and irradiated in the reaction vessel for 10–13 h (2 days for MIN), at room temperature (23 °C) with continuous argon degassing. The photolysate was acidified with 10 mL of 4 N HCl, 10 mL of brine was added, and the solution was extracted with EtOAc (4 × 20 mL). The combined extracts were washed with 25 mL of H_2O, dried (anhyd Na_2SO_4), filtered through glass wool, and evaporated to dryness under vacuum. The crude lumi product mixtures were purified using an E. M. Merck Lichrosorb RP-8 (size B, 43–60 μM) LoBar column. Eluent conditions were 10% v/v MeCN, 30% MeOH, and 60% 0.2 M NH_4OAc (pH 7), flow rate 6 mL/min, monitored at 272 nm. The mixtures were dissolved in 2–3 mL of MeOH and diluted to twice the volume with the buffer component of the eluent used. The resultant solution was loaded on to the column in 1–1.5-mL increments, injected over a period of up to 5 min. The lumi product was the first major peak to elute from the column, with the onset at 70–100 mL (solvent front ca. 50 mL) and the product completely eluted at ≤200–300 mL. The fraction containing the lumi product was acidified with up to 10 mL of 4 N HCl, concentrated in vacuo to 40–50% of the original volume, and extracted 4 times with 15–20-mL fractions of EtOAc. The combined fractions were washed once with 20 mL of H_2O, dried, treated with carbon black, and filtered through a medium-fritted glass funnel. The solution was evaporated in vacuo to ca. 3–4 mL, and ca. 150–300 mL of hexanes was added to precipitate the lumi products as flocculent off-white to yellow precipitates. These were collected through a 13-mm Nylon 66 0.45 μm membrane (Alltech) and dried to give isolated amounts of the lumi products ranged from 40 to 60 mg (ca. 8 mg for LMIN).

Quantum Efficiency Determinations. This experiment utilized the 366-nm mercury line isolated with a soft glass sleeve surrounding the lamp and a Corning CS7-37 366-nm bandpass filter. Quartz photolysis tubes (7.5 cm i.d.) were placed in a Merry-go-round (New England Ultraviolet Co.) mounted in front of the bandpass filter. Photolyses were carried out for 3 h at room temperature (22–25 °C) with benzophenone/benzhydrol actinometry.[8] Stock solutions of 0.5 mM tetracycline (OTc, DOX, CTc, DEM) in 50 mM phosphate buffer, pH 6.4, ionic strength of 0.15 (adjusted with NaCl), were prepared which had an absorbance of ≈3 at 366 nm (1-cm path length). Aliquots (5 mL) from each solution were placed in test tubes and covered with aluminum foil to serve as dark controls. Two 5-mL aliquots of each of the tetracyclines and of the actinometer solution were placed into the tubes and deoxygenated with Ar for 15 min, and the tubes were sealed with rubber septa. Analyses were by reverse-phase HPLC with an Alltech Econosil C-18 (4.6 mm × 25 cm) 10 μm column, using propiophenone as an internal standard.

Acknowledgment. We thank the National Institutes of Health (Grant 5 RO1 AR39286) for support of this research.

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Cytotoxic Metabolites of the Marine Sponge *Mycale adhaerens* Lambe[1]

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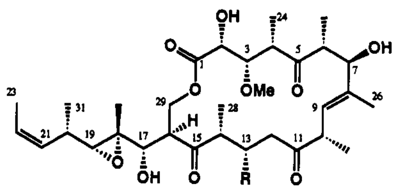
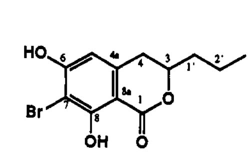
Marine sponges of the genus *Mycale* are a source of novel bioactive nitrogenous metabolites; e.g., mycalysins A and B,[2] mycalamides A and B,[3] and mycalolides A–C.[4] In our continuing search for cytotoxic metabolites from Japanese marine invertebrates, we found that the lipophilic extract of the marine sponge *Mycale adhaerens* showed potent cytotoxic activity. Bioassay-guided isolation yielded five active compounds, of which 13-deoxytedanolide and a brominated isocoumarin named hiburipyranone are new. This paper deals with the isolation and structure elucidation of these compounds.

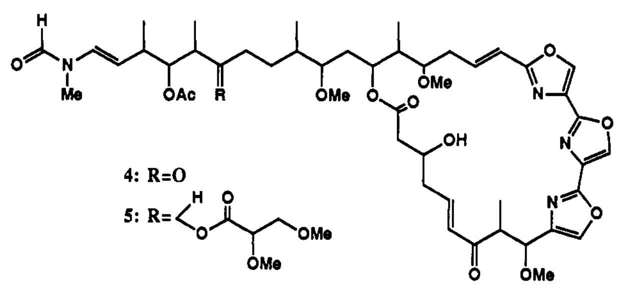
The EtOH extract of the sponge was partitioned between water and ether. The ether phase was fractionated by flash chromatography on silica gel, followed by gel filtration and reversed-phase HPLC to afford 13-deoxytedanolide (**1**, (5.5×10^{-3})% based on wet weight) and hiburipyranone (**3**, (2.1×10^{-4})%), together with three known compounds, mycalolides A (**4**, (2.1×10^{-4})%) and B (**5**, (6.8×10^{-5})%)[4] and a bromoindole **6** ((3.2×10^{-5})%).[5] The known compounds were identified by comparing spectral data with those reported in literature.



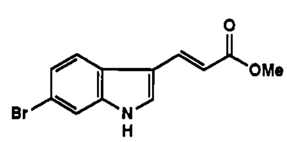
1: R=H
2: R=OH



3



4: R=O
5: R=



6

The new compound **1** had a molecular formula of $C_{32}H_{50}O_{10}$, which was established by the high-resolution FAB mass spectrum. The ^1H and ^{13}C NMR spectra indicated that **1** might be a macrolide containing three ketones that interrupted ^1H NMR coupling sequences. However, the ^1H NMR spectrum showed well-resolved signals and interpretation of the COSY and C–H correlation[6] spectra gave rise to four partial structures, a–d, which were eventually connected through ketones by tracing cross-peaks in the HMBC spectrum.[7]

The assignment of the C2–C4(C24) portion (partial structure a) was straightforward by interpretation of the

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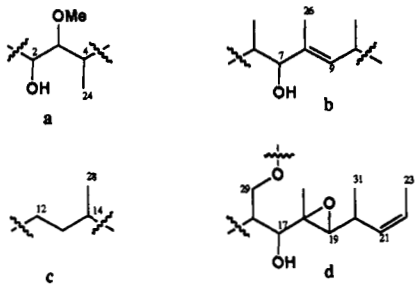

COSY spectrum, which revealed three contiguous methines including methylated C4. The presence of a methoxy group on C3 was indicated by the NOESY[8] cross-peaks between the H3 and the *O*-methyl signals, as well as by the low-field chemical shift for C3 (δ 85.1). The chemical shifts for H2 (δ 3.68) and H4 (δ 3.12) suggested that C2 was oxygenated and C4 was adjacent to a ketone.

Partial structure b was deduced by a combination of COSY and NOESY data. The COSY spectrum revealed the (C25)C6–C7 and C9–C10(C27) units. The H9 signal at δ 5.26 showed allylic coupling to the C26 methyl protons at δ 1.63. The connection between C7 and C8 was established by means of NOESY data, which gave cross-peaks between H6 and $H_3$26 and between H7 and H9. The ^{1}H shifts for H6 (δ 3.11) and H10 (δ 3.41) indicated that these protons were situated on the carbons adjacent to ketones.

Partial structures c and d were established by interpretation of the COSY spectrum. The contiguous nature of C29–C16–C17 in partial structure d was easily assigned from the COSY spectrum; C29 and C17 are oxygenated as judged by their ^{13}C chemical shifts (δ 65.7 and 77.7, respectively). The remaining portion was a methylated *Z*-olefin attached to a methylated methine, which was juxtaposed to a trisubstituted epoxide. Two cross-peaks assignable to *W* coupling from 30-methyl protons to H17 and to H19 were noteworthy.

Connection of partial structures a–d through an ester and three ketones was accomplished by interpretation of the HMBC spectrum. A ketone at δ 217.3 showing correlations with H4, H6, $H_3$24, and $H_3$25 could be assigned as C5; thus, partial structures a and b could be connected. A deshielded methine (δ_C 46.1, δ_H 3.41) located at the other end of partial structure b showed a cross-peak with a ketone at δ 213.8, which was in turn correlated with H13a and $H_2$12 in partial structure c. On the other hand, H14 (δ 2.77) and $H_3$28 (δ 1.12) were correlated to C15 ketone at δ 215.6. Though the HMBC cross-peak between C15 and H16 was faint, there were intense correlations between C15 and both C29 methylene protons. Therefore, connection between partial structures c and d was proved. Furthermore, the 29-methylene protons were correlated with an ester carbonyl at δ 173.5, thus completing gross structure 1. Considering the degree of unsaturation, oxygens on C2, C7, and C17 must be hydroxyl groups.

Gross structure 1 happened to be 13-deoxytedanolide; the parent compound, tedanolide, was isolated from the Caribbean sponge *Tedania ignis*, and structure 2 was unambiguously determined by X-ray crystallography.[9,10] Based on the *J* values in the ^{1}H NMR spectrum of tedanolide (2), we assumed that tedanolide has the same conformation in solution as in the solid state. For example, with regard to the C2–C4 unit, the substituents for C2–C3 and C3–C4 were both syn to each other. If we assume that this portion has a staggered conformation with larger substituents in the anti position, which we usually expect for aliphatic molecules, both coupling constants for H2–H3 and H3–H4 must fall within the 1–3 Hz range. The coupling constants reported for H2–H3 and for H3–H4 are 1.7 and 8.6 Hz, respectively, which are in accordance with the X-ray model, and reveal that C2 and C5 are in a gauche relationship on the basis of the C3-C4 bond, so that the dihedral angle between H3 and H4 was near 180°. Therefore, the solution conformation for the C1–C5 unit is most likely identical with that reported in the solid state. Similar arguments can be applied all through the molecule, leading to the conclusion that the solution conformation of tedanolide is the same as that in the solid state.[11]

Comparison of the ^{1}H NMR coupling constants between 1 and 2 indicated that 1 has the same conformation for partial structures a, b, and d. This was fully supported by the NOESY data. Due to the absence of the hydroxyl group on C13 and the degeneracy of the chemical shifts for the C12 methylene protons in 1, it was difficult to compare the conformation of this portion between the two compounds on the basis of coupling constants. However, the presence of a NOESY cross-peak between $H_2$12 and H14 and the absence of those between $H_2$12 and $H_3$28 indicated that C12 and C28 are anti based on the C13–C14 bond, differing from the solid-state conformation of tedanolide, which showed the gauche conformation for C12 and C28. Moreover, there was a transannular NOESY cross peak between H2 and $H_2$12, which can never be observed for the solid-state tedanolide conformer where H2 and $H_2$12 fall outside the lactone ring. A weak NOESY cross-peak between H2 and $H_3$26, another transannular NOE, was also observed.

Obviously, it is impossible to assign the total stereochemistry of 1 by means of coupling constants and NOESY data.[12] However, it is most likely that 13-deoxytedanolide has the structure as shown, since ^{1}H and ^{13}C chemical shifts are very similar in 1 and in tedanolide (2).

Hiburipyranone (3) has the molecular formula of $C_{12}H_{13}BrO_4$ as revealed by the high-resolution EI mass spectrum. The UV spectrum (λ_{max} 273 (ϵ 8200) and 306 (ϵ 3200) nm) was indicative of a conjugated phenolic chromophore.[13] Interpretation of the COSY spectrum led us to assign a 1,2-disubstituted pentane moiety, in which the terminal methylene protons were coupled to an aromatic proton at δ 6.42 (s). The H3 chemical shift of 4.53 ppm indicated that the oxygen on this carbon was esterified. There were two phenolic protons at δ 6.30 (br) and 11.97 (s), the latter of which was hydrogen bonded. As the remaining portion was composed of C_3Br, further structural assignment was carried out by interpretation of the HMBC spectrum.

The hydrogen-bonded C8 phenolic proton was coupled to C7, C8, and C8a. The H5 aromatic proton gave intense HMBC cross-peaks with C4, C7, and C8a, while the C4 methylene protons were strongly coupled to C3, C4a, C5, C8a, and C1′. In addition to these correlations, weak

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(10) It must be noted that the stereochemistry for C17 of tedanolide was incorrectly drawn in ref 9.
(11) Though we were unable to predict the conformation through the three ketones, it is reasonable to infer that the conformation is the same as in the solid state, because tedanolide is macrocyclic, and the coupling constants observed in partial structures a–d match well to the solid-state conformation.
(12) An intense NOESY cross-peak between H14 and H16 indicated that the stereochemical relationship for C14 and C16 are the same as the solid-state conformation of tedanolide.
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Table I. ^1H and ^{13}C NMR Data of 13-Deoxytedanolide (1) in CD_3OD

no.	^{13}C	^1H	HMBC	NOESY
1	173.5 (s)			
2	72.5 (d)	3.68 (d, 1.9)	1	3, 4, 12, 26
3	85.1 (d)	3.60 (dd, 9.6, 1.9)	4, 24, 32	2, 4, 24, 32
4	49.3 (d)	3.12 (dq, 9.6, 7.1)	3, 5, 24	2, 3, 24
5	217.3 (s)			
6	51.1 (d)	3.11 (dq, 10.1, 7.0)	5, 7, 8, 25	7, 25, 26
7	80.2 (d)	3.95 (d, 10.1)	6, 9, 25, 26	6, 9, 25
8	138.4 (s)			
9	130.1 (d)	5.26 (dq, 9.7, 1.3)	7, 10, 11, 26	7, 27
10	46.1 (d)	3.41 (dq, 9.7, 6.9)	8, 9, 11, 27	12, 26, 27
11	213.8 (s)			
12	38.8 (t)	2.30 (dd, 7.8, 7.8)	11, 13, 14	2, 10, 14
13a	26.0 (t)	1.57 (dtd, 13.8, 7.8, 3.1)	15, 28	13b
13b		1.96 (ddt, 13.8, 9.0, 7.8)	11, 12, 14, 15, 28	13a, 14
14	49.5 (d)	2.77 (dqd, 9.0, 7.1, 3.1)	12, 13, 15, 28	12, 13a, 16, 28
15	215.6 (s)			
16	53.2 (d)	3.35 (ddd, 11.9, 10.3, 4.3)	15, 29	14, 28, 30
17	77.7 (d)	3.17 (d, 10.3)	16, 18, 19, 29, 30	19, 29a, 30
18	64.0 (s)			
19	67.4 (d)	2.65 (d, 9.3)	17, 20, 21, 31	17, 20, 21, 29a, 30, 31
20	32.4 (d)	2.47 (ddq, 10.5, 9.3, 6.6)	19, 21, 22, 31	19, 23, 30, 31
21	131.8 (d)	5.31 (ddq, 10.9, 10.5, 1.7)	19, 22, 23	19, 22, 31
22	126.0 (d)	5.46 (dq, 10.9, 6.8)	20, 21, 23	21, 23
23	13.5 (q)	1.61 (dd, 6.8, 1.7)	21, 22	20, 22, 30
24	15.2 (q)	1.22 (d, 7.1)	3, 4, 5	3, 4, 26, 32
25	15.6 (q)	1.26 (d, 7.0)	5, 6, 7	6, 7
26	10.5 (q)	1.63 (d, 1.3)	7, 8, 9	2, 6, 10, 24, 27
27	16.2 (q)	1.01 (d, 6.9)	9, 10, 11	9, 10, 26
28	15.7 (q)	1.12 (d, 7.1)	13, 14, 15	14, 16
29a	65.7 (t)	4.01 (dd, 11.9, 10.5)	1, 15, 16, 17	17, 19, 29b
29b		4.17 (dd, 10.5, 4.3)	1, 15, 16	29a, 30, 32
30	11.4 (q)	1.34 (s)	17, 18, 19	16, 17, 19, 20, 23, 29b
31	18.7 (q)	1.10 (d, 6.6)	19, 20, 21	19, 20, 21
32	61.1 (q)	3.33 (s)	3	3, 24, 29b

HMBC cross-peaks were observed between 8-OH and C1 and C6; between H5 and C1, C6, and C8; between H4 and C1; and between H3 and C4a. These data led us to assign the brominated isocoumarin structure **3**. Similar isocoumarins were isolated from several sources including the brown alga *Caulocystis cephalornithos*,[14] the terrestrial plant *Ononis natrix*,[15] and fungi-infested wood samples.[16] The spectral data reported for these compounds are also consistent with our structural assignment.

13-Deoxytedanolide and hiburipyranone showed remarkable cytotoxicity against P388 murine leukemia cells with IC_{50}'s of 94 pg/mL and 0.19 μg/mL, respectively. 13-Deoxytedanolide was also highly antitumor-active against P388: T/C = 189% at a dose of 0.125 mg/kg. Detailed antitumor activity of 13-deoxytedanolide will be reported elsewhere.

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Table II. ^1H and ^{13}C NMR Data of 3 in $CDCl_3$

no.	^{13}C	^1H	HMBC[a]
1	169.4 (s)		
3	78.8 (d)	4.53 (m)	4a
4	32.5 (t)	2.84 (d, 6.5)	(1), 3, 4a, 5, 8a, 1′
4a	140.1 (s)		
5	105.9 (d)	6.42 (s)	(1), 4, 6, 7, (8), 8a
6	158.5 (s)		
7	97.0 (s)		
8	160.4 (s)		
8a	102.5 (s)		
1′	36.6 (t)	1.67 (m)	3, 4, 2′, 3′
		1.85 (m)	3, 4, 2′, 3′
2′	18.0 (t)	1.58 (m)	3, 1′, 3′
3′	13.7 (q)	0.96 (t, 7.3)	
6-OH		6.30 (br)	
8-OH		11.97 (s)	(1), (6), 7, 8, 8a

[a] Weak HMBC correlation peaks are indicated with parentheses.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on either Bruker AM500 or AC300 NMR spectrometers. Ultraviolet spectra were measured on a Hitachi 330 spectrophotometer. Infrared spectra were recorded on a JASCO IR-G infrared spectrometer. Optical rotations were determined by a JASCO DIP-140 polarimeter. Mass spectra were measured on either JEOL D300 (EIMS) or JEOL SX102 (FABMS) mass spectrometers.

Collection and Isolation. The sponges were collected by SCUBA off Hiburi Island (−10 to −15 m) of the Uwa Sea, 750 km southwest of Tokyo. The frozen sponges (1.9 kg) were extracted with EtOH in a Waring Blender, and the concentrated extract was partitioned between Et_2O and H_2O. The Et_2O-soluble portion was again partitioned between hexane and 90% aqueous MeOH, and the 90% aqueous MeOH fraction (3.9 g) was subjected to silica gel flash chromatography on Kieselgel 60 (E. Merck) with $CHCl_3$–MeOH, followed by gel filtration on Toyopearl HW40SF (Tosoh Co., Ltd.) with $CHCl_3$–MeOH (1:1) to yield three active fractions. The first fraction was subjected to ODS flash chromatography with aqueous MeOH and further purified by HPLC on Capcell Pak C_{18} (Shiseido Co., Ltd.) with 75% aqueous MeOH to obtain 13-deoxytedanolide (**1**, 105.2 mg) and fractions containing **4** and **5**. Compounds **4** and **5** were further purified by HPLC on Senshu Pak ODS H-4251 (Senshu Sci. Co., Ltd.) with 65 and 70% aqueous MeOH, respectively, to yield mycalolides A (**4**, 4.0 mg) and B (**5**, 1.3 mg). The second fraction from a gel filtration column was fractionated by flash chromatography on ODS with aqueous MeOH, followed by HPLC on Capcell Pak C_{18} with 60% aqueous MeOH to afford hiburipyranone (**3**, 4.0 mg). The third fraction was separated by flash chromatography on ODS with aqueous MeOH. The active fractions, eluted with 70 and 80% aqueous MeOH, were repeatedly chromatographed on Capcell Pak C_{18} with a solvent gradient from 50 to 70% aqueous MeOH to obtain **6** (0.6 mg).

13-Deoxytedanolide (**1**): $[\alpha]_D$ +84.4° (*c* 0.26, $CHCl_3$); IR (film) 3450, 3000, 2950, 1750, 1710, 1460, 1370, 1240, 1210, 1140, 1120, 1090, 1040, 980, 890, 860, 830, 810, 760, 740 cm^{-1}; HRFABMS *m/z* 595.3444 (MH^+; $C_{32}H_{51}O_{10}$, Δ −3.8 mmu); for ^1H and ^{13}C NMR, see Table I.

Hiburipyranone (**3**): $[\alpha]_D$ −2.30° (*c* 0.028, $CHCl_3$); λ_{max} (MeOH) 219 (ε 15 600), 227 (ε 12 600), 273 (ε 8200), 306 (ε 3200) nm; IR (KBr) 3450 (sh), 3050, 2950, 1610, 1490, 1430, 1380, 1310, 1260, 1190, 1140, 1120, 1060, 1030, 1000, 910, 830, 770 cm^{-1}; HREIMS *m/z* 299.9978 (M^+; $C_{12}H_{13}{}^{79}BrO_4$, Δ −2.0 mmu); for ^1H and ^{13}C NMR, see Table II.

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Registry No. 1, 134455-11-1; 3, 134419-24-2; 4, 121038-36-6; 5, 122752-21-0; 6, 134419-23-1.

Supplementary Material Available: ^1H NMR, DEPT, ^{13}C-^1H COSY, ^1H-^1H COSY, HMBC, and NOESY spectra of 1 and ^1H NMR, ^{13}C NMR, ^1H-^1H COSY, and HMBC spectra of 3 (10 pages). Ordering information is given on any current masthead page.

A Convenient Method for the Preparation of (Alkylsulfonyl)benzoic Acids

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(Alkylsulfonyl)benzoic acids are useful intermediates for a variety of synthetic compounds possessing pharmaceutical[1] and herbicidal[2] activity. Literature methods for the preparation of such compounds can be divided into two general categories. The first procedure involves the alkylation of a substituted thiophenol followed by oxidation of the resulting sulfide to the sulfone.[1b,3,4] Use of a strong oxidant such as potassium permanganate or sodium dichromate may allow for the simultaneous conversion of an aryl methyl group to the desired carboxylic acid moiety.[1a,5-7] The second method of preparation requires the reduction of the corresponding sulfonyl chloride followed by treatment of the intermediate sulfinate with an alkyl halide to give the (alkylsulfonyl)benzoic acid.[1c-e,3] The initial product of this process is often the corresponding ester, which must be hydrolyzed to the desired acid.[1f-g,8] All these procedures suffer from various deficiencies including low yields, the requirements for large excesses of alkylating reagent, or the need for further chemical manipulation (e.g., ester hydrolysis). We report a simple, one-pot method for the synthesis of these materials via reduction of a (chlorosulfonyl)benzoic acid to the corresponding sulfinate, selective alkylation with a 2-halo carboxylic acid, and side-chain decarboxylation. This approach affords a convenient, high-yielding preparation of a variety of (alkylsulfonyl)benzoic acids from readily available precursors that is suitable for large-scale application.

(Alkylsulfonyl)benzoic acids were prepared in the following manner (Scheme I). (Chlorosulfonyl)benzoic acid 1 was reduced with aqueous basic sodium sulfite, and the resulting aqueous solution of sulfinate 2 was treated with a slight excess of a 2-halo carboxylic acid 3. The reaction mixture was then heated until decarboxylation of the initial alkylation product, sulfonylacetic acid 4, was complete. (Alkylsulfonyl)benzoic acids 5 were obtained in overall yields of 66-95% (Table I). Although sulfinate 2 and sulfonylacetic acid 4 may be isolated, the procedure was most conveniently performed without isolation of intermediates. The starting materials for this process, (chlorosulfonyl)benzoic acid 1 and 2-halo carboxylic acid 3, are both readily available or easily prepared. A bis(acid chloride) (the chloride of both the carboxylic and sulfonic acid groups) may be substituted as the starting material with no loss in yield; additional base must be added in the reduction step to consume the acid generated by the hydrolysis of the carboxylic acid chloride. A cosolvent may be used to dissolve the bisacid chloride; however, if the solvent is not removed before the additon of the 2-halo carboxylic acid 3, the subsequent alkylation and decarboxylation reactions will be inhibited.

The reaction times required for complete conversion of (chlorosulfonyl)benzoic acids 1 to (alkylsulfonyl)benzoic acid 5 varied from 7 to 213 h. Although the reduction of (chlorosulfonyl)benzoic acid 1 required only 0.25-3.0 h, reaction times for the alkylation/decarboxylation step were much longer and were found to be dependent upon a number of factors. When chloroacetic acid was used as the alkylating reagent, total reaction times for the alkylation/decarboxylation were typically 7-21 h. Longer reaction times were necessary for the preparation of an (alkylsulfonyl)benzoic acid 5 bearing an ortho substituent (e.g., 4-chloro-3-(methylsulfonyl)benzoic acid, **5f**), presumably due to steric hindrance in the alkylation step. In this case, the use of 2-bromoacetic acid reduced the required reaction time from 42 to 24 h. The reaction times given in Table I are for reactions at reflux (ca. 105 °C). At other temperatures, the rate of decarboxylation was dramatically different. Below 80 °C, essentially no reaction occurred. At slightly elevated pressures, the higher reaction temperatures afforded a significant increase in the reaction rate; at 115 °C, the reaction time for the preparation of 2-chloro-4-(methylsulfonyl)benzoic acid (**5b**) was reduced from 21 to 3 h.

The chain length of the 2-halo carboxylic acid 3 also affected the rate of the decarboxylation. Reaction times increased as the size of the alkyl group of the 2-halo carboxylic acid 3 increased, peaking with 2-bromobutanoic acid and then decreasing at longer chain lengths. Two independent factors can account for this phenomenon. Substitution of a hydrogen on the intermediate sulfonylacetic acid 4 with an electron-donating alkyl group destabilizes the incipient carbanion 6, inhibiting the loss of carbon dioxide (Scheme II).[9] The effect observed for R = ethyl is greater than for R = methyl due to the greater inductive effect of the larger group ($\sigma_{Me} = -0.046$ vs $\sigma_{Et} = -0.057$).[10] As the size of the alkyl chain continues to

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