Solid and Solution Phase Synthesis and Biological Evaluation of Combinatorial Sarcodictyin Libraries

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Abstract: Isolated from certain species of soft corals, the sarcodictyins, eleutherobin, and eleuthosides have become important synthetic targets due the their novel molecular architectures, important biological activities, and potential in medicine. Of particular interest is their Taxol-like mechanism of action involving disturbance of the tubulin−microtubule interplay resulting in tumor cell death. Their scarcity and biological profile prompted us to initiate a program directed at exploring their chemical synthesis and chemical biology. Herein we report (a) the first total synthesis of sarcodictyins A (**7**) and B (**8**) by a combination of solution and solid-phase methods through the attachment of the common precursors **18** or **20** on solid support, thus generating conjugates **23** and **24**, followed by standard chemical manipulations; (b) the construction of a combinatorial library of sarcodictyins by solution and solid-phase chemistry modifying the C-8 ester, C-15 ester, and C-4 ketal functionalities, and, therefore, producing analogues of the general structures **33**, **37**, and **40**; (c) the tubulin polymerization properties of all members of the library; and (d) the cytotoxic actions of a selected number of these compounds against a number of tumor cells including Taxol-resistant lines. Several of the synthesized analogues were identified to be of equal or superior biological activities (e.g. **60**, **61**, **63**, **66**−**70**, **73**, **76**, **85**, **92**) as compared to the natural products, setting the stage for further developments in the field of cancer chemotherapy.

Introduction

Sarcodictyins A (**7**) and B (**8**) (Figure 1) were discovered in the Mediterranean stoloniferan coral *Sarcodictyon roseum* by Pietra et al. and originally reported in 1987.[1] The sarcodictyin family was enriched in 1988 with the disclosure of the structures of sarcodictyins C−F from the same group.[2] Their potent antitumor activity and Taxol-like mode of action (i.e. tubulin polymerization and microtubule stabilization)[3] were recognized in 1997 by an Upjohn-Pharmacia group.[4] These substances are related, both structurally and with regard to their biological action, to eleutherobin (**4**)[5] and to eleuthosides A (**5**) and B (**6**)[6] (Figure 1). Furthermore, all four marine-derived natural products (**4**−**8**) share the same mechanism of action with the soil-derived (myxobacteria) epothilones A (**2**) and B (**3**)[7−10] (Figure 1) and the forest-residing Taxol (**1**)[11] (Figure 1). The latter compound **1** is currently enjoying a billion-dollar drug status as an anticancer agent. Total syntheses of eleutherobin (**4**),[12−14] eleuthosides A (**5**) and B (**6**),[13] and sarcodictyins A (**7**) and B (**8**)[15,16] have recently been reported. Furthermore, the

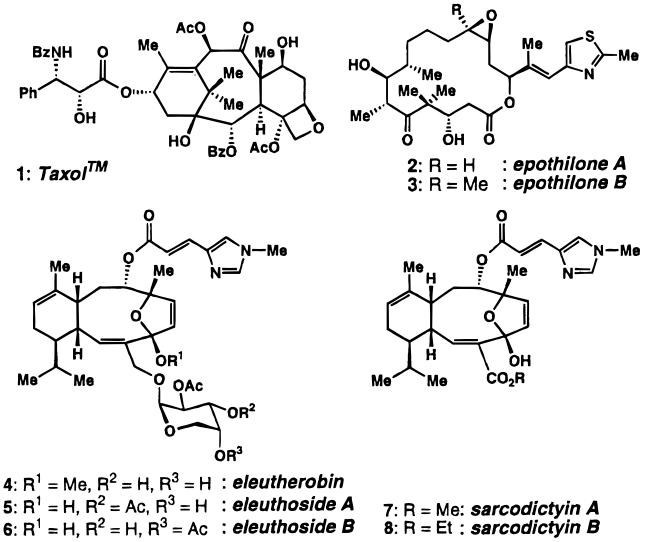

Figure 1. Molecular structures of Taxol (**1**), epothilones A (**2**) and B (**3**), eleutherobin (**4**), eleuthosides A (**5**) and B (**6**), and sarcodictyins A (**7**) and B (**8**) (Ac = acetyl, Bz = benzoyl).

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syntheses of a number of sarcodictyin analogues have also been accomplished in solution and recently disclosed from these laboratories.[17] In this article we describe the development of solid-phase chemistry that allowed the generation of a combinatorial sarcodictyin library and its biological evaluation leading to the discovery of analogues possessing higher antitumor potencies than those of the natural products. The gained knowledge provides important information regarding the structure−activity relationships within the sarcodictyin−eleutherobin molecular framework and sets the stage for further advances in the field.

Molecular Diversity Design. Solid Phase Strategy. Inspection of the structure of sarcodictyins A (**7**) and B (**8**) reveals the three branches of possible molecular diversification; those emanating from skeletal carbons C-3, C-4, and C-8 (see structure **IV**, Figure 2 for numbering). Furthermore, the ready availability of a suitable common intermediate for attachment to a solid support and the potential reactivity of the functional groups at C-3, C-4, and C-8 presented an attractive opportunity for the design and construction of a general sarcodictyin library depicted under structure **I** (Figure 2). Thus, compounds **I** could be obtained by *trans*-ketalization with a variety of alcohols with simultaneous cleavage from the resin **II**, whereas the latter structure **II** could be tailored from **III** by various functional group (FG) manipulations at the indicated positions. Structures **III**, in turn, could be obtained from **IV** by ester or carbamate bond formation. Finally, disconnection of the conjugates **IV** unravels possible precursors, sarcodictyin scaffold **V**, an appropriate linker **VI**, and resin **VII**.

Construction of Resins and Substrates for Attachment. In preparation for a solid phase synthesis of sarcodictyins A (**7**) and B (**8**) and libraries thereof, the functionalized resins **10**, **12**,[10,18,19c] and **14**[10,19c] (Scheme 1) were designed and constructed as shown in Scheme 1. Thus, hydroxymethyl polystyrene resin **9** was reacted with excess glutaric anhydride in the presence of Et_3N, followed by capping with pivaloyl chloride under the same conditions, to afford resin **10** in >90% overall yield. On the other hand, reaction of Merrifield resin **11** with excess of the monosodium alkoxide of 1,4-butanediol resulted in the formation of resin **12** in 99% yield. Iodination of the latter (**12**) with I_2−Ph_3P−imidazole then furnished iodide **13** (>95% yield) which was converted to its phosphonium salt by treatment with Ph_3P at 100 °C (95% yield) and hence to phosphorane **14** (>90% yield) by the action of LiHMDS (for abbreviations, see legends in schemes). These resins were then ready for coupling with suitable sarcodictyin scaffolds such as **16**−**18** and **20** (Scheme 2). The latter compounds were prepared from the previously synthesized intermediate **15**[16] as shown in Scheme 2. Thus, coupling of **15** with ethylene glycol or 1,4-butanediol in the presence of PPTS resulted in the formation of compounds **16** (91%) and **17** (94%), respectively. On the other hand, acetylation of **15** furnished **18** (96%) whose reaction with 1,6-hexanediol in the presence of PPTS led to **19** (92%). Oxidation of **19** with Dess−Martin reagent[20] gave the desired aldehyde **20** in 96% yield.

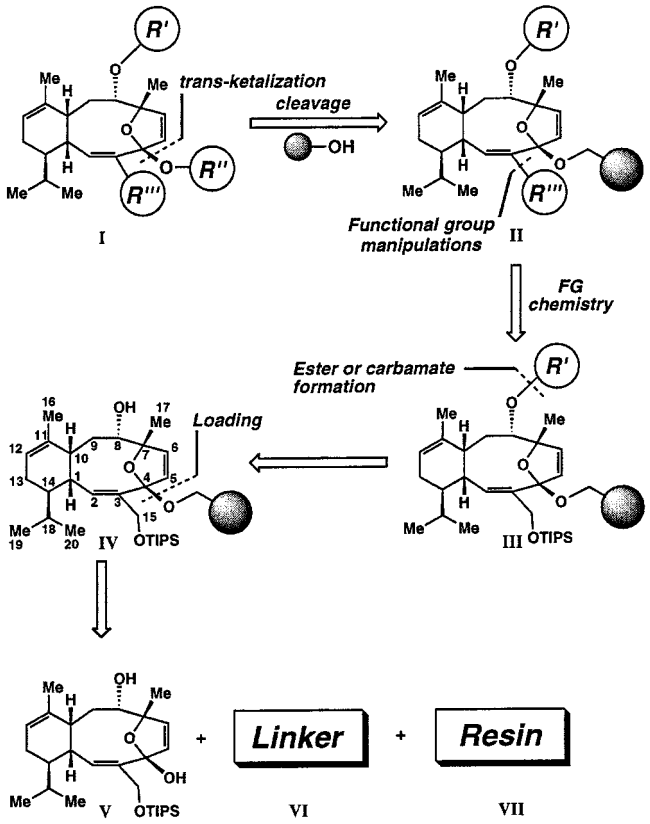

Figure 2. Retrosynthetic analysis of a sarcodictyin library (**I**).

Loading of Sarcodictyin Scaffolds onto the Solid Support. The reaction of sarcodictyin derivatives **16** and **17** with excess functionalized resin **10** in the presence of Et_3N and 4-DMAP

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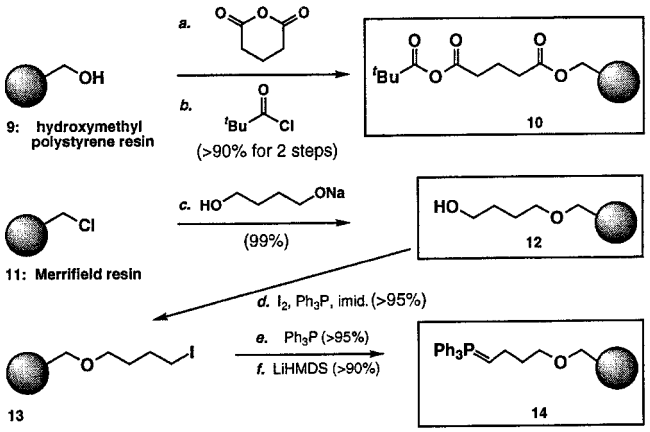
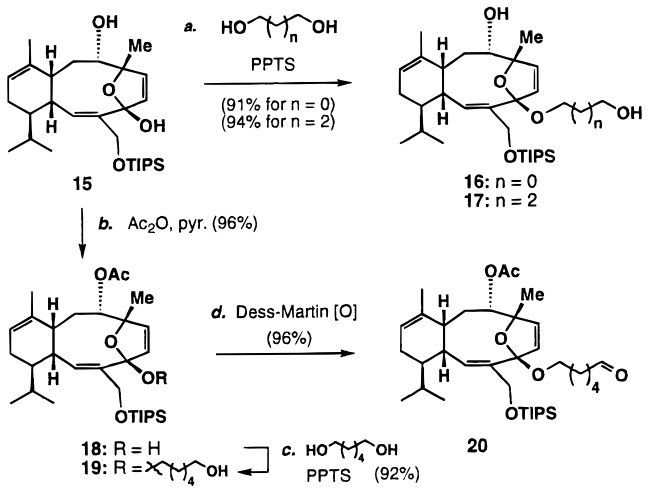
Scheme 1. Synthesis of Resins **10**, **12**, and **14** for the Loading of the Sarcodictyin Core on Solid Phase[a]



[a] Reagents and conditions: (a) glutaric anhydride (4.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 8 h; (b) ^{t}BuCOCl (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25 °C, 6 h, >90% for two steps; (c) 1,4-butanediol (4.0 equiv), NaH (4.0 equiv), ^{n}BuNI (0.1 equiv), DMF, 25 °C, 15 h, 99%; (d) I_2 (4.0 equiv), Ph_3P (4.0 equiv), imidazole (4.0 equiv), CH_2Cl_2, 0 °C, 4 h, >95%; (e) Ph_3P (10.0 equiv), 100 °C, 15 h, >95%; (f) LiHMDS (1.3 equiv), THF, 25 °C, 2 h, >90%. LiHMDS = lithium bis(trimethylsilyl)amide; THF = tetrahydrofuran; ● = polystyrene.

Scheme 2. Synthesis of Tethered Sarcoictyin Cores **16**−**18** and **20**[a]



[a] Reagents and conditions: (a) PPTS (1.0 equiv), diol:CH_2Cl_2 (2:1), 25 °C, 2 h, 91% for 1,2-ethanediol, 94% for 1,4-butanediol; (b) Ac_2O (3.0 equiv), pyridine (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 96%; (c) PPTS (1.0 equiv), 1,6-hexanediol (10 equiv), CH_2Cl_2, 92%; (d) Dess−Martin periodinane (2.0 equiv), pyridine (5.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 2 h, 96%. PPTS = pyridinium *p*-toluenesulfonate.

led, unexpectedly, to conjugates **21** and **22**, respectively, in >95% yield. The surprising fact that derivatives **16** and **17** attached themselves to the resin via their secondary, rather than primary, hydroxyl groups was evident from the resistance of **21** and **22** to undergo cleavage under acidic conditions and the ease by which these scaffolds could be recovered under basic conditions. This led us to the investigate the resins **12** and **14**. Thus, conjugation of **18** to resin **12** was accomplished in the presence of PPTS to afford **23**, but only in 50% yield despite several attempts to drive the reaction to completion with dehydrating agents. In contrast, coupling of aldehyde **20** with resin **14**, followed by capping with acetaldehyde, proceeded smoothly to afford conjugate **24** in >95% yield, making this resin a more attractive starting point for further chemical studies.

Solid Phase Synthesis of Sarcodictyins A and B. With resins **23** and **24** in hand, we proceeded to investigate their use in the synthesis of a sarcodictyin library. As a prelude to a library construction, and in order to develop the chemistry required for the operation, we first targeted the naturally occurring sarcodictyins A (**7**) and B (**8**). As demonstrated in Scheme 4, both resins performed equally well. Thus, NaOMe-induced deacetylation of **23** or **24** led smoothly to **25** (>95%) which coupled with mixed anhydride **26**[12,13,15−17] in the presence of Et_3N and 4-DMAP to afford conjugate **27** in ca. 90% yield. Desilylation of **27** (>95%), followed by Dess−Martin oxidation[20] (>95%), led efficiently to aldehyde **28**. Further oxidation of **28** with $NaClO_2$ (>95%) and esterification of the resulting carboxylic acid with MeOH or EtOH in the presence of DCC furnished, in ca. 90% yield, sarcodictyin A and B conjugates **29** and **30** respectively. Finally, generation of the natural substances (**7** and **8**) from the corresponding resins was achieved by exposure to CSA in CH_2Cl_2:H_2O (2:1). The overall yield of sarcodictyin A (**7**) was ca. 51% from **24** or 44% from **23** and of sarcodictyin B (**8**) was 48% from **24** or 42% from **23**. The spectroscopic properties (^{1}H, ^{13}C NMR, HRMS, α_D, IR) of **7** and **8** were identical to those exhibited by authentic samples previously obtained in these laboratories by a solution total synthesis.[16]

Construction of a Sarcodictyin Combinatorial Library. The sarcodictyin library shown in Table 1 was constructed by a combination of solid phase (Scheme 5) and solution (Scheme 6) methods. For the solid-phase chemistry, resin **24** was used because of its excellent profile in terms of formation, efficiency, and reactivity performance. Both parallel and combinatorial techniques were applied, the latter utilizing Radio frequency Encoded Combinatorial (REC) chemistry.[19]

Thus, individual flasks with resin **25** or IRORI Microkans[21] containing resin **25** were utilized to carry out the chemistry summarized in Scheme 5. Thus, **25** (derived by deacetylation of **24**) was reacted with LG-R_1 (acid anhydride, acid chloride, carboxylic acid, or isocyanate) under the appropriate coupling conditions to afford a series of esters and cabamates (90−95%) which were deprotected with TBAF, leading to hydroxy esters **31** (>95%). A portion of the reactant (resin or Microkans, **31**) was treated with LG-R_2 (acid anhydride, acid chloride, or isocyanate) under appropriate coupling conditions to afford, after PPTS-induced cleavage in the presence of HO−R_3 (60−90%), a series of sarcodictyins **33** via conjugates **32**.

A second portion of the reactant **31** was subjected to Dess−Martin oxidation to afford aldehyde resin **34** in >95% yield. Further oxidation of **34** with $NaClO_2$ led to carboxylic acid resin **35** (>95%) which was subjected to coupling reactions with either alcohols [HO−R_4] under Mitsunobu conditions or amines [H_2N−R_4] under DCC/4-DMAP conditions. The resulting esters or amides (**36**) were then exposed to acid (CSA) cleavage conditions in HO−R_3, affording sublibrary **37** (60−90%).

A third portion of the reactant **31** was converted to azide **38** in >95% yield by the action of $(PhO)_2PON_3$, DEAD, and Ph_3P. Reduction of the azido group in **38** with Ph_3P−H_2O gave the corresponding amine (95%) which was coupled with LG-R_5 [anhydride or acid chloride] to afford the amide derivatives **39**. Compounds **40** were then released from the resins **39** by exposure to PPTS in HO−R_3 (60−90%). Each library member was obtained in ca. 1−5 mg scale and was purified by silica gel chromatography (flash column or thin layer) or HPLC. The rather wide range in yield for the cleavage was attributed to

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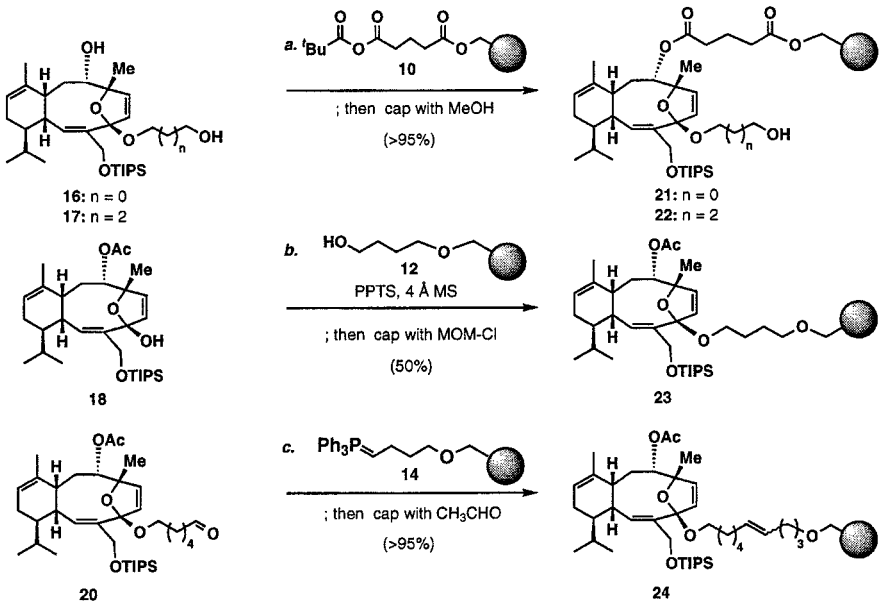
Scheme 3. Loading of Sarcodictyin Cores to Solid Supports[a]



[a] Reagents and conditions: (a) **10** (5.0 equiv), Et_3N (10.0 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, 25 °C, 8 h, >95%; then MeOH (20 equiv); (b) **12** (10 equiv), PPTS (1.0 equiv), 4 Å MS, CH_2Cl_2, 25 °C, 48 h, 50%; then MOM-Cl (20 equiv), $^iPr_2NEt$ (20 equiv), DMF, 25 °C, 24 h; (c) **14** (5.0 equiv), THF, −78 → 25 °C, 4 h, >95%; then CH_3CHO (20 equiv). 4-DMAP = 4-(dimethylamino)pyridine; PPTS = pyridinium *p*-toluenesulfonate, MOM-Cl = methoxymethyl chloride; DMF = dimethylformamide; THF = tetrahydrofuran; ● = polystyrene.

kinetic reasons and/or instability of the individual products to prolonged exposure to acidic conditions.

Due to the low yields obtained for the DCC-coupled products on solid phase, a number of sarcodictyin analogues were prepared by conventional solution methods. Specifically, sarcodictyins **42**−**54** were synthesized as outlined in Scheme 6. Thus, a number of ester side chains were introduced at C-8 and the appendage at C-4 was modified to include CH_2OH, CH_2-OAc, and CH_2F. Thus, DCC/4-DMAP-assisted coupling of **41**[16] with carboxylic acids **Ar-I**, **Ar-II**, and **Ar-III** (derived from the corresponding known pyridine, thiazole,[22] and oxazole[23] aldehydes by a Wittig olefination−saponification sequence in excellent yields) gave, after TBAF removal of the silyl protecting group, esters **42** (73%), **43** (61%), and **44** (79%), respectively. Dess−Martin oxidation[20] of these hydroxy esters led to aldehydes **45** (44%), **46** (40%), and **47** (84%), respectively. Further oxidation of **45**, **46**, and **47** with $NaClO_2$ and treatment of the resulting carboxylic acids with CH_2N_2 or CH_3CHN_2 led to the formation of sarcodictyins **48** (43%), **49** (71%), and **50** (87%), respectively. The fluorosarcodictyin **52**[17] was generated from the previously synthesized compound **51**[17] by the action of DAST (99%), whereas acetates **53**[17] and **54** were prepared from **51** by sequential treatment with Ac_2O/Et_3N/4-DMAP and CSA in CH_2Cl_2:H_2O as indicated in Scheme 6.

Biological Evaluation of Sarcodictyins. The synthesized sarcodictyin library (shown in Table 1) was screened for induction of tubulin polymerization using the filtration colorimetric assay and 100 μM compound at 37 °C (results are listed in Table 1).[8b] These investigations were then followed by cytotoxicity studies with ovarian cancer cells (1A9) including two Taxol-resistant lines (1A9PTX10 and 1A9PTX22).[24] Experiments showing IC_{50} values less than 2000 nM in any of the tested cell lines are tabulated in Table 2. The data reveal a number of important structure−activity relationships (SARs). Thus, compounds **60**, **73**−**75**, and **85** exhibited superior tubulin polymerization properties to those of either sarcodictyins A (**7**) or B (**8**). In the cytotoxicity studies compounds **60**, **61**, **63**, **66**−**70**, **73**, **76**, **85**, and **92** exhibited potencies comparable to or higher than those of the natural substances (**7** and **8**). Particularly striking were the cytotoxicities of compounds **60**, **61**, **67**, **68**, **73**, **76**, **85**, and **92** against the Taxol-resistant tumor cell lines. Interestingly, the tubulin polymerization potencies of some of these compounds were not always in line with their cytotoxicity effects (e.g. compounds **61** and **70**). These observations suggest an additional mechanism of action for these compounds such as DNA alkylation.[17]

The importance of the C-8 ester side chain became apparent by a number of substitutions. Thus, replacing the natural urocanic acid side chain with acetate (compound **107**, Table 1) or phenyl carbamate (compound **101**, Table 1) resulted in complete loss of activity. Likewise, substitution of the heterocycle with a phenyl group while maintaining the α,β-unsaturated portion of the ester side chain leads to only negligible biological activity (compound **99**, Table 1). Even the more subtle substitution of the imidazole-derived natural substituent for a pyridine (compound **48**, Tables 1 and 2), a thiazole (compound **49**, Tables 1 and 2), or an oxazole (compound **50**, Tables 1 and 2) moiety led to considerable loss of activity, thereby suggesting a role for both nitrogen atoms of the natural products in their mechanism of action. In contrast, modifications at the C-4 ketal center appear more tolerable for biological activity. Thus, replacement of the OH group of the natural products with an OMe moiety resulted in enhanced biological activity against the Taxol-resistant cell lines (compounds **60** and **61**, Tables 1

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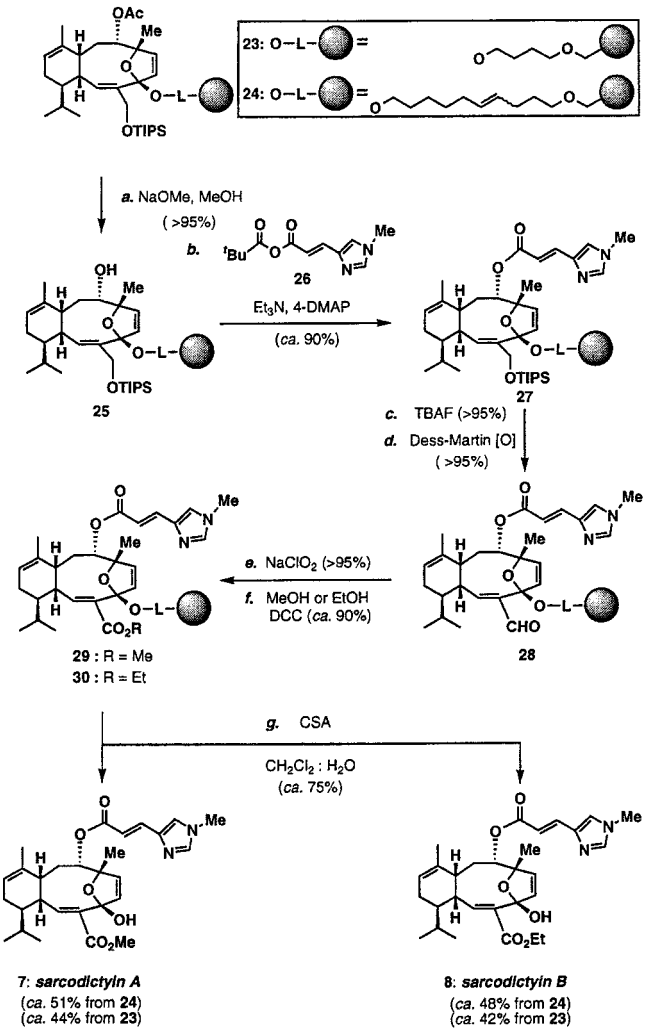
(25) Present work.

Scheme 4. Solid Phase Synthesis of Sarcodictyins A (**7**) and B (**8**)[a]



[a] Reagents and conditions: (a) NaOMe (5.0 equiv), MeOH:THF (1:3), 25 °C, 12 h, >95%; (b) **26** (5.0 equiv), Et_3N (10 equiv), 4-DMAP (2.0 equiv), CH_2Cl_2, 25 °C, 48 h, *ca.* 90%; (c) TBAF (10 equiv), THF, 25 °C, 8 h, >95%; (d) Dess−Martin periodinane (5.0 equiv), $NaHCO_3$ (15 equiv), pyridine (15 equiv), CH_2Cl_2, 25 °C, 2 h, 95%; (e) $NaClO_2$ (12 equiv), NaH_2PO_4 (12 equiv), 2-methyl-2-butene (50 equiv), THF−BuOH:H_2O (5:5:1) 25 °C, 48 h, >95%; (f) MeOH (10 equiv), DCC (10 equiv), 4-DMAP (5.0 equiv), DMF, 25 °C, 48 h, *ca.* 90%; (g) CSA (3.0 equiv), CH_2Cl_2:H_2O (2:1), 25 °C, 40 h, *ca.* 75%. Overall yield for sarcodictyin A: *ca.* 51% from **24** and *ca.* 44% from **23**. Overall yield of sarcodictyin B: *ca.* 48% from 24 and *ca.* 42% from **23**. 4-DMAP = 4-(dimethylamino)pyridine; TBAF = tetra-*n*-butylammonium fluoride; DCC = dicyclohexylcarbodiimide; THF = tetrahydrofuran; ● = polystyrene; CSA = camphorsulfonic acid.

and 2), whereas substitution with O^nPr or OCH_2CF_3 resulted in an overall decrease of cytotoxicity (compounds **74** and **84**, Tables 1 and 2). The C-15 reduced compound and derivatives thereof (e.g. compounds **51**−**53** and **55**−**59**, Tables 1 and 2) failed to exhibit strong tubulin polymerization or cytotoxicity properties, which is rather intriguing, given the potent biological actions of eleutherobin (**4**) whose C-15 position is reduced and glycosylated.

Interestingly, the C-15 dimethyl acetal (compound **73**, Tables 1 and 2) displayed biological activities comparable to those of the natural products (**7** and **8**, Tables 1 and 2), thus demonstrating that ester functionality is not a requirement for activity. Modification of the alcohol component of the C-3 ester group resulted in significant modulation of the biological actions of these compounds as compared to the natural products. Thus, substitution of the methyl (compound **60**, Tables 1 and 2) with an ethyl (compound **61**, Tables 1and 2), *n*-propyl (compound **68**, Tables 1 and 2), or allyl group (compound **70**, Tables 1 and 2) resulted in enhancement of the biological activity. A reversal of the trend was noted with bulkier substituents, such as *n*-butyl (compound **63**, Tables 1 and 2) or isopentyl (compound **71**, Tables 1 and 2). Interestingly, however, the bulky moieties of anthracenyl (compound **92**, Tables 1 and 2), benzyloxyethyl (compound **69**, Tables 1 and 2), and 4-butylphenyl (compound **66**, Tables 1 and 2) exhibited cytotoxicity comparable to, or better than, the natural products (even though their tubulin polymerization potencies were modest).

Figure 3 summarizes the SARs so far obtained within the sarcodictyin family of compounds.

Experimental Section

General Information. See the Supporting Information for general techniques. Substituted polystyrene resins (100−200 mesh, 1% DVB) were purchased from Novabiochem. All equipment utilized for the REC microchemistry is commercially available and can be purchased from IRORI Quantum Microchemistry, La Jolla, CA. The REC chemistry was carried out according to the recommendations provided by the manufacturer. All reactions carried out on solid phase were monitored by TLC analysis of the product obtained upon acidic cleavage from the resin. Unless otherwise stated, yields of solid phase reactions refer to the estimated conversion of the reaction precursor based on TLC analysis. Full experimental data are presented for compounds which were previously synthesized in solution and thus were fully characterized. All compounds obtained from solid phase chemistry, and which were biologically tested, were characterized by ^1H NMR spectroscopy and mass spectroscopy (see below and Supporting Information for data).

Synthesis of Mixed Anhydride Resin 10. A suspension of hydroxymethyl polystyrene resin (5.00 g, 4.00 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) at 25 °C was treated with Et_3N (2.79 mL, 20.0 mmol, 5.0 equiv) and glutaric anhydride (1.87 g, 16.0 mmol, 4.0 mmol). The reaction mixture was stirred gently (<300 rpm) over 8 h at 25 °C after which time it was poured into a fritted funnel, washed with CH_2Cl_2 (50 mL), MeOH (50 mL), CH_2Cl_2 (3 × 50 mL), and ether (2 × 200 mL), and dried to constant weight under high vacuum. The resulting resin was resuspended in CH_2Cl_2 (50 mL) at 25 °C and treated with Et_3N (2.79 mL, 20.0 mmol, 5.0 equiv) followed by pivaloyl chloride (1.44 g, 12.0 mmol, 3.0 equiv). The reaction mixture was stirred gently over 6 h at 25 °C after which time it was poured into a fritted funnel, washed with the following distilled solvents under an argon atmosphere: CH_2Cl_2 (50 mL), Et_2O (50 mL), CH_2Cl_2 (3 × 50 mL), and Et_2O (2 × 200 mL), and dried to constant weight under high vacuum (5.60 g). A two-step yield of >90% was determined by titration of the mixed anhydride resin with benzyl alcohol. Thus, in three separate experiments, the mixed anhydride resin (300 mg, 0.207 mmol, 1.0 equiv) was treated with benzyl alcohol (15.6 mg, 0.145 mmol, 0.7 equiv; 20.1 mg, 0.186 mmol, 0.9 equiv; and 24.5 mg, 0.227 mmol, 1.1 equiv) followed by Et_3N (43.2 μL, 0.310 mmol, 1.5 equiv) and 4-DMAP (5.0 mg, 0.041 mmol, 0.2 equiv). TLC analysis of the reaction mixtures revealed complete consumption of the benzyl alcohol for the experiments with 0.7 and 0.9 equiv of benzyl alcohol establishing the yield as at least 90%.

Synthesis of Hydroxy Resin 12. To a suspension of NaH (60% in mineral oil, 1.76 g, 44.0 mmol, 4.0 equiv) in DMF (100 mL) at 0 °C was added 1,4-butanediol (3.86 mL, 44.0 mmol, 4.0 equiv), and the reaction mixture was stirred for 1 h at 0 °C. Merrifield resin (10.0 g, 11.0 mmol, 1.0 equiv) was then added to the reaction mixture followed by tetra-*n*-butylammonium iodide (400 mg, 0.11 mmol, 0.1 equiv), and the mixture was stirred gently (<300 rpm) over 12 h. The resin was poured into a fritted funnel, washed with aq HCl (1 N, 200 mL), DMF (2 × 300 mL), MeOH (200 mL), CH_2Cl_2 (300 mL), MeOH (200 mL), CH_2Cl_2 (2 × 300 mL), and Et_2O (2 × 200 mL), and dried to constant weight under high vacuum (9.98 g, 99% yield). A sample of this resin was suspended in CH_2Cl_2 at 25 °C and treated with Fmoc-Cl (5.0 equiv)

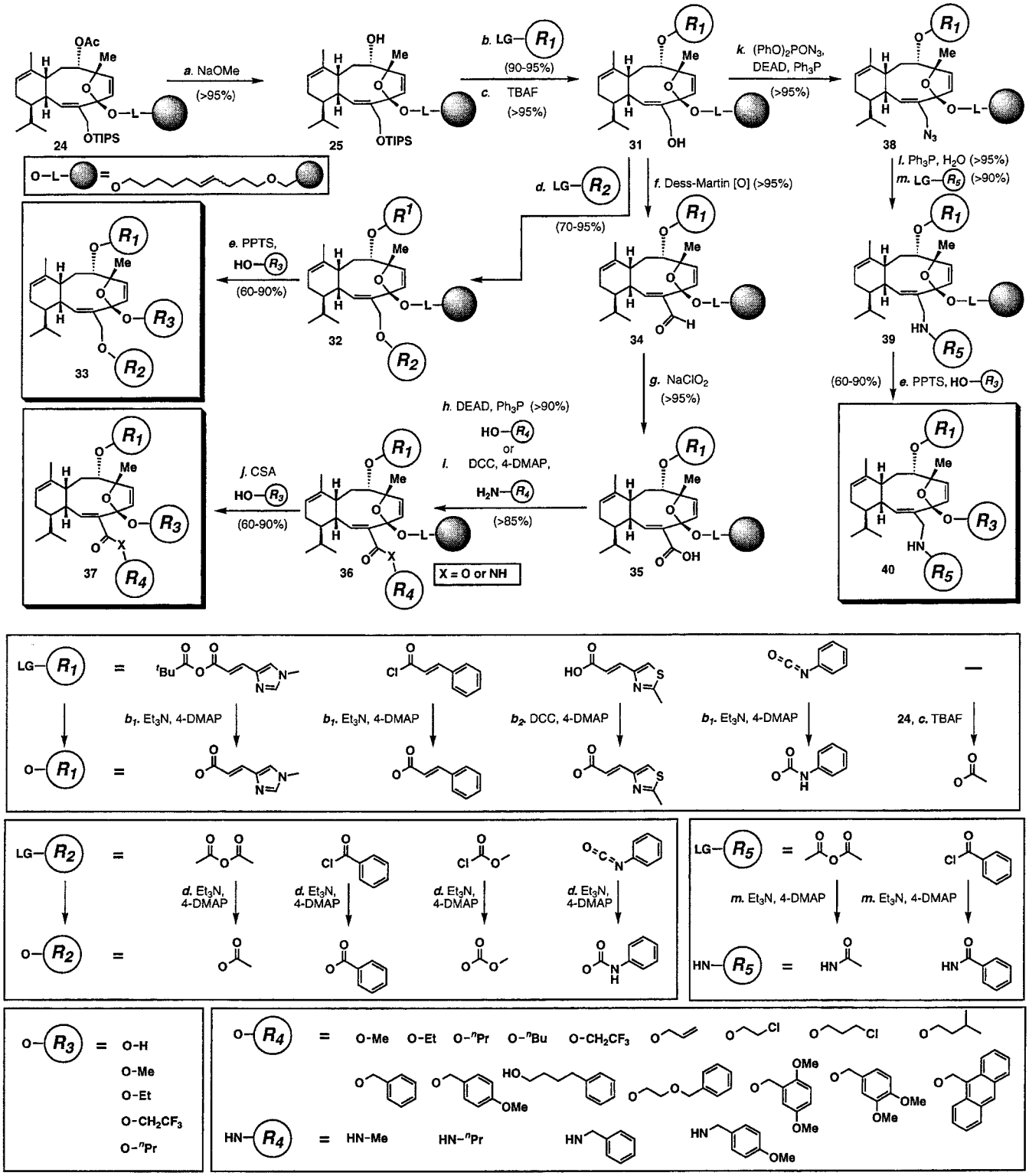
Table 1. Structures and Tubulin Polymerization Properties of Sarcodictyin Analogues

Ref.	Structure	% Tubulin polymerization [a]
15-17	**7:** R = Me	67
15-17	**8:** R = Et	71
16, 17	**51:** R = OH	37
17	**52:** R = F	27
17	**53:** R = OAc	37
17	**55:** R = OBz	12
17	**56:** R = N_3	24
17	**57:** R = OCONHPh	24
25	**58:** R = NHAc	30
25	**59:** R = NHBz	5
16, 17	**60:** R = Me	72
16, 17	**61:** R = Et	46
25	**62:** R = Bn	61
25	**63:** R = CH_2CH_2Cl	40
25	**64:** R = $(CH_2)_2CH_2Cl$	30
25	**65:** R = CH_2CF_3	31
25	**66:** R = $(CH_2)_3CH_2Ph$	38
25	**67:** R = ^{n}Bu	52
25	**68:** R = ^{n}Pr	69
25	**69:** R = CH_2CH_2OBn	54
25	**70:** R = $CH_2CH{=}CH_2$	51
25	**71:** R = $(CH_2)_2CH(CH_3)_2$	10
16	**72:** R = CHO	4
25	**73:** R = $CH(OMe)_2$	74
17	**74**	79
25	**75:** R = NHBn	75
25	**76:** R = NHMe	52
	77: R = NH^{n}Pr	15
25	**78:** R = OH	2
25	**54:** R = OAc	34
25	**79:** R = $(CH_2)_2CH_2Cl$	22
25	**80:** R = CH_2CH_2Cl	21
25	**81:** R = ^{n}Bu	23
25	**82:** R = CH_2Ph	38
25	**83:** R = $(CH_2)_3CH_2Ph$	1
25	**84:** R = Pr	21
17	**85:** R = Me	85
25	**86:** R = CH_2CH_2OBn	28
25	**87:** R = $(CH_2)_2CH(CH_3)_2$	20
25	**88**	22
25	**89:** R = Me	26
25	**90:** R = Et	18
25	**91**	16
25	**92:** R = Me	48
25	**93:** R = Et	24
25	**94:** R = CO_2Bn	1
25	**95:** R = CONHMe	3
25	**96:** R = CONHBn	2
25	**97:** R = CH_2NHAc	6
25	**98:** R = CH_2NHBz	5
25	**99:** R = CO_2Me	6
25	**100:** R = *p*-MeOBnNH	3
25	**101:** R = CO_2Me	4
25	**102:** R = CONHMe	2
25	**103:** R = CONHBn	2
25	**104:** R = CO_2Bn	1
25	**105:** R = CH_2NHAc	1
25	**106:** R = CH_2NHBz	2
25	**48**	18
25	**43**	5
25	**49**	42
25	**50:** R = CO_2Et	4
25	**47:** R = CHO	9
25	**107:** R = CO_2Me	0
25	**108:** R = CH_2NHAc	4
25	**109:** R = CHO	3

[a] See legend of Table 2.

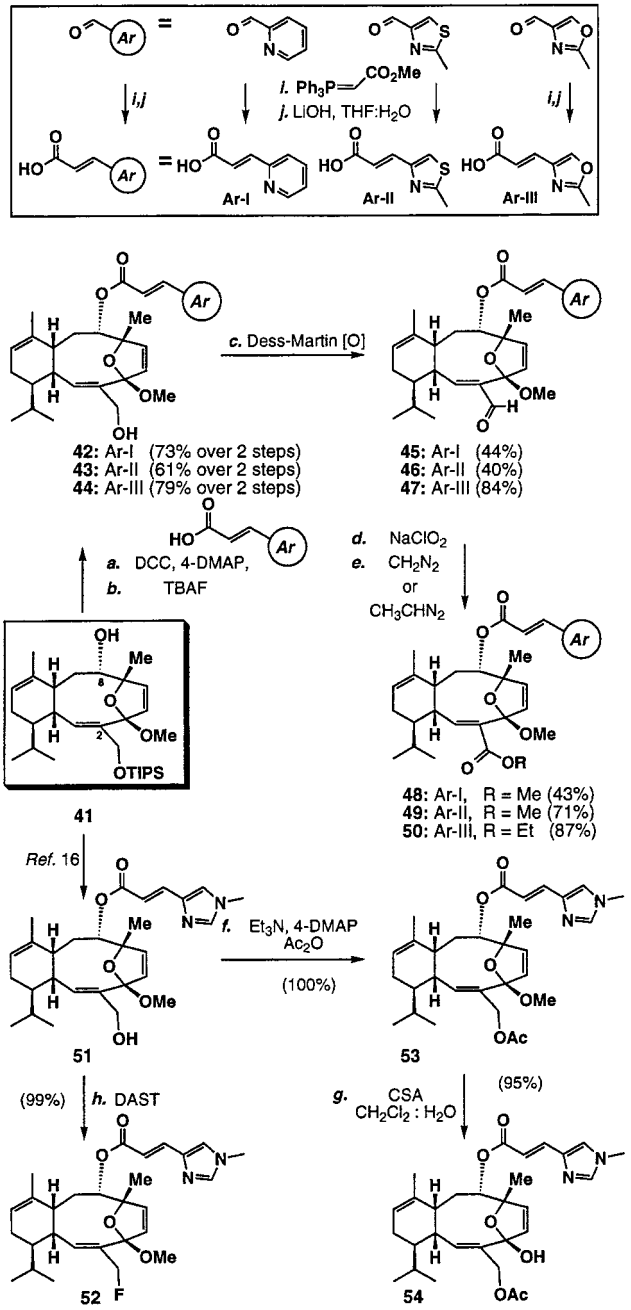
and pyridine (5.0 equiv) for 6 h. The reactive hydroxyl groups were photometrically quantified from the amount of Fmoc chromophore released upon treatment of the Fmoc-resin with 10% Et_3N in CH_2Cl_2 at 25 °C for 8 h.

Scheme 5. Synthesis of a Sarcodictyin Library on Solid Phase[a]



[a] Reagents and conditions: (a) NaOMe (5.0 equiv), MeOH:THF (1:3), 25 °C, 12 h, >95%; (b_1) LG-R_1 (5.0 equiv), Et_3N (10 equiv), 4-DMAP (2.0 equiv), DMF, 50 °C, 48 h, 90−95%; (b_2) LG-R_1 (10 equiv), DCC (10 equiv), 4-DMAP (2.0 equiv), DMF, 50 °C, 48 h, 90−95%; (c) TBAF (10 equiv), THF, 25 °C, 8 h, >95%; (d) LG-R_2 (10 equiv), Et_3N (10 equiv), 4-DMAP (2.0 equiv), CH_2Cl_2, 25 °C, 20 h, 70−95%; (e) PPTS (3.0 equiv), MeOH, 25 °C, 24 h, 60−90%; (f) Dess−Martin periodinane (5.0 equiv), $NaHCO_3$ (15 equiv), pyridine (15 equiv), CH_2Cl_2, 25 °C, 2 h, 95%; (g) $NaClO_2$ (25 equiv), KH_2PO_4 (25 equiv), 2-methyl-2-butene (50 equiv), THF:^{t}BuOH:H_2O (5:5:1) 25 °C, 48 h, >95%; (h) HO-R_4 (10 equiv), DEAD (10 equiv), Ph_3P (10 equiv), THF, 0 → 25 °C, 12 h, >95%; (i) H_2N-R_4 (10 equiv), DCC (10 equiv), 4-DMAP (5 equiv), DMF, 25 °C, 20 h, >95%; (j) CSA (3.0 equiv), HO-R_3, 25 °C, 15 h, 60−90%; (k) $(PhO)_2PON_3$ (10 equiv), DEAD (10 equiv), Ph_3P (10 equiv), THF, 0 → 25 °C, 4 h, >95%; (l) Ph_3P (10 equiv), H_2O (30 equiv), THF, 25 °C, 8 h, >95%; (m) LG-R_5 (10 equiv), Et_3N (15 equiv), CH_2Cl_2, 25 °C, 10 h, >90%. LG = leaving group; 4-DMAP = 4-(dimethylamino)pyridine; TBAF = tetra-*n*-butylammonium fluoride; DEAD = diethyl azodicarboxylate; DCC = dicyclohexylcarbodiimide; THF = tetrahydrofuran; DMF = dimethylformamide; ● = polystyrene; CSA = camphorsulfonic acid; PPTS = pyridinium *p*-toluenesulfonate.

Scheme 6. Synthesis of Sarcodictyin Analogues **48**−**54** in solution[a]



[a] Reagents and conditions: (a) acid **Ar-I** or **Ar-II** or **Ar-III** (1.3 equiv), DCC (2.0 equiv), 4-DMAP (0.5 equiv), CH_2Cl_2, 25 °C, 36 h; (b) TBAF (2.0 equiv), THF, 25 °C, 1 h, 73% for **42** over two steps, 61% for **43** over two steps, 79% for **44** over two steps; (c) Dess−Martin periodinane (2.5 equiv), $NaHCO_3$ (*ca.* 10 equiv), CH_2Cl_2, 25 °C, 0.5 h, 44% for **45**, 40% for **46**, 84% for **47**; (d) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (3.0 equiv), 2-methyl-2-butene (50 equiv), THF:^{t}BuOH:H_2O (5:5:1), 0 °C, 2 h; (e) CH_2N_2 or CH_3CHN_2, 0 °C, 10 min, 43% for **48** over two steps, 71% for **49** over two steps, 87% for **50** over two steps; (f) Ac_2O (5.2 equiv), Et_3N (6.8 equiv), 4-DMAP (1.6 equiv), CH_2Cl_2, 25 °C, 2 h, 100%; (g) CSA (cat., 10% mol), CH_2Cl_2:H_2O (10:1), 25 °C, 72 h, 95%; (h) DAST (2.0 equiv), CH_2Cl_2, −78 °C, 3 h, 99%; (i) Ph_3PCHCO_2Me (1.5 equiv), benzene, 80 °C, 95−98%; (j) LiOH (3.0 equiv), THF:H_2O (1:1). 25 °C, 100%. DCC = dicyclohexylcarbodiimide; 4-DMAP = 4-(dimethylamino)pyridine; TBAF = tetra-*n*-butylammonium fluoride; THF = tetrahydrofuran; CSA = camphorsulfonic acid; DAST = diethylaminosulfur trifluoride.

Synthesis of Iodo Resin 13. A suspension of hydroxy resin **12** (9.00 g, 9.39 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at 0 °C was treated sequentially with imidazole (2.55 g, 37.6 mmol, 4.0 equiv), Ph_3P (9.85 g, 37.6 mmol, 4.0 equiv), and iodine (9.55 g, 37.6 mmol, 4.0 equiv). The reaction mixture was stirred gently at 0 °C for 4 h after which time it was poured into a fritted funnel, washed with CH_2Cl_2 (3 × 200 mL), MeOH (200 mL), CH_2Cl_2 (2 × 200 mL), and Et_2O (2 × 200

Table 2. Cytotoxicity Data of Sarcodictyins and Related Compounds

compd no.	% tubulin polymerization[a]	inhibition of carcinoma cell growth,[b] IC_{50} (nM) 1A9	1A9PTX10	1A9PTX22
1 Taxol	65	2	50	40
2 epothilone A	73	2	19	4
3 epothilone B	97	0.04	0.035	0.04
7 sarcodictyin A	67	240	140	360
8 sarcodictyin B	71	2	160	80
48	18	430	1800	>2000
49	42	300	244	180
50	4	>2000	800	385
51	37	800	>2000	>2000
52	27	1850	>2000	>2000
53	37	1050	>2000	1620
54	34	1400	>2000	>2000
56	47	>2000	>2000	1800
58	30	800	1600	1200
60	72	70	4	84
61	46	2	1	60
62	61	360	1210	540
63	40	95	85	100
64	30	200	350	290
66	38	110	90	120
67	52	25	35	31
68	69	3	4	5
69	54	80	91	85
70	51	9	12	10
72	4	600	400	600
73	74	30	45	60
74	47	>2000	>2000	1800
75	75	500	1400	700
76	52	45	65	60
85	85	110	13	160
86	28	110	400	440
87	20	500	1240	1000
88	22	1400	1300	1400
89	26	640	1300	900
92	48	110	90	130

[a] The tubulin polymerization measurements were performed at 37 °C as described elsewhere[8b,19c] except for adjustments in drug concentration (100 μM) and incubation time (90 min). [b] The cytotoxicity experiments were carried out as previously described.[19c,24]

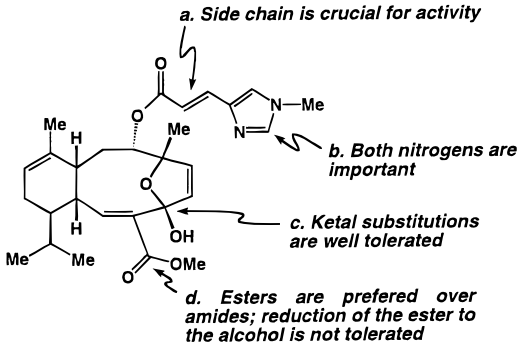


Figure 3. Structure activity relationships (SARs) of sarcodictyins: (a) replacement of side chain with acetate, phenyl carbamate, or cynamoyl ester is not tolerated; (b) replacement of the substituted imidazole heterocycle by a pyridine, thiazole, or oxazole led to reduced activity; (c) methyl and ethyl ketals are well tolerated, whereas propyl or trifluoroethyl ketals are not; (d) esters are more active than the corresponding amides; substitution of the ester group is well tolerated; reduction of the ester to the alcohol and derivatives thereof are not tolerated (except for the eleutherobin **4**).

mL), and dried to constant weight under high vacuum (9.95 g, >95% yield). Subjection of this resin to the Fmoc assay described in the synthesis of **12** indicated complete consumption of the alcohol.

Synthesis of Phosphorane Resin 14. A mixture of iodide resin **13** (5.00 g, 4.45 mmol, 1.0 equiv) and Ph_3P (11.7 g, 44.5 mmol, 10 equiv) in DMF (30 mL) was gently stirred at 100 °C for 15 h after which time it was poured into a fritted funnel, washed with warm (100 °C) DMF (3 × 200 mL), CH_2Cl_2 (2 × 200 mL), and Et_2O (3 × 300 mL) and dried to a constant weight of 6.10 g (>95% yield based on mass gain). A portion of this resin (2.2 g, 1.57 mmol, 1.0 equiv) was resuspended in THF (15 mL) at 25 °C, LiHMDS (1.0 M in THF, 2.04 mL, 2.04 mmol, 1.3 equiv) was added, and the reaction was allowed to stir for 2 h at ambient temperature after which time the resin adopted a deep red color. The supernatant solvent was removed by cannulation, the resin was washed with THF (3 × 15 mL), and the resulting resin was used for the next step without any additional treatment (>90% yield). The yield was determined as follows. The ylide was quenched with benzaldehyde (5.0 equiv, 25 °C, 6 h), and the resulting resin was subjected to ozonolysis (CH_2Cl_2, −78 °C, 30 min) followed by a reductive workup (Me_2S). The quantity of benzaldehyde recovered was quantified by HPLC absorption calibrated with an authentic benzaldehyde sample.

Acetate 18. A solution of hydroxy compound **15** (0.404 g, 0.806 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 25 °C was treated with pyridine (0.322 g, 4.03 mmol, 5.0 equiv) and Ac_2O (0.246 g, 2.42 mmol, 3.0 equiv). The reaction mixture was stirred for 1 h at 25 °C after which time TLC analysis indicated complete reaction. The reaction mixture was poured into Et_2O (150 mL), washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography (silica gel, EtOAc−hexane, 1:3) to furnish pure acetate **18** (0.421 g, 96% yield). $R_f = 0.20$ (silica gel, EtOAc−hexane, 1:3); $[\alpha]^{25}_D$ +47.8 (c = 2.32, $CHCl_3$); FT-IR (neat) ν_{max} 2942, 2866, 2363, 2334, 1739, 1720, 1459, 1364 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.11 (d, J = 7.5 Hz, 1 H), 6.03 (d, J = 7.5 Hz, 1 H), 5.43 (d, J = 11.5 Hz, 1 H), 5.23 (bs, 1 H), 5.07 (s, 1 H), 4.66 (d, J = 9.0 Hz, 1 H), 4.37 (d, J = 9.0 Hz, 1 H), 4.06 (d, J = 9.5 Hz, 1 H), 3.99 (m, 1 H), 2.55 (m, 1 H), 2.27 (m, 1 H), 2.05 (s, 3 H), 1.99 (m, 1 H), 1.60−1.49 (m, 3 H), 1.51 (s, 3 H), 1.45 (s, 3 H), 1.36−1.25 (m, 1 H), 1.04 (s, 21 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 135.6, 134.2, 134.1, 132.7, 132.0, 121.3, 112.5, 89.9, 81.5, 68.5, 42.2, 38.5, 33.9, 31.5, 28.9, 25.5, 24.4, 22.2, 22.0, 21.3, 20.5, 17.9, 11.7; HRMS (FAB) calcd for $C_{32}H_{52}O_5Si$ ($M + Cs^+$): 665.2638, found 665.2615.

Hydroxy Ketal 19. A solution of ketal **18** (0.421 g, 0.774 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 25 °C was treated with 1,6-hexanediol (0.913 g, 7.74 mmol, 10 equiv) and PPTS (0.194 g, 0.774 mmol, 1.0 equiv). The reaction mixture was stirred for 4 h at 25 °C after which time TLC analysis indicated complete reaction. The reaction mixture was loaded onto a short silica column and eluted with EtOAc−hexanes (1:2) to give pure hydroxy ketal **19** (0.450 g, 92% yield). $R_f = 0.15$ (silica gel, EtOAc−hexanes, 1:2); $[\alpha]^{25}_D$ +36.5 (c = 1.0, C_6H_6); FT-IR (neat) ν_{max} 3427, 2936, 2864, 1742, 1465, 1368 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.15 (d, J = 6.0 Hz, 1 H), 6.09 (d, J = 9.0 Hz, 1 H), 6.05 (d, J = 6.0 Hz, 1 H), 5.43 (bs, 1 H), 5.08 (dd, J = 9.0, 1.0 Hz, 1 H), 4.54 (d, J = 13.0 Hz, 1 H), 4.49 (d, J = 13.0 Hz, 1 H), 4.37 (m, 1 H), 3.55 (m, 2 H), 3.39 (t, 2 H), 2.90 (m, 1 H), 2.58 (m, 1 H), 2.06 (m, 1 H), 1.91−1.86 (m, 2 H), 1.73 (s, 3 H), 1.69 (s, 3 H), 1.67−1.53 (m, 3 H), 1.52 (s, 3 H), 1.42−1.36 (m, 6 H), 1.28−1.25 (m, 1 H), 1.18 (s, 21 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.0, 137.0, 134.3, 133.1, 131.5, 130.2, 121.6, 116.0, 89.6, 81.9, 65.2, 62.3, 61.9, 42.9, 39.0, 33.8, 32.9, 32.0, 30.0, 29.11, 26.3, 25.6, 24.9, 24.5, 22.1, 22.0, 20.5, 20.4, 18.0, 12.1; HRMS (FAB) calcd for $C_{37}H_{64}O_6Si$ ($M + Cs^+$): 765.3527, found 765.3548.

Aldehyde Ketal 20. To a solution of Dess−Martin periodinane (0.451 g, 1.07 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL) at 25 °C were added pyridine (0.280 g, 3.56 mmol, 5.0 equiv) and $NaHCO_3$ (0.598 g, 7.12 mmol, 10 equiv). The mixture was stirred for 15 min at ambient temperature and then cooled to 0 °C. Alcohol **19** (0.450 g, 0.712 mmol, 1.0 equiv) was added as a solution in CH_2Cl_2 (10 mL). The reaction mixture was removed from the cold bath after 15 min and stirred for an additional 2 h at 25 °C after which time TLC analysis indicated complete reaction. The crude mixture was loaded onto a short silica gel column and eluted with EtOAc−hexane (1:3) to yield pure product **20** (0.430 g, 96% yield). $R_f = 0.18$ (silica gel, EtOAc−hexane, 1:3); $[\alpha]^{25}_D$ +29.0 (c = 1.0, C_6H_6); FT-IR (neat) ν_{max} 2940, 2865, 1939, 1458, 1369 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.33 (t, J = 1.5 Hz, 1 H), 6.13 (d, J = 6.0 Hz, 1 H), 6.08 (d, J = 9.0 Hz, 1 H), 6.01 (d, J = 6.0 Hz, 1 H), 5.41 (bs, 1 H), 5.08 (d, J = 6.0 Hz, 1 H), 4.53 (d, J = 13.0 Hz, 1 H), 4.48 (d, J = 13.0 Hz, 1 H), 4.35 (m, 1 H), 3.55 (m, 2 H), 2.90 (m, 1 H), 2.59 (m, 1 H), 2.31 (m, 1 H), 1.92−1.56 (m, 2 H), 1.82 (dd, J = 12.5, 1.5 Hz, 2 H), 1.73 (s, 3 H), 1.70 (s, 3 H), 1.63 (m, 1 H), 1.51 (s, 3 H), 1.50−1.20 (m, 9 H), 1.16 (s, 21 H), 1.08 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.2, 168.7, 137.2, 134.1, 133.2, 131.3, 130.2, 121.6, 116.0, 89.6, 81.9, 65.6, 65.2, 61.6, 43.5, 42.9, 39.0, 33.8, 31.9, 29.7, 29.1, 25.9, 24.9, 24.4, 22.1, 22.0, 21.7, 20.5, 20.4, 18.0, 15.3, 12.1; HRMS (FAB) calcd for $C_{37}H_{62}O_6Si$ ($M + Cs^+$): 763.3370, found 763.3390.

Attachment of Sarcodictyin Core 18 on Resin 12 by Transketalization. To a suspension of resin **12** (0.563 g, 0.54 mmol, 10 equiv) in CH_2Cl_2 (3 mL) containing flamed-dried 4 Å molecular sieves (0.30 g) at 25 °C was added a solution of ketal **18** (28 mg, 0.054 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) followed by PPTS (13 mg, 0.054 mmol, 1.0 equiv). The reaction mixture was agitated gently on a wrist shaker at ambient temperature for 48 h and then filtered and washed with anhydrous CH_2Cl_2 (2 × 5 mL). The unreacted starting material in the combined filtrates was purified to recover 14 mg of pure **18** (50% yield based on recovered starting material). The excess alcohol on the resin was capped by resuspending the resin in DMF (3 mL) followed by addition of MOM-Cl (88 mg, 0.054 mmol, 20 equiv) and $^iPr_2NEt$ (126 mg, 1.1 mmol, 20 equiv) for 24 h at ambient temperature. The resin was filtered in a fritted funnel, washed with CH_2Cl_2 (3 × 50 mL) containing 1% Et_3N, and Et_2O (2 × 50 mL), and dried under high vacuum to a constant weight of 0.56 g (0.039 mmol/g loading of the sarcodictyin core).

Attachment of Sarcodictyin Core 20 on Resin 14 by a Wittig Reaction. To a suspension of ylide **14** (0.75 mmol, 7.0 equiv) in THF (2 mL) cooled to −78 °C was added a solution of aldehyde **20** (67.6 mg, 0.107 mmol, 1.0 equiv) in THF (5 mL). The reaction mixture was allowed to warm slowly to ambient temperature over 2 h and was stirred for an additional 2 h at 25 °C, after which time TLC analysis indicated complete consumption of the aldehyde (>95% yield). The excess ylide was quenched by the addition of acetaldehyde (99 mg, 2.25 mmol, 21 equiv), and the resin was collected on a fritted funnel, washed with THF (3 × 50 mL) containing 1% Et_3N, and Et_2O (2 × 50 mL), and dried under high vacuum to a constant weight of 836 mg (0.128 mmol/g loading of the sarcodictyin core). In a cleavage demonstration experiment, a sample of this resin (225 mg, 28.8 μmol, 1.0 equiv) was treated with PPTS (14.3 mg, 57.6 μmol, 2.0 equiv) in MeOH (0.5 mL) at 25 °C for 30 h to recover, after purification (silica gel, flash column chromatography), 14.2 mg of the corresponding methyl ketal (90% for two steps).

Hydrolysis of Acetate 24 and Formation of Polymer-Bound Alcohol 25. To a suspension of resin **24** (3.12 g, 0.40 mmol, 1.0 equiv) in THF (20 mL) was added NaOMe (0.5 M in MeOH, 4.0 mL, 2.0 mmol, 5.0 equiv). The reaction mixture was agitated on a wrist shaker for 12 h at ambient temperature. The resin was filtered and washed with MeOH containing 1% Et_3N (100 mL), CH_2Cl_2 containing 1% Et_3N (100 mL), and Et_2O (100 mL) and then dried under high vacuum. NMR analysis of the crude product obtained from the cleavage showed a single compound corresponding to the previously reported product **41** (Scheme 6) thereby establishing a yield of >95%. Although exact procedures for the sequence of reactions leading to sarcodictyins A (**7**) and B (**8**) are given only for resin **24**, similar procedures were followed for resin **23** and with similar results.

Attachment of the Urocanic Acid Side Chain and Synthesis of Resin 27. A suspension of hydroxy resin **25** (2.0 g, 0.256 mmol, 1.0 equiv) in DMF (6 mL) was treated with mixed anhydride **26** (0.302 g, 1.28 mmol, 5.0 equiv) in the presence of Et_3N (0.357 mL, 2.56 mmol, 10 equiv) and 4-DMAP (62 mg, 0.512 mmol, 2.0 equiv) for 24 h at 50 °C. The resin was filtered, washed with CH_2Cl_2 containing 1% Et_3N

(2 × 25 mL), Et_2O (25 mL), CH_2Cl_2 containing 1% Et_3N (2 × 25 mL), and Et_2O (3 × 20 mL), and then dried under high vacuum. TLC analysis after cleavage of the product from the resin by the action of PPTS (*ca.* 3 equiv) and MeOH also revealed the presence of 5−10% of a less polar byproduct presumed to be derived from impurities in reagent **26**. NMR analysis of the crude product obtained from the cleavage confirmed its identity[16] and led to an estimated yield of 90%.

Desilylation and Oxidation of Alcohol 27. Synthesis of Solid-Supported Aldehyde 28. A suspension of resin **27** (300 mg, 38.4 μmol, 1.0 equiv) in THF (1.5 mL) was treated with TBAF (1.0 M in THF, 384 μmol, 10 equiv) for 8 h at 25 °C. The resin was filtered, washed with THF containing 1% Et_3N (4 × 10 mL) and Et_2O (3 × 10 mL), and then dried under high vacuum. NMR analysis of the crude product so obtained confirmed its identity[16] and established a yield of >95% for the deprotection steps. The resin (250 mg, 32 μmol, 1.0 equiv) was resuspended in CH_2Cl_2 (1.0 mL) containing pyridine (12.8 mg, 160 μmol, 5.0 equiv) and treated with a preformed suspension of Dess−Martin periodinane (67.2 mg, 160 μmol, 5.0 equiv), $NaHCO_3$ (40.3 mg, 480 μmol, 15 equiv), and pyridine (25.6 mg, 64 μmol, 10 equiv) in CH_2Cl_2 (1.5 mL). The mixture mixture was allowed to react for 2 h at ambient temperature. The resin was then filtered, washed with CH_2Cl_2 (4 × 10 mL), H_2O (3 × 10 mL), MeOH (2 × 5 mL), CH_2Cl_2 (2 × 5 mL), and Et_2O (3 × 5 mL), and dried under high vacuum. The completion of the reaction, the identity of the resulting product, and the yield of the reaction (>95%) were established by TLC and NMR analysis after subjecting a sample the resin to cleavage with CSA (ca. 3 equiv) and MeOH.

Oxidation of Aldehyde 28 and Esterification of the Resulting Carboxylic Acid. Synthesis of Polymer-Bound Sarcodictyins A (29) and B (30). A mixture of resin **28** (220 mg, 28.2 μmol, 1.0 equiv), sodium chlorite (63.3 mg, 704 μmol, 25 equiv), KH_2PO_4 (83.7 mg, 704 μmol, 25 equiv), and isobutylene (2 M in THF, 1.40 mmol, 50 equiv) in THF:^{t}BuOH:H_2O (4:4:1) was allowed to react for 48 h at ambient temperature (>95% conversion). The resulting resin was filtered, washed with water (3 × 10 mL), MeOH (2 × 10 mL), 0.5 M PPTS in CH_2Cl_2 (3 × 10 mL), CH_2Cl_2 (2 × 10 mL), and Et_2O (2 × 10 mL), and then dried under high vacuum. The resin was then split into two portions (100 mg each, 12.8 μmol, 1.0 equiv) and each was treated with a solution of DMF (0.5 mL) containing DCC (26 mg, 128 μmol, 10 equiv) and 4-DMAP (7.7 mg, 64 μmol, 5.0 equiv). To the first portion of resin was added MeOH (4.0 mg, 128 μmol, 10 equiv), and to the second portion of resin was added EtOH (5.9 mg, 128 μmol, 10 equiv). The reaction vessels were agitated on a wrist shaker for 48 h after which time each resin was filtered, washed with CH_2Cl_2 (4 × 5 mL), MeOH (2 × 5 mL), CH_2Cl_2 (3 × 5 mL), and Et_2O (3 × 5 mL), and dried under high vaccum (>90% estimated yield).

Cleavage of Polymer-Bound Sarcodictyins A an B with CSA/H_2O. Synthesis of Sarcodictyins A (7) and B (8). A suspension of resin **29** (92 mg, 11.7 μmol, 1.0 equiv) or **30** (90 mg, 11.5 μmol, 1.0 equiv) in CH_2Cl_2/H_2O (2:1, 2.0 mL) at 25 °C was treated with CSA (8 mg, 35.1 μmol, 3.0 equiv) and stirred vigorously over the course of 40 h. The reaction mixture was then quenched with $NaHCO_3$ (9.8 mg, 117 μmol, 10 equiv) and filtered and the aqueous layer washed with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated, and the product was purified by PTLC (3% MeOH in CH_2Cl_2) to yield 3.0 mg of natural sarcodictyin A (**7**) (ca. 75% yield from **29**, ca. 51% overall yield from **24)** or 2.6 mg sarcodictyin B (**8**) (*ca.* 75% yield from **30**, *ca.* 44% overall yield from **24)**.

Reaction of Resin 25 with *trans*-Cinnamoyl Chloride. Toward the Synthesis of Cinnamoate Ester 31. To a suspension of resin **25** (600 mg, 0.077 mmol) in DMF (5.0 mL) were added cinnamoyl chloride (128 mg, 0.77 mmol, 10 equiv), Et_3N (0.215 mL, 1.54 mmol, 20 equiv), and 4-DMAP (46.5 mg, 0.385 mmol, 5.0 equiv), and the reaction mixture was heated at 50 °C for 12 h. The resin was then filtered, washed with CH_2Cl_2 containing 1% Et_3N (5 × 20 mL), and Et_2O (2 × 100 mL), and then dried under high vacuum(>95% estimated yield).

DCC-Mediated Esterification of Resin 25 with Thiazole Acid Side Chain Ar-II. Toward the Synthesis of Thiazole Ester 31. To a suspension of resin **25** (200 mg, 0.026 mmol) in DMF (3.0 mL) was added thiazole acid side chain **Ar-II** (Schemes 5 and 6) (48 mg, 0.26 mmol, 10 equiv), DCC (52 mg, 0.26 mmol, 10 equiv), and 4-DMAP (6.3 mg, 0.052 mmol, 2.0 equiv), and the reaction mixture was heated at 50 °C for 48 h. The resin was then filtered, washed with CH_2Cl_2 containing 1% Et_3N (5 × 20 mL), and Et_2O (2 × 100 mL), and then dried under high vacuum (90−95% estimated yield).

Reaction of Alcohol 25 with Phenyl Isocyanate. Toward the Synthesis of Phenyl Carbamate 31. To a suspension of resin **25** (500 mg, 0.064 mmol, 1.0 equiv) in DMF (4.0 mL) were added phenyl isocyanate (77 mg, 0.64 mmol, 10 equiv) and 4-DMAP (39 mg, 0.32 mmol, 5 equiv), and the reaction mixture was shaken on a wrist shaker for 10 h. The resin was filtered, washed with CH_2Cl_2 containing 1% Et_3N (3 × 15 mL), and Et_2O (2 × 15 mL), and then dried under high vacuum (>95% estimated yield).

General Desilylation Procedure. Synthesis of Hydroxy Resins 31. A suspension of the silylated resin (1.0 equiv) in THF was allowed to react with TBAF (10 equiv, 1.0 M in THF) at 25 °C for 6 h. The resin was then filtered, washed with THF containing 1% Et_3N, CH_2Cl_2 (containing 1% Et_3N), and Et_2O, and then dried under high vacuum (>95% estimated yield).

General Procedure for the Functionalization of Hydroxy Resins 31. Synthesis of Compounds 32. A suspension of resin **31** (1.0 equiv) in CH_2Cl_2 at 25 °C was treated with Et_3N (10 equiv), 4-DMAP (2.0 equiv), and acetic anhydride (10 equiv) or benzoyl chloride (10 equiv) or methyl chloroformate (10 equiv) or phenylisocyanate (10 equiv). After 15 h, the resin was filtered, washed with CH_2Cl_2 containing 1% Et_3N, and Et_2O, and then dried under high vacuum. The acylation, benzoylation, and formation of carbamate were found to proceed smoothly (>95%) whereas the carbonate formation proceeded in 70% yield along with the formation of two less polar unidentified byproducts.

General Procedure for the Dess−Martin Oxidation of Solid-Supported Hydroxy Resins 31. Synthesis of Aldehyde Resins 34. To a suspension of hydroxy resin **31** (1.0 equiv) in CH_2Cl_2 containing pyridine (5.0 equiv) was added a preformed suspension of Dess−Martin periodinane (5.0 equiv), $NaHCO_3$ (15 equiv), and pyridine (10 equiv) in CH_2Cl_2. The mixture was allowed to react for 2 h at ambient temperature. The resin was then filtered, washed with CH_2Cl_2, H_2O, MeOH, and Et_2O, and dried under high vacuum (>95% estimated yield).

General Procedure for the Sodium Chlorite Oxidation of Aldehyde Resins 34. Synthesis of Carboxylic Acids 35. A mixture of aldehyde resin **34** (1.0 equiv), sodium chlorite (25 equiv), KH_2PO_4 (25 equiv), and isobutylene (2 M in THF, 50 equiv) in THF:^{t}BuOH:H_2O (4:4:1) was allowed to react for 48 h at ambient temperature. The resulting resin was filtered, washed with water, MeOH, 0.5 M PPTS in CH_2Cl_2, CH_2Cl_2, and Et_2O, and dried under high vacuum (>95% estimated yield).

General Procedure for the DCC/4-DMAP-Mediated Formation of Ester or Amide Sarcodictyin Analogues 36. To a suspension of resin **35** (1.0 equiv) in DMF were added DCC (10 equiv), 4-DMAP (5.0 equiv), and an alcohol or an amine (10 equiv, amines were used as HCl or PPTS salts), and the reaction mixture was allowed to react for 20 h at ambient temperature. The resin was then filtered, washed with CH_2Cl_2, MeOH, and Et_2O, and dried under high vacuum (>85% estimated yield).

General Procedure for the Ph_3P/DEAD-Mediated Formation of Ester Sarcodictyin Analogues 36. A suspension of resin **35** (1.0 equiv) in THF containing Ph_3P (10 equiv) and an alcohol (10 equiv) was cooled to 0 °C. DEAD (10 equiv) was then added dropwise, and the reaction mixture was allowed to warm to 25 °C. After 12 h, the resin was filtered, washed with CH_2Cl_2 and Et_2O, and dried under high vacuum (>90% estimated yield).

General Procedure for the Formation of Azides 38 via a Mitsunobu Reaction. A suspension of resin **31** (1.0 equiv) in THF containing Ph_3P (10 equiv) and $(PhO)_2P(O)N_3$ (10 equiv) was cooled to 0 °C and treated with DEAD (10 equiv, dropwise addition). After completion of the addition, the reaction mixture was allowed to warm to 25 °C. After 4 h, the resin was filtered, washed with CH_2Cl_2 (containing 1% Et_3N) and Et_2O, and dried under high vacuum (>95% yield based on NMR analysis of crude product, see compound **56** in Supporting Information for spectroscopic data).

General Procedure for the Ph_3P/H_2O-Mediated Reduction of Azides 38. Toward the Syntheses of Amides 39. A suspension of resin **38** (1.0 equiv) in THF containing Ph_3P (10 equiv) and H_2O (50 equiv) was heated to 50 °C and stirred at that temperature for 8 h. The resin was then filtered, washed with CH_2Cl_2 containing 1% Et_3N and Et_2O, and dried under high vacuum (>95% estimated yield).

General Procedure for the Synthesis of Amides 39. A suspension of the resin-bound amines (1.0 equiv) in CH_2Cl_2 at 25 °C was treated with Et_3N (15 equiv) and acetic anhydride (10 equiv) or benzoyl chloride (10 equiv) for 10 h at ambient temperature. The resin was then filtered, washed with CH_2Cl_2 containing 1% Et_3N, and Et_2O, and dried under high vacuum (>90% estimated yield).

General Procedure for the Cleavage with PPTS/ROH. Synthesis of Sarcodictyin Analogues 33 and 40. A suspension of resins **32** or **39** (1.0 equiv) in ROH at 25 °C was treated with PPTS (3.0 equiv). After 15 h, the reaction was quenched with solid $NaHCO_3$ (10 equiv), filtered, and washed with CH_2Cl_2 and MeOH. The combined filtrates were concentrated, and the product was purified by PTLC (60−90%, see individual compounds in Supporting Information for exact overall yields).

General Procedure for the Cleavage with CSA/H_2O. Synthesis of Sarcodictyin Analogues 37. A suspension of resins **29** or **30** (1.0 equiv) in CH_2Cl_2/H_2O (2:1) at 25 °C was treated with CSA (3.0 equiv). After 40 h, the reaction was quenched with solid $NaHCO_3$ (10 equiv), filtered, and washed with CH_2Cl_2. The organic layer of the combined filtrates was collected, dried over $MgSO_4$, and concentrated, and the product was purified by PTLC (60−90%, see individual compounds in Supporting Information for exact overall yields).

General Procedure for the Transketalization with CSA/ ROH. Synthesis of Sarcodictyin Analogues 37. A suspension of resins **36** in ROH (0.5 mL) at 25 °C was treated with CSA (3.0 equiv). After 15 h, the resin was quenched with $NaHCO_3$ (10 equiv), filtered, and washed with CH_2Cl_2 and MeOH. The combined filtrates were concentrated, and the products were purified by PTLC (60−90%, see individual compounds in Supporting Information for exact overall yields).

Preparation of Pyridine Carboxylic Acid Ar-I. To a solution of 2-pyridinecarboxaldehyde (2.0 g, 18.7 mmol, 1.0 equiv) in benzene (37 mL) was added Ph_3PCHCO_2Me (9.36 g, 28.0 mmol, 1.5 equiv), and the reaction mixture was heated at reflux temperature for 2 h. After the end of the reaction was established (TLC), the solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography (silica gel, Et_2O−hexanes, 1:1, R_f = 0.26) furnishing the expected α,β-unsaturated methyl ester (2.9 g, 95% yield). The so prepared methyl ester (1.5 g, 9.2 mmol, 1.0 equiv) was treated in THF:H_2O (1:1, 30 mL) with $LiOH\cdot H_2O$ (1.16 g, 27.6 mmol, 3.0 equiv) at ambient temperature for 3 h after which time the end of the reaction was established (TLC). The reaction mixture was extracted with saturated aqueous $NaHCO_3$ (3 × 20 mL), and the combined aqueous extracts were acidified with 1 M HCl to pH 4 and further extracted with EtOAc (4 × 20 mL). Concentration of the combined organic solutions furnished, in quantitative yield, essentially pure carboxylic acid **Ar-I** (1.4 g, 100% yield). R_f = 0.35 (silica gel, EtOAc); mp 141−142 °C (EtOAc); FT-IR (neat) ν_{max} 3434, 3091, 1700, 1644, 1595, 1568, 1464 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.34 (d, J = 5.0 Hz, 1 H), 7.65 (dt, J = 8.0, 1.5 Hz, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 16.0 Hz, 1 H), 7.17 (m, 1 H), 6.63 (d, J = 16.0 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.5, 154.5, 150.8, 143.6, 138.9, 125.7, 125.2, 125.2; HRMS (FAB) calcd for $C_8H_7NO_2$ (MH^+): 150.0555, found 150.0551.

Preparation of Thiazole Carboxylic Acid Ar-II. According to the procedure described for the synthesis of pyridine derivative **Ar-I**, the corresponding thiazole aldehyde (2.0 g, 16 mmol, 1.0 equiv) was reacted with Ph_3PCHCO_2Me (8.0 g, 24.0 mmol, 1.5 equiv) in benzene (32 mL) to yield after chromatographic purification (silica gel, Et_2O−hexanes, 3:1), the expected α,β-unsaturated thiazole methyl ester (2.8 g, 97% yield). R_f = 0.42 (silica gel, Et_2O−hexanes, 3:1); FT-IR (neat) ν_{max} 3095, 3048, 1707, 1631, 1431, 1300 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 15.5 Hz, 1 H), 7.26 (s, 1H), 6.70 (d, J = 15.5 Hz, 1 H), 3.77 (s, 3 H), 2.71 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 166.8, 151.3, 136.4, 121.5, 119.8, 51.6, 19.3; HRMS (FAB) calcd for $C_8H_9NO_2S$ (MH^+): 184.0432, found 184.0437.

The so obtained methyl ester (0.50 g, 2.73 mmol, 1.0 equiv) was saponified by the action of $LiOH\cdot H_2O$ (0.33 g, 8.19 mmol, 3.0 equiv) in THF:H_2O (1:1, 7 mL) as described for pyridine acid **Ar-I** above, to produce thiazole acid **Ar-II** (0.46 g, 100% yield) as a white crystaline solid. R_f = 0.32 (silica gel, EtOAc); mp 172−173 °C (EtOAc); FT-IR (neat) ν_{max} 3413, 2919, 1690, 1672, 1625, 1496 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.47 (s, 1 H), 7.40 (d, J = 15.5 Hz, 1 H), 6.43 (d, J = 15.5 Hz, 1 H), 2.55 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.4, 169.3, 152.4, 137.8, 123.5, 121.3, 18.9; HRMS (FAB) calcd for $C_7H_7NO_2S$ (MH^+): 170.0276, found 170.0270.

Preparation of Oxazole Carboxylic Acid Ar-III. According to the procedure described for the synthesis of pyridine derivative **Ar-I** above, the corresponding oxazole aldehyde (0.7 g, 6.3 mmol, 1.0 equiv) was reacted with Ph_3PCHCO_2Me (3.16 g, 9.45 mmol, 1.5 equiv) in benzene (13 mL) to yield, after chromatographic purification (silica gel, EtOAc), the expected α,β-unsaturated oxazole methyl ester (2.7 g, 96%) yield. R_f = 0.61 (silica gel, EtOAc); FT-IR (neat) ν_{max} 3132, 3088, 1716, 1646, 1439, 1388 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1 H), 7.32 (d, J = 15.5 Hz, 1 H), 6.44 (d, J = 15.5 Hz, 1 H), 3.61 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.2, 138.9, 132.3, 118.8, 51.3, 13.4; HRMS (FAB) calcd for $C_8H_9NO_3$ (MH^+): 168.0661, found 168.0668.

The so obtained methyl ester (0.3 g, 1.80 mmol, 1.0 equiv) was saponified by the action of $LiOH\cdot H_2O$ (0.22 g, 5.4 mmol, 3.0 equiv) in THF:H_2O (1:1, 15 mL) as described for pyridine carboxylic acid **Ar-I**, to produce thiazole carboxylic acid **Ar-III** (0.28 g, 100%) in quantitative yield as a white crystaline solid. R_f = 0.33 (silica gel, EtOAc); mp 165−166 °C (EtOAc); FT-IR (neat) ν_{max} 3085, 2938, 2546, 1668, 1636, 1598, 1566, 1429 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.90 (s, 1 H), 7.35 (d, J = 15.5 Hz, 1 H), 6.34 (d, J = 15.5 Hz, 1 H), 2.34 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.9, 164.7, 141.6, 138.2, 133.9, 120.6, 13.5; HRMS (FAB) calcd for $C_7H_7NO_3$ (MH^+): 154.0504, found 154.0508.

Attachment of the Pyridine Side Chain and Desilylation. Synthesis of Compound 42. To a solution of hydroxy compound **41** (23.0 mg, 0.046 mmol, 1.0 equiv) in CH_2Cl_2 (2.2 mL) were added 4-DMAP (2.8 mg, 0.023 mmol, 0.5 equiv), pyridine carboxylic acid **Ar-I** (10.2 mg, 0.068 mmol, 1.5 equiv), and DCC (18.8 mg, 0.091 mmol, 2.0 equiv) at 25 °C. The reaction mixture was stirred for 20 h at that temperature and then concentrated. The crude mixture was purified by flash chromatography (silica gel, EtOAc−hexane, 1:4, R_f = 0.28) to furnish the corresponding ester (24.5 mg, 85%). The latter compound was desilylated as follows: A solution of the silyl ether (24.5 mg, 0.038 mmol, 1.0 equiv) in THF (1 mL) was treated with TBAF (1.0 M in THF, 77 μL, 2.0 equiv), and the reaction mixture was stirred for 1 h at 25 °C. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (silica gel, EtOAc−hexane, 1:1) to yield alcohol **42** (16.1 mg, 87%). R_f = 0.10 (silica gel, EtOAc−hexane, 1:1); $[\alpha]^{25}_D$ −13.8 (c = 0.8, $CHCl_3$); FT-IR (neat) ν_{max} 3410, 2961, 1713, 1647, 1583, 1468, 1434 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.64 (d, J = 5.5 Hz, 1 H), 7.72 (dt, J = 9.0, 2.0 Hz, 1 H), 7.67 (d, J = 15.5 Hz, 1 H), 7.43 (d, J = 7.5 Hz, 1 H), 7.28 (dd, J = 9.0, 5.5 Hz, 1 H), 6.95 (d, J = 15.5 Hz, 1 H), 6.24 (d, J = 7.5 Hz, 1 H), 6.05 (d, J = 7.5 Hz, 1 H), 5.50 (d, J = 11.5 Hz, 1 H), 5.27 (bs, 1 H), 4.83 (d, J = 8.5 Hz, 1 H), 4.17 (d, J = 14.0 Hz, 1 H), 3.97−3.87 (m, 1 H), 3.75−3.69 (m, 2 H), 3.24 (s, 3 H), 2.65−2.57 (m, 1 H), 2.36−2.28 (m, 1 H), 2.03−1.95 (m, 1 H), 1.63−1.47 (m, 4 H), 1.51 (s, 3 H), 1.47 (s, 3 H), 1.00 (d, J = 7.5 Hz, 3 H), 0.92 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 150.1, 136.9, 136.8, 135.4, 135.1, 133.8, 129.4, 124.5, 122.3, 121.5, 117.1, 90.2, 82.1, 67.9, 67.3, 49.6, 42.0, 38.7, 33.9, 31.5, 28.9, 25.6, 23.9, 22.2, 21.0; HRMS (FAB) calcd for $C_{29}H_{37}NO_5$ ($M + Na^+$): 502.2569, found 502.2556.

Attachment of the Thiazole Side Chain and Desilylation. Synthesis of Compound 43. According to the procedure described above for compound **42**, to a solution of hydroxy compound **41** (15 mg, 0.030 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL) were added 4-DMAP (1.8 mg, 0.015 mmol, 0.5 equiv), thiazole carboxylic acid **Ar-II** (6.5 mg, 0.039 mmol, 1.3 equiv), and DCC (11.3 mg, 0.055 mmol, 1.7 equiv) at 25 °C to provide, after flash chromatography (silica gel, EtOAc−hexane, 1:4), the corresponding ester (12 mg, 61% yield). Desilylation of the latter compound (6.0 mg, 9.1 mmol, 1.0 equiv) in THF (1 mL) with

TBAF (1.0 M in THF, 18 μL, 2.0 equiv) furnished after flash chromatography (silica gel, EtOAc−hexane, 1:2) alcohol **43 (**5.5 mg, 100%). R_f = 0.18 (silica gel, EtOAc−hexane, 1:2); $[\alpha]^{25}_D$ +19.6 (*c* = 0.55, $CHCl_3$); FT-IR (neat) ν_{max} 3414, 2961, 1711, 1636, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 15.5 Hz, 1 H), 7.29 (s, 1 H), 6.73 (d, *J* = 15.5 Hz, 1 H), 6.21 (d, *J* = 6.0 Hz, 1 H), 6.04 (d, *J* = 6.0 Hz, 1 H), 5.55 (d, *J* = 9.5 Hz, 1 H), 5.27 (bs, 1 H), 4.82 (d, *J* = 7.5 Hz, 1 H), 4.15 (d, *J* = 12.0 Hz, 1 H), 3.95−3.88 (m,2 H), 3.23 (s, 3 H), 2.72 (s, 3 H), 2.62−2.54 (m, 2 H), 2.32 (m, 1 H), 1.99 (m, 1 H), 1.59−1.55 (m, 2 H), 1.50 (s, 3 H), 1.45 (s, 3 H), 1.44−1.35 (m, 1 H), 1.30−1.25 (m, 1 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 0.92 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 166.3, 151.3, 136.8, 136.7, 135.5, 135.1, 133.9, 129.4, 121.8, 121.5, 120.2, 117.1, 90.2, 81.9, 67.3, 49.6, 42.1, 38.7, 33.9, 28.0, 26.0, 24.3, 23.9, 22.2, 22.1, 20.5, 19.4; HRMS (FAB) calcd for $C_{28}H_{37}NO_5S$ (M + Cs^+): 632.1447, found 632.1469.

Attachment of the Oxazole Side Chain and Desilylation. Synthesis of Compound 44. According to the procedure described for the synthesis of compound **42**, alcohol **41** (21 mg, 0.042 mmol, 1.0 equiv) was treated with 4-DMAP (2.5 mg, 0.020 mmol, 0.5 equiv), oxazole carboxylic acid **Ar-III** (8.4 mg, 0.055 mmol, 1.3 equiv), and DCC (16.9 mg, 0.082 mmol, 2.0 equiv) in CH_2Cl_2 (2 mL) to produce, after chromatographic purification (silica gel, EtOAc−hexane, 1:4, R_f = 0.43), the desired ester (23 mg, 86%). The latter compound (23 mg, 0.036 mmol, 1.0 equiv) was deprotected by the action of TBAF (1.0 M in THF, 72 μL, 2.0 equiv) according to the procedure described above for compound **42** to afford, after chromatographic purification (flash column, silica gel, EtOAc−hexane, 1:1), alcohol **44** (16 mg, 92%). R_f = 0.21 (silica gel, EtOAc−hexane, 1:1); $[\alpha]^{25}_D$ +8.1 (*c* = 1.6, $CHCl_3$); FT-IR (neat) ν_{max} 3410, 2961, 2865, 1712, 1651, 1451 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.44 (d, *J* = 15.5 Hz, 1 H), 6.59 (d, *J* = 15.5 Hz, 1 H), 6.19 (d, *J* = 6.0 Hz, 1 H), 6.03 (d, *J* = 6.0 Hz, 1 H), 5.54 (d, *J* = 9.5 Hz, 1 H), 5.25 (bs, 1 H), 4.78 (d, *J* = 7.5 Hz, 1 H), 4.14 (d, *J* = 12.0 Hz, 1 H), 3.93−3.87 (m, 2 H), 3.22 (s, 3 H), 2.65 (bd, *J* = 7.5 Hz, 1 H), 2.58 (m, 1 H), 2.47 (s, 3 H), 2.30 (m, 1 H), 1.98 (m, 1 H), 1.59−1.51 (m, 2 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.40−1.34 (m, 1 H), 1.28−1.27 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 162.6, 139.2, 137.1, 136.7, 135.4, 135.1, 133.9, 132.7, 129.3, 121.5, 119.5, 117.1, 90.2, 81.9, 67.3, 49.6, 42.0, 38.6, 33.8, 31.4, 28.9, 24.3, 23.8, 22.2, 22.1, 20.5, 13.9; HRMS (FAB) calcd for $C_{28}H_{37}NO_6$ (M + Na^+): 506.2519, found 506.2502.

Oxidation of Alcohol 44. Synthesis of Aldehyde 47. To a solution of alcohol **44** (16 mg, 0.033 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) were added $NaHCO_3$ (20 mg, 0.238 mmol, ca. 7 equiv) and Dess−Martin periodinane (25 mg, 0.060 mmol, ca. 2 equiv) in CH_2Cl_2 (1.5 mL), and the reaction mixture was stirred for 50 min at 25 °C after which time 2-propanol (excess) was added followed by EtOAc (2.0 mL). The precipitates were filtered off through a short plug of silica, and the filtrates were concentrated and purified by flash chromatography (silica gel, EtOAc−hexane, 1:1) to yield the desired aldehyde **47** (13.3 mg, 84%). R_f = 0.56 (silica gel, EtOAc−hexane, 1:1); $[\alpha]^{25}_D$ +85.0 (*c* = 1.3, $CHCl_3$); FT-IR (neat) ν_{max} 2962, 1697, 1650, 1450, 1301 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.27 (s, 1 H), 7.69 (s, 1 H), 7.44 (d, *J* = 15.5 Hz, 1 H), 6.59 (d, *J* = 15.5 Hz, 1 H), 6.47 (d, *J* = 10.0 Hz, 1 H), 6.30 (d, *J* = 6.0 Hz, 1 H), 6.15 (d, *J* = 6.0 Hz, 1 H), 5.32 (bs, 1 H), 4.77 (d, *J* = 7.5 Hz, 1 H), 3.27 (m, 1 H), 3.24 (s, 3 H), 2.75 (m, 1 H), 2.47 (s, 3 H), 2.39 (m, 1 H), 2.10 (m, 1 H), 1.65−1.61 (m, 2 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.38−1.35 (m, 1 H), 1.25−1.19 (m, 1 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.94 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.9, 166.0, 162.7, 159.4, 142.0, 139.3, 137.0, 135.4, 133.9, 132.9, 129.8, 121.5, 119.4, 114.6, 89.3, 81.6, 50.3, 41.3, 39.0, 35.6, 31.5, 28.9, 24.3, 24.2, 22.1, 22.0, 20.5, 13.9; HRMS (FAB) calcd for $C_{28}H_{35}NO_6$ (M + Na^+): 504.2362, found 504.2345.

Preparation of Sarcodictyin Analogue 48 via Aldehyde 45. According to the procedure described above for the synthesis of compound **47**, alcohol **42** (16.0 mg, 0.033 mmol, 1.0 equiv) was treated with $NaHCO_3$ (26.6 mg, 0.334 mmol, ca. 10 equiv) and Dess−Martin periodinane (35.4 mg, 0.083 mmol, ca. 2.5 equiv) in CH_2Cl_2 (1.5 mL) to produce, after chromatographic purification (silica gel, EtOAc−hexane, 1:4, R_f = 0.35), the corresponding aldehyde (7.0 mg, 44%). The so obtained aldehyde **45** (7.0 mg, 0.015 mmol, 1.0 equiv) was treated with 2-methyl-2-butene (2.0 M in THF, 1.5 mL), NaH_2PO_4 (5.3 mg, 0.044 mmol, ca. 3 equiv), and $NaClO_2$ (8.0 mg, 0.088 mmol, ca. 6 equiv) in THF:^{t}BuOH:H_2O (5:5:1, 2.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h after which time a solution of CH_2N_2 in Et_2O (excess) was added and stirring was continued for an additional 10 min at 25 °C. The excess CH_2N_2 was removed by a stream of argon, and the reaction mixture was extracted with Et_2O (3 × 8 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (silica gel, EtOAc−hexane, 1:4) to afford sarcodictyin analogue **48** (3.2 mg, 43% for two steps). R_f = 0.56 (silica gel, EtOAc−hexane, 1:1); $[\alpha]^{25}_D$ −37.14 (*c* = 0.07, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.0 Hz, 1 H), 7.76 (m, 1 H), 7.69 (d, *J* = 16.0 Hz, 1 H), 7.43 (d, *J* = 11.0 Hz, 1 H), 7.31 (m, 1 H), 7.05 (d, *J* = 16.0 Hz, 1 H), 6.80 (d, *J* = 10.0 Hz, 1 H), 6.51 (d, *J* = 5.5 Hz, 1 H), 6.22 (d, *J* = 5.5 Hz, 1 H), 5.30 (bs, 1 H), 4.82 (d, *J* = 7.5 Hz, 1 H), 4.15−4.08 (m, 1 H), 3.71 (s, 3 H), 3.24 (s, 3 H), 2.70−2.65 (m, 1 H), 2.42−2.36 (m, 1 H), 2.15−1.97 (m, 1 H), 1.70−1.46 (m, 4 H), 1.52 (s, 3 H), 1.37 (s, 3 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 152.6, 150.1, 137.2, 137.0, 136.8, 136.6, 135.4, 135.1, 133.8, 129.4, 124.5, 122.3, 121.5, 117.1, 90.2, 82.1, 68.0, 67.3, 49.6, 42.0, 38.7, 33.9, 31.5, 29.0, 25.6, 24.3, 23.9, 22.2, 20.5; HRMS (FAB) calcd for $C_{30}H_{37}NO_6$ (MH^+): 508.2699, found 508.2681.

Preparation of Sarcodictyin Analogue 49 via Aldehyde 46. According to the procedure described above for the synthesis of compound **47**, to a solution of alcohol **43** (5.0 mg, 0.010 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) were added $NaHCO_3$ (6.7 mg, 0.080 mmol, 8.0 equiv) and Dess−Martin periodinane (8.5 mg, 0.02 mmol, 2.0 equiv), and the reaction mixture was stirred for 30 min at 25 °C to afford after flash chromatography (silica gel, EtOAc−hexane, 1:4; R_f = 0.45) the corresponding aldehyde **46** (2.0 mg, 40%) which was used directly in the next step. Thus, aldehyde **46** (2.0 mg, 0.004 mmol, 1.0 equiv) in ^{t}BuOH:H_2O (5:1, 0.6 mL) was treated with 2-methyl-2-butene (2.0 M in THF, 0.5 mL, 1.0 mmol), NaH_2PO_4 (1.4 mg, 0.012 mmol, 3.0 equiv), and $NaClO_2$ (2.2 mg, 0.024 mmol, 6.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h after which time a solution of CH_2N_2 (excess) in Et_2O was added, and stirring was continued for an additional 10 min at 25 °C. The excess CH_2N_2 was removed by a stream of argon, and the reaction mixture was extracted with Et_2O (3 × 5 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography (silica gel, EtOAc−hexane, 1:4) to yield sarcodictyin analogue **49** (1.5 mg, 71% for 2 steps). R_f = 0.45 (silica gel, EtOAc−hexane, 1:4); $[\alpha]^{25}_D$ −13.4 (*c* = 0.10, $CHCl_3$); FT-IR (neat) ν_{max} 2960, 2360, 2337, 1714, 1636, 1436, 1268, 1157 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 15.5 Hz, 1 H), 7.29 (s, 1 H), 6.73 (d, *J* = 15.5 Hz, 1 H), 6.73 (d, *J* = 10.0 Hz, 1 H), 6.50 (d, *J* = 6.0 Hz, 1 H), 6.17 (d, *J* = 6.0 Hz, 1 H), 5.29 (bs, 1 H), 4.80 (d, *J* = 7.5 Hz, 1 H), 4.14 (m, 1 H), 3.70 (s, 3 H), 3.23 (s, 3 H), 2.72 (s, 3 H), 2.70−2.64 (m, 1 H), 2.38 (m, 1 H), 2.04 (m, 1 H), 1.63−1.55 (m, 2 H), 1.51 (s, 3 H), 1.45 (s, 3 H), 1.36−1.28 (m, 1 H), 1.26−1.11 (m, 1 H), 0.98 (d, *J* = 6.5 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 166.4, 154.9, 151.3, 146.4, 136.7, 134.8, 133.9, 132.0, 131.2, 121.9, 121.5, 120.1, 115.6, 100.8, 89.5, 81.8, 51.9, 50.2, 41.7, 38.8, 34.7, 31.5, 28.9, 24.4, 22.2, 22.0, 20.5, 19.4; HRMS (FAB) calcd for $C_{29}H_{37}NO_6S$ (M + Cs^+): 660.1396, found 660.1416.

Preparation of Sarcodictyin Analogue 50. According to the procedure described above for the synthesis of compound **49**, aldehyde **47** (8.5 mg, 0.017 mmol, 1.0 equiv) was treated with 2-methyl-2-butene (2.0 M in THF, 1.0 mL), NaH_2PO_4 (6.3 mg, 0.053 mmol, ca. 3 equiv), and $NaClO_2$ (9.6 mg, 0.106 mmol, ca. 6 equiv) in ^{t}BuOH:H_2O (5:1, 1.2 mL) to furnish, after diazoethane treatment and chromatographic purification (silica gel, EtOAc−hexane, 1:2), sarcodictyin analogue **50 (**8.0 mg, 87% for two steps). R_f = 0.35 (silica gel, EtOAc−hexane, 1:2); $[\alpha]^{25}_D$ +3.6 (*c* = 0.8, $CHCl_3$); FT-IR (neat) ν_{max} 2963, 1713, 1650, 1449, 1301 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1 H), 7.44 (d, *J* = 15.5 Hz, 1 H), 6.72 (d, *J* = 10.0 Hz, 1 H), 6.60 (d, *J* = 15.5 Hz, 1 H), 6.50 (d, *J* = 6.0 Hz, 1 H), 6.14 (d, *J* = 6.0 Hz, 1 H), 5.29 (bs, 1 H), 4.78 (d, *J* = 7.5 Hz, 1 H), 4.18−4.10 (m, 3 H), 3.22 (s, 3 H), 2.66 (m, 1 H), 2.47 (s, 3 H), 2.39 (m, 1 H), 2.03 (m, 1 H), 1.63−1.57 (m, 2 H), 1.51 (s, 3 H), 1.44 (s, 3 H), 1.34−1.31 (m, 2 H), 1.26

(t, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 166.0, 162.6, 146.1, 139.2, 137.1, 134.6, 133.8, 132.7, 132.3, 131.3, 121.5, 119.5, 115.6, 89.4, 81.8, 60.6, 50.2, 41.7, 38.8, 34.7, 31.5, 28.9, 24.3, 22.2, 22.0, 20.5, 14.1, 13.9; HRMS (FAB) calcd for $C_{30}H_{39}NO_7$ (M + Cs^+): 658.1781, found 658.1762.

Preparation of Sarcodictyin Analogue 52. A solution of alcohol **51** (2.5 mg, 0.0052 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at −78 °C was treated with DAST [(diethylamino)sulfur trifluoride] (1.3 μL, 0.010 mmol, ca. 2 equiv) and stirred at that temperature for 3 h. The reaction mixture was quenched by the addition of solid $NaHCO_3$ (30 mg), warmed to 25 °C, concentrated, and purified by flash chromatography (silica gel, EtOAc:CH_2Cl_2:MeOH, 10:10:1) to afford the desired sarcodictyin analog **52** (2.5 mg, 99% yield). R_f = 0.31 (silica gel, EtOAc:CH_2Cl_2:MeOH, 10:10:1); $[\alpha]^{25}_D$ − 32.4 (c = 0.25, $CHCl_3$); FT-IR (neat) ν_{max} 2961, 1762, 1637, 1451, 1384 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, J = 15.5 Hz, 1 H), 7.44 (s, 1 H), 7.08 (s, 1 H), 6.56 (d, J = 15.5 Hz, 1 H), 6.14 (d, J = 6.0 Hz, 1 H), 5.97 (dd, J = 6.0, 3.0 Hz, 1 H), 5.67 (dd, J = 9.5, 5.0 Hz, 1 H), 5.26 (bs, 1 H), 5.02 (dd, J = 49.0, 10.0 Hz, 1 H), 4.80 (d, J = 7.5 Hz, 1 H), 4.62 (dd, J = 48.0, 10.0 Hz, 1 H), 3.98−3.93 (m, 1 H), 3.69 (s, 3 H), 3.22 (s, 3 H), 2.62 (m, 1 H), 2.29 (m, 1 H), 1.99 (m, 1 H), 1.64−1.55 (m, 2 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.23−1.20 (m, 2 H), 0.96 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 139.2, 138.9, 138.8, 138.4, 136.4, 134.4, 134.3, 130.6, 122.7, 121.2, 116.0, 115.6, 90.1, 87.4, 81.5, 49.8, 42.2, 38.7, 34.1, 33.6, 31.4, 29.0, 24.4, 24.2, 22.2, 22.1, 20.5; HRMS (FAB) calcd for $C_{28}H_{37}N_2O_4F$ (M + Cs^+): 617.1792, found 617.1813.

Preparation of Sarcodictyin Analogue 53. To a solution of alcohol **41** (5.0 mg, 0.01 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) there were added acetic anhydride (5.0 mg, 0.052 mmol, 5.2 equiv), Et_3N (10 μL, 0.07 mmol, 6.8 equiv), and 4-DMAP (2.0 mg, 0.016 mmol, 1.6 equiv), and the reaction mixture was stirred at ambient temperature for 2 h. After completion of the reaction was established (TLC), quenching with saturated $NaHCO_3$ solution (2 × 2 mL), removal of the solvents under reduced pressure, and flash chromatographic purification (silica gel, EtOAc) afforded sarcodictyin analogue **53** in quantitative yield (5.2 mg, 100%). R_f = 0.41 (silica gel, EtOAc); $[\alpha]^{25}_D$ − 16.2 (c = 0.55, $CHCl_3$); FT-IR (neat) ν_{max} 2961, 1737, 1704, 1638, 1450, 1381 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 15.5 Hz, 1 H), 7.45 (s, 1 H), 7.07 (s, 1 H), 6.55 (d, J = 15.5 Hz, 1 H), 6.15 (d, J = 6.0 Hz, 1 H), 6.01 (d, J = 6.0 Hz, 1 H), 5.60 (d, J = 9.5 Hz, 1 H), 5.26 (bs, 1 H), 4.79 (d, J = 7.5 Hz, 1 H), 4.55 (d, J = 12.5 Hz, 1 H), 4.51 (d, J = 12.5 Hz, 1 H), 3.96 (m, 1 H), 3.69 (s, 3 H), 3.19 (s, 3 H), 2.59 (m, 1 H), 2.27 (m, 1 H), 2.02 (s, 3 H), 1.98 (m, 1 H), 1.61−1.53 (m, 2 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.43−1.40 (m, 1 H), 1.24−1.21 (m, 1 H), 0.96 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 166.7, 139.2, 138.4, 136.8, 136.3, 134.7, 134.3, 132.8, 130.0, 122.7, 121.2, 116.0, 115.9, 90.2, 81.5, 67.0, 49.7, 42.3, 38.8, 34.1, 33.6, 31.5, 29.1, 24.5, 24.3, 22.2, 22.0, 21.2, 20.5; HRMS (FAB) calcd for $C_{30}H_{40}N_2O_6$ (M + Cs^+): 657.1941, found 657.1922.

Preparation of Sarcodictyin Analogue 54. To a stirring solution of ketal **53** (5.2 mg, 0.01 mmol, 1.0 equiv) in CH_2Cl_2:H_2O (10:1) at ambient temperature there was added a catalytic amount of CSA (10% mol), and stirring was continued for 72 h. After completion of the reaction was established by TLC (40 h), quenching with solid $NaHCO_3$, filtration, and chromatographic purification (silica gel, EtOAc) afforded sarcodictyin analogue **54** (5.1 mg, 95% yield). R_f = 0.37 (silica gel, EtOAc); $[\alpha]^{25}_D$ −28.9 (c = 0.35, $CHCl_3$); FT-IR (neat) ν_{max} 3348, 2962, 1737, 1704, 1638, 1233, 1155 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 15.5 Hz, 1 H), 7.46 (s, 1 H), 7.08 (s, 1 H), 6.55 (d, J = 15.5 Hz, 1 H), 6.14 (d, J = 6.0 Hz, 1 H), 6.11 (d, J = 6.0 Hz, 1 H), 5.58 (d, J = 9.5 Hz, 1 H), 5.26 (bs, 1 H), 4.79 (d, J = 7.5 Hz, 1 H), 4.59 (s, 2 H), 3.98 (m, 1 H), 3.70 (s, 3 H), 3.25 (bs, 1 H), 2.60 (m, 1 H), 2.29 (m, 1 H), 2.04 (s, 3 H), 2.00 (m, 1 H), 1.68−1.53 (m, 2 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 1.41−1.33 (m, 1 H), 1.25−1.22 (m, 1 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.7, 139.2, 138.3, 136.9, 136.3, 134.2, 133.9, 133.4, 131.7, 122.7, 121.2, 115.9, 112.2, 90.4, 81.2, 67.4, 42.3, 38.7, 34.2, 33.7, 31.6, 29.1, 25.8, 24.4, 22.2, 22.1, 21.2, 20.6; HRMS (FAB) calcd for $C_{29}H_{38}N_2O_6$ (M + Cs^+): 643.1784, found 643.1763.

Conclusion

In this article, we described the development of solid phase chemistry for the chemical synthesis of the naturally occurring sarcodictyins A (**7**) and B (**8**) and its application to the construction of a sarcodictyin combinatorial library. This library was complemented with compounds synthesized by solution methods and was subjected to biological evaluation with regards to tubulin polymerization and cytotoxicity. The results were useful both in terms of new synthetic methodology development and structure−activity relationships in this new structural class of compounds. Furthermore, the chemistry described herein demonstrates the use of REC chemistry[19] in chemical biology studies and sets the stage for further developments in the field of cancer chemotherapy.

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Supporting Information Available: Selected physical data for **55**−**59**, **62**−**71**, **73**−**77**, **79**−**109** (52 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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