e) [Rh(nbd)(dppb)]BF_4 (0.05 equiv), H_2, acetone, 25 °C, 10 min; f) PPTS (0.5 equiv), MeOH, 25 °C, 10 min, 80 % over two steps; g) **10** (5.0 equiv), Et_3N (20 equiv), DMAP (2.0 equiv), CH_2Cl_2, 25 °C, 48 h, 83 %; h) TBAF (2.0 equiv), THF, 25 °C, 2 h, 100 %; i) Dess–Martin periodinane (2.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 0.5 h; j) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (3.0 equiv), 2-methyl-2-butene (50 equiv), THF, *t*BuOH, H_2O; k) CH_2N_2 or CH_3CHN_2, Et_2O, 88 % (**12**) and 90 % (**13**) over three steps; l) CSA (2.0 equiv), CH_2Cl_2:H_2O (10:1), 25 °C, 48 h, 80 (**1**) and 86 % (**2**); m) Ac_2O (3.0 equiv), Et_3N (5.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 1 h, 95 %; n) DCC (2.0 equiv), (*E*)-3-(2-methyloxazole-4-yl)propenoic acid (1.3 equiv), DMAP (0.5 equiv), CH_2Cl_2, 25 °C, 36 h, 86 %. CSA = 10-camphorsulfonic acid, DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, dppb = 1,4-bis(diphenylphosphanyl)butane, LiHMDS = lithium hexamethyldisilazanide, nbd = 2,5-norbornadiene, PPTS = pyridinium *p*-toluenesulfonate, TBAF = tetra-*n*-butylammonium fluoride, TIPSOTf = trisisopropylsilyl trifluoromethanesulfonate.

relies on the use of more effective protecting groups (**6**) and hydrogenation catalysts (**8**→**9**), and includes a number of alternative esterification protocols. Thus, the previously synthesized alcohol **6**[8] was protected as a TIPS ether (**6**→**7**, 79 %; for abbreviations, see the scheme legend) prior to ring closure (LiHMDS, −20 °C) and Dess–Martin[9] oxidation to afford ten-membered ring enynone **8** (89 % over two steps). Desilylation of **8** with 3 HF · Et_3N (78 %) followed by selective hydrogenation[10] in the presence of [Rh(nbd)(dppb)]BF_4 led through ring closure of a short-lived dihydroxydienone to the tricyclic skeleton. The resulting intermediate was converted to its methoxy acetal **9** (80 % over two steps), which served as a common intermediate for the total synthesis of sarcodictyin B (**2**) and the construction of a sarcodictyin library. Three methods of esterification used in the generation of the library are exemplified in Scheme 1 by the syntheses of **11**, **14**, and **15**. Specifically, treatment of alcohol **9** with mixed anhydride **10** in the presence of DMAP resulted in the formation of urocanic ester derivative **11** in 83 % yield. Subsequent cleavage of the silyl ether group with TBAF (100 % yield) followed by a series of standard transformations (Dess–Martin and $NaClO_2$ oxidations and diazoalkane esterification) led to the isolation of methyl and ethyl esters **12** and **13** (88 and 90 %, relatively, over three steps). The natural sarcodictyins A (**1**) and B (**2**) were obtained after acidic hydrolysis with 10-camphorsulfonic acid in CH_2Cl_2/H_2O (80 and 86 %, respectively). In a second approach, treatment of **9** with acetic anhydride in the presence of DMAP provided acetate **14** (95 % yield), which was in turn transformed into sarcodictyin A analogue **16** by the previously described sequence.[7] Finally, reaction of **9** with (*E*)-3-(2-methyloxazol-4-yl)propenoic acid in the presence of DCC and DMAP gave a number of other side-chain analogues (Table 1).

The synthetic sarcodictyins were evaluated for tubulin-polymerization and cytotoxic properties, and were compared with taxol and epothilones A and B (Table 1). The colorimetric-filtration assay for tubulin polymerization[11, 12] was utilized to determine the tubulin effects of sarcodictyins **1**, **2**, **11**–**13**, and **16**–**25**. They exhibited varying degrees of polymerizing properties ranging from 4.0 to 85 % (for comparison: taxol, 65 %; epothilone A, 72 %; epothilone B, 97 %). Cytotoxicity studies were conducted with the parental ovarian carcinoma cell line 1A9 and the taxol-resistant tumor-cell lines PTX10 and PTX22[13] derived from 1A9. The observed activity of the synthetic compounds proved to be highly dependent upon their precise structures (Table 1).

A number of conclusions can be drawn from these studies with respect to structure–activity relationships (SARs). The C8 side chain is crucial for both tubulin-polymerization and cytotoxic properties, as shown by a comparison of compounds **13** and **16**. Reduction of the ester group at C15 to a primary alcohol (**11**) resulted in a decrease in activity. The sarcodictyin pharmacophore appears in fact to be rather sensitive to modification at C15 (reduction), as is apparent from the properties of compounds **21**–**25**. An increase in the size of the alkyl group on the C4 acetal seems to have only a small effect on the biological activity of the compounds (see **1**, **12**, **18**, and **19**).

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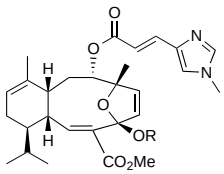
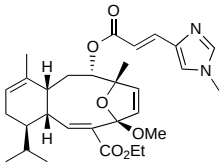
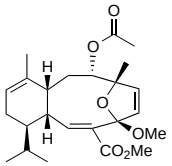
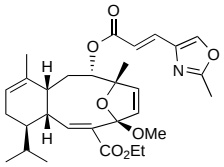
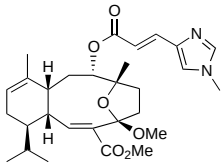
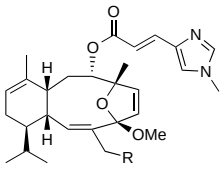
Table 1. Tubulin-polymerizing and cytotoxic characteristics of the sarcodictyins.

Compound			Induction of tubulin polymerization [%]	Inhibition of cancer-cell growth (IC_{50} [nM]) 1A9	1A9PTX10	1A9PTX22
		taxol	65.0	2.0	50	40
		epothilone A	72.7	2.0	1.9	4.0
		epothilone B	97.0	0.04	0.035	0.04
1		sarcodictyin A	67.0	340	140	360
2		sarcodictyin B	71.0	2.0	160	80
12		R = Me	72.0	70	3.6	84
18[c]		R = Et	85.0	110	13	160
19[d]		R = *n*Pr	79.0	170	> 2000	130
13			46.0	2.0	0.6	6.0
16			4.0	> 2000	1300	> 2000
17			4.0	> 2000	800	385
20[e]			52.0	510	1700	1800
11		R = OH	37.5	800	> 2000	> 2000
21[f]		R = F	27.4	1850	> 2000	> 2000
22[g]		R = OAc	37.2	1050	> 2000	1620
23[h]		R = OBz	34.1	> 2000	> 2000	> 2000
24[i]		R = N_3	47.0	> 2000	> 2000	1800
25[j]		R = OCONHPh	37.0	> 2000	> 2000	> 2000

[a] Tubulin-polymerization measurements were carried out at 37 °C as described,[11, 12] apart from adjustments in the concentration of active agents (100 μM) and incubation time (90 min). [b] The cytotoxicity investigations were carried out as described.[12, 13] [c] From sarcodictyin A (**1**) by treatment with CSA/EtOH in CH_2Cl_2 (98 %). [d] From sarcodictyin A (**1**) by treatment with CSA/*n*PrOH in CH_2Cl_2 (90 %). [e] By-product from overreduction of the triple bond and subsequent acetalization. [f] From **11** by treatment with DAST (99 %). [g] From **11** by treatment with Ac_2O, Et_3N, and DMAP (100 %). [h] From **11** by treatment with BzCl, Et_3N, and DMAP (95 %). [i] From **11** by treatment with $(PhO)_2PON_3$, DEAD, and Ph_3P (74 %). [j] From **11** by treatment with PhNCO and Et_3N (95 %). Bz = benzyl, CSA = 10-camphorsulfonic acid, DAST = (diethylamino)sulfur trifluoride, DEAD = diethyl azodicarboxylate, DMAP = 4-(dimethylamino)pyridine.

The apparent inconsistency between tubulin-polymerization activity and cytotoxicity for a number of these compounds (e.g., **13**, **17**, **20**) may be indicative of the availability of an additional mechanism of action in some cases. Indeed, inspection of the structures of sarcodictyins and eleutherobins reveals their potential as alkylating agents under acidic conditions (Figure 2), so they may be capable of interacting with DNA and other cellular receptors. Experiments directed toward confirming this hypothesis are in progress.

  1433-7851/98/3710-1420 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 10

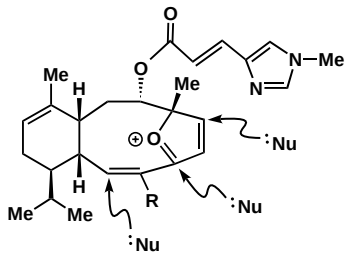


Figure 2. Alkylating properties of sarcodictyins and eleutherobins.

The chemistry and biological activity presented here shows the sarcodictyins to be a new class of potential anticancer agents. Access to additional derivatives and closer investigation are now possible through the use of molecular design and chemical synthesis. The first structure – activity information on sarcodictyins, reported here, should provide valuable guidelines for further chemical and biological studies.[14]

Received: January 22, 1998 [Z 11393 IE]
German version: *Angew. Chem.* **1998**, *110*, 1484 – 1487

Keywords: antitumor agents · sarcodictyins · structure – activity relationships · total synthesis · tubulin polymerizations

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Cooperative Hairpin Dimers for Recognition of DNA by Pyrrole – Imidazole Polyamides**

John W. Trauger, Eldon E. Baird, and Peter B. Dervan*

Small molecules which permeate cells and bind to specific DNA sequences can potentially control the expression of specific genes.[1, 2] Recently, a polyamide with eight heterocyclic units which binds to a target site consisting of six base pairs was shown to inhibit gene transcription in a cell culture.[2] Polyamides that recognize longer DNA sequences should provide more specific biological activity,[3] which could be achieved by synthesizing larger polyamides.[4] However, the upper limit of polyamide size with regard to efficient cell permeation is not known.

Alternatively, a more biomimetic approach is to bind larger DNA sequences while maintaining the size of the polyamide. Natural transcription factors often bind large DNA sequences by formation of cooperative protein dimers at adjacent half-sites.[5] In cooperatively binding extended pyrrole – imidazole (Py – Im) polyamide dimers, the two ligands can slip sideways with respect to one another to allow recognition of other sequences.[6] Polyamides containing the turn-specific γ-aminobutyric acid linker[7] adopt a hairpin conformation in which the DNA binding sites are fully overlapped and the slipped-motif option is precluded. Here we report a cooperative six-ring extended hairpin polyamide which dimerizes to specifically bind a predetermined sequence of ten base pairs.

As target site, we chose a sequence contained in the regulatory region of the HIV-1 genome.[8] To design the ligand we considered the polyamide ring-pairing rules,[9–13] the need to incorporate β-alanine (β) to relax the ligand curvature,[6, 13] and the preference of γ-aminobutyric acid (γ) for a hairpin-turn conformation in polyamide – DNA complexes.[6, 7a,e] This analysis suggested that the six-ring polyamide having the core sequence ImPyβImPyγImPy might bind the target sequence 5′-AGCAGCTGCT-3′ by formation of a cooperative hairpin dimer (Figure 1). To avoid a collision between the N-terminal end of one ligand and the C-terminal end of the other in the complex, the positively charged β-alaninedimethylaminopropylamide C terminus used in standard polyamides was replaced with the shorter, uncharged $(CH_2)_2OH$ group (C_2 – OH). The cationic turn residue (*R*)-2,4-diaminobutyric acid ($(R)^{H_2N}\gamma$)[14] maintains the overall positive charge needed for optimal solubility in water.

Polyamide ImPyβImPy$(R)^{H_2N}\gamma$ImPyC_2-OH (**1**) was synthesized by solid-phase methods[15] on glycine – PAM resin,[16] reductively cleaved from the solid support with $LiBH_4$,[17]

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[**] We are grateful to the National Institutes of Health for support (GM-27681), to the National Science Foundation and the Ralph M. Parsons Foundation for predoctoral fellowships to J.W.T., and to the Howard Hughes Medical Institute for a predoctoral fellowship to E.E.B. Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/98/3710-1421 $ 17.50+.50/0