Regioselective Alkylation of 3-(Trimethylsilyl)-3-sulfolene: Route to Stereospecific 2-Silylated Butadiene Derivatives

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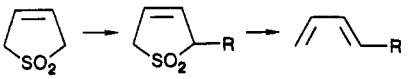
Dichotomous regiochemistry in the alkylation of 3-(trimethylsilyl)-3-sulfolene (1) can be achieved by controlling the amount of base used (to generate the monoanion or the dianion) and the sequence of its addition. In this way, a variety of 2-silyl-1,3-butadiene derivatives can be prepared.

2-Silyl-1,3-butadiene is a functionally versatile butadiene derivative in Diels–Alder reactions.[1,2] However, the existing methods[3,4] for its preparation are limited, and a more general method for preparing various substituted 2-silyl-1,3-butadienes would be desirable. The recent findings that certain substituted butadienes[5,6] can be readily prepared by the deprotonation/alkylation of 3-sulfolenes (eq 1) suggest that a similar reaction with 3-silylated 3-



(1)

sulfolene may provide a general route to other substituted 2-silyl-1,3-butadiene derivatives. Indeed, we find that, with a trimethylsilyl group at the 3-position, the monoanion of 1 can be alkylated regioselectively at the 5-position while the dianion leads to a mixture of products, with the monoalkylated derivative at the 2-position predominating. The second alkylation also occurs regioselectively. Thus 1 could serve as common starting material for various 2-silylated butadiene derivatives.

Results and Discussion

3-(Trimethylsilyl)-3-sulfolene (1) can be prepared directly from commercially available 3-sulfolene[7] or indirectly from 1,4-dichlorobutyne.[3]

Alkylation of the Monoanion of 1. When 1 was deprotonated at −105 °C with 1 equiv of *n*-butyllithium and then reacted with alkyl iodide, the 5-alkylated product 2 was obtained in 70–90% yield. The observed regiochemistry can be attributed to the stabilizing effect provided by the trimethylsilyl group on the resulting allyl anion. Furthermore, when the second alkylation was carried out on 2, again alkylation occurred only at the 5-position to give 5,5-dialkylated product 3. This is in sharp contrast with the behavior of parent sulfolene, in which case the second deprotonation occurs at the site opposite to that of the first.[9] Apparently, the strong anion-stabilizing effect of the TMS substituent[10] outweighs any anion-destabilizing effect of the alkyl group in guiding the observed regiochemistry of the deprotonation. The 5,5-dialkylated product 3 can also be prepared in one pot by the sequential addition of 1 equiv of base, 1 equiv of electrophile, another equivalent of base and another equivalent of electrophile. If an α,ω-diiodoalkane is used as the electrophile, the spiro product is obtained.[11] These results are summarized in Table I and Scheme I.

Alkylation of the Dianion of 1. When 1 was treated with 2 equiv of *n*-butyllithium at −105 °C, a light yellow solution was obtained. Addition of 1 equiv of electrophile, followed by quenching with aqueous NH_4Cl solution and workup, afforded the 2-alkylated derivative 4 as the major product. Apparently, a dianion with the second negative

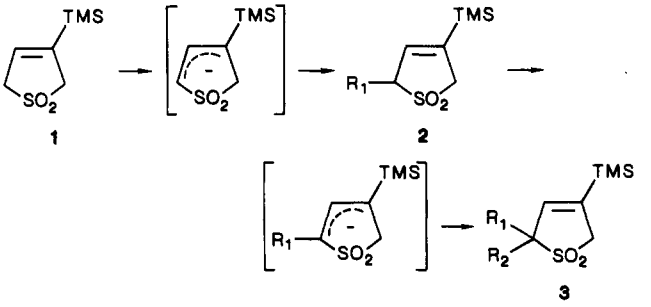
Table I. Alkylation of the Monoanion of 1

electrophile			
R_1I	R_2I	product	yield, %
CH_3		**2a**	90
C_2H_5		**2b**	86
C_4H_9		**2c**	85
C_6H_{11}		**2d**	68
CH_3	CH_3	**3a**	75
C_2H_5	C_2H_5	**3b**	90
CH_3	C_6H_{11}	**3c**	78
$-(CH_2)_4-$		**3d**	55
$-(CH_2)_5-$		**3e**	50

Table II. Alkylation of the Dianion of 1

electrophile			
R_1I	R_2I	product	yield, % (ratio)
CH_3		**4a**	60
C_4H_9		**4b/5b/6b**	70 (13:2.8:1)
C_6H_{11}		**4c/5c/6c**	67 (10:2.5:1)
i-C_3H_7		**5d**	60
CH_3	CH_3	**7a**	55
C_4H_9	C_4H_9	**7b**	50

Scheme I



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(11) Metal exchange between *n*-butyllithium and iodide undermines the yield. In these cases, lithium hexamethyldisilazide is used for the second equivalent base.

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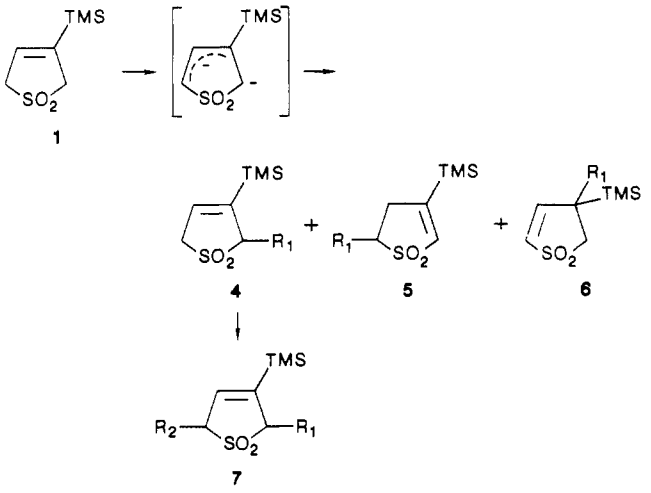
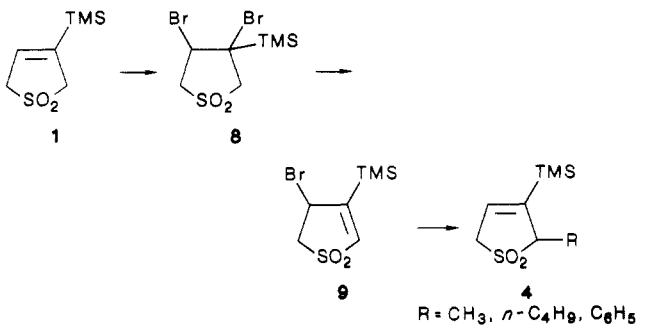
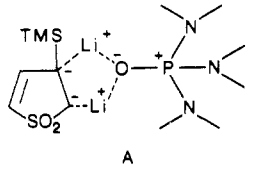
Scheme II



Scheme III



charge on the 2-position was formed. In addition to compound **4**, compounds **5** and **6**, which resulted from alkylation at the 5- and 3-positions, respectively, were also obtained. The formation of **6** is intriguing. In the alkylation of the monoanion of **1**, **2** is the only product. This has been attributed to the higher charge density at the α-position of a sulfone group[5] and also perhaps the steric hindrance at the 3-position.[8] In the dianion of **1**, one might expect even less charge density at the 3-position because of the electrostatic repulsion between neighboring negative charges. The sizable amount of **6** produced might hint to partial contribution of an unusual five membered ring complex, in which electron density is "drawn" to the 3-



A

position. The relative yields of **4**, **5**, and **6** appear to be very sensitive to the steric bulkiness of the electrophile. With methyl iodide as electrophile, **5** and **6** were not detected, yet with 2-iodopropane as electrophile, **5** became the major product. Presumably this is the result of steric hindrance. If 2 equiv of electrophile were added, 2,5-dialkylated product **7** was obtained as the major product with trans stereochemistry.[9] Second alkylation of **4** also yielded **7**. The results are summarized in Table II and Scheme II.

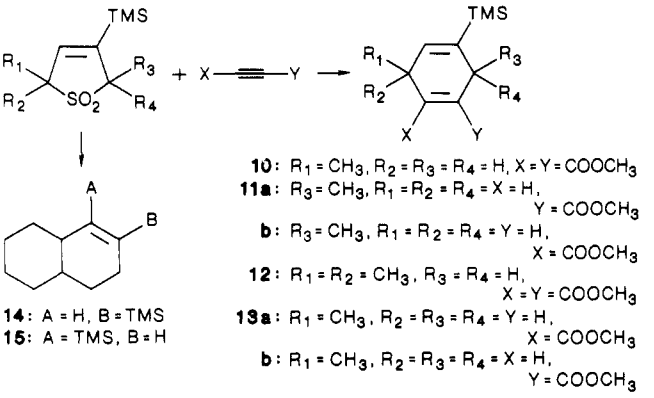
Alternatively, **4** can also be prepared via a different route, which involves the nucleophilic substitution of 4-bromo-3-(trimethylsilyl)-2-sulfolene (**9**), which can be prepared readily from **1** and dialkylcuprates (Scheme III). For example, **4** was prepared in this way in 78%, 75%, and 71% yield for R = CH_3, n-C_4H_9, and C_6H_5, respectively.

Table III. Diels–Alder Reactions of 3-Sulfolene Derivatives

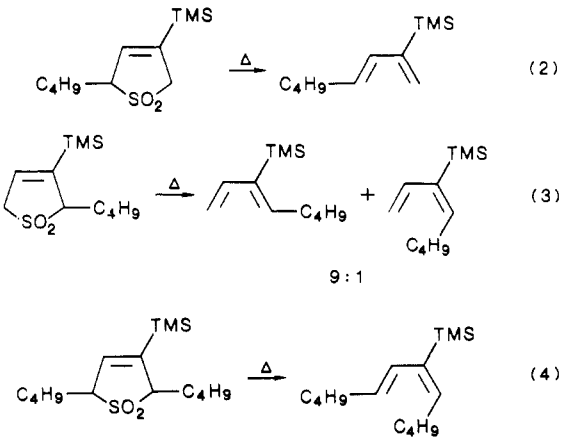
entry	sulfolene	dienophile[a]	product	yield,[b] % (ratio)
1	**2a**	DMAD	**10**	78
2	**4a**	MP	**11a/11b**	58 (2:1)
3	**3a**	DMAD	**12**	50
4	**2a**	MP	**13a/13b**	64 (5:1)
5	**2d**		**14**	60[c,d]
6	**4c**		**15**	40[c,e]

[a] DMAD: dimethylacetylenedicarboxylate. MP: methyl propiolate. [b] Conditions: toluene, 140 °C, sealed tube, 10 h, unless otherwise noted. [c] Conditions: *N,N*-dimethylaniline,[16] 220 °C, sealed tube, 10 h. [d] Cis/trans, 1:1. [e] Trans only.

Scheme IV



Generation of 2-Silyl-1,3-butadienes and Diels–Alder Reaction. The thermal extrusion of SO_2 from 3-sulfolene is a well-studied reaction.[12] The behavior of the 3-(trimethylsilyl)-3-sulfolene derivatives is similar and within expectation. The stereochemistry of the dienes, generated upon direct thermolysis in a GC injection port at 220 °C, is typified by the n-butylated derivatives as shown in eq 2–4. In eq 3, the stereospecificity is lower,



presumably, due to the steric interaction in the transition state leading to the isomer with the n-butyl group cis to the bulky TMS group. In eq 4, the sole product confirms that the starting sulfolene has a trans stereochemistry.

In situ generation of the diene and reaction with a reactive dienophile also proceeded as expected. Some examples are described in Table III and Scheme IV. The major influence on the regiochemistry of the Diels–Alder adduct comes from the alkyl substituent (entries 2 and 4), in agreement with Fleming's conclusion.[13] While 1,1-di-

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substituted butadienes are known[14] to give a poor yield of normal Diels–Alder product due to an unfavorable transoid conformation, the silylated derivative, nevertheless, reacts smoothly (entry 3). The intramolecular Diels–Alder reaction of **4c** (entry 6) is highly stereospecific, yielding only the trans isomer. The origin of this stereochemical outcome has precedence.[15]

Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR spectra were taken on a Bruker AW-80 NMR spectrometer or a Bruker MSL-200 NMR spectrometer with $CDCl_3$ as solvent. IR spectra were taken on a Perkin-Elmer 297 IR spectrometer. Mass spectra were obtained on a Finnigan MAT 112S spectrometer. Elemental analyses were performed with a Perkin-Elmer 240B elemental analyzer at the Food and Drug Bureau, Department of Health, Taipei.

General Procedure for Deprotonation/Alkylation for 5-Alkylation. The starting sulfolene 1 (60 mg, 0.316 mmol) and HMPA (1.26 mmol) were dissolved in 6 mL of dry THF and were stirred efficiently at −105 °C under nitrogen. *n*-BuLi (1.38 M, 0.316 mmol) was added dropwise. After the mixture was stirred for 10 min, the alkyl iodide in 1 mL of THF was added to the resulting light reddish-brown solution in one shot. The reaction mixture was allowed to warm up gradually to −30 °C before quenching with saturated aqueous ammonium chloride solution. The product was extracted with ethyl acetate and washed with saturated sodium chloride solution. The residue after evaporation of solvent was eluted through a silica gel column (hexane/EtOAc, 1:1) to remove HMPA. Products were separated and purified by HPLC. For sequential alkylation in one pot, after the addition of the first equivalent of electrophile, the reaction mixture was allowed to warm up to −80 °C slowly and then cooled down to −105 °C again and the steps of adding base and electrophile were repeated just as for the first equivalent. The workup procedure is the same as described above.

Procedure for Deprotonation/Alkylation at 2-Position via the Dianion. The starting sulfolene 1 (100 mg, 0.527 mmol) and HMPA (2.11 mmol) were dissolved in 10 mL of dry THF and stirred efficiently at −105 °C. *n*-BuLi (1.38 M, 1.05 mmol) was added dropwise. The solution turned light yellow after being stirred for 10 min. The alkyl iodide dissolved in 8 mL of dry THF was cooled to −105 °C before being transferred to the dianion solution through a short cannula. Stirring was continued for 20 min, after which the temperature of the cooling bath was raised to −80 °C. One milliliter of saturated ammonium chloride solution was added while the mixture was brought to vigorous stirring. The reaction mixture was extracted with ethyl acetate and washed with saturated sodium chloride solution. After removal of HMPA through a silica gel column, the products were separated and purified by HPLC.

5-Methyl-3-(trimethylsilyl)-3-sulfolene (2a): ^1H NMR δ 0.13 (9 H, s), 1.39 (3 H, d, J = 7 Hz), 3.71 (3 H, m), 6.08 (1 H, br s); IR (liquid) 1590, 1300, 1240, 1120 cm^{-1}; MS, m/z 204 (M^+), 140, 125, 73 (base). Anal. Calcd for $C_8H_{16}SSiO_2$: C, 47.05; H, 7.84. Found: C, 46.6; H, 7.92.

5-Ethyl-3-(trimethylsilyl)-3-sulfolene (2b): ^1H NMR δ 0.10 (9 H, s), 1.04 (3 H, t, J = 7 Hz), 1.70 (2 H, m), 3.65 (2 H, s), 3.55 (1 H, m), 6.10 (1 H, br s); IR (liquid) 1590, 1300, 1240, 1120 cm^{-1}; MS, m/z 218 (M^+), 203, 154, 73 (base). Anal. Calcd for $C_9H_{18}SSiO_2$: C, 49.54; H, 8.26. Found: C, 49.18; H, 8.23.

5-Butyl-3-(trimethylsilyl)-3-sulfolene (2c): ^1H NMR δ 0.10 (9 H, s), 0.90 (3 H, t, J = 7 Hz), 1.0–2.0 (6 H, m), 3.69 (3 H, m), 6.11 (1 H, br s); MS, m/z 182 ($M^+ - SO_2$), 167, 73. Anal. Calcd for $C_{11}H_{22}O_2SSi$: C, 53.61; H, 9.00. Found: C, 54.05; H, 9.22.

5-(5-Hexenyl)-3-(trimethylsilyl)-3-sulfolene (2d): ^1H NMR δ 0.10 (9 H, s), 1.01–2.00 (8 H, m), 3.55 (3 H, m), 4.60–5.00 (2 H, m), 5.30–5.9 (1 H, m), 5.95 (1 H, br s); IR (liquid) 1640, 1590, 1300, 1250, 1120 cm^{-1}; MS, m/z 208 ($M^+ - SO_2$), 193, 73. Anal. Calcd for $C_{13}H_{24}SSiO_2$: C, 57.30; H, 8.88. Found: C, 57.80; H, 8.51.

5,5-Dimethyl-3-(trimethylsilyl)-3-sulfolene (3a): ^1H NMR δ 0.13 (9 H, s), 1.40 (6 H, s), 3.67 (2 H, d, J = 2 Hz), 6.06 (1 H, t, J = 2 Hz); IR 2960, 1590, 1310, 1250 cm^{-1}; MS, m/z 154 ($M^+ - SO_2$), 139, 73. Anal. Calcd for $C_9H_{18}SSiO_2$: C, 49.5; H, 8.25. Found: C, 49.27; H, 8.19.

5,5-Diethyl-3-(trimethylsilyl)-3-sulfolene (3b): ^1H NMR δ 0.13 (9 H, s), 0.98 (6 H, t, J = 7 Hz), 1.4–2.2 (4 H, m), 3.62 (2 H, d, J = 2 Hz), 6.03 (1 H, t, J = 2 Hz); IR 2960, 1590, 1305, 1250 cm^{-1}; MS, m/z 246 (M^+), 182, 167, 73. Anal. Calcd for $C_{11}H_{22}SSiO_2$: C, 53.6; H, 9.0. Found: C, 54.0; H, 9.0.

5-(5-Hexenyl)-5-methyl-3-(trimethylsilyl)-3-sulfolene (3c): ^1H NMR δ 0.12 (9 H, s), 1.34 (3 H, s), 1.2–1.8 (6 H, m), 1.97 (2 H, m), 3.62 (2 H, d, J = 2 Hz), 4.6–5.1 (2 H, m), 5.3–6.0 (1 H, m), 6.0 (1 H, t, J = 2 Hz); IR (liquid) 1640, 1590, 1310, 1250 cm^{-1}; MS, m/z 222 ($M^+ - SO_2$), 207, 73.

3-(Trimethylsilyl)-1-thiaspiro[4.4]non-3-ene 1,1-dioxide (3d): solid; mp 63 °C; ^1H NMR δ 0.10 (9 H, s), 1.4–2.0 (6 H, m), 2.45 (2 H, m), 3.68 (2 H, s), 6.06 (1 H, s); MS, 180 ($M^+ - SO_2$), 165, 73, 64. Anal. Calcd for $C_{11}H_{20}SSiO_2$: C, 54.10; H, 8.20. Found: C, 54.08; H, 8.19.

3-(Trimethylsilyl)-1-thiaspiro[4.5]dec-3-ene 1,1-dioxide (3e): solid; mp 75–76 °C; ^1H NMR δ 0.0 (9 H, s), 1.2–1.8 (10 H, m), 3.56 (2 H, s), 6.08 (1 H, s); IR (liquid) 2950, 1595, 1310, 1140 cm^{-1}; MS, 194 ($M^+ - SO_2$), 179, 73, 45. Anal. Calcd for $C_{12}H_{22}SSiO_2$: C, 55.76; H, 8.57. Found: C, 55.91; H, 8.4.

2-Methyl-3-(trimethylsilyl)-3-sulfolene (4a): ^1H NMR δ 0.16 (9 H, s), 1.4 (3 H, d, J = 7 Hz), 3.7 (3 H, m), 6.18 (1 H, br s); MS, m/z 204 (M^+), 140, 125. Anal. Calcd for $C_8H_{16}SSiO_2$: C, 47.05; H, 7.84. Found: C, 47.20; H, 7.81.

2-Butyl-3-(trimethylsilyl)-3-sulfolene (4b): ^1H NMR δ 0.16 (9 H, s), 0.9 (3 H, t, J = 7 Hz), 1.36–1.84 (6 H, m), 3.7 (3 H, m), 6.19 (1 H, br s); IR (liquid) 2975, 1600, 1305, 1125 cm^{-1}; MS, m/z 246 (M^+), 182, 167.

5-*n*-Butyl-3-(trimethylsilyl)-2-sulfolene (5b): ^1H NMR δ 0.20 (9 H, s), 0.88 (3 H, t, J = 7 Hz), 1.1–2.0 (6 H, m), 3.2 (3 H, m), 6.54 (1 H, s).

4-*n*-Butyl-4-(trimethylsilyl)-2-sulfolene (6b): ^1H NMR δ 0.10 (9 H, s), 0.90 (3 H, t, J = 7 Hz), 1.1–2.0 (6 H, m), 3.05 (2 H, s), 6.45 (2 H, s).

2-(5-Hexenyl)-3-(trimethylsilyl)-3-sulfolene (4c): ^1H NMR δ 0.19 (9 H, s), 1.2–2.4 (8 H, m), 3.67 (3 H, m), 4.94 (1 H, d, J = 12 Hz), 5.21 (1 H, d, J = 17 Hz), 5.75 (1 H, dd, J = 12, 17 Hz), 6.18 (1 H, br s); IR (liquid) 3100, 1645, 1305, 1130 cm^{-1}.

5-(5-Hexenyl)-3-(trimethylsilyl)-2-sulfolene (5c): ^1H NMR δ 0.21 (9 H, s), 1.2–1.5 (6 H, m), 1.8–2.2 (2 H, m), 3.2 (3 H, m), 4.94 (1 H, d, J = 10 Hz), 4.98 (1 H, d, J = 18 Hz), 5.62 (1 H, dd, J = 10, 18 Hz), 6.54 (1 H, s).

4-(5-Hexenyl)-4-(trimethylsilyl)-2-sulfolene (6c): ^1H NMR δ 0.09 (9 H, s), 1.0–2.0 (8 H, m), 3.07 (2 H, s), 4.90 (1 H, d, J = 10 Hz), 4.94 (1 H, d, J = 18 Hz), 5.62 (1 H, dd, J = 10, 18 Hz), 6.43 (2 H, s).

5-Isopropyl-3-(trimethylsilyl)-2-sulfolene (5d): ^1H NMR δ 0.25 (9 H, s), 0.77 (3 H, d, J = 7 Hz), 0.99 (3 H, d, J = 7 Hz), 1.8–2.3 (1 H, m), 2.8–3.3 (3 H, m), 6.60 (1 H, s); IR 3050, 1620, 1280, 1120 cm^{-1}; MS, m/z 232 (M^+), 217, 190, 125. Anal. Calcd for $C_{10}H_{20}O_2SSi$: C, 51.70; H, 8.68. Found: C, 51.54; H, 8.67.

2-Phenyl-3-(trimethylsilyl)-3-sulfolene (4e): ^1H NMR δ 0.0 (9 H, s), 3.80 (2 H, br s), 4.80 (1 H, s), 6.4 (1 H, s), 7.35 (5 H, m); IR (liquid) 3100, 1600, 1590, 1315, 1120 cm^{-1}; MS, m/z 202 ($M^+ - SO_2$), 73.

2,5-Dimethyl-3-(trimethylsilyl)-3-sulfolene (7a): ^1H NMR δ 0.10 (9 H, s), 1.38 (6 H, d, J = 7 Hz), 3.64 (2 H, q, J = 7 Hz), 5.98 (1 H, s); IR (liquid) 2975, 1595, 1310, 1130 cm^{-1}; MS, m/z 182 ($M^+ - SO_2$), 167, 73. The stereochemistry was determined to be trans by thermal extrusion of SO_2 and a 2-D NOESY experiment on the resulting diene.

2,5-Di-*n*-butyl-3-(trimethylsilyl)-3-sulfolene (7b): ^1H NMR δ 0.11 (9 H, s), 0.90 (6 H, t, J = 7 Hz), 1.0–2.2 (12 H, m), 3.3–3.8 (2 H, m), 6.10 (1 H, s); IR (liquid) 2880, 1600, 1320, 1120 cm^{-1}; MS, m/z 238 ($M^+ - SO_2$), 223, 164, 73. The stereochemistry was determined to be trans by extrusion of SO_2 and a 2-D NOESY

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experiment on the resulting diene.

Diels–Alder Adducts. 10: ^{1}H NMR δ 0.0 (9 H, s), 1.0 (3 H, d, J = 7 Hz), 2.85 (1 H, m), 2.90 (2 H, s), 3.62 (6 H, s), 5.80 (1 H, br s); IR 1737, 1660, 1620 cm^{-1}; MS, m/z 282 (M^+), 267, 235. **12:** ^{1}H NMR δ 0.11 (9 H, s), 1.15 (6 H, s), 2.97 (2 H, s), 3.74 (3 H, s), 3.78 (3 H, s), 5.68 (1 H, br s); IR 1735, 1620 cm^{-1}; MS, m/z 296 (M^+), 281, 73. For **2a** with methyl propiolate, both GC and NMR show that two isomers were obtained, with a 5:1 ratio. From aromatization experiment, the major product was assigned as 2-carbomethoxy-3-methyl-5-(trimethylsilyl)-1,4-cyclohexadiene (**13a**): ^{1}H NMR δ 0.1 (9 H, s), 1.10 (3 H, d, J = 7 Hz), 2.8–3.0 (3 H, m), 3.72 (3 H, s), 6.0 (1 H, br s), 7.0 (1 H, br s); MS, m/z 224 (M^+), 209. Minor product, 1-carbomethoxy-3-methyl-5-(trimethylsilyl)-1,4-cyclohexadiene (**13b**): ^{1}H NMR δ 0.2 (9 H, s), 1.10 (3 H, d, J = 7 Hz), 2.8–3.0 (3 H, m), 3.72 (3 H, s), 5.84 (1 H, br s), 6.85 (1 H, br s); MS, 224 (M^+), 209. For **4a** with methyl propiolate, both GC and NMR show two isomers obtained with a 2:1 ratio. From aromatization experiment, the major product was assigned as 2-carbomethoxy-3-methyl-4-(trimethylsilyl)-1,4-cyclohexadiene (**11b**): ^{1}H NMR δ 0.09 (9 H, s), 1.06 (3 H, d, J = 7 Hz), 2.8–3.0 (3 H, m), 3.72 (3 H, s), 5.97 (1 H, br s), 6.97 (1 H, br s); IR 1737, 1660, 1620 cm^{-1}; MS, m/z 224 (M^+), 209. The minor product, 1-carbomethoxy-3-methyl-4-(trimethylsilyl)-1,4-cyclohexadiene (**11b**): ^{1}H NMR δ 0.08 (9 H, s), 1.06 (3 H, d, J = 7 Hz), 2.8–3.0 (3 H, m), 3.72 (3 H, s), 6.05 (1 H, br s), 6.92 (1 H, br s); IR 1735, 1660, 1620 cm^{-1}; MS, m/z 224 (M^+), 209. 7-(Trimethylsilyl)-1,2,3,4,5,6,4a,8a-octahydronaphthalene (**14**): GC shows two isomers with a 1:1 ratio; NMR shows two vinyl protons at δ 5.68 and 5.78 (total 1 H), 0.8–2.2 (14 H, m), 0.0 (9 H, s); MS, m/z 208 (M^+). 8-(Trimethylsilyl)-1,2,3,4,5,6,4a,8a-octahydronaphthalene (**15**): ^{1}H NMR δ 0.0 (9 H, s), 0.8–2.2 (14 H, m, three multiple bands, pattern identical with that of the trans 8-methyl analogue[15]), 5.92 (1 H, br s); MS, m/z 208 (M^+).

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Registry No. **1**, 104692-94-6; **2a**, 104664-80-4; **2b**, 111379-20-5; **2c**, 111379-21-6; **2d**, 111379-22-7; **3a**, 111379-23-8; **3b**, 111379-24-9; **3c**, 111379-25-0; **3d**, 111379-26-1; **3e**, 111379-27-2; **4a**, 111379-28-3; **4b**, 111379-29-4; **4c**, 111379-32-9; **4d**, 111379-48-7; **5b**, 111379-30-7; **5c**, 111379-33-0; **5d**, 111379-35-2; **6b**, 111379-31-8; **6c**, 111379-34-1; **7a**, 111379-36-3; **7b**, 111379-37-4; **8**, 111379-46-5; **9**, 111379-47-6; **10**, 106212-32-2; **11a**, 111379-38-5; **11b**, 111379-39-6; **12**, 111379-40-9; **13a**, 111379-41-0; **13b**, 111379-42-1; *cis*-**14**, 111379-43-2; *trans*-**14**, 111379-44-3; **15**, 111379-45-4; MP, 922-67-8; DMAD, 762-42-5; MeI, 74-88-4; EtI, 75-03-6; BuI, 542-69-8; $C_6H_{11}I$, 626-62-0; $I(CH_2)_4I$, 628-21-7; $I(CH_2)_5I$, 628-77-3; (*E*)-BuCH=CHC(TMS)=CH_2, 111379-49-8; (*Z*)-CH_2=CHC(TMS)=CHBr, 111379-50-1; (*E*)-CH_2=CHC(TMS)=CHBu, 111379-51-2; (*E*,*E*)-BuCH=C(TMS)=CHBu, 111379-52-3; *i*-PrI, 75-30-9.

Total Syntheses of Marchantin A and Riccardin B, Cytotoxic Bis(bibenzyls) from Liverworts

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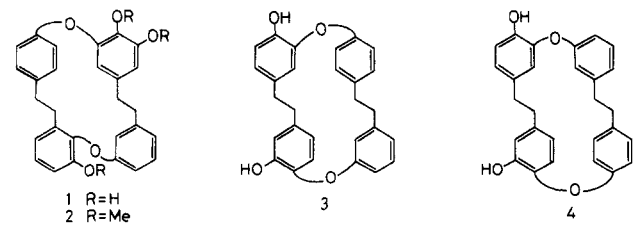
Marchantin A (**1**) and riccardin B (**3**) have been synthesized in twelve steps. The novel macrocyclic bis(bibenzyl) frameworks have been constructed by the intramolecular Wadsworth–Emmons olefination of the phosphonates **24** and **37**. The key intermediate **24** was prepared by the sequential connection of methyl 7-(4-formylphenoxy)-2,2-dimethyl-1,3-benzodioxole-5-carboxylate (**15**), diethyl [[2,3-bis(benzyloxy)phenyl]methyl]phosphonate (**16**), and *m*-bromobenzaldehyde, while **37** was synthesized from diethyl [4-[2-methoxy-5-(1,3-dioxan-2-yl)-phenoxy]benzyl]phosphonate (**32**) and methyl 3-methoxy-4-(3-formylphenoxy)benzoate (**33**). The synthesis established the structure of riccardin B as the formula **3**.

Liverworts have been shown to produce various types of natural products including terpenoids, phenolic compounds, lipids, and so on.[1] Among them, cyclic bis(bibenzyls) are particularly interesting because they constitute a new class of natural products and some of them exhibit cytotoxic activity against KB cell and P388 lymphocytic leukemia.[2] To date, more than 20 substances have been isolated from liverworts.[3,4] A representative compound of this family is marchanchin A (**1**) (Chart I), isolated as the major component of *Marchantia polymorpha* and related liverworts.[2] In this molecule, two unsymmetrically substituted bibenzyls are joined by two ether linkages forming a macrocyclic ionophor-like structure. The novel

Chart I



structure **1** was deduced on the basis of spectral analysis and chemical degradations and confirmed by X-ray crystallographic analysis of its trimethyl ether **2**. Riccardin B is another type of cyclic bis(bibenzyl) obtained from *Riccardia multifida*.[5] While the structure of this compound has been proposed by Asakawa et al.[5] as **3** on the basis of spectral analysis and biogenetic considerations, alternative structure **4** could not be fully excluded.

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