Longicaudatine has strong reserpine-like activity, which is different from the activities described by Sandberg et al.[18] for fractionated extracts of *S. longicaudata*.

Experimental Section

Longicaudatine (1): mp 350 °C dec; $[\alpha]_D$ +141° (*c* 0.5, $CHCl_3$); UV λ_{max} 223 nm (log ϵ 4.66), 270 (sh), 284 (4.28), 290 (4.26), 307 (sh, 3.97); in perchloric acid a strong absorption maximum appears at 268 nm; IR λ_{max} (KBr) 3420, 2900, 1630, 1600, 1480, 740 cm^{-1}. The 400-MHz ^1H NMR spectrum was recorded in $CDCl_3$ on material containing 0.25 molecule of acetone of crystallization (Table I). ^{13}C NMR spectra were recorded at 62 and 25.15 MHz, in $CDCl_3$. Proton-noise-decoupled, off-resonance-decoupled, and selective decoupled (δ 9.6, 6.06, and 4.27 in the ^1H NMR spectrum) spectra were determined (see Table II). On TLC plates a blue color is obtained with the spray reagents 0.2 M iron(III) chloride in 35% aqueous perchloric acid and 1% cerium(IV) sulfate in 10% aqueous sulfuric acid.

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Bisnor-C-alkaloid H (3b): UV λ_{max} 293, 322 nm (sh); IR ν_{max} (KBr) 2920, 1640, 1600, 1480, 1460, 740 cm^{-1}. The 300-MHz ^1H NMR spectrum was recorded in $CDCl_3$ (see text). On TLC plates a blue color was obtained with the spray reagent 0.2 M iron(III) chloride in 35% aqueous perchloric acid and a purple color with 1% cerium(IV) sulfate in 10% aqueous sulfuric acid.

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Photodimerization of Coumarins in Micelles: Limitations of Alignment Effect

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Organized media such as micelles have shown great promise in achieving regio- and stereoselectivity in photochemical cycloaddition reactions as has been shown by recent reports. 7-Alkoxy- and 4-methyl-7-alkoxycoumarins dimerize in organic solvents to give the syn head–tail dimer. However, dimerization of these coumarins in SDS and CTAB micelles did not show any reversal in this trend. The results probably indicate that the micellar orientational effect is most effective only in those systems where the forces that control regiochemistry are weaker than hydrophobic association energies.

Photochemical cycloaddition is a useful synthetic tool which has been frequently exploited.[1] The two possible orientations commonly referred to as the head–head and head–tail regioisomers are formed in a variable ratio during the photoannelation of cyclopentenones and cyclohexenones.[2] Some control may be achieved by substitution in the enone or by variation of solvent polarity. Very recently, micellar alignment effects have been utilized to bring about regioselectivity during photoannelation reactions. This has been demonstrated in the case of cyclopentenones,[3] cyclohexenones,[4] and pyridinones.[5] Enhancement of regioselectivity during the dimerization of 9-(hydroxymethyl)anthracene has recently been observed.[6] Thus, the feasibility of exploiting preorientational effects of the micellar structure for selective synthesis has been demonstrated. Results of our study on 7-alkyl- and 4-methyl-7-alkoxycoumarins presented below demonstrate the limitations of micellar effects on photoannelation reactions.

Coumarins have been chosen for our investigation as their photochemical behavior is fairly well understood,[7,8] and therefore the environmental influence which is the subject of our concern would be easily understandable. Recently, we have demonstrated the use of micelles in enhancing the reactivity of coumarin and bringing about stereoselective dimerization.[9] This was attributed to the micellar polarity effect. Presently, we have chosen 7-alkoxy- and 4-methyl-7-alkoxycoumarins to study the micellar orientational effect. Our choice was dictated by the fact that 7-methoxy- and 4-methyl-7-methoxycoumarins generally give head–tail dimers upon excitation in organic solvents. Unlike the earlier systems studied,[3-5] these do not exhibit polarity-dependent product distribution, and therefore polarity effects of micelles can be excluded. Micellar solubilized 7-alkoxy- and 4-methyl-7-alkoxycoumarin molecules are expected to be arranged in such

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Table I. Photodimerization of 7-Alkoxycoumarins in Organic, Aqueous, and Micellar Media

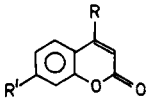
compd	media	[coumarin], M	duration of irradiation,[a] h	product formed[b]	yield,[c] %
7-*O*-methylcoumarin (1)	methylene chloride	0.25	72	syn HT	40
	water	2.1×10^{-3}	24	syn HT	65
	SDS (0.032 M)	1.1×10^{-2}	5	syn HT	70
	CTAB (0.01 M)	6.0×10^{-3}	72	syn HT	10
	methylene chloride/ benzophenone (0.1 M)	0.15	72	no reaction	
7-*O*-butylcoumarin (2)	chloroform-*d*	0.5	24	syn HT	35
	water	$<10^{-5}$		no reaction	
	SDS (0.05 M)	1.4×10^{-2}	30	syn HT	50
	CTAB (0.02 M)	1.1×10^{-2}	30	syn HT	5
	chloroform-*d*/ benzophenone (0.2 M)	0.25	30	no reaction	
7-*O*-hexylcoumarin (3)	chloroform-*d*	0.75	45	syn HT	75
	water	$<10^{-5}$		no reaction	
	SDS (0.05 M)	1.4×10^{-2}	45	syn HT	42
	CTAB (0.025 M)	1.6×10^{-2}	45	syn HT	5
	chloroform-*d*/ benzophenone (0.2 M)	0.25	45	no reaction	
7-*O*-heptylcoumarin (4)	chloroform-*d*	0.25	50	syn HT	54
	water	not soluble			
	SDS (0.05 M)	6×10^{-3}	50	syn HT	50
	CTAB (0.025 M)	6×10^{-3}	50	syn HT	6
	chloroform-*d*/ benzophenone (0.2 M)	0.25	50	no reaction	
7-*O*-octylcoumarin (5)	chloroform-*d*	0.25	50	syn HT	25
	water	not soluble			
	SDS (0.05 M)	6×10^{-3}	50	syn HT	25
	CTAB (0.025 M)	6×10^{-3}	50	syn HT	<5
	chloroform-*d*/ benzophenone (0.2 M)	0.25	50	no reaction	
7-*O*-dodecylcoumarin (6)	chloroform-*d*	0.25	50	syn HT	17
	water	not soluble			
	SDS (0.05 M)	5×10^{-3}	50	syn HT	10
	CTAB (0.025 M)	5×10^{-3}	50	syn HT	<5
	chloroform-*d*/ benzophenone (0.2 M)	0.25	50	no reaction	

[a] All irradiations were conducted in Pyrex vessels by using a 450-W medium-pressure mercury lamp. [b] Structures of the dimers were identified by their spectral properties. [c] Yields presented correspond to TLC isolated yields.

a way that the polar carbonyl groups are directed toward the polar regions of the micellar surfaces while aromatic and alkoxy parts of the molecules lie towards the hydrocarbon like interior of the micelles. The formation of head-head photodimers is expected to be favoured by this organization. Results presented below on 7-alkoxy and 4-methyl-7-alkoxycoumarins provide some insight into the micellar structure and the molecular forces that dictate regiochemistry and the hydrophobic interactions that control molecular orientation in micelles.

Results

The coumarins studied in organic solvents and cationic (CTAB) and anionic (SDS) micelles are shown below. Excitation of 7-alkoxycoumarins **1–6** in organic solvents



1 R = H; R′ = OCH_3 **7** R = CH_3; R′ = OCH_3
2 R = H; R′ = $O(CH_2)_3CH_3$ **8** R = CH_3; R′ = $O(CH_2)_3CH_3$
3 R = H; R′ = $O(CH_2)_5CH_3$ **9** R = CH_3; R′ = $O(CH_2)_5CH_3$
4 R = H; R′ = $O(CH_2)_6CH_3$ **10** R = CH_3; R′ = $O-(CH_2)_6CH_3$
5 R = H; R′ = $O(CH_2)_7CH_3$ **11** R = CH_3; R′ = $O-(CH_2)_7CH_3$
6 R = H; R′ = $O(CH_2)_{11}CH_3$ **12** R = CH_3; R′ = $O-(CH_2)_{11}CH_3$

(chloroform, acetonitrile, and benzene) gave a single dimer in all cases. Only 7-methoxycoumarin is found to be soluble in water, and excitation of 7-methoxycoumarin (2 $\times 10^{-3}$ M) in water readily gave a single dimer. However, at such low concentrations no dimerization was observed in organic solvents. The dimers obtained in all of these cases is established to have syn head–tail configurations by comparison of their spectral data with the syn head–tail dimer of 7-methoxycoumarin whose structure has been established through x-ray structural investigation.[10] Attempts to look for other isomers in the product mixture did not reveal their presence. Although the rate of dimerization for **1–6** was comparatively higher in chloroform than in benzene, the syn head–tail dimer is the only product in all organic solvents. Further, triplet sensitization with benzophenone did not bring any reaction. Thus we conclude that 7-alkoxycoumarins **1–6** in general dimerize from the lowest excited singlet state to give the syn head–tail dimer in all organic solvents and that the triplet state is not reactive.

The 7-alkoxycoumarins **1–6** were irradiated under the conditions indicated in Table I in SDS and CTAB micelles. The mean occupancy number never exceeded 10 both in SDS and CTAB micelles. The irradiations of **1–6** both in SDS and CTAB gave a single dimer namely the syn head–tail dimer. This is most unexpected on the basis of expected organization of coumarin molecules in micelles. The reactivity of **1–6**, under the same concentrations, was tremendously enhanced in micellar media compared to that in organic solvents. It is of interest to note that at

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Table II. Photodimerization of 4-Methyl-7-alkoxycoumarins in Organic, Aqueous, and Micellar Media

compd	media	[coumarin], M	duration of irradiation, h	product formed	yield, %
4-methyl-7-methoxycoumarin (7)	methylene chloride	0.25	72	syn HT	~10
	water	1.3×10^{-4}			
	SDS (0.03 M)	4.38×10^{-3}	72	syn HT	40
	CTAB (0.01 M)	3.95×10^{-3}	72	syn HT	<5
	methylene chloride/ benzophenone (0.15 M)	0.2	72	anti HT	50
	SDS (0.03 M)/ benzophenone (0.003 M)	0.8×10^{-3}	72	anti HT	70
	CTAB (0.01 M)/ benzophenone (0.001 M)	1.3×10^{-3}	72	anti HT	20
4-methyl-7-*O*-butylcoumarin (8)	chloroform-*d*	0.50	24	syn HT	45
	water	$\sim 10^{-5}$			
	SDS (0.05 M)	1.34×10^{-2}	60	syn HT	60
	CTAB (0.025 M)	1.34×10^{-2}	60	syn HT	40
	chloroform/ benzophenone (0.22 M)	0.34	60	anti HT	10
	SDS (0.05 M)/ benzophenone (0.01 M)	1.25×10^{-2}	60	no dimer	
4-methyl-7-*O*-hexylcoumarin (9)	chloroform-*d*	0.50	30	syn HT	54
	water	$\sim 10^{-5}$			
	SDS (0.05 M)	2.23×10^{-2}	72	syn HT	65
	CTAB (0.025 M)	1.62×10^{-2}	72	syn HT	22
	chloroform/ benzophenone (0.25 M)	0.38	72	anti HT	10
	SDS (0.05 M)/ benzophenone (0.013 M)	2.0×10^{-2}	72	no dimer	
4-methyl-7-*O*-heptylcoumarin (10)	chloroform-*d*	0.25	65	syn HT	60
	water	not soluble			
	SDS (0.05 M)	0.91×10^{-2}	65	syn HT	51
	CTAB (0.025 M)	0.85×10^{-2}	65	syn HT	35
4-methyl-7-*O*-octylcoumarin (11)	chloroform-*d*	0.25	60	syn HT	70
	water	not soluble			
	SDS (0.05 M)	0.91×10^{-2}	100	syn HT	47
	CTAB (0.025 M)	0.75×10^{-2}	100	syn HT	40
4-methyl-7-*O*-dodecylcoumarin (12)	chloroform-*d*	0.25	80	syn HT	35
	water	not soluble			
	SDS (0.05 M)	0.3×10^{-2}	100	syn HT	35
	CTAB (0.025 M)	0.3×10^{-2}	100	syn HT	10

such concentrations (10^{-2} M) no dimerization of **1–6** occurred in organic solvents. Such an enhancement in reactivity in micellar media could simply be due to the local concentration effect. Further, **1–6** were found to dimerize more readily in SDS than in CTAB micelles. No attempt was made to measure the quantum yield of dimerization as most of these reactions required long irradiation times. However, the dimer yields obtained for the same duration of irradiation under identical conditions are presented in Table I.

4-Methyl-7-alkoxycoumarins studied in organic and micellar media are shown above (**1–12**), and the results are presented in Table II. Similar to 7-alkoxycoumarins, direct excitation of **7–12** in organic solvents readily gave syn head–tail dimer in each case. The structure of the dimer was assigned on the basis of the comparison of their spectral properties with literature reports on similar systems.[8,10] However, as opposed to **1–6**, triplet sensitization of **7–12** readily gave anti head–tail dimer. Once again contrary to general expectation, direct excitation of **7–12** in SDS and CTAB micelles gave only syn head-tail dimer; the expected head–head dimer was found to be absent. Although triplet sensitization of 4-methyl-7-methoxycoumarin in SDS and CTAB micelles gave anti head–tail dimer, **8–12** failed to react in the presence of benzophenone in micelles.

Discussion

The emphasis of the present study is on the use of micelles to orient organic molecules and bring about regioselectivity during dimerization reactions. In this connection, the failure to induce the formation of head-head dimer upon excitation of **1–12**, solubilized in micelles, is noteworthy. The above observation is interesting in view of the reported behavior of cyclopentenones,[3] cyclohexenones,[4] pyridinones,[5] and 9-(hydroxymethyl)-anthracene.[6]

Cyclopentenones[3] and cyclohexenones[4] have been demonstrated to yield head–head dimers in micellar media. On the other hand, in our systems even the introduction of a hydrophobic chain failed to reverse the formation of syn head–tail dimer. While introduction of a butyl group had a powerful effect on cyclopentenone dimerization in micellar media, in our systems even a dodecyl group was unable to effect head–head dimer formation, even in small amounts. This contrasting behavior can result from two features. Either the 7-alkoxycoumarin molecules are not suitably oriented with the carbonyl group at the interface or the hydrophobic energy introduced by alkyl chains is not sufficient to affect the inherent molecular forces that control the regiochemistry. We expect that introduction of a long chain such as heptyl, octyl, and dodecyl would ensure that the carbonyl portion of coumarin molecules are at the interface with the long hydrocarbon chain buried inside the micelle. In this context, we suggest that molecular forces controlling regiochemistry are much stronger in **1–12** than the hydrophobic interaction introduced by alkyl chains. Therefore, the former continues to control the regiochemistry. The results with **1–12**, we believe, clearly indicate that the micellar orientational effect can be profitably utilized only in systems where the forces that control regiochemistry are weaker than hydrophobic as-

Table III. Physical and Spectral Data of Selected Coumarins

compd	mp, °C	IR, cm^{-1} (C=O)	UV,[b] λ_{max}, nm (ϵ_{max}, M^{-1} cm^{-1})	H^1 NMR[d,e] (Me_4Si), δ
3		1730[a]	324 (18 340)	0.93 (m, 3 H), 1.13-1.93 (m, 8 H), 3.90 (t, 2 H, J = 6 Hz), 6.025 (d, 1 H, J = 9 Hz), 6.56-6.73 (m, 2 H), 7.25 (d, 1 H, J = 10 Hz), 7.52 (d, 1 H, J = 9 Hz)
6	57-59	1740[b]	322 (15 500)	0.90 (m, 3 H), 1.00-1.95 (m. 20 H), 4.00 (t, 2 H, J = 6 Hz), 6.1 (d, 1 H, J = 10 Hz), 6.73 (m, 2 H), 7.28 (d, 1 H, J = 10 Hz), 7.54 (d, 1 H, J = 10 Hz)
8	47-48	1720[c]	324 (16 670)	1.00 (m, 3 H), 1.32-1.87 (m, 4 H), 2.32 (br s, 3 H); 3.92 (t, 2 H, J = 6 Hz), 5.88 (br s, 1 H), 6.57-6.72 (m, 2 H), 7.29 (d, 1 H, J = 9 Hz)
11	40-41	1730[b]	323 (16 800)	0.90 (m, 3 H), 1.10-1.90 (m, 12 H), 2.36 (br s, 3 H), 3.96 (t, 2 H, J = 6 Hz), 6.00 (br s, 1 H), 6.60-6.80 (m, 2 H), 7.46 (d, 1 H, J = 10 Hz)

[a] Neat. [b] In $CHCl_3$. [c] In Nujol. [d] In CCl_4. [e] d = doublet, t = triplet, m = multiplet, and br s = broad singlet.

Table IV. Physical and Spectral Data of a Few Selected Dimers

compd	mp, °C	IR, cm^{-1} (C=O)	UV,[b] λ_{max}, nm (ϵ, M^{-1} cm^{-1})	H^1 NMR (Me_4Si),[c,d] δ
syn-HT dimer of 3	115-116	1750	280 (4020), 247 (6700)	0.93 (t, 6 H), 1.1-1.83 (m, 16 H), 3.77 (t, 4 H, J = 6 Hz), 4.10 (s, 4 H), 6.07 (d, 2 H, J = 2 Hz), 6.53 (dd, 2 H, J = 2, 9 Hz), 6.92 (d, 2 H, J = 9 Hz)
syn-HT dimer of 6	96-97	1750	279 (1400), 244 (2450)	0.90 (t, 6 H), 1.20-1.80 (m, 20 H), 4.00 (t, 2 H, J = 6 Hz), 4.10 (s, 4 H), 6.05 (d, 2 H, J = 2 Hz), 6.70 (dd, 2 H, J = 2, 10 Hz), 7.20 (d, 2 H, J = 10 Hz)
syn-HT dimer of 8	135-136	1745	280 (3210), 249 (3970)	0.92 (t, 6 H), 1.13-1.80 (m, 14 H), 3.34 (s, 2 2 H), 3.76 (t, 4 H, J = 6 Hz), 5.98 (d, 2 H, J = 2 Hz), 6.57 (dd, 2 H, J = 2, 9 Hz), 7.04 (d, 2 H, J = 9)
syn-HT dimer of 11	70-72	1745	278 (4100), 244 (7850)	0.90 (t, 6 H), 1.10-1.50 (m, 24 H), 1.66 (s, 6 H), 3.36 (s, 2 H), 3.76 (t, 4 H, J = 6 Hz), 6.10 (d, 2 H, J = 2 Hz), 6.63 (dd, 4 H, J = 2, 10 Hz), 7.16 (d, 2 H, J = 10 Hz)
anti-HT dimer of 7	202-204	1745	275 (2000), 246 (3900)	1.25 (s, 6 H), 3.39 (s, 2 H), 3.84 (s, 6 H), 6.64 (d, 2 H, J = 2.6 Hz), 6.78 (dd, 2 H, J = 2.6, 8.5 Hz), 7.1 (d, 2 H, J = 8.5 Hz)

[a] In Nujol. [b] In chloroform. [c] In $CDCl_3$. [d] s = singlet, d = doublet, t = triplet, m = multiplet, and dd = douplet of douplet.

sociation energy. A study of a series of closely related systems varying in the nature of forces that control regiochemistry would be revealing.

As expected, at comparable substrate concentrations, the efficiency of intermolecular cycloaddition of **1–12** is higher for a micellar solution than for a homogeneous solution (Tables I and II). This expectation is based on the high local concentrations of a substrate that are achieved by solubilization of the substrate into micellar aggregates. However, the difference in the efficiency of dimerization of **1–12** between SDS and CTAB was not expected. In all of the systems studied dimerization was generally more efficient (by an order of magnitude) in SDS than in CTAB. This can originate from the bromide quenching of the excited singlet state (heavy atom induced intersystem crossing to the triplet state), thus resulting in poor efficiency of dimerization from S_1. This appears to be a true possibility as fluorescence of **1–12** was found to be quenched by potassium bromide. However, if this is the main cause of the decreased efficiency in CTAB, it is not obvious why the triplet anti head–tail dimer is not formed in the case of **7–12** when excitation is conducted in CTAB. Therefore, at this stage, the likely reasons for the variation in the efficiency of dimerization between SDS and CTAB micelles escape our comprehension.

Experimental Section

Materials. Sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) from Sigma were recrystallized twice from 95% ethanol and methanol–ether mixture, respectively. Benzophenone (Aldrich) was used as received. Double-distilled water was used. All organic solvents were distilled before use.

Synthesis of Hydroxycoumarins and Bromoalkanes. 7-Hydroxy- and 4-methyl-7-hydroxycoumarins[11] were prepared by condensing malic acid and ethyl acetoacetate, respectively, with resorcinol in the presence of concentrated sulfuric acid. The hydroxycoumarins thus obtained were purified by repeated crystallization from alcohol–water mixture. 7-Hydroxycoumarin separated as pale pink prisms (decolorizing carbon was used), mp 225–227 °C (lit.[11] mp 227–228 °C). 4-Methyl-7-hydroxycoumarin crystallizes as colorless needles, mp 185 °C (lit.[11] mp 185 °C).

1-Bromoalkanes were prepared from the corresponding alcohols either by treatment with $HBr–H_2SO_4$ or with PBr_3 following the prescribed procedure.[12]

Synthesis of 7-Alkoxy- and 4-Methyl-7-alkoxycoumarins. General Method. 7-Methoxy- and 4-methyl-7-methoxycoumarins (**1** and **7**) were prepared by following the reported procedure.[8] All the other 7-alkoxy- and 4-methyl-7-alkoxycoumarins were prepared by refluxing for 20–30 h the corresponding hydroxycoumarins (0.05 mol) with the bromoalkanes (0.062 mol) in the presence of anhydrous potassium carbonate (0.1 mol) either in dry acetone (**2, 3, 8, 9**) or in dry dimethylformamide (**4–6, 10–12**). The solvent was partially distilled off, and the residual mixture was transferred into an excess of cold water. The suspended organic material was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate. The residue obtained after distilling off chloroform was passed through a silica

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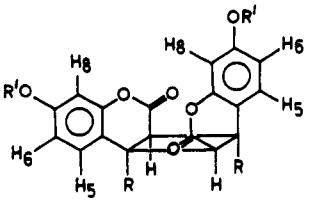
gel column and eluted with a benzene–hexane mixture. The yields of the alkoxycoumarins were 40–60%. The physical and spectral characteristics of a few coumarins as representatives are given in Table III.

Solubilization of Reactants in Micellar Solutions. Weighed amounts of powdered alkoxycoumarins were stirred for 12–24 h with 60–80 mL of the surfactant solutions (SDS, CTAB) of concentrations well above critical micelle concentrations (cmc's of SDS and CTAB are 8×10^{-3} and 9.5×10^{-4} M, respectively). The micellar solutions were filtered through Whatman No. 1 filter paper to remove suspended particles, if any. By a similar procedure micellar solutions containing both coumarin and benzophenone were also prepared.

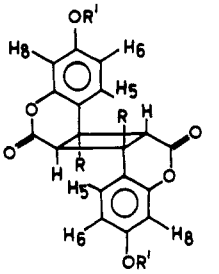
Irradiation and Workup Procedure. The clear transparent micellar solutions were irradiated in Pyrex tubes with a 450-W medium-pressure mercury arc lamp (Applied Photophysics Ltd.) for 5–72 h. Bulk irradiations in organic solvents and in aqueous media were also carried out in Pyrex vessels under similar conditions. Irradiations in deuterated organic solvents were carried out in Pyrex NMR tubes. During the course of irradiation the dimer formed in the micellar and aqueous phases precipitate out, on account of its lower solubility in the medium. Due to this, some of the irradiation mixtures become turbid after few hours of exposure. However, prolonged irradiation resulted in neat separation of crystalline products.

These precipitated products from the micellar solutions were collected by filtering the solutions through either a G-4 sintered crucible or Whatman No. 1 filter paper, washed thoroughly with water, and dried slowly in air/air oven. The filtrates were diluted to a concentration that was approximately one-third of the respective cmc's and extracted with ether or chloroform. The contents of the aqueous irradiation mixture were collected by extracting with chloroform. The products in the organic residue were separated from the reactants by preparative TLC (silica gel/benzene–chloroform mixture), purified by recrystallization (chloroform–carbon tetrachloride mixture), and analyzed spectroscopically.

Structure of the Dimers. All dimers had elemental analyses (C, H) within calculated values (0.35%). Spectral properties of a few selected dimers are presented in Table IV. The dimers formed upon direct irradiation of **1–12** in organic, aqueous, and micellar media show a closely similar pattern for the aromatic protons (H_5, H_6, and H_8) in the NMR spectrum. All these dimers have been assigned the syn head–tail configuration on the basis of the structure of 7-methoxycoumarin (**1**) dimer which has been unequivocally solved by X-ray analysis.[10] The protons H_5, H_6, and H_8 of the dimers of **1–12** can be described as part of an AMX system. In comparison with the same protons of the monomer, H_5 and H_6 are slightly shifted upfield while H_8 is shifted to a higher field by over 0.6 ppm. This strong shielding effect on H_8 caused by the diamagnetic anisotropy of a phenyl nucleus situated in front of this proton is possible only in the syn head–tail configuration[8] shown below.



Syn head-tail dimer



Anti head-tail dimer

The benzophenone-sensitized irradiation products of 4-methyl-7-alkoxycoumarins **7–12** were assigned the anti head–tail configuration by the ^1H NMR spectrum of the dimer obtained from **7**. At δ 3.39 and 1.25 two peaks were observed due to cyclobutane protons and cyclobutane methyl protons, respectively. These protons absorb considerably higher than the corresponding protons in the syn configuration. This shielding effect due to diamagnetic anisotropy effect of both the carbonyl group and the phenyl nucleus is possible in the anti head–tail configuration.

Registry No. **1**, 531-59-9; **2**, 71783-00-1; **3**, 71783-02-3; **3** (syn-HT dimer), 85389-91-9; **4**, 85389-84-0; **5**, 85405-69-2; **6**, 85389-85-1; **6** (syn-HT dimer), 85389-92-0; **7**, 2555-28-4; **7** (anti-HT dimer), 85389-95-3; **8**, 85389-86-2; **8** (syn-HT dimer), 85389-93-1; **9**, 85389-87-3; **10**, 85389-88-4; **11**, 85389-89-5; **11** (syn-HT dimer), 85389-94-2; **12**, 85389-90-8.

Synthesis of Novel 3-Methylstatine Analogues. Assignment of Absolute Configuration[1a]

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The synthesis and stereochemical assignments of two new analogues of statine are reported. Boc-L-leucine was reacted with methyllithium in dimethoxyethane to produce the corresponding methyl ketone in 45–75% yield. Addition of ethyl lithioacetate at −78 °C to the methyl ketones gave Boc-(*S*)-4-amino-3-hydroxy-3,6-dimethylheptanoic acid ethyl ester [Boc-Me^{3}Sta-OEt] in 75–78% yield as a mixture of 3-position diastereomers. The corresponding Me^{3}AHPPA derivatives [(*S*)-4-amino-3-hydroxy-3-methyl-5-phenylpentanoic acid] were synthesized as a pair of diastereomers starting from Boc-L-Phe-OH. The absolute configurations of both Me^{3}Sta and Me^{3}AHPPA diastereomers were established by converting the free amino acids to the corresponding trideuteriomethyl ester oxazolidones by reaction with phosgene followed by esterification with ^2H_3CI and Cs_2CO_3. ^{13}C NMR and ^1H nuclear Overhauser effect difference spectra established the following chiralities for the oxazolidone obtained from Me^{3}AHPPA: major diastereomer (70%) 3*S*,4*S*; minor diastereomer (30%) 3*R*,4*S*. Similarly the major Me^{3}Sta diastereomer (>90% of mixture) was shown to have the 3*S*,4*S* configuration and the minor diastereomer to have the 3*R*,4*S* configuration. Pepstatin analogues containing the 3*R*,4*S* diastereomer of Me^{3}Sta or Me^{3}AHPPA are better inhibitors of pepsin and cathepsin D than the corresponding 3*S*,4*S* diastereomers.

Pepstatin, isovaleryl-L-valyl-L-valyl-[(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]-L-alanyl-(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (**1**), abbreviated Iva-Val-Val-Sta-Ala-Sta, a pentapeptide first isolated by

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