Nuclear Synthons: Mesyltriflone as an Olefin Polyanion Equivalent[1]

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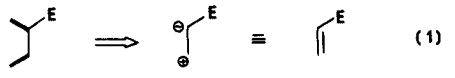
Abstract: Mesyltriflone ($CF_3SO_2CH_2SO_2CH_3$) is developed as a nuclear synthon reagent capable first of multiple constructions such as alkylations then of Ramberg–Bäcklund elimination to a substituted olefin. The alkylations are clean and regiospecific, often amenable to one-pot operation, and in most cases the elimination is smooth. A variety of examples is presented to establish the scope of the method, and the mechanism and stereochemistry are discussed.

Nuclear Synthons. In our examination of the logic of synthesis design[2] we directed attention to the central importance of minimizing steps and of utilizing primarily construction reactions. A major corollary of these ideas is the prime importance of multiple constructions, allowing two or more constructions in one operation. Typical examples of the concept are illustrated in eq 1–4, in which the product directs the use of a particular small-



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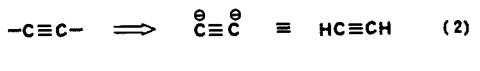

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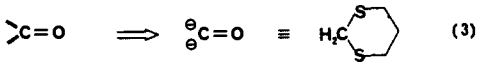

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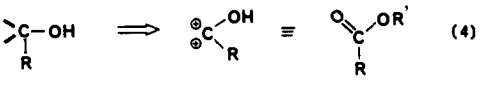

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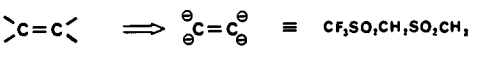


(5)

molecule unit capable of initiating multiple constructions, usually either as a nucleophile (−) or electrophile (+) as designated; the constructed product bonds are shown in boldface. The Diels–Alder reaction (1) and acetylene dialkylation (2) are simple examples. Less direct are the masked functional group equivalents like the carbonyl anion equivalent (3) or the "alcohol electrophile" (4).

Such small units we term "nuclear synthons" since they provide a nucleus of reactivity capable of rapidly elaborating around it a large product skeleton. It is possible to deduce a number of formal examples of nuclear synthons of one to three carbons activating two or more constructions like examples 1–4. Our interest has focused on nuclear synthons capable of a maximal number of constructions, and one of these is explored in this paper: the olefin polyanion equivalent[1] of eq 5, which offers construction of up to four bonds onto a two-carbon olefin equivalent unit acting successively as nucleophile. One important feature of the nuclear synthon concept is that it dictates to a large extent the synthesis design. Mapping the nuclear synthon onto a target structure determines a partial bondset and so directs the remaining synthons

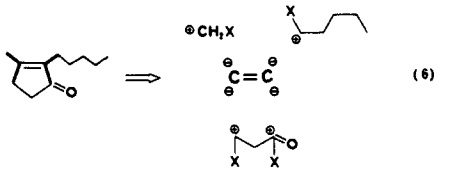
Table I. Alkylations of α,α-Dianion **1**

$CF_3SO_2C^{2-}SO_2CH_3 + RX \rightarrow CF_3SO_2CH(R)SO_2CH_3$

product	RX	mp (°C)	yield (%)
2a	CH_3I	70	95
2b	$CH_3(CH_2)_2I$	oil	84
2c	$CH_3(CH_2)_4I$	47	55
2d	$C_6H_5CH_2Br$	111	94
2e	$(CH_3)_2C{=}CHCH_2CH_2I$	oil	75
2f[a]		oil	50

[a] Product, R = CH_2CH_2OH.

necessary for the synthesis. The more bonds which can be constructed by the nuclear synthon, the more the plan and the resultant starting materials are simplified. Thus the synthesis of dihydrojasmone is dictated from the olefin polyanion in eq 5 as illustrated in eq 6; the required synthons are now quite simple, and the execution[3] is reviewed below.



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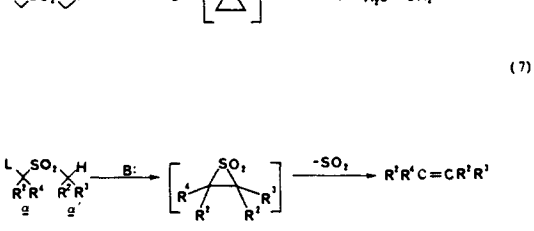
Mesyltriflone Alkylation. Since design of the olefin polyanion reagent requires both carbons as carbanions, we looked to the Ramberg–Bäcklund reaction (eq 7)[4] as an olefin source in order to utilize its sulfone for α-carbanion activation. Further required is a leaving group L which can also serve to stabilize the carbanion on the α-position in order to create the differential activation necessary to control the regioselectivity of alkylations at α and α', adding R^1 to R^4. For this purpose the trifyl group is ideal (L = $-SO_2CF_3$) since it is both powerfully electron-withdrawing and also known to be a leaving group at least in three-membered ring displacements such as eq 7.[5]



(7)

(1) A preliminary communication of this work: Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S. *Tetrahedron Lett.* **1984**, 4617.
(2) (a) Hendrickson, J. B.; Braun-Keller, E.; Toczko, A. G. *Tetrahedron Suppl.* **1981**, *37*, 359. (b) Hendrickson, J. B.; Grier, D. L.; Toczko, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5228.
(3) Hendrickson, J. B.; Palumbo, P. S. *J. Org. Chem.* **1985**, *50*, 2110.
(4) Paquette, L. A. *Org. React. (N.Y.)* **1977**, *25*, 1.
(5) Hendrickson, J. B.; Sternbach, D. D.; Bair, K. W. *Acc. Chem. Res.* **1977**, *10*, 306.

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Table II. Dialkylation of α,α,α'-Trianion **9**

$CF_3SO_2C^{2-}SO_2CH_2^- + 2RX \rightarrow CF_3SO_2CH(R)SO_2CH_2R$

product	2RX	mp (°C)	yield (%)
6a	CH_3I	oil	95
6b	$CH_3(CH_2)_2I$	oil	69
6c	$CH_3(CH_2)_4I$	oil	65
6d	$Br(CH_2)_3Br$	95	87
6e	$C_6H_5CH_2Br$	72–74	92
6f	α: CH_3I, α': $CH_3(CH_2)_4Br$	oil	30[a]

[a] Successive addition: amyl bromide followed by methyl iodide.

The requisite reagent is the disulfone, mesyltriflone, $CF_3SO_2C^{\alpha}H_2SO_2C^{\alpha'}H_3$, a stable crystalline compound (mp 116–117 °C). This is readily made either by triflation of dimethyl sulfone in base with trifyl fluoride (CF_3SO_2F)[3] or triflic anhydride ($(CF_3SO_2)_2O$) or by analogous acylation of methyltriflone[6] with methanesulfonic anhydride. The α-hydrogen is very acidic (pK_a = 4.3 in water),[7] indeed more acidic than acetic acid and similar in acidity to ditrifylmethane,[6,7] $(CF_3SO_2)_2CH_2$. With 2 mol of butyllithium/THF/−78 °C the dianion is formed, precipitating as an insoluble white solid, which readily dissolves between −50 and 20 °C after addition of methyl iodide or other alkylating agents, to form exclusively the product of monoalkylation at the α-position; examples are listed in Table I. Thus deprotonation of the α-monoanion removes the second α-hydrogen in preference to the α'-hydrogen; this parallels the easy abstraction of the second hydrogen from the anion of ditrifylmethane.[6] The α-monoanion itself is very stable and difficult to alkylate.

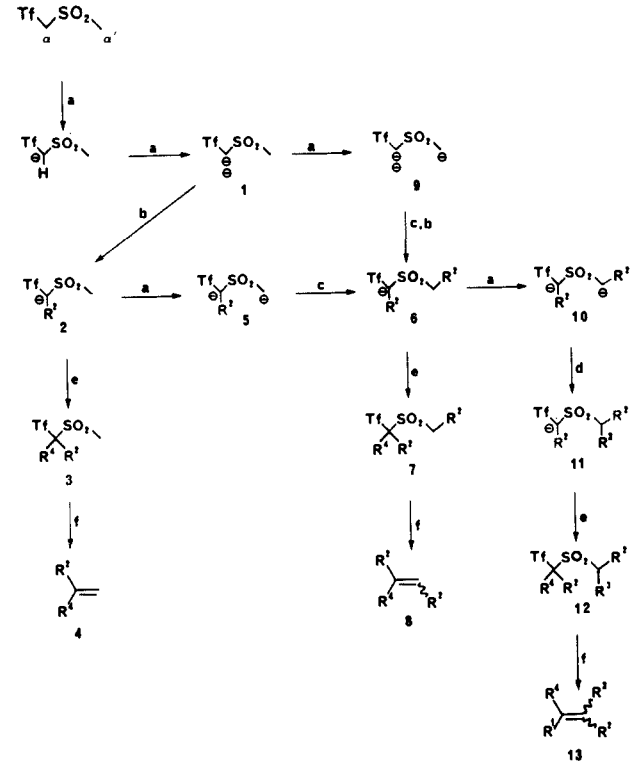
With this background the general approach to olefin synthesis via alkylations of mesyltriflone is outlined in Scheme I. The insoluble α,α-dianion of the reagent (**1**) redissolves on addition of a third equiv of butyllithium, apparently to the α,α,α'-trianion (**9**), which cleanly yields the α,α'-dialkyl product **6** ($R^1 = R^2$) with 2 equiv of alkylating agent (Table II). It is not, however, so regiospecific with 1 equiv, cf., successive alkylation of the trianion with pentyl bromide followed by methyl iodide afforded mixtures containing only 30% of **6** ($R^1 = CH_3$; $R^2 = C_5H_{11}$). After alkylation of the dianion to **2** (Table I), deprotonation from α is now readily achieved (butyllithium/−78 → −55 °C) to form the α,α'-dianion (**5**), from which as expected alkylation proceeds exclusively at α' to give **6** (Table III). Further alkylation at α' is accomplished without difficulty by repeating the process, i.e., **6** → **10** → **11**.

In this way multiple alkylations can be carried out with a high degree of regiocontrol, producing the alkylated monoanions (**2**, **6**, **11**). Indeed the reactions are facile enough to allow several operations successively in one vessel, as in the conversion of mesyltriflone to **6** ($R^1 = CH_3$; $R^2 = C_5H_{11}$) in 70% yield or of **2** ($R^1 = CH_3$) to **11** ($R^1 = R^2 = CH_3$; $R^3 = PhCH_2$) in 89%, without intermediate isolations. Without strict control of stoichiometry, however, three successive different alkylations, in one vessel, to form **11** tend as expected to give lower yields. Side products from further alkylation of the α-monoanion are not found, however, owing to the insignificant reactivity of these species at lowered temperatures. Indeed it is the presence of the α-monoanion throughout the alkylation sequence that protects the molecule from premature Ramberg–Bäcklund elimination when the α'-anions are formed. Furthermore, these α-monoanion products are freely water-soluble stable salts, facilitating their separation from neutral by-products; aqueous acidification then provides the conjugate acid for extraction.

Further alkylation of the α-substituted α-anion (**2**, **6**, **11**) is somewhat more facile than that of the unsubstituted reagent monoanion but still requires very reactive alkylation agents and elevated temperatures, as evidenced by the examples in Table IV which were carried out on the isolated conjugate acids of these

(6) Koshar, R. J.; Mitsch, R. A. *J. Org. Chem.* **1973**, *38*, 3358.
(7) For comparison, the pK_a of ditrifylmethane is 1.2. The acidity measurements were kindly determined for us by Professor R. Bergeron at the University of Florida, in 20% MeOH and extrapolated to water.

Scheme I. Olefin Synthesis Paths from Mesyltriflone[a]

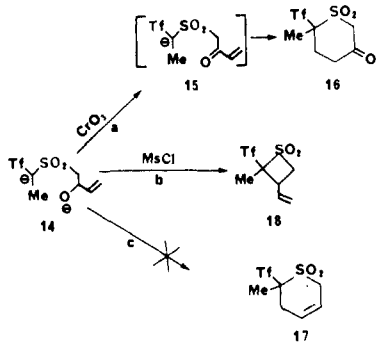


[a] Reagents: (a) *n*-BuLi (1 equiv), (b) R^1X, (c) R^2X, (d) R^3X, (e) R^4X, (f) potassium *tert*-butoxide.

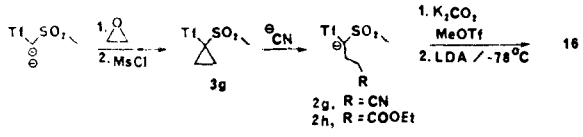
anions with added base. When the alkylation was internal, the reaction was more facile, the three-membered ring proceeding at room temperature (see below), while large rings required heating, as in examples **7j–l** and **12f,g** in Table IV. A smooth internal conjugate addition is also described below. While Ramberg–Bäcklund elimination did not significantly occur during these alkylations, 1,2-elimination of triflinate ion may occur if carbonyl activation exists, giving rise to β-acylvinyl sulfones, as in alkylation of **2a** with ethyl bromoacetate to form $CH_3SO_2C(CH_3)$=CHCOOEt. Finally, unsuccessful alkylations using the potassium salt were also attempted with the silver salt but with no more success, cf., with $C_6H_5CH_2OCH_2Cl$, $C_6H_5CH_2Br$, and $C_6H_5SCH_2Cl$.

Other Electrophiles. The use of carbon electrophiles other than alkylating agents is also viable. Acylation proved to be even more facile, most commonly on the α'-position via the α,α'-dianion; acid chlorides, anhydrides, esters, and chloroformates all reacted in good yield at −78 °C, as surveyed in Table III. An additional equivalent of base (commonly LDA) is supplied for complete reaction since the product β-keto sulfones are more acidic than the starting sulfones. Aldehydes and ketones reacted similarly to give the β-hydroxy sulfones, and carboxylation gave the β-sulfo acid, all expected reactions of α-sulfone carbanions. The reactions of the stable α-monoanion, however, offered some surprises. First, since the α'-acryloyl derivative **15** was not available from acrylic esters or chloride owing to polymerization, it was approached by oxidation of the alcohol **14** from acrolein and **2a**, but the unsaturated ketone initially formed **15** spontaneously cyclized by conjugate addition to give the ketone **16**. Second, an attempt to explore the parallel reaction at the next lower level of oxidation employed mesyl chloride with the alcohol **14**, which gave the four-membered direct displacement product **18** instead of the allylic substitution to the six-membered ring **17**. A variety of attempts to convert **18** to **17** including heating with iodide ion or acetic acid failed to alter **18**.

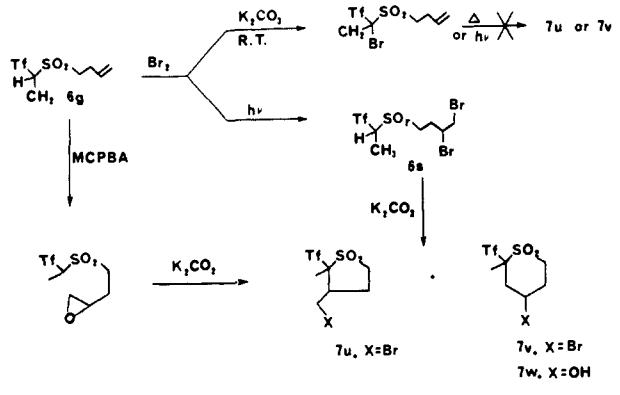
Alkylation of the α,α-dianion with ethylene oxide followed directly by mesyl chloride afforded the cyclopropyl derivative **3g** at room temperature. The activation of this ring was apparent in its reaction with cyanide to give **2g** which could be ethanolyzed



in acid to the ester **2h**. α-Methylation of the monoanion followed by base led to **16**. In other cyclization attempts, bromination



of the allyl derivative **6g** in the presence of light saturated the double bond to **6s** but treatment with mild base cyclized to a mixture of ring sizes, **7u** and **7v**. The epoxide of **6g**, however, gave only a single alcohol (**7w**) on cyclization.



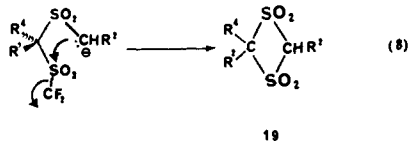
Further, reaction of formaldehyde with the stable α-monoanion proceeded smoothly at room temperature to eliminate triflate ion and create α-methylene sulfones in high yield.[8] The reaction apparently involves a four-membered transition akin for sulfur to the Wittig and Petersen reactions for phosphorus and silicon. With higher aldehydes the α-monoanions were unreactive, however. In contrast the α-monoanions readily and quantitatively brominate at low temperature (examples **7h** and **12h**, Table IV).

Underlying all these clarifications of construction reactions on the reagent has been the idea that the α'-anion of α-disubstituted compounds invariably led to elimination. However, the faster acylation reaction (−78 °C) at α' is successful, as demonstrated in Table V, for the Ramberg–Bäcklund reaction does not proceed significantly at −78 °C. Acid chlorides with enolizable hydrogens were not successful, e.g., example **7p**, presumably owing to by-products from generated ketenes.

Ramberg–Bäcklund Elimination. Only when the α-position is dialkylated can the Ramberg–Bäcklund reaction proceed. When these compounds (**3**, **7**, and **12** in Scheme I) are treated with bases, triflinate ($CF_3SO_2^-$) ion is ejected and cheletropic sulfur dioxide extrusion follows spontaneously to give the corresponding olefins (**4**, **8**, and **13**) as in eq 7. With the lower-energy carbanions of the α'-acylated or carboxylated compounds the reaction proceeds smoothly in high yield with phase-transfer alkali or on heating with potassium carbonate. Results are tabulated in Table VI.

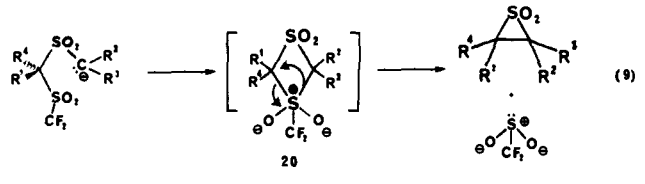
With simple α'-alkylated compounds stronger bases were required. When butyllithium was used for the alkylations themselves, the NMR spectra of the crude products invariably exhibited considerably extra hydrocarbon absorption indicative of incorporation of the butyl nucleophile. Indeed in one case (**2**, R^1 = Ph; R^2 = CH_2Ph) some 42% of the $PhCH_2CH(Ph)Tf$ was isolated, implying attack of butyl on the sulfone to eliminate the stabilized benzyltriflone anion.

The use of *tert*-butoxide as base was successful on the simple dialkylated compounds (3 → 4) and on the tetraalkyl (12 → 13) or cyclic cases documented in Table VI. However, several bases used on the trialkyl compounds (7 → 8) and some dialkyl ones (3 → 4) afforded the desired olefin mixed with a competitive reaction product, the cyclic disulfone **19**. This competitive reaction presumably involves internal attack by the α'-anion on trifyl sulfonyl group with elimination of CF_3^- (or F^- and $:CF_2$) as in the haloform reaction (eq 8). Bimolecular examples of this reaction have been seen in the attack of alkoxide bases on simple triflones to form alkyl sulfonate esters, ($RSO_2CF_3 + {}^-OR^1 \rightarrow RSO_2OR^1$).[9]



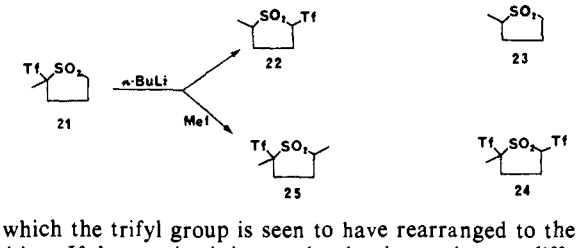
Of the several bases tried (Table VII) *tert*-butoxide appeared to be the most satisfactory, but no clear correlation of olefin product preference with either base or substrate structure appeared to emerge. Few of these cyclic disulfones **19** have previously been reported,[10] and none with the asymmetric substitution pattern available here. These compounds are stable, modestly acidic (pK_a 12.5),[10] and unchanged by pyrolysis to 300 °C.

The intervention of intramolecular attack on the trifyl sulfonyl led us to query the accepted mechanism of the Ramberg–Bäcklund reaction,[4] in which we considered that initial attack on the trifyl sulfonyl instead might create an intermediate hypervalent sulfur form **20** which could conceivably collapse directly to the episulfone (eq 9). It should be noted that the same hypervalency could be



attributed to halogen leaving groups (L in eq 7) but would not occur with sulfonates, which indeed shown an otherwise unexpectedly low rate in the elimination.[11]

The only other evidence we have seen for this alternative came in the conversion of **21** (made analogously from sulfolane) to **22**



in which the trifyl group is seen to have rearranged to the α'-position. If the reaction is intramolecular, it constitutes a different path from **20**, presumably forced by ring strain from the sulfolane. If it is intermolecular, one would expect other products such as **23** and **24**, and these were clearly absent. To date, however, no

(8) Hendrickson, J. B.; Palumbo, P. S. *Tetrahedron Lett.* **1985**, 2849. A referee suggested that a discrete β-sulfone intermediate might be formed by reaction of oxygen anion on SO_2CF_3 to displace CF_3 anion. This would be followed by extrusion of SO_3 to give the alkene and reaction of the SO_3 with CF_3^- to give triflate. Each mechanism affords the same products, and a resolution of this slight distinction cannot be made from our evidence.

(9) Skipper, P. Ph.D. Thesis, Brandeis University, 1975.

(10) Block, E.; Corey, E. R.; Penn, R. E.; Renken, T. L.; Sherwin, P. F.; Bock, H.; Hirabayashi, T.; Mohmand, S.; Colouki, B. *J. Am. Chem. Soc.* **1982**, *104*, 3119.

(11) Meyers, C. Y.; Hua, D. H.; Peacock, N. J. *J. Org. Chem.* **1980**, *45*, 1719.

Table III. Reactions of α,α'-Dianions **5** and **10**

$$CF_3SO_2\bar{C}(R^1)\text{-}SO_2\bar{C}(R^2)\text{-}H + R^3X \longrightarrow CF_3SO_2CH(R^1)SO_2CH(R^2)R^3$$

product	reagent (R^3X)	R^1	R^2	R^3	mp	yield (%)	method[a]
6f	$CH_3(CH_2)_4I$	CH_3	H	$(CH_2)_4CH_3$	oil	90	A[b]
6g	CH_2=$CHCH_2Br$	CH_3	H	CH_2CH=CH_2	oil	63	A
6h	$C_6H_5CH_2Br$	CH_3	H	$CH_2C_6H_5$	oil	87	A
6i	$C_6H_5CH_2Br$	$CH_2C_6H_5$	H	$CH_2C_6H_5$	72–73 °C	90	A
6j[25]	CH_3I	C_6H_5	H	CH_3	136–138 °C	95	A
6k	CH_2=$CHCHO$	CH_3	H	$CH(OH)CH$=CH_2		*c*	A
6l	$Cl(CH_2)_3COOEt$	CH_3	H	$CO(CH_2)_3Cl$	55–56 °C	60	B
6m		CH_3	H		62–63 °C	60	B
6n		CH_3	H		69–74 °C	53	B
6o	CO_2	CH_3	H	COOH	99–100 °C	56	A
6p	$ClCOOCH_3$	CH_3	H	$COOCH_3$	oil	100	B
6q	$ClCOOCH$=CH_2	CH_3	H	$COOCH$=CH_2	52–53 °C	94	B
11a	$C_6H_5CH_2Br$	CH_3	CH_3	$CH_2C_6H_5$	87 °C	90	A[b]
11b	$C_6H_5CH_2Br$	$-(CH_2)_2-$		$CH_2C_6H_5$	146–149 °C	100	A
11c	$C_6H_5CH_2Br$	$-(CH_2)_3-$		$CH_2C_6H_5$	154–157 °C	72	A
11d	CH_2=$CHCHO$	CH_3	CH_3	$CH(OH)CH$=CH_2	oil	94	A
11e	C_6H_5COCl	CH_3	CH_3	COC_6H_5	82–87 °C	68	B
11f	$CH_3(CH_2)_4I$	CH_3	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	oil	66	A

[a] Methods: (A) 1. *n*-BuLi (2 equiv)/THF/−78 °C, 2. RX (1 equiv), 3. warm to RT and acidify; (B) 1. *n*-BuLi (2 equiv)/LDA (1 equiv)/THF/−78 °C, 2. RCOCl (1 equiv)/−78 °C, 3. acidify. [b] Carried out in one operation with two successive alkylations. [c] Not isolated but carried on by oxidation/cyclization (**14** → **16**).[3]

Table IV. Reactions of α-Monoanions (**2**, **6**, and **11**)

$$CF_3SO_2\bar{C}(R^1)\text{-}SO_2CH(R^2)R^3 + R^4X \longrightarrow CF_3SO_2C(R^1)(R^4)SO_2CH(R^2)R^3$$

product	reagent (R^4X)	R^1	R^2	R^3	R^4	mp	yield (%)	method
3a	CH_3I	$(CH_2)_2CH_3$	H	H	CH_3	oil	90	A
3b	CH_3OTf	$(CH_2)_2COOEt$	H	H	CH_3	oil	66	B
3c	CH_3SCH_2Cl	CH_3	H	H	CH_2SCH_3	oil	90	C
3d	$C_6H_5CH_2OCH_2Cl$	CH_3	H	H	$CH_2OCH_2C_6H_5$	oil	50	C
3e	$I(CH_2)_3COOEt$	CH_3	H	H	$(CH_2)_3COOEt$	oil	50	A
3f	CH_3I	$(CH_2)_2CH$=$C(CH_3)_2$	H	H	CH_3	oil	92	A
7a	C_2H_5OTf	CH_3	CH_3	H	C_2H_5	oil	95	B
7b	CH_3OTf	CH_3	$CH_2C_6H_5$	H	CH_3	oil	83	B
7c	C_2H_5OTf	CH_3	$CH_2C_6H_5$	H	C_2H_5	oil	73	B
7d	C_2H_5OTf	$CH_2C_6H_5$	$CH_2C_6H_5$	H	C_2H_5	oil	69	B
7e[25]	CH_3OTf	C_6H_5	CH_3	H	CH_3	70–72 °C	82	B
7f	CH_3I	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	H	CH_3	oil	94	A
7g	CH_3I	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	H	CH_3	oil	91	A
7h	Br_2	CH_3	CH_2CH=CH_2	H	Br	oil	97	D
7i	CH_3SCH_2Cl	$-CH_2CH_2CH_2-$		H	CH_2SCH_3	oil	63	C
7j	$Br(CH_2)_3Br$[b]	CH_3	H	$-CH_2CH_2CH_2-$		83–90 °C	71	E[b]
7k	$Br(CH_2)_4Br$[b]	CH_3	H	$-CH_2CH_2CH_2CH_2-$		95–97 °C	67	E[b]
7l	$Br(CH_2)_3Br$[b]	$(CH_2)_4CH_3$	H	$-CH_2CH_2CH_2-$		oil	66	E[b]
12a	C_2H_5OTf	CH_3	CH_3	$CH_2C_6H_5$	C_2H_5	oil	69	A
12b	$C_6H_5CH_2Br$	CH_3	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	oil	64	A
12c	CH_3I	CH_3	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	CH_3	oil	95	A
12d	CH_3I	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	CH_3	oil	*b*	A
12e	CH_3OTf	$-CH_2CH_2-$		$CH_2C_6H_5$	CH_3	oil	46	B
12f	$Br(CH_2)_3Br$[b]	CH_3	$(CH_2)_4CH_3$	$-CH_2CH_2CH_2-$		oil	93[b]	E
12g	$Br(CH_2)_4Br$[b]	CH_3	$(CH_2)_4CH_3$	$-CH_2CH_2CH_2CH_2-$		oil	87	E
12h	Br_2	CH_3	CH_3	$CH_2C_6H_5$	Br	oil	100	D

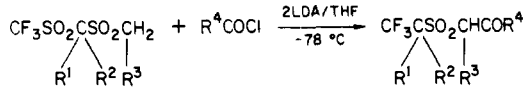
[a] Methods: (A) RX (1–3 equiv)/K_2CO_3 (anhydrous)(3 mol)/DMF/70–90 °C/3–24 h; (B) 1. K_2CO_3, 2. $ROTf/CH_2Cl_2$ or CCl_4/Δ; (C) RX (1.2 mol)/K_2CO_3 (anhydrous)(3 mol)/THF/Δ 1–3 days; (D) K_2CO_3 (1 mol)/Br_2 (1 mol)/CH_2Cl_2–THF/0 °C; (E) 1. *n*-BuLi (2 equiv), 2. $Br(CH_2)_xBr$/−78 °C, 3. CH_3CN/80 °C (x = 3) or DMF/120 °C (x = 4). [b] Two alkylations without isolation; cyclization requires heat. [c] Incomplete after days at 90 °C/K_2CO_3/DMF.

definitive experiment to distinguish these alternatives has been found. It may be noted that, unlike the unstrained cases, the anion of **21** will alkylate cleanly to **25**, presumably owing to the slow competitive rate of elimination, again owing to ring strain.

Stereochemistry. For optimal synthetic use the attachment of substituents to the reagent must be regiospecific, and this appears to be well-controlled. Further, the elimination to olefin should also be stereospecific, and indeed this is known to be the case in the traditional Ramberg–Bäcklund reaction. In an elegant demonstration of the stereochemistry, Bordwell showed that each separated diastereomer (eq 7: $R^1 = R^3 = CH_3$; $R^2 = R^4 = C_6H_5$; L = Br) gave mainly only one olefin isomer with a selectivity of about 20:1, i.e., the meso-bromide gave the cis-olefin, and the DL-bromide gave the trans.[12] This translates to a stereochemistry

(12) Bordwell, F. G.; Doomes, E.; Corfield, P. W. R. *J. Am. Chem. Soc.* **1970**, *92*, 2581. Bordwell, F. G.; Doomes, E.; Corfield, P. W. R. *J. Org. Chem.* **1974**, *39*, 2526.

Table V. Acylation of α-Disubstituted Compounds **3** and **7**

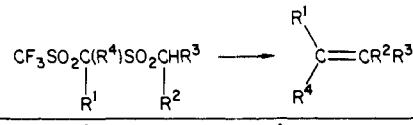


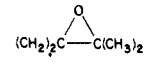
3 or **7** **7** or **12**

product	R^1	R^2	R^3	R^4	mp	yield (%)
7m	CH_3	$CH_2OCH_2C_6H_5$	H	OCH_3	oil	64
7n	CH_3	CH_3	H	$C(CH_3)_3$	117–119 °C	91
7o	CH_3	CH_3	H	C_6H_5	86–88 °C	100[a]
7p	CH_3	CH_3	H	CH_3		0
7q	CH_3	CH_3	H	$C(CH_3)_2CH{=}CH_2$	81–82 °C	100[a]
7r	CH_3	$(CH_2)_2CH_3$	H	OCH_3	oil	87
7s	CH_3	CH_2SCH_3	H	OCH_3	oil	64
7t	CH_3	$(CH_2)_2C{=}C(CH_3)_2$	H	OCH_3	oil	68
12i	CH_3	$-CH_2CH_2CH_2-$		OCH_3	109–125 °C	94
12j	CH_3	$-CH_2CH_2CH_2CH_2-$		OCH_3	111–120 °C	80
12k	CH_2SCH_3	$-CH_2CH_2CH_2-$		OCH_3	oil	85
12l	CH_3	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	OCH_3	oil	20[b]

[a] Crude yield only. [b] Also obtained 36% cyclic disulfone **19** and 13% elimination to α,β-dipentyl crotonate (1:1 *E*/*Z* ratio).

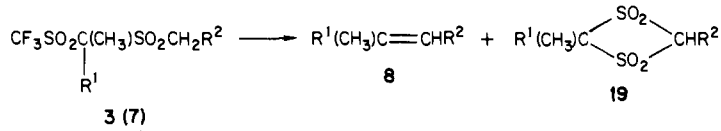
Table VI. Ramberg–Bäcklund Eliminations



substrate	product[a]	R^1	R^2	R^3	R^4	yield (%)	method[b]	ref
3a	**4a**	$(CH_2)_2CH_3$	H	H	CH_3	80	A	16
3e	**4e**	CH_3	H	H	$(CH_2)_3COOEt$	83	A	17
7l	**8l**	$(CH_2)_4CH_3$	H	$-CH_2CH_2CH_2-$		65	A	
12d	**13d**	CH_3	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	64	A	
12f	**13f**	CH_3	$(CH_2)_4CH_3$	$-CH_2CH_2CH_2-$		64	A	
12g	**13g**	CH_3	$(CH_2)_4CH_3$	$-CH_2CH_2CH_2CH_2-$		70	A	
16		CH_3	H	$-COCH_2CH_2-$		50	B	3
		CH_3	CH_3	$-COCH_2CH_2-$		100	B	3
		CH_3	$(CH_2)_4CH_3$	$-COCH_2CH_2-$		100	B	3
12h	**13h**	CH_3	$COOCH_3$	$-CH_2CH_2CH_2-$		72	B	18
12i	**13i**	CH_3	$COOCH_3$	$-CH_2CH_2CH_2CH_2-$		100	B	18
12l	**13l**	CH_3	$(CH_2)_4CH_3$	$COOCH_3$	$(CH_2)_4CH_3$	100	C	
7m	**8m**	$CH_2OCH_2C_6H_5$	H	$COOCH_3$	CH_3	91	C	
7n	8n	CH_3	H	$COC(CH_3)_3$	CH_3	67	C	20
7o	**8o**	CH_3	H	COC_6H_5	CH_3	86	C	21
7q	**8q**	CH_3	H	$COC(CH_3)_2CH{=}CH_2$	CH_3	90	C	13
7r	**8r**	CH_3	H	$COOCH_3$	CH_3	62	C	22
7t	8t	$(CH_2)_2C{=}C(CH_3)_2$	H	$COOCH_3$	CH_3	89	C	19
7t′	**8t′**		H	$COOCH_3$	CH_3	84	C	

[a] The olefins prepared were pure or purified by chromatography and were homogeneous by GLC, TLC, and NMR; where, already known, the references for comparison are listed. The three products not labeled are described in ref 3. [b] Methods: (A) *t*-BuOK (1.2 equiv)/THF/0 °C/1 h; (B) K_2CO_3 (1.2 mol)/THF/Δ/3–5 h; (C) 10% aqueous $NaOH/CH_2Cl_2/Bu_4N^+HSO_4^-$.[15]

Table VII. Ramberg–Bäcklund Eliminations with Disulfone Formation

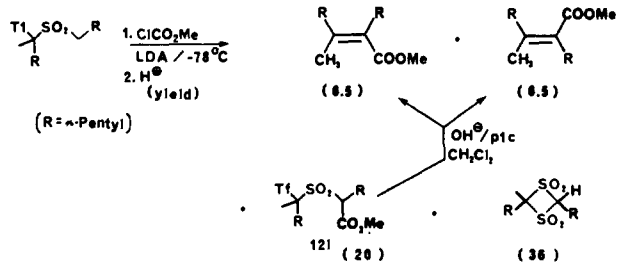


3 (**7**) **8** **19**

substrate	R^1	R^2	yield (%) **3** (**7**)	yield (%) **8**	yield (%) **19**	*E*/*Z* ratio[a] **8**	*E*/*Z* ratio[a] **19**	method[b]
3a	$(CH_2)_2CH_3$	H	~0	80[c]	20			B
3b	$(CH_2)_2COOEt$	H	11	83	7			B
3c			~0	68	17			D
7f	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	38	24[c]	38			A
			~0	38[c]	62		3/2	B
			~0	*d*	45			C
7g	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	~0	45	53	2.2/1	3/2	B
					83		3/2	D

[a] *E*/*Z* ratio by NMR.[23] [b] (A) ptc. $BzMe_3N^+Cl^-/CH_2Cl_2/OH^-$; (B) *t*-BuOK/THF/0 °C; (C) LDA/THF −78 °C; (D) $Bu_4N^+F^-$ (4 equiv)/THF/room temperature. [c] Volatile olefin not isolated; yield by difference. [d] Little or no olefin by TLC.

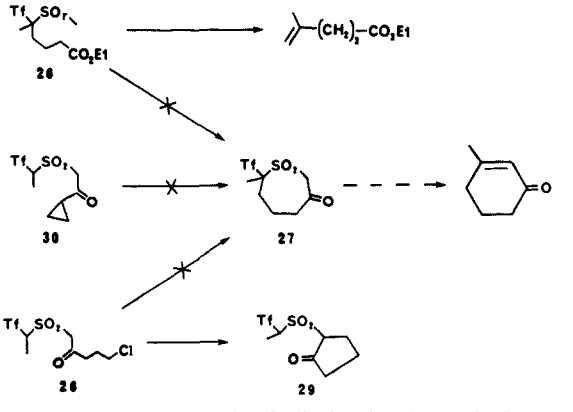
Scheme II. Stereochemistry of Elimination



with inversion at each carbon en route to the epi-sulfone intermediate and implies an initial planar W-conformation for the L–C–SO_2–C–H array. Bordwell's result also removes the question of stereocontrol in our case to control of the alkylation of the final substituent at the α-position, i.e., **11** → **12**. In view of the known preference of α-sulfonylcarbanions for the projection of the carbanion orbital to bisect the O–S–O angle of the sulfonyl,[13] we felt that an irreversible alkylation at the α-center should produce a single diastereomer of **12**. However, since the alkylation conditions commonly require elevated temperatures owing to the low reactivity of the α-monoanions, inversion of the anion configuration is apparently facile, for the tetrasubstituted precursors **12** have generally been around 1:1 mixtures of diastereomers, and the α-bromo compound (**12**, Table IV) is the same despite rapid formation at −78 °C. The examples in Table VII also reflect these mixtures.

On the assumption that, if the last reaction is done irreversibly at −78 °C by acylation at α', more stereocontrol might result, we acylated **7g** with chloroformate at −78 °C and directly quenched with acid. The results are outlined in Scheme II: small but equal amounts of the isomeric elimination products were observed directly as well as the expected product **12l** and also the cyclic disulfone, formed faster than the acylation itself. While the NMR spectrum of **12l** suggested it was only a single diastereomer, nevertheless, the quantitative phase-transfer alkali elimination from **12l** yields the same Z/E isomer mixture of olefins.

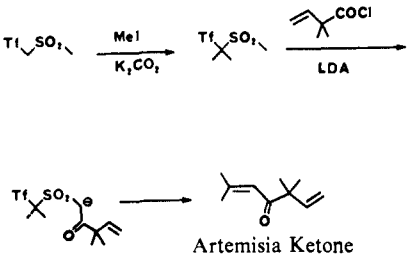
Synthetic Applications. Seen overall as a synthetic tool, the procedure fulfills its promise for making certain kinds of olefins by multiple construction. 1,1-Disubstituted olefins are available directly without complications of stereocontrol or cyclic disulfone intervention, and the unexpected elimination of triflate from the formaldehyde reaction affords a near-quantitative preparation of α-methylenesulfones, $CH_2{=}C(R)SO_2R'$.[8] The lack of stereocontrol is not a factor in the preparation of five- and six-membered cyclic olefins, and the route to cyclopentenones like jasmone is particularly facile.[3] Similar paths to cyclohexenones have not succeeded despite preparation of substituted cyclohexenes themselves (cf., **13g** in Table VI). Thus treatment of **26** with bases



underwent Ramberg–Bäcklund elimination instead of internal α'-acylation to **27** despite the quantitative cyclization of the next

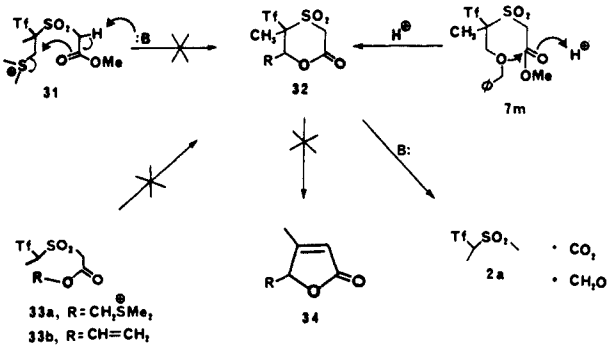
(13) Corey, E. J.; Lowry, T. H. *Tetrahedron Lett.* **1965** *593*, 803. Bordwell, F. G.; Phillips, D. D.; Williams, J. M., Jr. *J. Am. Chem. Soc.* **1968** *90*, 426, 5298.

Scheme III. Synthesis of Artemisia Ketone



lower homologue to **16**, and in reverse **28** exhibited a faster cylization to **29** while the cyclopropyl analogue **30** of **15** could not be induced to form **27** under a variety of conditions.

We devoted much attention to the parallel synthesis of butenolides **34** from **32**. Of several precursors, **31** and **33a** could not be induced to cyclize with bases, and **33b** with either acid or



halogen also failed to cyclize. However, debenzylation of **7m** with acid did yield the desired lactone (**32**, R = H) only to find that warming with potassium carbonate served only to fragment the lactone to form the starting **2a** by elimination of formaldehyde and carbon dioxide (the α'-carboxylic acid, $TfCH(CH_3)SO_2CHCOOH$, readily decarboxylates in mild base). When the trisubstituted **7m** is instead allowed to react with base, it smoothly eliminates (Table VI) in the normal mode to an E/Z (~1:1) mixture of acrylic esters **8**, one of which formed the butenolide **34** (R = H) on treatment with acid.

Application of the synthetic concept to the synthesis of artemisia ketone is outlined in Scheme III. This is the simplest of the syntheses of this natural ketone,[14] proceeding in two steps in 86% overall yield, and it illustrates the effectiveness of the concept in quickly assembling olefinic compounds from much simpler, available starting materials. The foregoing survey should outline the usefulness and scope of the method.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Infrared (IR) spectra were determined on either a Perkin-Elmer 683 or 137 spectrometer as solutions, neat films, or potassium bromide pellets. The data are presented in wave numbers (cm^{-1}) and are referenced to the 1601 polystyrene absorption. Proton nuclear magnetic resonance (NMR) spectra were recorded on Varian EM390, EM360, and XL300 spectrometers, in the designated solvent, by using tetramethylsilane as an internal standard. Carbon-13 NMR were determined by using pulsed Fourier transform techniques on either a Varian CFT-20 or XL300 spectrometer, operating at 25.03 and 75.43 MHz, respectively. The NMR results are reported in chemical shift (δ), followed by the signal shape: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The multiplicity is followed by the coupling constant, where applicable, and the integrated signal intensity. Gas chromatographic (GC) analyses were carried out with a Hewlett-Packard 5890 instrument equipped with an Alltech 30 m × 0.25 mm Heliflex capillary column, packed with RSC-150 polydimethyl-

(14) Prior syntheses of artemisia ketone required 3–5 steps and offered overall yields of 27–77%: (a) Pillot, J.-P.; Dunogues, J.; Calas, R. *Tetrahedron Lett.* **1976**, 1871. (b) Michelot, D.; Linstrumelle, G.; Julia, S. *Synth. Commun.* **1977** *7*, 95. (c) Huynh, C.; Julia, S. *Ibid.* **1977** *7*, 103. (d) Gosselin, P.; Masson, S.; Thuillier, A. *Tetrahdron Lett.* **1978**, 2717. (e) Stella, L.; Amrollah-Madjdabadi, A. *Synth. Commun.* **1984**, 1141.

siloxane. Mass spectral analyses were run on a Hewlett-Packard 5985 spectrometer, and the data are presented as m/e (intensity relative to parent ion). Microanalyses were run by Galbraith Labs, Knoxville, TN.

Silica used in chromatography refers to Kieselgel 60 (0.04–0.06 mm) supplied by EM Reagents; flash[26] techniques were generally used. All thin-layer chromatography (TLC) was performed on Anal Tech (GHLF) precoated, 0.25-mm, glass-backed silica gel plates. Spots were visualized under UV and by treatment with one or more of the following: iodine vapor, alcoholic potassium permanganate, or vanillin solution.[27] All solvents were distilled "dry" immediately prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and methylene chloride from phosphorus pentoxide. "Ether" refers to anhydrous diethyl ether which was supplied by Fisher Scientific. "Petroleum ether" refers to the analyzed reagent grade hydrocarbon fraction, bp 35–60 °C, also supplied by Fisher, and was not further purified. Brine refers to a saturated aqueous solution of sodium chloride. n-Butyllithium solution in hexane was periodically titrated with isopropyl alcohol (1,10-phenenthroline as indicator[28]). Gaseous trifluoromethanesulfonyl fluoride (trifyl fluoride), a gift of the 3M Co., was dried by passing through a calcium sulfate glass tube. Other commercially supplied chemicals were purified and/or distilled, when appropriate, and stored under an atmosphere of nitrogen in the freezer.[29]

All reaction flasks and syringes were flame-dried and cooled under a stream of dry nitrogen just prior to use. Unless otherwise indicated, all reactions were run under a positive pressure of dry nitrogen. Transfer of moisture-sensitive liquids was performed by hypodermic syringe or cannula through rubber septa.

Preparations and spectra of representative compounds only are shown for each experimentally different procedure used. However, some general comments about the spectra are in order. In the infra red spectra of the substituted mesyltriflones there are two strong absorptions at about 1320 and 1125 cm^{-1} for the mesyl sulfone as well as three strong characteristic absorptions for the trifyl group: 1360 and 1160 cm^{-1} for sulfonyl and 1200 cm^{-1} for the trifluoromethyl group. These five absorptions are diagnostic for these derivatives.

In the NMR spectra in deuteriochloroform the α-proton is commonly found at 4.3–5.3 δ with clear characteristic splitting corresponding to the attached alkyl, while the α'-protons are found at 3.2–3.4 δ. The acidity of the α-proton does not result in any serious line broadening but deuterium exchange with D_2O is facile. Carbon-13 spectra reveal a quartet at about u20 ppm (J = 330 Hz) assigned to CF_3 and signals at 70–90 and 40 ppm are typical for the α- and α'-carbons, respectively.

Synthesis of the Reagent Mesyltriflone. To a mechanically stirred, room temperature solution of 20 g (0.212 mol) of dimethyl sulfone in 400 mL of THF was dropwise added 127.5 mL (0.255 mol) of a 2 M THF solution of ethyl magnesium bromide, over 30 min. Stirring was continued for 1 h, during which time the initially formed gummy precipiate became a suspended powder. A low-temperature condenser (dry ice–acetone) was attached, and trifyl fluoride was bubbled directly into the stirred solution, periodically, until all of the solid had dissolved, and no further exotherm was observed upon further addition of the gas. The solution was allowed to stand overnight and then cautiously acidified with 75 mL of 3 N hydrochloric acid. The resulting two-phase mixture was transferred to a separatory funnel, the aqueous phase was extracted with an additional ether portion, then the combined organics were washed with brine and dried over magnesium sulfate (anhydrous), and the solvent was removed under reduced pressure. The crude product was recrystallized from water, vacuum dried over phosphorus pentoxide, and recrystallized again from petroleum ether–methylene chloride to afford 17 g (70%) of mesyltriflone as colorless plates: mp 115–116 °C; ^1H NMR (acetone-d_6) δ 3.4 (s, 3 H), 5.75 (s, 2 H); IR (KBr) 3040, 3020, 3000, 2940, 2930, 1360 (s), 1320 (s), 1220 (s), 1205 (s), 1160, 1125 (s), 985, 970, 865, 780, 750 cm^{-1}. Anal. Calcd for $C_3H_5S_2O_4F_3$: C, 15.93; H, 2.23; S, 28.35; F, 25.20. Found: C, 15.93; H, 2.11; S, 28.53; F, 24.68. Potassium and silver salts were generated by stirring in absolute methanol with 0.6 mol of potassium carbonate and silver carbonate, respectively, followed by evaporation of the methanol and recrystallization from acetone–methylene chloride: silver salt, mp dec >150 °C; potassium salt, mp dec 250 °C; IR (KBr) 3095, 3080, 1312, 1308, 1278, 1210, 1160, 1148, 1095, 980, 970 cm^{-1} (same spectra for both salts).

α,α-Dimethylmesyltriflone. To a stirred solution of 500 mg (2.21 mmol) of mesyltriflone in 5 mL of dry DMF were added 1.53 g (11.05 mmol) of roasted potassium carbonate and 0.69 mL (11.05 mmol) of methyl iodide, and then the mixture was heated at 70 °C overnight. The solution was then cooled to room temperature, transferred to a separatory funnel with 50 mL of ether, and washed with 10 mL of water. The aqueous phase was extracted with an additional ether portion (25 mL), and then the combined organics were washed with saturated sodium bisulfite and brine, dried under magnesium sulfate (anhydrous), and evaporated under reduced pressure. The resulting colorless oil was taken in methylene chloride and passed down a short silica plug, and the solvent was evaporated to give crystalline product. Recrystallization from petroleum ether–methylene chloride gave 500 mg (90%): mp 39–40 °C; ^1H NMR ($CDCl_3$) δ 3.23 (s, 3 H), 1.95 (q, 6 H, J = 0.9 Hz); IR (CH_2Cl_2) 1365, 1335, 1210, 1130, 1100 cm^{-1}.

Alkylation of the α,α-Dianion of Mesyltriflone. α-Methylmesyltriflone (2a). The following procedure is representative for the preparation and subsequent alkylation of the α,α-dianion of mesyltriflone. A stirred solution of 392 mg (1.73 mmol) of mesyltriflone in 10 mL of THF, at −78 °C, was treated dropwise with 2.04 mL (3.55 mmol) of a 1.74 M solution of n-butyllithium in hexane. The resulting fine, white suspension was allowed to slowly warm to −55 °C over 30 min and was then recooled to −78 °C. To this solution was added 0.11 mL (1.82 mmol) of methyl iodide, dropwise, and the resultant mixture was allowed to warm slowly to room temperature and stirred overnight. The solution was diluted with 50 mL of ether and washed with 1 N hydrochloric acid (2 × 2 mL). The aqueous phase was extracted with an additional ether portion, and then the combined organic layers were washed with saturated bisulfate solution and brine and dried over magnesium sulfate (anhydrous), and the solvent was evaporated under reduced pressure, to afford a solid residue, which was recrystallized from methylene chloride–petroleum ether to give 390 mg (95%) of pure product: mp 74–75 °C; ^1H NMR ($CDCl_3$) δ 4.60 (q, J = 7 Hz, 1 H), 3.30 (s, 3 H), 1.95 (d, J = 7 Hz, 3 H); IR (CH_2Cl_2) 1376, 1342, 1205, 1155, 1120 cm^{-1}. Anal. Calcd for $C_4H_7S_2O_4F_3$: C, 20.00; H, 2.94; S, 26.69; F, 23.73. Found: C, 20.19; H, 2.75; S, 26.93; F, 23.37.

Alkylation of the α,α,α'-Trianion of Mesyltriflone. α,α'-Dimethylmesyltriflone (6a). The following preparation is representative for the generation and subsequent alkylation of the α,α,α'-trianion of mesyltriflone. To a stirred solution of 500 mg (2.2 mmol) of mesyltriflone in 40 mL of THF at −78 °C was added 4.42 mL (7.07 mmol) of a 1.6 M hexane solution of n-butyllithium, dropwise, and then the bath was allowed to warm to −50 °C. After 1.5 h, during which time the initially formed insoluble α,α-dianion of mesyltriflone is further deprotonated to afford the soluble α,α,α'-trianion, the mixture was recooled to −78 °C, and 0.35 mL (4.86 mmol) of methyl iodide was added dropwise. The bath was allowed to slowly warm to room temperature, and the resultant mixture was stirred overnight. The reaction mixture was diluted with 70 mL of ether, transferred to a separatory funnel, and shaken with 5 mL 1 N HCl. The organic phase was then successively treated with saturated sodium bisulfate and brine and then dried over magnesium sulfate (anhydrous). The organic layer was concentrated under reduced pressure to give a pale yellow oil, which on chromatography on silica gel (methylene chloride) afforded 530 mg (95%) of dimethylmesyltriflone (**6a**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.5 (t, J = 7 Hz, 3 H), 1.95 (d, J = 7 Hz, 3 H), 3.5 (q, J = 7 Hz, 2 H), 4.6 (q, J = 7 Hz, 1 H); IR (film) 3000, 2940, 1450, 1370, 1330, 1200, 1140, 1115, 1060, 1035 cm^{-1}. Anal. Calcd for $C_5H_9S_2O_4F_3$: C, 23.62; H, 3.57. Found: C, 23.95; H, 3.61.

Reactions of the α,α'-Dianion of α-Monosubstituted Mesyltriflones. α-Methyl-α'-pentylmesyltriflone (6f). Method A. The following is representative for the formation and subsequent alkylation of the α,α'-dianion of mesyltriflone derivatives. To a stirred solution of 670 mg (2.79 mmol) of compound **2a** in 10 mL of THF, at −78 °C, was added 3.18 mL (5.86 mmol) of a 1.84 M hexane solution of n-butyllithium, dropwise. The resultant homogeneous mixture was warmed to −55 °C, stirred for 20 min, and then recooled to −78 °C. To this solution was added 0.36 mL (2.79 mmol) of n-pentyl iodide, dropwise, and the bath was allowed to slowly warm to room temperature. After acidification with 5 mL of 1 N hydrochloric acid, the mixture was extracted into 50 mL of ether and dried over magnesium sulfate (anhydrous), and the solvent was removed under reduced pressure. The resulting residue was chromatographed on silica gel (1:1 petroleum ether–methylene chloride) to afford 730 mg (85%) of **6f** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.9 (br t, 3 H), 1.2–1.65 (m, 6 H), 1.95 (d, J = 8 Hz, 3 H), 1.7–2.1 (m, 2 H), 3.3–3.55 (m, 2 H), 4.55 (q, J = 8 Hz, 1 H); IR (CH_2Cl_2) 1375, 1330, 1210, 1145, 1110 cm^{-1}; Anal. Calcd for $C_9H_{17}S_2O_4F_3$: C, 34.83; H, 5.52. Found: C, 34.97; H, 5.77.

α'-Cyclopropylketomethyl-α-methylmesyltriflone (6m). Method B. The following preparation is representative for the general acylation of the α,α'-dianion of α-substituted mesyltriflones. To a stirred solution of 500 mg (2.08 mmol) of α-methylmesyltriflone (**2a**) and 0.32 mL (2.29 mmol) of diisopropyl amine in 25 mL of THF, at −78 °C, was added 3.7 mL (6.24 mmol) of a hexane solution of n-butyllithium, dropwise. The bath was allowed to warm to −55 °C, stirred 15 min, and recooled to −78 °C. To the resultant mixture was added 0.19 mL (2.08 mmol) of cyclopropane–carboxyl chloride, dropwise, and the bath was allowed to warm slowly to −30 °C. The reaction was then quenched with acid and worked up as in method A above. The product was purified by chromatography on silica gel (1:9 acetone–methylene chloride) to afford 384

mg (60%) of compound **6m** as a colorless crystalline solid: mp 62–63 °C, ^{1}H NMR ($CDCl_3$) δ 5.54 (q, 7 Hz, 1 H), 4.73 (AB quartet, J = 15 Hz, 2 H), 1.93 (d, J = 7 Hz, 3 H), 2.0 (m, 1 H), 1.05–1.35 (m, 4 H); IR (CH_2Cl_2) 1720, 1360, 1335, 1200, 1150, 1110, 1040, 1010 cm^{-1}; Anal. Calcd for $C_8H_{11}S_2O_5F_3$: C, 31.17; H, 3.60. Found: C, 31.49; H, 3.56.

Alkylation of the α-Monoanion of Substituted Mesyltriflones. α-Methyl-α,α′-dipentylmesyltriflone (7g). Method A. The following procedure is representative for the preparation and subsequent alkylation of the α-monoanion of an α-monosubstituted mesyltriflone. A solution of 1.23 g (3.4 mmol) of compound (**6c**) in 10 mL of DMF was charged with 1.76 g (12.7 mmol) of roasted potassium carbonate and 0.63 mL (10.0 mmol) of methyl iodide. The resultant mixture was stirred and heated at 60 °C for an overnight period. The solution was cooled to room temperature, diluted with 100 mL of ether, and then washed with 20 mL of water. The aqueous phase was extracted with an additional ether portion, and the combined organic layers were washed with water (20 mL), saturated sodium bisulfate (20 mL), and saturated brine (20 mL). The organic layer was then dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure to afford 1.33 g colorless oil. This residue was purified by dissolving in methylene chloride and passing down a short silica plug, to provide 1.23 g (95%) of trisubstituted sulfone (**7g**): ^{1}H NMR ($CDCl_3$) δ 3.5–3.25 (m, 2 H), 2.5–2.2 (m, 2 H), 1.95 (br s, 3 H), 2.1–1.1 (m, 14 H), 1.1–0.75 (m, 6 H); IR (film) 2960, 2940, 2880, 1465, 1360, 1335, 1190, 1100 cm^{-1}. Anal. Calcd for $C_{14}H_{27}S_2O_4F_3$: C, 44.20; H, 7.15. Found: C, 44.71; H, 7.57.

α,α-Dimethyl-α′-benzylmesyltriflone (7b). Method B: prepared from compound **6h** as its potassium salt (165 mg, 0.45 mmol), added to a solution of methyl triflate (0.9 mmol) in methylene chloride, and stirred overnight at room temperature; suspension filtered and solution evaporated to 128 mg (83%) of **7b** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 6 H), 3.15–3.40 (m, 2 H), 3.55–3.70 (m, 2 H), 7.30 (s, 5 H); IR (CH_2Cl_2) 1360, 1325, 1205, 1124, 1093 cm^{-1}.

α-Benzyloxymethyl-α-methylmesyltriflone (3d). Method C: prepared from compound **2a**, chloromethyl benzyl ether (1.2 equiv), and potassium carbonate (3.3 mol); yield, 50%; reaction time, 4 days at room temperature in THF (compounds **3c** and **7i** required refluxing THF for 24 h); chromatographed on silica gel (3:7 petroleum ether–methylene chloride); colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.78 (br s, 3 H), 3.43 (s, 3 H), 4.15 (s, 2 H), 4.63 (br s, 2 H), 7.38 (s, 5 H); IR (film) 3238, 3127, 3041, 1448, 1359, 1318, 1192, 1144, 1094, 962 cm^{-1}; MS (15 eV), m/e (relative intensity) 360 (18), 121 (47), 107 (100), 106 (55), 105 (32), 91 (40). Anal. Calcd for $C_{12}H_{15}S_2O_5F_3$: C, 40.00; H, 4.20. Found: C, 41.51; H, 4.36.

α′-Allyl-α-bromo-α-methylmesyltriflone (7h). Method D: prepared from compound **6g**, bromine (1 equiv), and potassium carbonate (1.1 mol); yield, 97%; reaction time, 1 h at room temperature in THF–methylene chloride; volatiles removed on the rotary evaporator to afford a colorless oil which slowly crystallized in freezer: ^{1}H NMR ($CDCl_3$) δ 5.6–6.08 (m, 1 H), 5.04–5.34 (m, 2 H), 3.44–4.05 (m, 2 H), 2.5–2.95 (m, 2 H), 2.54 (s, 3 H); IR (CH_2Cl_2) 1380, 1370, 1340, 1200, 1140, 1100 cm^{-1}. Anal. Calcd for $C_7H_{10}S_2O_4BrF_3$: C, 23.41; H, 2.81; Br, 22.25. Found: C, 23.70; H, 2.87; Br, 22.12.

2-Methyl-2-trifyltetrahydrothiopyran 1,1-Dioxide (7j). Method E. The following is representative for the formation of mesyltriflone ring compounds. To a stirred solution of 300 mg (1.25 mmol) of **2a** in 15 mL of THF at −78 °C was added 1.47 mL (2.50 mmol) of *n*-butyllithium (1.7 M in hexane), dropwise, and the bath was allowed to slowly warm to −55 °C. After 15 min, the bath was recooled to −78 °C, and 0.63 mL (6.24 mmol) of 1,3-dibromopentane was added in one quick portion. The mixture was slowly warmed to room temperature and stirred for 15 min and then the solvent was evaporated under reduced pressure. The crude residue was taken in 12 mL of acetonitrile, and a spatula tip of finely ground, anhydrous potassium carbonate was added and then refluxed for 30 min. The solution was then cooled to room temperature, and the solvent was evaporated to dryness. The residue was dissolved in ether, washed with water (3×), dried over magnesium sulfate (anhydrous), and evaporated to afford **7j** as a crystalline solid: 248 mg (71%); mp 82.5–90 °C (petroleum ether–methylene chloride); ^{1}H NMR ($CDCl_3$) δ 1.68–2.45 (m, 5 H), 1.9 (br s, 3 H), 2.52–2.95 (m, 1 H), 3.22 (dt, J_1 = 15 Hz, J_2 = 3 Hz, 1 H), 3.68–4.05 (m, 1 H); IR (CH_2Cl_2) 3041, 1350, 1321, 1189, 1129, 1098, 1077, 816 cm^{-1}. Anal. Calcd for $C_7H_{11}S_2O_4F_3$: C, 30.00; H, 3.96. Found: C, 30.08; H, 3.88.

For the synthesis of the next higher homologue, substitute 1,4-dibromobutane for 1,3-dibromopropane and DMF (120 °C/1–2 h) for CH_3CN (reflux).

Acylation of the α′-Monoanion of α,α-Disubstituted Mesyltriflone. 6-Carbomethoxy-2-methyl-2-trifyltetrahydrothiopyran 1,1-Dioxide (12i). The following is representative for the general acylation of the α′-anion of an α,α-disubstituted mesyltriflone. To a stirred solution of 200 mg (0.714 mmol) of **7j** and 0.055 mL (0.714 mmol) of methyl chloroformate in 5 mL of THF, at −78 °C, was dropwise added LDA (freshly prepared in 3 mL of THF from 0.21 mL (1.50 mmol) of diisopropylamine and 0.84 mL (1.43 mmol) of a 1.7 M solution of *n*-butyllithium in hexane), and the bath was allowed to slowly warm to 0 °C. The reaction mixture was quenched with 2 mL of saturated ammonium chloride solution, transferred to a separatory funnel with 50 mL of ether, and washed with 2 mL of 1 N HCl. The aqueous phase was extracted with an additional 25 mL of ether, and the combined organic phase was dried over magnesium sulfate and evaporated to dryness to afford 227 mg (94%) **12i** as a crystalline solid, homogeneous on TLC (silica–methylene chloride): mp 109–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.72–2.55 (m, 5 H), 1.88 (br s, 3 H), 2.78 (br d, J = 12 Hz, 1 H), 3.9 (s, 3 H), 4.85 (br t, J = 8 Hz, 1 H); IR (CH_2Cl_2) 3051, 1755, 1357, 1330, 1198, 1091 cm^{-1}; MS (10 eV), m/e (relative intensity) 338 (4.6), 205 (100), 187 (11.3), 140 (13.2), 113 (5.6). Anal. Calcd for $C_9H_{13}S_2O_6F_3$: C, 31.95; H, 3.87. Found: C, 32.30; H, 4.06.

Ramberg-Bäcklund Reactions. Ethyl 5-Methyl-5-hexenoate (4e). Method A. To a stirred solution of 98 mg (0.28 mmol) of compound **3e** in 4 mL of THF, at 0 °C, was added 37 mg (0.33 mmol) of potassium *tert*-butoxide, in one portion from a dry test tube. After 30 min, the mixture was treated with 1 mL of saturated ammonium chloride solution, extracted into 30 mL of ether, dried, and evaporated to afford a colorless liquid bearing a strong odor. Chromatography on silica gel (methylene chloride) gave 36 mg (83%) of compound **4e** as a colorless liquid, the spectral data of which was identical with that reported in the literature.[17] ^{1}H NMR ($CDCl_3$) δ 4.66 (m, 2 H), 4.12 (q, J = 7 Hz, 2 H), 2.3 (t, J = 7 Hz, 2 H), 1.55–2.2 (m, 4 H), 1.72 (br s, 3 H), 1.25 (t, J = 7 Hz, 3 H); IR (CH_2Cl_2) 3075, 2980, 2950, 1725, 1375, 910, 890 cm^{-1}. Also formed in the reaction and isolated in the chromatography was a small amount (15%) of 2-methyl-2-(3-carbethoxypropyl)-1,3-dithietane 1,1,3,3-tetraoxide (**19b**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.54 (br s, 2 H), 4.13 (q, J = 7 Hz, 2 H), 2.25–2.55 (m, 4 H), 2.0 (s, 3 H), 1.65–2.1 (m, 2 H), 1.25 (t, J = 7 Hz, 3 H); IR (CH_2Cl_2) 3030, 2960, 1730, 1450, 1350, 1170, 1085 cm^{-1}; MS (15 eV), m/e (relative intensity) 285 (5.3), 239 (60.3)8 211 (8.1), 174 (8.8), 141 (16.6), 113 (76.7), 95 (56.2), 85 (100), 71 (63.4), 68 (58.2), 67 (54.8), 55 (42.6).

1-Carbomethoxy-2-methylcyclopentane (13h). Method B. A solution of 100 mg (0.296 mmol) of **12h** and 82 mg (0.591 mmol) of finely ground, anhydrous potassium carbonate in 5 mL of THF was refluxed 8 h. TLC of the solution at this point revealed that the starting material had been quantitatively converted to one new, less polar product. The solvent was evaporated, and the residue was extracted into ether. Suction filtration through Celite and subsequent evaporation of the filtrated yielded **13h** as a colorless liquid.[18] ^{1}H NMR ($CDCl_3$) δ 1.8 (q, J = 7 Hz, 2 H), 2.1 (br s, 3 H), 2.3–2.77 (m, 4 H), 3.75 (s, 3 H); IR ($CDCl_3$) 3032, 1698, 1648, 1431, 1344, 1327, 1253, 1211, 1106, 1051 cm^{-1}; MS (70 eV), m/e (relative intensity) 140 (53.9), 109 (76.7), 81 (100), 79 (80).

Artemisia Ketone (Scheme III). Method C. A mixture of 2 mL of 10% sodium hydroxide, 345 mg (0.985 mmol) of ketosulfone (**7q**), and 334 mg (0.985 mmol) of tetrabutylammonium hydrogen sulfate was combined and stirred vigorously in 4 mL of methylene chloride for an overnight period. Thin-layer chromatographic analysis (silica–methylene chloride) of the mixture revealed a single new compound, of higher R_f and stronger UV absorption, relative to starting material. The two-phase mixture was transferred to a separatory funnel, and the aqueous phase was extracted with an additional methylene chloride portion. The combined organics were dried over sodium sulfate (anhydrous), and the solvent was evaporated. The resulting oil was taken in 20 mL of ether, washed with water (2 × 3 mL) and brine (1 × 3 mL), and dried over magnesium sulfate (anhydrous), and the solvent was evaporated to afford a pale yellow liquid, 133 mg (89%). This material (92% pure by GC analysis) was further purified by passing through a silica plug in methylene chloride. Pure artemisia ketone was thus obtained, the spectral properties of wich were identical with those reported in the literature.[30]

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^{1}H NMR ($CDCl_3$) δ 6.23 (m, 1 H), 5.93 (dd, J_1 = 17 Hz, J_2 = 10 Hz, 1 H), 5.3-5.0 (m, 2 H), 2.1 (s, 3 H), 2.86 (s, 3 H), 1.2 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 220.71 (s), 155.78 (s), 143.1 (d), 120.43 (d), 113.63 (t), 50.03 (s), 28.0 (q), 23.55 (q), 21 (q); IR (film) 2980, 2920, 1685, 1625, 1470, 1450, 1382, 1367, 1108, 1028 cm^{-1}.

Reactions of Trisubstituted Sulfone (7g) with Base. (a) Potassium *tert*-Butoxide. To a stirred solution of 107 mg (0.28 mmol) of **7g** in 4 mL of THF, at 0 °C, was added 63 mg (0.56 mmol) of potassium *tert*-butoxide, in one solid portion. The resultant mixture was stirred at 0 °C overnight and than at room temperature for 1 h. The solution was then diluted with 20 mL of ether and treated with I mL of saturated ammonium chloride. The aqueous phase was extracted with an additional ether portion, and the combined organics were washed with brine, dried over magnesium sulfate (anhydrous), and then concentrated under reduced pressure. This affords 70 mg of pale yellow oil, NMR analysis of which reveals a mixture of 53% (syn/anti)-2-methyl-2,4-dipentyl-1,3-dithietane 1,1,3,3-tetraoxide (**19g**) and 45% (*E*/*Z*)-6-methyl-6-dodecene (**8g**). Chromatography of this crude oil on silica gel (petroleum ether) provided 20 mg (39%) of **8g** with an *E*/*Z* ratio of 2.2:1 (obtained from 300-MHz integral comparison of the vinyl methyl region[31]): ^{1}H NMR ($CDCl_3$) δ 5.12 (br t, 1 H), 2.04-1.90 (m, 4 H), 1.67 (br s, 0.94 H, CH_3 of *Z* isomer), 1.57 (br s, 2.06 H, CH_3 of *E* isomer), 1.45-1.1m (m, 12 H), 0.95-0.84 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 135.34 (s), 135.09 (s), 125.30 (d), 124.57 (d); IR (film) 2960, 2938, 2880, 2860, 1465, 1382, 1130, 1115 cm^{-1}. Further elution (7:3 petroleum ether-methylene chloride) provided 40 mg (46%) of **19g** as an oil (1.6:1 mixture of isomers[32]): ^{1}H NMR ($CDCl_3$) δ 5.51 (t, *J* = 7.5 Hz, 0.6 H), 5.45 (t, *J* = 7.5 Hz, 0.4 H), 2.35-1.15 (m, 4 H), 1.96 (s, 1.8 H), 1.82 (s, 1.2 H), 1.57-1.27 (m, 12 H), 0.95-0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 105.47 (s), 105.13 (s), 100.33 (d), 99.19 (d), 32.41 (t), 31.36 (t), 30.88 (t), 30.80 (t), 30.78 (t), 26.24 (t), 26.09 (t), 25.84 (t), 24.62 (t), 24.24 (t), 24.0k (t), 22.06 (t), 22.00 (t), 16.97 (q), 13.70 (q), 13.74 (q), 13.67 (q); IR (film) 2970, 2940, 2880, 2860, 1470, 1450, 1340, 1160, 1110, 922 cm^{-1}. Anal. Calcd for $C_{13}H_{26}S_2O_4$: C, 50.29; H, 8.44; S, 20.65. Found: C, 50.31; H, 8.63; S, 20.70.

(b) *n*-Butyllithium (2 equiv). To a stirred solution of 127 mg (0.334 mmol) of **7g** in 4 mL of THF, at -78 °C, was added 0.42 mL (0.667 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The bath was allowed to slowly warm to room temperature and stir overnight. Workup (ammonium chloride-ether as above) gave a colorless oil which was analyzed by NMR to contain **7g**, **19g**, and **8g** in a ratio of 2:1:2.5, respectively. The yields calculated based on weight obtained are as follows: **7a**, 24%; **19g**, 11.6%; **8g**, 30%; (34.4% unaccounted for).

(c) *n*-Butyllithium (3 equiv). Procedure was identical with (b) above. Affords a crude oil, which by NMR contains **7g**, **19g**, and **8g** in a ratio of 0:1:1, respectively. Actual yields based on weight: **7g**, <1%; **19g**, 37%; **8g**, 37%; (25% unaccounted for). Chromatography as in (a) above lead to isolated yields: **19g**, 15%; **8g**, 29%.

(d) Tetrabutylammonium Fluoride. To a stirred solution of 63 mg (0.166 mmol) of **7q** at room temperature was added dropwise 0.66 mL (0.662 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. The resultant solution was stirred for 3 h, diluted with 30 mL of ether and washed with water (2×) and then brine. The organic layer was dried over magnesium sulfate (anhydrous) and concentrated under reduced pressure to afford 43 mg of pale yellow oil. NMR analysis of this residue reveals >90% **19g** (actual yield = 83%). The experiment was repeated starting at -78 °C, warming to room temperature over 1.5 h, and then stirring for 1 h. The yield of **19g** was 92% with barely a trace of **8g** visible by thin-layer chromatographic analysis (silica-methylene chloride).

Acknowledgment. We are indebted to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

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Stereochemistry of Hydrogen Elimination in the Biosynthesis of Polyprenols in Higher Plants[1]

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Abstract: In the biosynthesis of polyprenols in the leaves of *Mallotus japonicus*, the elimination of the C(4) prochiral hydrogen of mevalonate during the formation of their (*E*)-prenyl chain followed Cornforth's basic principle for isoprenoid biosynthesis, but the formation of their (*Z*)-prenyl chain involved, contrary to the basic principle, the elimination of the *pro*-4*S* hydrogen of mevalonate. The reversed hydrogen elimination during the formation of the (*Z*)-prenyl chain was confirmed by tracer experiments using geranylgeranyl pyrophosphate and stereospecifically ^{3}H-labeled isopentenyl pyrophosphate as a prerequisite substrate. The biological formation of the (*Z*)-prenyl chain of polyprenols was demonstrated to result from the successive addition of isopentenyl pyrophosphate to geranylgeranyl pyrophosphate. The elimination of the reversed hydrogen was found to be a common occurrence in the formation of the (*Z*)-prenyl chain of polyprenols in the leaves of 11 other higher plants examined hitherto.

The basic principle of the mechanism in the biological formation of prenyl pyrophosphate was established by the studies on the biosynthesis of squalence in yeast and mammalian enzymes[2-4] and of polyprenol in rubber latex.[5] The principle involves the stereochemical picture that the *pro*-4*S* hydrogen of mevalonic acid (MVA) is lost in the formation of an (*E*)-prenyl unit, while the *pro*-4*R* hydrogen is eliminated in the formation of a (*Z*)-prenyl

(1) This paper forms Part 1 in the series "The Biosynthesis of Isoprenoids in Higher Plants" and in part has been presented in preliminary forms (a-c) and communications (d and e): (a) the ACS/CSJ Chemical Congress, Honolulu, HI, April 1979. (b) 23rd Symposium on the Cnemistry of Natural Products, Nagoya, Japan, Oct 1980. (c) 2nd U.S.-Japan Seminar on the Biosynthesis of Natural Products, Honolulu, HI, Sept 1982. (d) Suga, T.; Hirata, T.; Aoki, T.; Shishibori, T. *J. Am. Chem. Soc.* **1983**, *105*, 6178-6179. (e) Suga, T.; Aoki, T.; Hirata, T.; Saragai, Y. *Chem. Lett.* **1983**, 1467-1470.

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