NMR, IR, MS) were identical to those of **13**: $[\alpha]^{23}_{D}$ = +1.12° (*c* = 2.68, $CHCl_3$).

(2*S*,8*S*)-(+)-8-Methyldec-2-yl Propanoate (8a). Ethylmagnesium cuprate was prepared by dropwise addition of ethylmagnesium bromide (3.92 mL of 1 M solution in THF, 3.92 mmol) to a heterogeneous mixture of CuI (373 mg, 1.96 mmol) in THF (8 mL) at −40 °C followed by stirring at the same temperature for 30 min. The mixture was cooled to −78 °C, compound **13** was slowly added, and the mixture was stirred for 5 days at −35 °C. A saturated aqueous solution of ammonium chloride was added, and the mixture was stirred for 5 min at the same temperature and then extracted with diethyl ether. Solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane:ethyl acetate 50:1) to give **8a** (66 mg, 74%) in the form of a colorless oil: $[\alpha]^{23}_{D}$ = +8.58° (*c* = 1.2, $CHCl_3$) [lit.[11] +8.5972° (*c* = 12.7, $CHCl_3$)]. ^1H NMR: 4.92–4.84 (m, 1 H), 2.28 (q, *J* = 7.6, 2 H), 1.94–1.06 (m, 13 H), 1.18 (d, *J* = 6.4, 3 H), 1.12 (t, *J* = 7.6, 3 H), 0.83 (t, *J* = 7.1, 3 H), 0.82 (d, *J* = 6.4, 3 H).

(2*S*,8*R*)-(−)-8-Methyldec-2-yl Propanoate (8c). The reaction was carried out as described above using tosylate **14** (104 mg, 0.28 mmol) and ethylmagnesium cuprate that was prepared from ethylmagnesium bromide (2.8 mL, 2.8 mmol) and cuprous iodide (267 mg, 2.8 mmol) in THF (8 mL) to produce **8c** (46 mg, 72%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of **8a**: $[\alpha]^{23}_{D}$ = −4.12° (*c* = 1.62, $CHCl_3$) [lit.[11] −3.77° (*c* = 15, $CHCl_3$)]; [lit.[10] −4.25° (*c* = 1.11, $CHCl_3$)].

(2*R*,8*S*)-(+)-8-Methyldec-2-yl Propanoate (8b). Compound **8a** (66 mg, 0.29 mmol) was dissolved in methanol (1 mL) and mixed with 3 N aqueous KOH (1 mL). The mixture was stirred at rt for 24 h and then worked up with CH_2Cl_2 and water. Solvent was removed under reduced pressure and the residue was filtered through a short silica gel column using hexane:ethyl acetate: 4:1, affording (2*R*,8*S*)-(+)-8-methyldecan-2-ol (42 mg, 84%): $[\alpha]^{23}_{D}$ = +15.64° (*c* = 1.0, $CHCl_3$) [lit.[11] +15.782° (neat, *d* = 0.8307)]. ^1H NMR: 3.80–3.71 (m, 1 H), 1.63–1.07 (m, 13 H), 1.15 (d, *J* = 6.0, 3 H), 0.82 (t, *J* = 7.1, 3 H), 0.81 (d, *J* = 6.4, 3 H). ^{13}C NMR: 68.11, 39.34, 36.55, 34.33, 29.96, 29.43, 27.02, 25.78, 23.41, 19.15, 11.36.

The above-mentioned alcohol (40 mg, 0.23 mmol) was dissolved in benzene (1 mL) together with triphenylphosphine (73 mg, 0.28 mmol) and propanoic acid (21 mg, 0.28 mmol). Diethyl azodicarboxylate (DEAD) was added at rt, and the mixture was stirred at the same temperature for 24 h and then worked up with CH_2Cl_2 and water. Solvent was removed under reduced pressure and the residue was filtered through a short silica gel column using hexane:ethyl acetate: 49:1, affording **8b** (32 mg, 57%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of **8a**: $[\alpha]^{23}_{D}$ = +4.02° (*c* = 1.57, $CHCl_3$) [lit.[11] −4.054° (*c* = 21, $CHCl_3$)].

(2*R*,8*R*)-(−)-8-Methyldec-2-yl Propanoate (8d). Hydrolysis of **8c** (46 mg, 0.2 mmol) in MeOH was carried out with 3 N KOH as described above for **8a** to give (2*R*,8*R*)-(−)-8-methyldecan-2-ol (30 mg, 87%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of the alcohol obtained by hydrolysis of **8a**: $[\alpha]^{23}_{D}$ = −1.32° (*c* = 1.41, $CHCl_3$) [lit.[11] +0.925° (*c* = 12, $CHCl_3$)]; [lit.[10] −1.32° (*c* = 1.19, $CHCl_3$)].

The above-mentioned alcohol (30 mg, 0.17 mmol) was dissolved in benzene (1 mL) together with triphenylphosphine (52 mg, 0.2 mmol) and propanoic acid (15 mg, 0.2 mmol) and reacted with DEAD (32 mL, 0.2 mmol) as described above, affording **8d** (28 mg, 72%). All the spectral data (^1H NMR, ^{13}C NMR, IR, MS) were identical to those of **8a**: $[\alpha]^{23}_{D}$ = −8.43° (*c* = 1.74, $CHCl_3$) [lit.[11] −7.967° (*c* = 15, $CHCl_3$)]; [lit.[10] −7.57° (*c* = 1.05, $CHCl_3$)]; [lit.[17] −8.02° (*c* = 1.18, $CHCl_3$)].

Acknowledgment. We thank the United States–Israel Binational Science Foundation and the joint research program of the National Council for Research and Development, Israel, and the GSF, Germany, for their generous support.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of compounds **10**, **11**, **12**, **12a**, and **13** and ^1H NMR spectrum of **8d** (11 pages). Ordering information is given on any current masthead page.

Total Syntheses of the Marine Sponge Pigments Fascaplysin and Homofascaplysin B and C

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The *Fascaplysinopsis* spp. marine sponge pigments fascaplysin (**1**), homofascaplysin B (**4**), and homofascaplysin C (**5**) have been synthesized by peracid oxidation, reaction with oxalyl chloride/methanol, or Vilsmeier formylation, respectively, of the keystone intermediate 12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (**7**). The versatile **7** was prepared from indole (**17**) in six steps (78% yield), a sequence in which the key reaction is the trifluoroacetic acid-induced ring closure of diindole **15**, followed by Pd/C-catalyzed dehydrogenation of the crude mixture of cyclized products **25**, **26**, to give **7** in 93% yield from **15**.

The red pigment, fascaplysin (**1**), was isolated in 1988 from the marine sponge *Fascaplysinopsis* Bergquist sp., collected in the South Pacific near the Fiji islands.[1] Fascaplysin has anti-microbial activity and is cytotoxic against L-1210 mouse leukemia.[1] More recently, this pigment, with the counterion dehydroluffariellolide diacid monoanion (**2**), was extracted from the Fijian sponge *F. reticulata*, along with the other novel β-carbolines homofascaplysin A (**3**) (accompanied by counterion **2**), homofascaplysin B (**4**), homofascaplysin C (**5**), and secofascaplysin A (**6**).[2]

The fascaplysins possess the novel 12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (**7**) ring system, unprecedented amongst natural products,[3] but related to the relatively small group of natural products having two indoles interconnected at their respective C-2 positions. Well-known examples of

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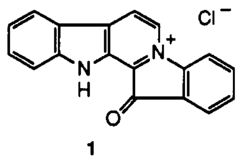
(1) Roll, D. M.; Ireland, C. M.; Lu, H. S. M.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 3276.

(2) Jimènez, C.; Quiñoá, E.; Adamczeski, M.; Hunter, L. M.; Crews, P. *J. Org. Chem.* **1991**, *56*, 3403.

(3) The synthesis of two examples of 6,7-dihydro-12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole have been reported: Harley-Mason, J.; Waterfield, W. R. *Chem. Ind.* (*London*) **1960**, 1478.

0022-3263/92/1957-3636$03.00/0



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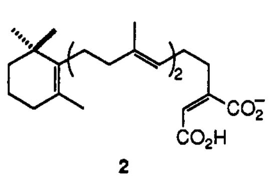

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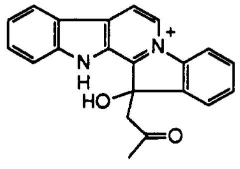

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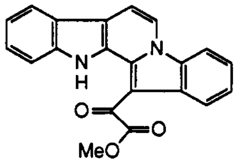

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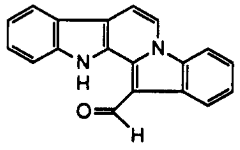

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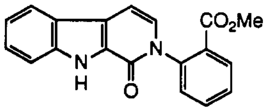

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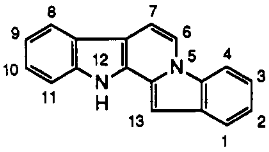

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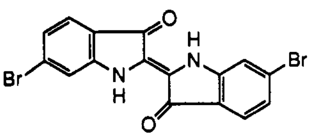

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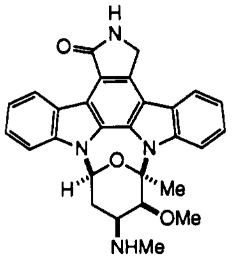

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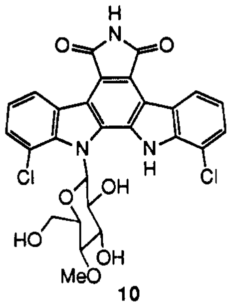

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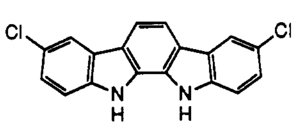

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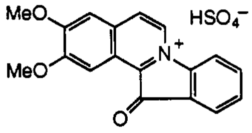

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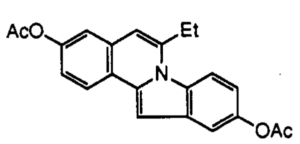

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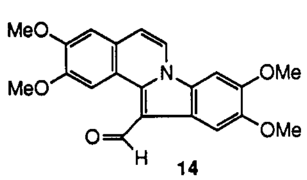

14

this class are Tyrian purple (8), the ancient Mediterranean dye,[4] and several microbial indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole natural products,[5] such as staurosporine (9)[6] and rebeccamycin (10).[7] More recently, some 15 indolo[2,3-*a*]carbazoles were isolated from a blue-green alga (e.g., tjipanazole D (11)).[8] Also of interest in this regard is indoloisoquinoline 12, which was formed as a byproduct in a synthesis of lysicamine[9] and which parallels the oxidation level of fascaplysin (1). Although biological activity has not been reported for 12, a series of structurally related indoloisoquinolines (e.g., 13 and 14) and, especially, their dihydro derivatives have cytostatic activity and bind to the estrogen receptor.[10]

We now describe the first total syntheses of fascaplysin (1) and homofascaplysins B (4) and C (5).[11]

Results and Discussion

Our approach to the pyrido[1,2-*a*:3,4-*b*′]diindole ring system was predicated on the belief that diindole 15 would undergo tandem regioselective electrophilic attack at the presumed more reactive unsubstituted indole-3-position[12,13] followed by cyclization to 16 (Scheme I). Subsequent dehydration and/or oxidation would provide 7 and/or 1, and, by suitable modification, homofascaplysins B (4) and C (5). In addition to being convergent, this strategy has the additional attractive feature that diindole 15 would be crafted from indole and, therefore, the readily available substituted indoles would lead to fascaplysin derivatives.

The pivotal intermediate diindole 15 was synthesized from indole (17) according to Scheme II. Thus, indole (17) and oxalyl chloride smoothly react to form 3-indolylglyoxylyl chloride (18),[14] which on treatment with the sodium salt of indole gave keto amide 19 in 86% yield. Reduction of the carbonyl groups of 19 was problematic due to the well-known propensity of *N*-acylindoles to suffer reductive cleavage.[15] Indeed, treatment of 19 with $LiAlH_4$ resulted in cleavage of the amide bond to give indole (17) and tryptophol. However, this cleavage reaction could be thwarted by the use of sodium (mono)trifluoroacetoxyborohydride,[16] which afforded 15 in 60% yield (47% overall yield from indole).

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[4] For an excellent, colorful review, see: Baker, J. T. *Endeavour* 1974, *33*, 11.

[5] For reviews, see: (a) Bergman, J. *Stud. Nat. Prod. Chem., Part A*, *1*, 1988, 3. (b) Bergman, J. *Chem. Scr.* 1987, *27*, 539. (c) Gill, M.; Steglich, W. *Prog. Chem. Org. Nat. Prod.* 1987, *51*, 216. (d) Gribble, G. W.; Berthel, S. J. *Stud. Nat. Prod. Chem.*, in press.

[6] (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* 1977, *30*, 275. (b) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *J. Chem. Soc., Chem. Commun.* 1978, 800. (c) Furusaki, A.; Hashiba, N.; Matsumoto, T.; Hirano, A.; Iwai, Y.; Omura, S. *Bull. Chem. Soc. Jpn.* 1982, *55*, 368.

[7] (a) Nettleton, D. E.; Doyle, T. W.; Krishnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.* 1985, *26*, 4011. (b) Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T.; Tomita, K. *J. Antibiot.* 1987, *40*, 668.

[8] Bonjouklian, R.; Smitka, T. A.; Doolin, L. E.; Molloy, R. M.; Debono, M.; Shaffer, S. A.; Moore, R. E.; Stewart, J. B.; Patterson, G. M. L. *Tetrahedron* 1991, *47*, 7739.

[9] Pabuccuoglu, V.; Rozwadowska, M. D.; Brossi, A.; Clark, A.; Hufford, C. D.; George, C.; Flippen-Anderson, J. L. *Arch. Pharm. (Weinheim)* 1991, *324*, 29. We thank Dr. Brossi for providing us with a preprint of this work.

[10] (a) Ambros, R.; Schneider, M. R.; von Angerer, S. *J. Med. Chem.* 1990, *33*, 153. (b) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* 1988, *321*, 743. (c) Ambros, R.; von Angerer, S.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* 1988, *321*, 481.

[11] For a preliminary account of a portion of our work, see: Pelcman, B.; Gribble, G. W. *Tetrahedron Lett.* 1990, *31*, 2381. Some of this work was also presented at the 199th National Meeting of the American Chemical Society, Boston, MA, April 22–27, 1990; Abstract ORGN-169. 13th International Congress of Heterocyclic Chemistry, Corvallis, OR, Aug 11–16, 1991; Abstract GE 12-141.

[12] For example, *N*-methylindole is 1100 times more reactive than 3-methylindole with the Vilsmeier reagent formed from phosgene/dimethylacetamide (C-3 and C-2 attack, respectively): Cipiciani, A.; Clementi, S.; Linda, P.; Marino, G.; Savelli, G. *J. Chem. Soc., Perkin Trans. 2* 1977, 1284.

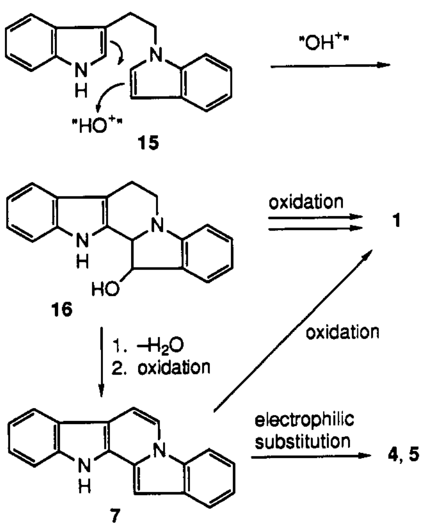
[13] For other examples and leading references, see: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; Chapter 1, pp 83–85. (b) Remers, W. A. In *The Chemistry of Heterocyclic Compounds. Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, Part I, pp 70–126.

[14] (a) Giua, M. *Gazz. Chim. Ital.* 1924, *54*, 593. (b) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* 1954, *76*, 6208. (c) Shaw, K. N. F.; McMillan, A.; Gudmundson, A. G.; Armstrong, M. D. *J. Org. Chem.* 1958, *23*, 1171.

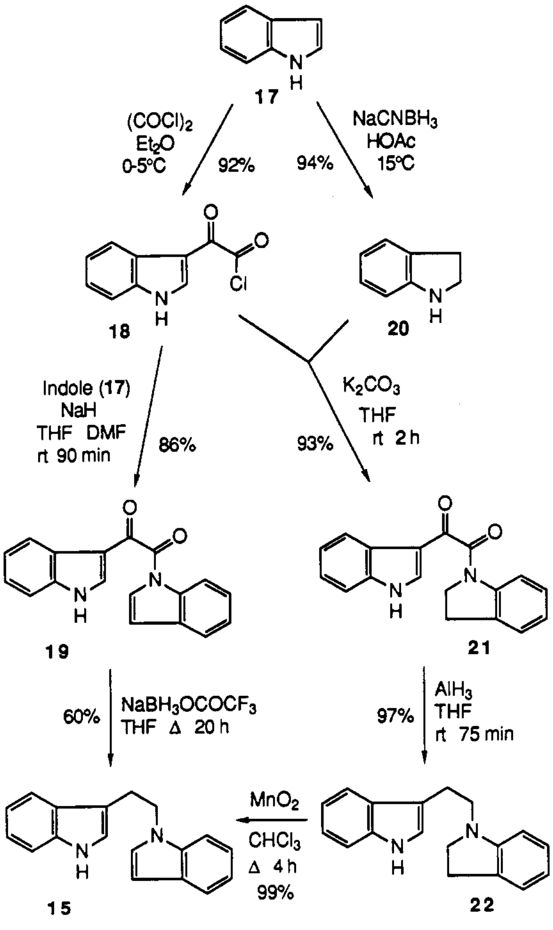
[15] Micovic, V. M.; Mihailovic, M. Lj. *J. Org. Chem.* 1953, *18*, 1190.

[16] Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* 1976, 763. For a review of the use of this and related reagents, see: Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* 1985, *17*, 317.

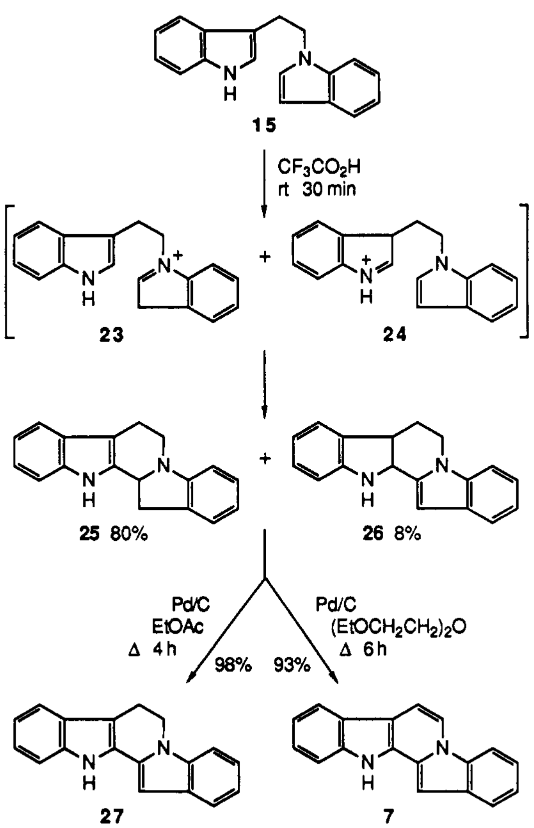
Scheme I



Scheme II



Scheme III



The modest yield in the reduction of keto amide **19** prompted us to develop an alternative synthesis of diindole **15**. Treatment of 3-indolylglyoxylyl chloride (**18**) with indoline (**20**), which was prepared from indole (**17**) by reduction with $NaCNBH_3$ in glacial acetic acid,[17] gave keto amide **21** as two rotamers.[18] Since indolinyl anion is a much poorer leaving group than indolyl anion, we anticipated that keto amide **21** would be less susceptible to reductive *N*-acyl cleavage than keto amide **19**. However, treatment of **21** with $LiAlH_4$ invariably led to mixtures of the desired indolylindoline **22** (30–58%), tryptophol, and indoline (**20**).[19] Other reducing agents, such as $NaBH_3O_2CCF_3$ or B_2H_6, gave more complex reaction mixtures and even lower yields of **22** (38% using $NaBH_3O_2CCF_3$). We observed that old batches of $LiAlH_4$ gave higher yields of **22** than newly purchased $LiAlH_4$ (98% in one experiment), suggesting that AlH_3 present in "aged" $LiAlH_4$ might be the active reagent in producing **22**. Indeed, treatment of keto amide **21** with AlH_3, prepared in situ from $LiAlH_4$ and concd H_2SO_4,[20] resulted in the clean reduction of both carbonyl groups to give the desired indolylindoline **22** in nearly quantitative yield. Dehydrogenation of **22** with MnO_2 in refluxing $CHCl_3$ gave indolylindole **15**, also in essentially quantitative yield. Although this alternative synthesis of **15** involves an extra step compared to the synthesis via keto amide **19**, the overall yield of **15** from indole (**17**) is 82% and the synthesis can be accomplished without the need for chromatography.

Having secured the advanced intermediate **15**, we turned our attention to the construction of the pentacyclic pyrido[1,2-*a*:3,4-*b*′]diindole skeleton. What began as only a model study of the reactivity of **15** with electrophiles ultimately became the route to fascaplysin. We initially examined the protonation of **15**, a choice based on the well-studied acid-catalyzed dimerizations of indoles.[21] Whereas indole itself gives a 2,3′-dimer with acid, 3-substituted indoles afford 2,2′-dimers. Although no intra-

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[17] Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859.

[18] The amide **21** was obtained as a mixture of rotamers (~4:1) due to restricted rotation of the amide C–N bond, as evident from the ^1H and ^{13}C NMR spectra in which several peaks appeared as "doublets" (only the shifts of the major isomer are given in the Experimental Section). For another example where rotamer mixtures were observed for indoleglyoxalamides, see: Raucher, S., Klein, P. *J. Org. Chem.* **1986**, *51*, 123.

[19] This type of cleavage of the amide bond is well known, cf. ref 15.

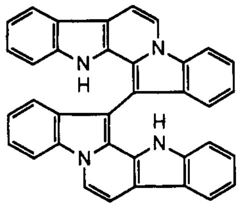
[20] Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927. See also: Schindlbauer, H. *Monatsh. Chem.* **1969**, *100*, 1413.

[21] For a review, see: Remers, W. A. In *The Chemistry of Heterocyclic Compounds. Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, Part I, pp 66–70.

molecular examples of acid-promoted indole dimerization appear to have been described, it was anticipated that **15** would afford the desired 2,2′-diindole irrespective of which indole moiety would be protonated. Since indoles undergo C-3 protonation in neat carboxylic acids,[22] we exposed **15** to neat CF_3CO_2H at room temperature (Scheme III).[23] To our delight, this resulted in the smooth cyclization to a 10:1 mixture of **25** and **26** in high yield. This ratio reflects the approximate 2.2 pK_a difference in basicity between a 3-unsubstituted indole and a 3-substituted indole,[24] leading to preferential formation of **25** via indolenium ion **23**, which arises by protonation of the more basic (unsubstituted) indole double bond in **15**. The isomers **25** and **26** were separated by flash chromatography, and their structures were established by NMR spectroscopic techniques (COSY, APT, and selective proton decoupling). They were also easily distinguished by TLC, as **26**, having an unsubstituted, and therefore more nucleophilic, indole C-3 position, gave a color reaction with van Urk's reagent (4-(dimethylamino)benzaldehyde, aqueous HCl, EtOH)[25] much more readily than did **25**.

Since it was more convenient and more efficient not to purify or separate **25** and **26** prior to the next step, the crude mixture of **25** and **26** was dehydrogenated with 10% Pd/C in refluxing EtOAc to give diindole **27** in 98% yield from **15**. More vigorous conditions were required for the introduction of the second double bond. Treatment of the **25**–**26** crude mixture with 10% Pd/C in refluxing 2-ethoxyethyl ether (180–190 °C) gave the fully aromatic pentacycle **7** in 93% yield from **15**. The structure of this pale green solid was fully supported by its spectral properties and by subsequent chemistry.

From early dehydrogenation reactions in 2-ethoxyethyl ether solvent, we isolated a bright yellow solid, which precipitated during this reaction. Spectral data indicated that this compound is probably the dimeric compound 13,13′-bis(12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole) (**28**), the product of oxidative coupling of **7**.[26] The mass spectrum exhibited a base peak at *m/e* 510 (M^+) and an intense peak at *m/e* 255. The ^1H NMR spectrum was similar to that of **7** but was missing the characteristic upfield signal corresponding to the indole C-3 proton. The ^{13}C NMR spectrum displayed the expected 18 signals. The formation of **28** likely involves a radical process, as its formation was suppressed by adding hydroquinone to the reaction mixture or by using freshly distilled 2-ethoxyethyl ether.[27]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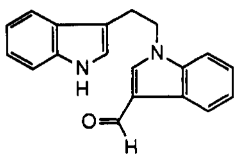
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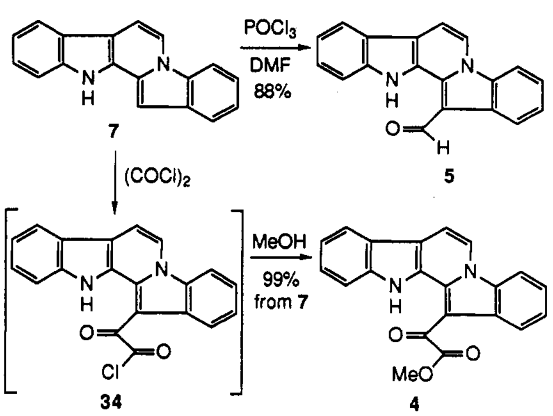
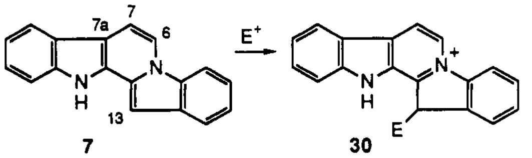
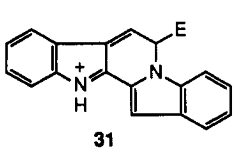
Scheme IV

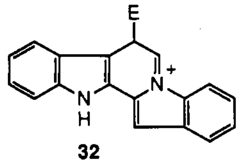


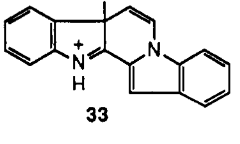
Unfortunately, attempts to induce the cyclization of **15** to **16**, according to Scheme I, with electrophiles ($Pb(OAc)_4$; peracids; MoOPH; DDQ, HOAc) or their synthetic equivalents (NBS; *t*-BuOCl; $CuCl_2$, HOAc) have been discouraging, and this approach to fascaplysin has been temporarily abandoned. Likewise, treatment of **15** with a Vilsmeier reagent ($POCl_3$, DMF) at room temperature did not result in cyclization but, rather, gave aldehyde **29** in 90% yield. Prolonged heating of this reaction mixture in the presence of Pd/C gave only **29**, with no evidence of cyclization to homofascaplysin C (**5**). It is possible to cyclize **22** directly to **27** using $Hg(OAc)_2$ or modified Polonovski conditions (*m*-CPBA/trifluoroacetic anhydride), but the reactions are unclean and the yield of **27** is only about 10%.

The reluctance of **15** to cyclize with electrophiles, other than CF_3CO_2H, steered our attention to the utilization of pentacycle **7** as a vehicle for the synthesis of the alkaloids **1**, **4**, and **5**. We anticipated that the C-13 position would be the preferred site of electrophilic attack in **7** since the resulting species would be the highly stabilized *N*-phenyl-β-carbolinium ion **30**. In contrast, electrophilic attack at C-6, C-7, or C-7a would generate the clearly less stable species **31**–**33**, respectively.


7 **30**


31


32


33

Indeed, treatment of **7** with the Vilsmeier reagent gave homofascaplysin C (**5**) in 88% yield (Scheme IV). Treatment of **7** with oxalyl chloride followed by methanol

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[22] (a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812. (b) Gribble, G. W.; Johnson, J. L.; Saulnier, M. G. *Heterocycles* **1981**, *16*, 2109.

[23] For examples of trifluoroacetic acid-induced 2,2′-indole dimerization, see: (a) Bach, N. J.; Kornfeld, E. C. *Tetrahedron Lett.* **1973**, 3315. (b) Hashizume, K.; Shimonishi, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3806. (c) Omori, Y.; Matsuda, Y.; Aimoto, S.; Shimonishi, Y.; Yamamoto, M. *Chem. Lett.* **1976**, 805. See also: (d) Black, D. St. C.; Kumar, N.; Wong, L. C. H. *J. Chem. Soc., Chem. Commun.* **1985**, 1174.

[24] Reference 21, pp 11-15.

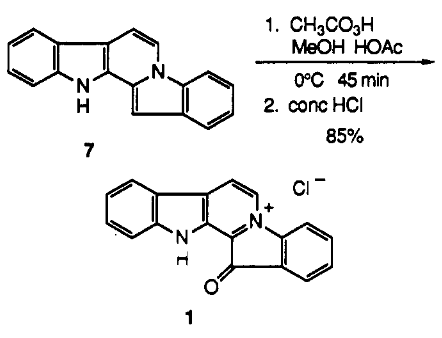
[25] Waldi, D. In *Thin Layer Chromatography. A Laboratory Handbook*; Stahl, E., Ed.; Springer-Verlag: New York, 1965; p 490.

[26] For the formation of similar dimers in the indolo[2,1-*a*]isoquinoline series, see: (a) Hess, U.; Hiller, K.; Schroeder, R.; Gründemann, E. *J. Prakt. Chem.* **1977**, *319*, 568. (b) Mak, C.-P.; Brossi, A. *Heterocycles* **1979**, *12*, 1413. (c) Yasuda, S.; Hirasawa, T.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull.* **1989**, *37*, 1682.

[27] Another indication that a radical process is involved is that dimerization has been induced in the indolo[2,1-*a*]isoquinoline series electrolytically[26a] or by air.[26b,c]

gave homofascaplysin B (4) in essentially quantitative yield from 7. Lower yields of 4 resulted when 7 was treated with methyl oxalyl chloride. Both 5 and 4 exhibited spectra identical to those of the natural products.

For the synthesis of fascaplysin (1) from 7, an electrophilic oxygen species was obviously needed. Although a number of such reagents are known to be able to introduce an oxygen into an unsubstituted indole C-3 position,[28] they have found limited utility, usually resulting in side reactions which give complex mixtures and low yields. In the present case, treatment of 7 with *m*-chloroperbenzoic acid, magnesium monoperoxyphthalate, H_2O_2, or, preferably, peracetic acid in methanol, followed by treatment with aqueous concd HCl, afforded fascaplysin (1) as a red powder in 85% yield, identical with a sample and spectra of the natural product. Although the oxidation of 7 with peracetic acid appears to be nearly quantitative by TLC, significant material losses are incurred upon isolation and chromatography.



In summary, we have described very efficient syntheses of fascaplysin (1) and homofascaplysins B (4) and C (5) in overall yields from indole (seven steps) of 65%, 76%, and 67%, respectively. All three syntheses proceed from the versatile intermediate pentacycle 7. Except for the last step in the synthesis of 1, none of the steps involve chromatography. Of particular note is the fact that indole is used to craft both "halves" of fascaplysin, and therefore, our syntheses should be readily adaptable to the preparation of indole-ring-substituted fascaplysin and homofascaplysin analogues.

Experimental Section

Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 599 or, for FTIR, on a Bio-Rad FTS 40 spectrometer. NMR spectra were obtained with a Varian EM-360 instrument, MS on a Finnigan EI-CI 4023 spectrometer (70 eV, unless otherwise stated), and UV spectra on a Hewlett-Packard 8451A spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Solvents and chemicals were used as purchased unless otherwise stated. THF was dried by distillation from sodium/benzophenone ketyl, DMF was dried over activated 4-Å molecular sieves, and MeOH was distilled from Mg. All reactions were performed under nitrogen unless otherwise stated.

1-(1,2-Dioxo-2-(3-indolyl)ethyl)indole (19). A solution of indole (17) (5.88 g, 50 mmol) in dry THF (50 mL) was added dropwise over 30 min to a stirred suspension of NaH (1.32 g, 55 mmol) in THF (50 mL) keeping the temperature <30 °C. After 30 min at rt a solution of 18[14] in THF (50 mL) and dry DMF (10 mL) was added dropwise over 30 min, again keeping the temperature <30 °C. The mixture was stirred at rt for 90 min and poured into water (1000 mL). The resulting precipitate was collected by filtration, washed with water, air-dried, and then dried in vacuo (~1 Torr) at 60 °C to give 19 (12.37 g, 86%) as a tan solid. Recrystallization from EtOH gave pale yellow flakes, mp 228–229 °C: IR (KBr) 3300 (broad), 1690, 1600, 1515, 1445, 1395, 1340, 780, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.57 (s, 1 H), 8.42–8.32 (m, 2 H), 8.28–8.22 (m, 1 H), 7.70 (d, 1 H), 7.64–7.58 (m, 2 H), 7.47–7.31 (m, 4 H), 6.83 (d, 1 H); ^{13}C NMR (DMSO-d_6) δ 182.1, 164.8, 138.9, 137.0, 134.7, 130.6, 126.6, 125.1, 124.5, 124.1, 123.1, 121.3, 121.1, 115.9, 112.9, 112.6, 110.3, 110.2; MS *m/e* 288 (M$^+$), 144, 116, 89 (100); UV (MeOH) λ_{max} 318, 250 nm. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.98; H, 4.20; N, 9.72. Found: C, 75.06; H, 4.24; N, 9.71.

3-(2-(1-Indolyl)ethyl)indole (15). Sodium borohydride (3.8 g, 100 mmol) was added in one portion to a stirred solution of 19 (2.88 g, 10 mmol) in THF (100 mL) at rt. The mixture was cooled in an ice bath, and CF_3COOH (7.7 mL, 100 mmol) was added dropwise over 10 min (vigorous gas evolution). The mixture was slowly heated to reflux (more gas was produced). After 20 h at reflux the mixture was allowed to cool to rt and concentrated in vacuo. The residue was partitioned between water (75 mL) and EtOAc (75 mL), and the two phases were separated. The aqueous layer was extracted with EtOAc (75 mL). The combined organic extract was washed with water (100 ml) and brine and dried ($MgSO_4$). Concentration in vacuo gave a yellow oil which was dissolved in warm *i*-PrOH. On standing, crystals separated which were collected by filtration, washed with *i*-PrOH, and dried in vacuo (~1 Torr) to give 1.12 g of 15 as a pale yellow solid. A second crop (0.43 g) was obtained by flash chromatography of the mother liquor. The total yield was 60%. The material was identical (TLC, ^{1}H and ^{13}C NMR) to 15 obtained by oxidation of 22 (vide infra).

3-(1,2-Dioxo-2-(1-indolinyl)ethyl)indole (21). A solution of 18[14] (20.85 g, 100 mmol) in THF (300 mL) was added dropwise over 45 min to an ice-cooled mechanically stirred mixture of indoline (20) (11.97 g, 100 mmol), K_2CO_3 (27.6 g, 200 mmol), and THF (200 mL). A voluminous ppt formed. The mixture was stirred at rt for 2 h and poured into water (2000 mL) to give a white solid which was collected by filtration, washed with water, air-dried, and dried in vacuo (~1 Torr) at 60 °C to give 21 (27.10 g, 93%) as a white solid, mp 231–232 °C. The analytical sample was obtained as fluffy white needles from EtOH, mp 233.5–234 °C: IR (KBr) 3160 (broad), 1630, 1600, 1490, 1440, 1250, 1165, 750 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.41 (s, 1 H), 8.37–8.17 (m, 3 H), 7.59–7.55 (m, 1 H), 7.37–7.24 (m, 4 H), 7.10 (t, 1 H), 4.08 (t, $J = 8.3$ Hz, 2 H), 3.12 (t, $J = 8.3$ Hz, 2 H);[18] ^{13}C NMR (DMSO-d_6) δ 184.7, 164.7, 141.9, 137.8, 137.0, 132.6, 127.1, 125.3, 125.1, 124.5, 123.6, 122.6, 121.0, 116.6, 112.7, 112.4, 48.0, 27.7;[18] MS *m/e* 290 (M$^+$), 262, 144 (100), 128, 119, 117; UV λ_{max} 314, 252 nm. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 74.46; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.90; N, 9.62.

3-(2-(1-Indolinyl)ethyl)indole (22). AlH_3 was prepared[20] by dropwise addition of H_2SO_4 (3.6 mL, 65 mmol, 96%, *d* 1.84) over 10 min to a stirred mixture of $LiAlH_4$ pellets (5.1 g, 134 mmol) and THF (200 mL) keeping the temperature below 20 °C. **Caution!** *Very* exothermic. The mixture was stirred at rt for 45 min after which time nearly all of the $LiAlH_4$ pellets had dissolved. A solution of 21 (11.61 g, 40 mmol) in THF (400 mL) was added dropwise over 1 h, keeping the temperature <10 °C. After 75 min at rt the mixture was cooled again and the excess AlH_3 was decomposed by *careful* addition of water/THF (1:1, 50 mL) followed by a solution of NaOH (10 g) in water (200 mL). A white gummy material formed. The supernatant was decanted and concentrated in vacuo to ~150 mL. The white gum was extracted with EtOAc (5 × 75 mL), and the combined extract was added to the concentrated supernatant along with water (150 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (100 mL) and the combined organic extract was washed with water (300 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo to give 22 (10.19 g, 97%) as a beige solid, mp 130–3 °C. The analytical sample was crystallized from *i*-PrOH, mp 135.5–136 °C: IR (KBr) 3370, 2700, 1600, 1455, 1250, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (broad s, 1 H), 7.65 (d, 1 H), 7.37 (d, 1 H), 7.25–7.05 (m, 5 H), 6.65 (t, 1 H), 6.52 (d, 1 H), 3.48–3.40 (m, 4 H), 3.06 (t, 2 H), 2.98 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 152.3, 136.1, 130.0, 127.4, 127.3, 124.4, 121.9, 121.6, 119.2, 118.6, 117.3, 113.7, 111.1, 52.9, 49.6, 28.5, 22.9; MS *m/e* 262 (M$^+$), 143, 132 (100), 130, 117, 115, 105, 103; UV (MeOH) λ_{max} 292, 260, 222 nm. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.40; H, 6.91; N, 10.68. Found: C, 82.28; H, 6.93; N, 10.64.

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(28) Reference 21, pp 145–160.

1-(2-(3-Indolyl)ethyl)indole (15). A mixture of **22** (6.57 g, 25 mmol), activated MnO_2 (8.7 g, 100 mmol), and $CHCl_3$ (125 mL) was refluxed for 4 h, cooled to rt, and filtered through Celite. Concentration in vacuo gave **15** (6.45 g, 99%) as a tan solid, mp 150–2 °C. The analytical sample was crystallized from *i*-PrOH, mp 157.5–158 °C: IR (KBr) 3390, 1455, 1315, 1225, 1170, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.93 (broad s, 1 H), 7.64 (t, 2 H), 7.39 (d, 1 H), 7.38 (s, 1 H), 7.27–7.10 (m, 4 H), 6.97 (d, 1 H), 6.77 (d, 1 H), 6.45 (d, 1 H), 4.44 (t, 2 H), 3.29 (t, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.2, 135.8, 128.6, 128.0, 127.0, 122.2, 122.1, 121.3, 120.9, 119.5, 119.2, 118.4, 112.5, 111.2, 109.4, 100.8, 46.9, 26.2; MS *m/e* 260 (M^+), 149, 131, 130 (100); UV (MeOH) λ_{max} 284, 224 nm. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 82.94; H, 6.25; N, 10.75.

6,7,12b,13-Tetrahydro-12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (25) and 6,7,7a,12a-Tetrahydro-12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (26). Diindole **15** (2.60 g, 10 mmol) was dissolved in CF_3COOH (25 mL) at rt. The red solution was allowed to stand at rt for 30 min and was then poured into ice–water (200 mL). A pink precipitate formed which was extracted with EtOAc (2 × 100 mL). The combined extracts were washed with water (100 mL), ice-cold aqueous NaOH (3 M, 100 mL), water (100 mL), and brine, dried ($MgSO_4$), and evaporated. Flash-chromatography (hexanes/EtOAc (7:3)) gave **26** (0.22 g, 8%) as a colorless oil that crystallized on standing, mp 49–55 °C: IR (KBr) 3390, 3060, 1615, 1490, 1465, 1340, 1255, 755, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1 H), 7.25–7.00 (m, 5 H), 6.78 (t, 1 H), 6.60 (d, 1 H), 6.46 (s, 1 H), 5.20 (d, 1 H), 4.05 (m, 2 H), 3.80–3.70 (m, 1 H), 2.43–2.18 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 150.2, 137.1, 135.8, 130.2, 128.1, 127.9, 123.7, 121.2, 120.3, 119.8, 119.2, 110.0, 109.0, 99.0, 55.5, 39.0, 39.0, 26.3; MS, *m/e* 260 (M^+), 259, 149, 130, 117, 57 (100); UV (MeOH) λ_{max} 286, 224, 206 nm.

Further elution gave **25** (2.08 g, 80%) as a white solid, mp 189–193 °C. The analytical sample was obtained from benzene, mp 195–197 °C: IR (KBr) 3420, 3170 (broad), 1615, 1490, 1470, 1335, 1235, 1135, 1015, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1 H), 7.39 (d, 1 H), 7.24 (d, 1 H), 7.18–6.99 (m, 4 H), 6.74 (d, 1 H), 6.64 (t, 1 H), 5.03 (dd, 1 H), 4.03 (dd, 1 H), 3.44–3.32 (m, 2 H), 3.09 (d, 1 H), 2.92 (m, 1 H), 2.57 (dd, 1 H); ^{13}C NMR ($CDCl_3$) δ 150.3, 136.0, 134.6, 129.1, 127.4, 127.2, 125.2, 121.8, 119.5, 118.6, 118.0, 110.7, 109.5, 108.2, 59.3, 42.3, 34.6, 17.3; MS *m/e* 260 (M^+), 259 (100), 245, 232, 143, 130, 115; UV (MeOH) λ_{max} 292, 284, 226 nm. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76. Found: C, 83.05; H, 6.21; N, 10.75.

6,7-Dihydro-12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (27). Diindole **15** (9.81 g, 37.7 mmol) was dissolved in CF_3COOH (75 mL) at rt, and the red solution was allowed to stand at rt for 30 min and poured into ice–water (300 mL). The resulting pink precipitate was extracted with EtOAc (2 × 250 mL). The extract was washed with water (250 mL), ice-cold aqueous NaOH (3 M, 350 mL), water (250 mL), and brine and dried ($MgSO_4$). The $MgSO_4$ was filtered off, Pd/C (10%, ~1 g) was added, and the mixture was refluxed for 4 h, cooled to rt, and filtered through Celite. Concentration in vacuo gave **27** (9.57 g, 98%) as a light tan solid, mp 263–265 °C dec (from EtOAc): IR (KBr) 3400, 1435, 1285, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.62 (s, 1 H), 7.58 (d, 1 H), 7.56 (d, 1 H), 7.49 (d, 1 H), 7.41 (d, 1 H), 7.19–7.11 (m, 2 H), 7.09–6.99 (m, 2 H), 6.74 (s, 1 H), 4.34 (t, 2 H), 3.23 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 137.2, 137.1, 130.7, 128.5, 127.6, 126.3, 122.0, 121.5, 120.2, 119.5, 119.2, 118.4, 111.4, 109.6, 107.8, 95.1, 40.9, 20.4; MS *m/e* 258 (M^+, 100), 128; UV (MeOH) λ_{max} 360, 340, 228 nm.[29] Anal. Calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.66; H, 5.48; N, 10.83.

12*H*-Pyrido[1,2-*a*:3,4-*b*′]diindole (7). Diindole **15** (1.30 g, 5.0 mmol) was dissolved in CF_3COOH (12 mL) at rt, and the red solution was allowed to stand at rt for 30 min and poured into ice–water (100 mL). The resulting pink precipitate was extracted with EtOAc (2 × 50 mL), and the extract was washed with water (100 mL), ice-cold aqueous NaOH (3 M, 100 mL), water (100 mL), and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in freshly distilled 2-ethoxyethyl ether (25 mL), Pd/C (10%, ~0.1 g) was added, and the mixture was refluxed for 6 h, cooled to rt (a precipitate formed during the reaction), and filtered through Celite. Concentration of the filtrate in vacuo gave **7** (0.69 g) as a greenish solid. The filter cake was extracted with acetone in a Soxhlet extractor, and the extract was concentrated in vacuo to give another crop (0.50 g) of **7**. Total yield 93%. The analytical sample was obtained by sublimation to afford mustard colored crystals, mp 264–268 °C (the mp of a sample after chromatographic purification on silica gel was 229–232 °C): IR (KBr) 3390, 1530, 1440, 1340, 1300, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.20 (s, 1 H), 8.60 (d, 1 H), 8.23 (d, 1 H), 8.03 (d, 1 H), 7.83 (d, 1 H), 7.59 (d, 1 H), 7.38–7.17 (m, 5 H), 6.99 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 138.2, 130.8, 128.4, 128.3, 123.8, 123.3, 122.3, 120.1, 119.7, 119.6, 119.5, 117.9, 111.6, 111.4, 111.1, 102.8, 88.8;[30] MS *m/e* 256 (M^+, 100), 128; UV (MeOH) λ_{max} 410, 388, 350, 334, 312, 282, 262 nm. Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.32; H, 4.73; N, 11.00.

From reactions using unpurified 2-ethoxyethyl ether, there was obtained a compound tentatively assigned as 13,13′-bis(12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole) (**28**): mp 319–322 °C; IR (KBr) 3460, 3410, 1525, 1410, 1340, 1315, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.38 (s, 1 H), 8.80 (d, 1 H), 8.41 (d, 1 H), 7.99 (d, 1 H), 7.46 (d, 1 H), 7.38–7.07 (m, 6 H); ^{13}C NMR (DMSO-d_6) δ 138.3, 131.3, 129.7, 128.5, 127.0, 123.2, 122.7, 122.0, 119.9, 119.5, 119.0, 118.9, 118.4, 112.2, 112.2, 111.3, 102.8, 95.2; MS (35 eV) *m/e* 510 (M^+, 100), 343, 255; UV (MeOH) λ_{max} 420, 354, 288, 262 nm. Anal. Calcd for $C_{36}H_{22}N_4$: C, 84.68; H, 4.34; N, 10.97. Found: C, 84.04; H, 4.44; N, 10.94.

1-(2-(3-Indolyl)ethyl)indole-3-carboxaldehyde (29). Phosphorus oxychloride (0.2 mL, 2.1 mmol) was added slowly via a syringe to ice-cold dry DMF (5 mL). The solution, protected from moisture with a drying tube, was stirred for 15 min at rt and then recooled. A solution of diindole **15** (0.52 g, 2 mmol) in DMF (5 mL) was then added over 2 min, and the solution was stirred at rt for 3 h, poured into a mixture of ice and aqueous NaOH (100 mL, 1 M), and extracted with EtOAc (2 × 50 mL). The extract was washed with water (3 × 50 mL) and brine and dried ($MgSO_4$). Concentration in vacuo gave **29** (0.52 g, 90%) as a pale yellow solid. The analytical sample was obtained from benzene/MeOH, mp 185.5–186.5 °C: IR (KBr) 3300 (broad), 1630, 1525, 1385, 1175, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1 H), 9.84 (s, 1 H), 8.20 (s, 1 H), 8.12 (d, 1 H), 7.64 (d, 1 H), 7.56 (d, 1 H), 7.36–7.22 (m, 3 H), 7.10–6.96 (m, 3 H), 4.54 (t, 2 H), 3.26 (t, 2 H); ^{13}C NMR (DMSO-d_6) δ 184.3, 140.7, 140.7, 136.9, 136.1, 126.9, 124.7, 123.4, 123.2, 122.4, 121.0, 118.4, 118.2, 117.0, 111.4, 111.0, 110.3, 47.1, 25.4; MS *m/e* 288 (M^+), 158, 130 (100), 103; UV (MeOH) λ_{max} 292, 252, 222 nm. Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.44; H, 5.71; N, 9.44.

Homofascaplysin C (5). Phosphorus oxychloride (0.2 mL, 2.2 mmol) was added slowly via a syringe to ice-cold dry DMF (5 mL). The solution, protected from moisture with a drying tube, was stirred for 15 min at rt and then recooled. A solution of compound **7** (0.53 g, 2 mmol) in DMF (10 mL) was then added over ~2 min, and the solution was stirred at rt for 3 h and poured into ice–water (50 mL). The yellow mixture was made alkaline with 2 M NaOH, and the precipitate that formed was collected by filtration, washed thoroughly with water, and dried (50 °C (~1 Torr)) to give **5** (0.50 g, 88%) as a yellow solid, mp 237–242 °C (starts to sinter at 220 °C), which could be recrystallized from AcOH, mp 243–247 °C: IR (KBr) 3250, 1656, 1624, 1606, 1507, 1483, 1457, 1334, 1313, 1212, 736 cm^{-1}; the ^{1}H and ^{13}C NMR ($CDCl_3$) spectra correspond excellently with the data reported for authentic **5**[2] MS, *m/e* 284 (M^+, 100), 255, 227, 127.

Homofascaplysin B (4). Oxalyl chloride (0.57 mL, 6.0 mmol) was added slowly via a syringe to an ice-cooled suspension of **7** (1.28 g, 5.0 mmol) in dry THF (50 mL). The mixture was stirred for 1 h at 0 °C, and dry MeOH (25 mL) was added in one portion. After 15 min at 0 °C and 3 h at rt the mixture was poured into a mixture of ice and saturated aqueous $NaHCO_3$ (250 mL). The mixture was saturated with NaCl, and the precipitate was filtered off, washed with water, and dried in vacuo to give **4** (1.69 g, 99%) as a yellow solid, mp 216–218 °C (starts to sinter at 210 °C). An analytical sample was obtained from $CHCl_3$/*i*-PrOH, mp 225–227 °C: IR (KBr) 3215 (broad), 1735, 1644, 1573, 1470, 1430, 1330,

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(29) This corresponds well to the UV spectrum of 2,2′-diindolyl (350, 332, 226 nm), a sample of which was generously donated by Professor Jan Bergman, Royal Institute of Technology, Stockholm.

(30) Only 17 peaks could be found in the ^{13}C NMR spectrum.

1270, 1160, 1075, 990, 735 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$) correspond excellently with the data reported for authentic **4**;[2] MS *m/e* 342 (M^+), 283 (100), 255, 128, 127. UV (MeOH) λ_{max} 432, 408, 388, 364, 274, 226 nm. Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.67; H, 4.12; N, 8.18. Found: C, 73.57; H, 4.11; N, 8.18.

Fascaplysin (1). Peracetic acid (32%, 0.6 mL, 3 mmol) was added slowly to a stirred ice-cooled solution of **7** (0.26 g, 1 mmol), in THF (15 mL). The dark red solution was stirred at 0 °C for 20 min, and excess peracetic acid was decomposed by addition of a catalytic amount of 10% Pd/C. After 15 min the mixture was filtered through a pad of Celite, which was washed thoroughly with MeOH. The MeOH extract was concentrated in vacuo, and the residue was absorbed on silica gel and purified by vacuum liquid chromatography[31] (silica gel 60, Merck, 230–400 mesh, elution with gradually increasing amounts of AcOH [0–5%] in EtOH). The eluent was concentrated and redissolved in MeOH. Concentrated aqueous HCl (0.3 mL) was added, and the solution was allowed to stand for 1 h, concentrated, and dried (60 °C, ~1 Torr) to give **1** (0.26 g, 85%) as a red brown solid, which was identical (FTIR, ^{1}H NMR, MS, UV, and TLC) with an authentic sample.[32]

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(31) (a) Pelletier, S. W.; Chokshi, H. P.; Desai, H. K. *J. Nat. Prod.* **1986**, *49*, 892. (b) Coll, J. C.; Bowden, B. F. *J. Nat. Prod.* **1986**, *49*, 934.

(32) A sample of fascaplysin and spectra were kindly provided by Professor Chris Ireland, University of Utah.

Synthesis of a Branched-Chain Inosose Derivative, a Versatile Synthon of N-Substituted Valiolamine Derivatives from D-Glucose[1]

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The synthesis of (1*S*)-(1(OH),2,4/1,3)-2,3,4-tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-oxo-1,2,3,4-cyclohexanetetrol (**7**), which is an important synthon for the synthesis of valiolamine (**8**)[2] and its N-substituted derivatives such as AO-128 (**9**)[3] having strong α-D-glucosidase inhibitory activity, is described. This branched-chain inosose derivative **7** has been prepared from the D-glucono-1,5-lactone derivative **2** which is readily available from D-glucose (**1**). The key step in the synthesis involves the stereospecific intramolecular carbocyclic ring closure of the 1-deoxy-2,6-heptodiulose derivatives **5a** and **5b** obtained by the oxidation of 2,3,4,6-tetra-*O*-benzyl-1-*C*-[bis(methylthio)methyl]-D-glucitol (**4a**) and 2,3,4,6-tetra-*O*-benzyl-1-*C*-(dichloromethyl)-D-glucitol (**4b**). The resulting branched-chain bis(methylthio)inosose derivative **6a** and dichloroinosose derivative **6b** have been converted to the desired branched-chain inosose derivative **7** by desulfurization of **6a** and dechlorination of **6b**.

Introduction

Valiolamine (**8**), (1*S*)-(1(OH),2,4,5/1,3)-5-amino-1-*C*-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol is a pseudoamino sugar first isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* and later semisynthesized by stereospecific conversion of valienamine to valiolamine.[2]

Valiolamine and its N-substituted derivatives have potent α-D-glucosidase inhibitory activity, and one of these derivatives, *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]valiolamine (**9**; AO-128) is presently undergoing clinical trials as an oral antidiabetic agent.[3]

In this paper, we report a stereospecific synthetic method for preparing (1*S*)-(1(OH),2,4/1,3)-2,3,4-tri-*O*-benzyl-1-*C*-[(benzyloxy)methyl]-5-oxo-1,2,3,4-cyclohexanetetrol (**7**), an important key compound in the synthesis of valiolamine and its N-substituted derivatives, which has been synthesized via its 6,6-bis(methylthio) and 6,6-dichloro derivatives (**6a** and **6b**) starting from 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**2**) which is readily available from D-glucose (**1**).

It is known that an intramolecular cyclization reaction (Wordworth–Emmons reaction) of the 1-deoxy-1-(dimethoxyphosphoryl)-D-*xylo*-2,6-heptodiulose derivative, obtained by chain-extension of tetra-*O*-benzyl-D-glucono-1,5-lactone (**2**) with lithium dimethyl methylphosphonate, results in the formation of an unsaturated inosose derivative, because an elimination reaction in the β-hydroxy

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(1) Part of this work and related experimental results are disclosed in the following patent application: Horii, S.; Fukase, H. (Takeda Chemical Industries, Ltd.). Eur. Pat. Appl. EP 260,121, 1988; *Chem. Abstr.* 1988, *109*, 129587v. Portions of this work were presented in Sept 1989 at the 198th National Meeting of the American Chemical Society. See: *Abstracts of Papers*. 198th National Meeting of the American Chemical Society; Washington, DC, 1989; Abstr. CARB 19.

(2) Horii, S.; Fukase, H.; Kameda, Y. *Carbohydr. Res.* **1985**, *140*, 185.

(3) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. AO-128 is the preclinical study code number of **9**.

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