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Isoprene Synthons. Silicon- and Tin-Mediated Terpene Synthesis[1]

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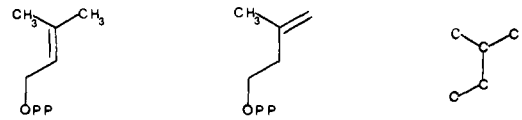
Abstract: Methodology for the construction of terpenes via reactive five-carbon "isoprene synthons" and applications of this strategy to the synthesis of various naturally occurring substances are discussed. The generation and chemistry of 1-cyclobutenylmethyllithium (**7**) and its conversion to 2-trimethylsilylmethylenecyclobutane (**10a**), trimethylsilylisoprene (**19a**), and trimethylstannylisoprene (**19b**) are described. Thermolysis of **10a**/**10b** leads to allylic isomerization followed by cyclobutene ring opening to **19a**/**19b**. Compounds **7**, **10a**, **19a**, and **19b** are useful terpene synthons. Compound **10a** reacts with isovaleraldehyde/$TiCl_4$ to yield cyclobutene **18** which can be thermolyzed to tagetol (**17**). Dienes **19a** and **19b** are used in a Diels–Alder reaction with methyl acrylate leading to a synthesis of δ-terpinol **22b**.

A terpene is a compound whose carbon skeleton is either directly constructed of isoprene units or has had at some state of its biosynthesis a carbon skeleton so constructed. The great majority of terpenes can thus be regarded as built up from the head-to-tail union of isoprene residues. Although methods for the head-to-tail linking of isoprene units have been the objective of much research in organic synthesis, the original isoprene synthon is used by nature herself. Dimethylallyl pyrophosphate (**1**) and isopentenyl pyrophosphate (**2**) condense to form ger-

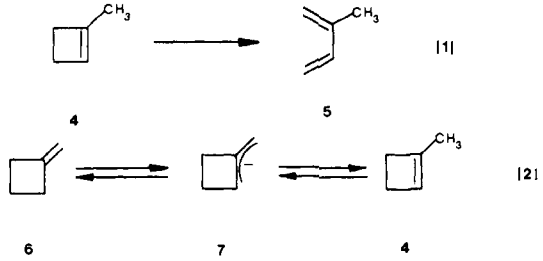


1 2 3

anyl pyrophosphate in the initial stages of the biosynthesis of many terpenes.[2]

Biogenetic-type[3] syntheses are basically synthetic routes designed to mimic as closely as possible steps in the biosynthesis. The use of isoprene synthons in terpene construction is not necessarily "biogenetic", although the regularity with which the repeating unit **3** appears in a large number of important compounds from nature means that 5-carbon *reagents* with the connectivity of **3** find wide applicability.

1-Cyclobutenylmethyllithium. Investigations of cyclobutene derivatives as reactive synthons for the introduction of isoprene residues have recently occupied our attention.[4] The strain energy of such small rings provides a strong driving force for chemical reactions. Thus, thermolysis[5] of 1-methylcyclobutene (**4**) to isoprene (**5**) (eq 1) is a well-known example of a con-

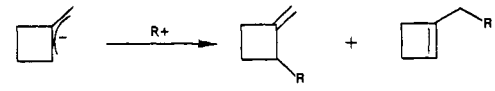


4 5 [1]

6 7 4 [2]

certed electrocyclic process. Simple generation of families of 1-substituted cyclobutenes is clearly a major objective if they are to become useful isoprene synthons. Therefore, the intermediacy of **7** in the reported[6] base-catalyzed isomerization (eq 2) of methylenecyclobutane (**6**) gave us the suggestion that the *quantitative* generation of **7** would yield an intermediate of unique applicability in this connection.

We found[4a] that metalation of methylenecyclobutane (**6**) with the *n*-butyllithium/TMEDA complex[7,8] in hexane occurred smoothly to give **7**.[9] Reaction of **7** with a proton was studied by D_2O quench. ^2H NMR (Figure 1) of the reaction mixture showed an encouraging 67% deuteration of the methylene group. CO_2 likewise reacts preponderantly at the methylene group as evidenced by the ratio of characteristic NMR signals at δ 4,8 (methylene) and 5.75 (cyclobutene H). However, the regioisomer problems typical of allyl anions[10,11] are clearly seen in the reactions of many other electrophiles (Table I). The **8**/**9** ratio was readily determined by NMR integration of vinyl proton signals at ca. δ 4.8 and 5.8 and the



7 8 9

results shown in the tables. A trend at least can be seen in the studies using $PhCH_2X$ and TMSX shown in Tables II and III. By varying the solvent and substrate it is possible to modify[12] the proportions of products within wide limits.[13] Higher temperatures and more reactive E^+ tend to favor reaction on the methylene yielding cyclobutene **9** whereas less reactive electrophiles and lower temperatures favor reaction on the ring to give **8**.

Mechanistic pathways to products **8** and **9** are shown in Scheme I. Because of the presence of TMEDA-complexed organolithium species, ion pairs, and aggregates, regioisomer control in the reactions of **7** proved fruitless.

Allylsilanes. We now describe the salient features of a silicon/tin based methodology which solves the regioisomer problems and allows additional flexibility in the incorporation of C-5 isoprene units. The unique reactivity of allylsilanes[15] has proved them to be functional groups with considerable

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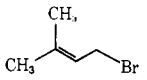
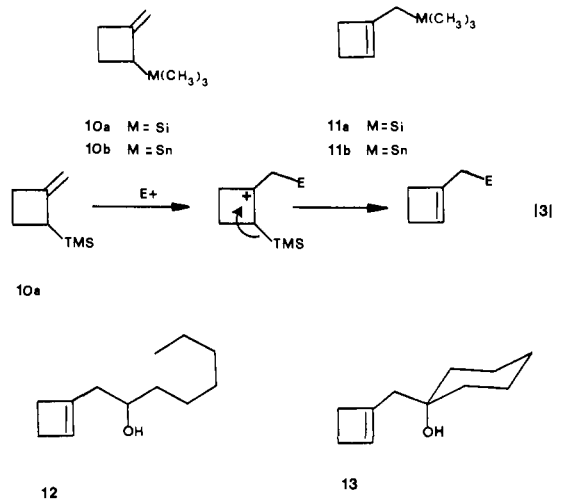
Table I. Reaction of **7** with Electrophiles

electrophile E^+	solvent	temp, °C	% yield	ratio **8/9**
D_2O	THF	25		33/67
CO_2	THF	−78	21	34/66
	hexane	25	75	52/48
adamantanone	THF	25	29	78/22
isovaleraldehyde	hexane	25	80	70/30
	hexane	−78	85	68/32[12]
	hexane	−78	93	85/15[12]
Me_3SnCl	hexane	25	85	20/80

potential for synthesis.[16-18] The regiochemical consequences of their reaction with electrophiles have already been used for specific synthesis of head-to-tail[17] and head-to-head[18] terpenes. Silylation or stannylation of **7** gave mixtures of allylic products (Tables I and III). In particular, the reaction of **7** with Me_3SiCl in hexane at −78 °C gave a 60/40 ratio of **10a/11a.** Distillation at atmospheric pressure in the presence of maleic anhydride induced ring opening of **11a** to **19a** which was trapped as the Diels–Alder adduct. Pure **10a** could be obtained in this manner and is a useful synthon for the synthesis of 1-substituted cyclobutenes,

Allylsilane **10a** reacts in the expected way with electrophiles leading to exclusive allylic isomerization[19] (eq 3). Thus, re-



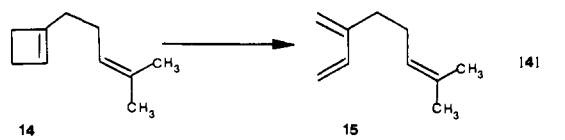
[3]

10a

12 13

action of **10a** with heptaldehyde ($TiCl_4$, CH_2Cl_2, 0 °C) gave 82% yield of **12** or reaction with cyclohexanone gave cyclobutene **13** (55%).

A common structural feature among a number of terpenoids is the terminal 1,3-diene unit,[20] Application of the cyclobutene method to terpenes of this type has already been reported.[4a] Cyclobutene **14** (Table I) on heating at 215 °C for 3 min was quantitatively converted to myrcene (**15**), The use of this



[4]

14 15

general method in the synthesis of a component of the *Ips confusus* pheromone[21] is now described. The male bark bettle *Ips confusus* produces a pheromone complex containing **16** and **17** (tagetol or ipsenol). The synthesis of tagetol (**17**) has been the subject of a number of reports.[22,4a] Our original route[4a] to

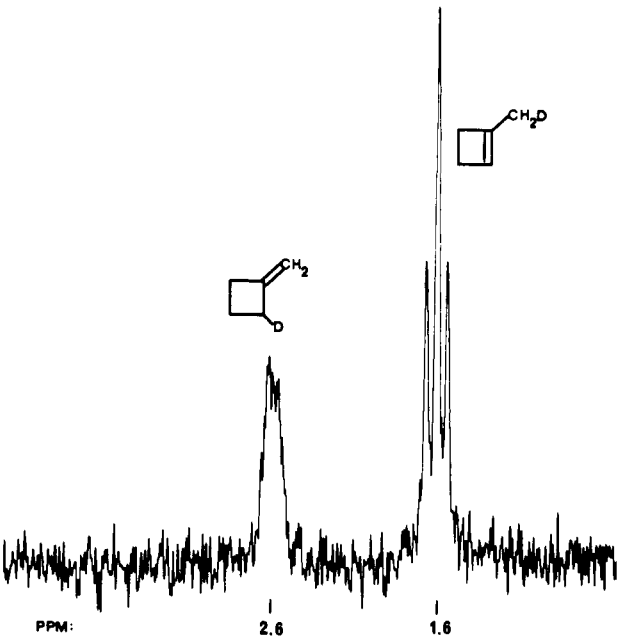
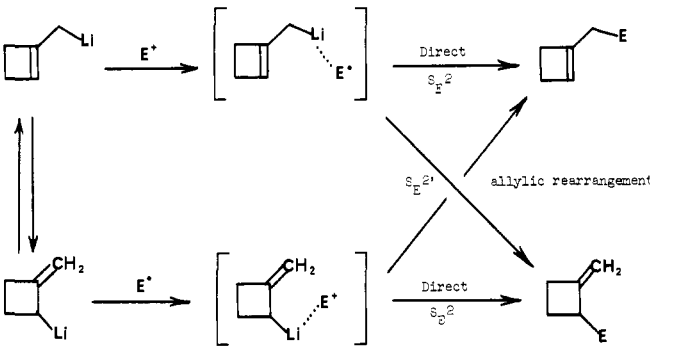


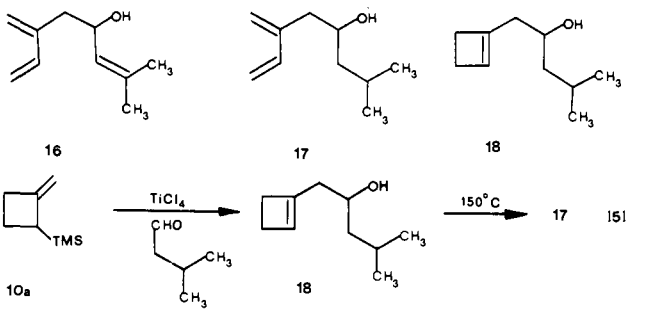
Figure 1. ^2H NMR of the reaction **7** + D_2O.

Scheme I



17 involved direct reaction of **7** with isovaleraldehyde (Table I), separation of isomer **18** by $AgNO_3$/silica chromatography, and thermolysis.

Application of our allylsilane chemistry to the synthesis of tagetol (**17**) involves reaction of **10a** with isovaleraldehyde/$TiCl_4$ yielding **18** (86%). Cyclobutene **18,** identical with material prepared earlier,[4a] is uncontaminated with the regioisomeric compound (**8**, Table I) obtained as major product



16 17 18

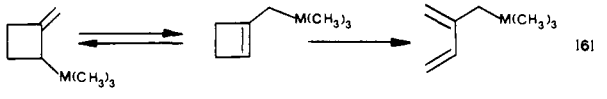
(70:30) in the *direct* reaction of **7** with isovaleraldehyde. Thermolysis of **18** yields tagetol (**17**) (eq 5).

Metalloisoprenes. The ready availability of silyl-substituted isomers **10a/11a** suggested that we might take advantage of another useful property of allylsilanes: the [1,3]-sigmatropic shift. Allylsilanes[23] and stannanes[24] are known to undergo thermal allylic isomerization with an activation energy in the silicon case of 47.7 kcal/mol, well above the 35.1 kcal/mol[5] required for the cyclobutene ring opening. Thus, we reasoned

Table II. Reaction of 7 with $PhCH_2X$

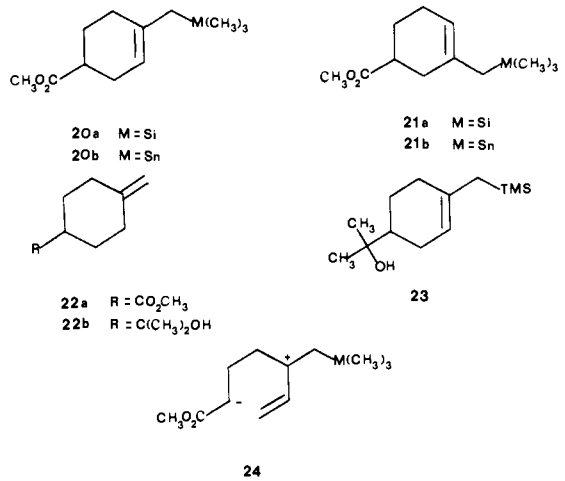
X	solvent	temp, °C	% yield	ratio 8/9
Cl	hexane	−78	71	100/0
Cl	hexane	25	92	66/34
Cl	hexane	70	85	62/38
Br	hexane	25	73	50/50
I	hexane	25	43	39/61
I	THF	25	64	51/59
I	DME	25	59	64/36

that thermolysis of a *mixture* of **10a/11a** might lead exclusively to trimethylsilylisoprene (**19a**) via transformations in eq 6. When a 60:40 mixture of **10a/11a** is passed through a hot tube at ~400 °C, the product is a 60:40 mixture of **19a/10a,**



10a,b 11a,b 19a M = Si 19b M = Sn

the result of ring opening of **11a** only. When the temperature is raised to >450 °C, some allylic isomerization occurs but byproduct formation, possibly via a methylenecyclobutene rearrangement,[25] increases. Compound **19a** reacts readily with methyl acrylate (6 h, 110 °C) to yield the Diels–Alder adduct **20a/21a** (80:20) in 75% yield.[26] The Diels–Alder reaction of **19a** produces *another* allylsilane which may be used in reactions with electrophiles. For example, methanolic HCl treatment of **20a** leads to **22a** (84%), which on reaction with methyllithium gives the monoterpene δ-terpinol (**22b**).[27] The



alternative pathway from **20a** to **22b** was also employed. Reaction of **20a** with methyllithium gave the tertiary alcohol **23** which was reacted with acid (CH_3OH/HCl) giving protonation of the double bond[28] and loss of Me_3Si to **22b.**

Since allylic stannanes undergo even more ready[24] [1,3]-sigmatropic isomerization the 80:20 mixture **10b/11b**[29] may be thermolyzed at 350 °C to yield *only* **19b** (61%), Diels–Alder reaction of **19b** with methyl acrylate gave adduct **20b/21b** (90:9) in 93% yield. Subsequent treatment with acid[30] yielded the same **22a** as obtained in the silicon route.

The Diels–Alder orientation[31] is interesting. It is well-known that silicon or tin can stabilize positive charge on the β carbon.[15b] Thus, the increased[31b] proportion of para (1,4) isomer **20a,b** in the reaction of methyl acrylate with metalloisoprenes **19a** and **19b** (compared to 70:30 for isoprene) reflects stabilization of the dipolar transition state **25** in the Diels–Alder reaction by the electropositive Si and Sn.

In summary, we have shown that new terpene synthons **7, 10a, 19a,** and **19b** may be used effectively to incorporate the C-5 isoprene unit.

Table III. Reaction of 7 with Me_3SiX

X	solvent	temp, °C	% yield	ratio 8/9
Cl	hexane	25	85	50/50
Cl	hexane	−78	77	60/40
Cl	THF	−78	75	80/20
Br	hexane	0	96	30/70
Br	hexane	25	91	25/75
I	hexane	0	90	25/75

Experimental Section

General. ^1H NMR spectra were recorded on Varian HR-220, T60-A, or EM360 spectrometers. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on Varian MAT CH-7 and AEI MS-9 spectrometers and IR spectra on a Perkin-Elmer 137 Infracord. Analytical gas chromatography was performed with a Varian Aerograph Model 3700 (or 940) on a 1.5% OV-101 (Chromosorb G) column (5 ft × 1/8 in.). Column chromatography used MCB silica gel, 100–200 mesh, grade 923. Distillations were performed with a Büchi/Brinkmann micro distillation oven, and boiling points reported are approximate.

Additions of Electrophiles to 1-Cyclobutenylmethyllithium (7). Methylenecyclobutane (**6**, 1.43 mL, 14.7 mmol) was added to a stirred solution of TMEDA (7.4 mmol) and *n*-butyllithium (7.4 mmol) in 3 mL of hexane under argon. The solution was stirred at room temperature overnight. Prior to reaction with an electrophile 2–3 mL of additional solvent (hexane or THF) was added. The electrophile (Tables I–III) was dissolved in ~5 mL of solvent. The solution of **7** prepared above was then brought to the selected temperature and the electrophile solution added dropwise with stirring. After 30 min, the reaction mixture was poured into a separatory funnel containing water and ether. The ether layer was washed with dilute acid, saturated sodium bicarbonate solution, and brine, then dried over calcium sulfate, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation and/or column chromatography gave **8** and **9.**

A. Reaction with D_2O. A hexane solution containing 2.5 mmol of **7** was added by syringe to 5 mL of D_2O cooled to ~0 °C under argon. The mixture was then extracted with cold 10% HCl and brine and dried over $MgSO_4$. ^1H NMR of the hexane solution showed signals for the cyclobutene hydrogen at δ 5.7 and the methylene hydrogens at δ 4.8. Integration indicated (after correction for excess **6**) ~28% **8** and ~72% **9.** The ^2H NMR spectrum (Figure 1) was obtained on a Varian HR-220 at 33.8 MHz with a Hewlett-Packard white noise decoupler centered at 220 002 587 Hz. Chemical shifts were determined relative to external $CDCl_3$. Integration of the ^2H NMR spectrum showed 33% **8** and 67% **9.**

B. Reaction with CO_2. After esterification (CH_3OH/HCl) a 21% yield of **8/9** (1:2) was obtained: bp 200 °C (40 Torr); IR (neat) 5.75 μ; NMR ($CDCl_3$) δ 5.75 (s, cyclobutene), 4.8 (m, exo methylene), 3.8 (s), 3.1 (bs), 2.5 (m); MS *m/e* (rel intensity) 126 (32), 68 (51), 67 (100), 59 (58). Calcd for $C_7H_{10}O_2$: 126.0681. Found: 126.0679.

C. Reaction with 3-Methyl-1-bromo-2-butene. A 75% yield of **8/9** (52/48) was obtained: bp 90 °C (40 Torr); GC (3/8 in. × 5 ft Carbowax 20M) three peaks (5:44:51); IR (neat) 3.29, 6.1 μ; NMR ($CDCl_3$) δ 5.75 (s, cyclobutene), 5.1 (m), 4.8 (m, exo methylene), 1.3–2.5 (m). Calcd for $C_{10}H_{16}$: 136.1253. Found: 136.1264.

D. Reaction with Adamantanone. A 25% yield of **8** (R_f 0.28, silica gel, 5% ether/95% petroleum ether) was obtained: IR ($CHCl_3$) 2.75, 6.00 μ; NMR ($CDCl_3$) δ 4.9 (2 H, m), 3.8 (1 H, s), 1.0–2.8 (19 H, m). Calcd for $C_{15}H_{22}O$: 218.1671. Found: 218.1677. A 5% yield of **9** (R_f 0.19, silica gel, 5% ether/95% petroleum ether) was obtained: IR ($CHCl_3$) 2.85, 6.15 μ; NMR ($CDCl_3$) δ 5.9 (1 H, s), 1.3–2.8 (21 H, m). Calcd for $C_{15}H_{22}O$: 218.1671. Found: 218.1670.

E. Reaction with Benzyl Halides. After alkylation under the described conditions (Table II) the products **8/9** were isolated by bulb-to-bulb distillation at 100 °C (20 Torr) in 43–71% yield. Compound **8** (R = $-CH_2Ph$): IR (neat) 6.00 μ; NMR ($CDCl_3$) δ 7.3 (5 H, m), 4.8 (2 H, m), 1.0–3.8 (7 H, m). Compound **9** (R = $-CH_2Ph$): NMR ($CDCl_3$) δ 7.3 (5 H, m), 5.8 (1 H, s), 1.0–3.0 (8 H, s). Calcd for $C_{12}H_{14}$: 158.1095. Found: 158.1088.

F. 1-(1-Cyclobutenyl)-5-methylhexan-3-ol (18). Addition of **7** to isovaleraldehyde in THF gave a 90% yield of **8/9** (70/30, **9** = **18**) after distillation, bp 100 °C (2.5 Torr). Compound **18** could be purified by chromatography on $AgNO_3$-impregnated silica gel (R_f 0.13, 10%

ether/90% petroleum ether). Compound **18** (19%): IR (neat) 2.90 μ; NMR ($CDCl_3$) δ 5.85 (1 H, s), 3.88 (1 H, m), 0.90 (6 H, d, J = 6 Hz). Calcd for $C_{10}H_{18}O$: 154.1359. Found: 154.1343. Compound **8** (R = $HOCHCH_2CH(CH_3)CH_3$) eluted later: IR (film) 2.90 μ; NMR ($CDCl_3$) δ 4.90 (2 H, s), 1.0–4.0 (16H, m). Calcd for $C_{10}H_{18}O$: 154.1359. Found: 154.1343.

G. Reaction with Trimethylsilyl Chloride. A solution of **7** (118 mmol) was brought to −78 °C and 146 mmol (21.6 mL) of trimethylchlorosilane (distilled from tri-*n*-butylamine) was added rapidly. The solution was stirred for 4 h, then poured into water and extracted with ether. The ether layer was washed twice with water, dried under magnesium sulfate, filtered, and concentrated under reduced pressure, yielding a light green oil which distilled at 130 °C (760 Torr) yielding 12.68 g (77%) of a mixture of 2-trimethylsilylmethylenecyclobutane (**10a**) and 1-trimethylsilylmethylcyclobutene (**11a**) (60:40): IR (neat) 3.0–3.3, 5.8 μ; NMR δ 5.45 (1 H, s, cyclobutene 40%), 4.5 (2 H, m, exo methylene 60%), 1.5–2.8 (5 H, m), 0 (9 H, s); MS *m/e* (rel intensity) 140 (10), 97 (10), 73 (100). Calcd for $C_8H_{16}Si$: 140.1022. Found: 140.1030.

H. Reaction with Trimethylstannyl Chloride. A hexane solution of $ClSn(CH_3)_3$ added dropwise to **7** at 0 °C gave **10b**/**11b** (20/80) (55%): IR (neat) 3.0–3.3, 5.95 (w), 6.09 μ; NMR δ 5.15 (1 H, s), 2.2 (4 H, s), 1.6 (2 H, s), 0 (9 H, s); MS *m/e* (rel intensity) 232 (2), 231 (0.6), 230 (2), 169 (18), 167 (16), 165 (80), 154 (35), 163 (61), 162 (25), 161 (55), 150 (14), 148 (10), 135 (33), 133 (29), 131 (19), 114 (20), 97 (16), 95 (23), 93 (19), 85 (70), 75 (63), 71 (40), 70 (64), 69 (67), 67 (73), 58 (83), 57 (73), 56 (72), 55 (75), 43 (100), 31 (100). The vinyl protons of minor component **10b** could be observed at δ 4.3 (2 H, m).

1-(1-Cyclobutenyl)-5-methylhexan-3-ol (18). Into a clean, dry 15-mL two-necked flask fitted with an argon bubbler and a rubber septum was placed 172 mg (2 mmol) of isovaleraldehyde in 30 mL of dichloromethane. After cooling to 0 °C, 188 mg (1 mmol, 0.1 mL) of $TiCl_4$ was added dropwise with a syringe and stirred for an additional 5 min. Then 280 mg of **10a** (2 mmol) was added rapidly. The reaction was followed by GC and was complete in 5 min. Water was added to the mixture and it was extracted with ether. The ether layer was washed twice with water, dried under $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation of the product yielded 265 mg (86%) of **18**: IR (neat) 2.90, 6.06 μ; NMR ($CDCl_3$) δ 5.8 (1 H, s), 3.8 (1 H, m), 0.8 (6 H, d); MS *m/e* (rel intensity) 154 (1), 68 (100). Calcd for $C_{10}H_{18}O$: 154.1359. Found: 154.1357.

1-(1-Cyclobutenyl)-2-hydroxyoctane (12). Into a clean, dry 25-mL two-necked flask fitted with an argon bubbler and a rubber septum were placed 228 mg (2 mmol) of heptaldehyde and 3.0 mL of dichloromethane. The solution was cooled to 0 °C in an ice bath and 188 mg (1 mmol, 0.11 mL) of $TiCl_4$ was added dropwise by syringe. The mixture was stirred for 5 min and then 280 mg (2 mmol) of **10a** was added rapidly. Reaction was complete in 5 min, when water was added and the mixture extracted with ether. The ether layer was washed twice with water, dried under $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation yielded 340 mg (82%) of a colorless liquid: IR 2.8–3.2, 3.35–3.55 μ; NMR δ 5.78 (1 H, s), 3.62 (1 H, m), 2.25 (4 H, s), 1.0–1.6 (13 H, m), 0.9 (3 H, t); MS *m/e* (rel intensity) 182 (0.3), 97 (28), 70 (12), 69 (20), 68 (100), 67 (27). Calcd for $C_{12}H_{22}O$: 182.1672. Found: 182.1656.

Compound 13. Into a clean, dry 25-mL two-necked flask fitted with an argon bubbler and a rubber septum were placed 196 mg (2 mmol) of cyclohexanone and 3 mL of dichloromethane. The solution was cooled to 0 °C and 188 mg (1 mmol, 0.11 mL) of $TiCl_4$ was added dropwise by syringe. After the solution was stirred for 5 min, 280 mg (2 mmol) of **10a** was added. The reaction was complete after 5 min. Water was then added and the mixture extracted with ether. The ether layer was washed twice with water, dried under $MgSO_4$, filtered, and concentrated under reduced pressure. Preparative thin layer chromatography (5% ether/pentane) yielded 270 mg of a colorless oil (86%): IR 2.7–3.0, 6.18 μ (weak); NMR δ 5.77 (1 H, s), 2.05–2.6 (4 H, m), 2.05 (2 H, bs), 1.9 (1 H, bs), 1.2–1.6 (10 H, m); MS *m/e* (rel intensity) 166 (0.3), 99 (100), 86 (17), 84 (27), 81 (57). Calcd for $C_{11}H_{18}O$: 166.1359. Found: 166.1344.

2-Methyl-6-methylene-7-octen-4-ol (17). Cyclobutene **18** (10 mg) in 0.5 mL of $CDCl_3$ was degassed and sealed. Heating of the sample at 150 °C ($t_{1/2} \simeq$ 1 h) for 4 h gave essentially quantitative conversion to **17**, whose NMR spectrum exactly matched that reported:[20c] δ 6.34 (dd, J = 16, 10 Hz, 1 H), 5.01–5.4 (m, 4 H), 3.74 (m, 1 H), 2.12–2.38 (m, 3 H), 1.7 (m, 2 H), 1.28 (m, 2 H), 0.92 (dd, J = 7, 2 Hz, 6 H).

1-Trimethylsilylmethyl-4-carbomethoxycyclohexene (20a).[26] A 60/40 mixture of **10a** and **11a** was heated for 10 h at 150 °C yielding a 60/40 mixture of **10a** and trimethylsilylisoprene (**19a**). Compound **19a** could not be isolated in pure form: NMR δ 6.25 (1 H, dd, J = 17, 10 Hz), 4.4–5.2 (3 H, m), 1.6 (2 H, s), 0 (9 H, s). To the mixture of **10a** and **19a** (6 g, 43 mmol) was added excess methyl acrylate and the mixture was heated to 110 °C under nitrogen for 24 h, yielding a mixture of 2-trimethylsilylmethylenecyclobutane (**10a**) and **20a**/**21a** (80/20). Fractional distillation gave 3.4 g (93% recovery) of 2-trimethylmethylenecyclobutane (**10a**) [bp 130 °C (760 Torr); IR (neat) 5.8 μ; NMR δ 4.5 (2 H, m), 1.5–2.8 (5 H, m), 0 (9 H, s); MS *m/e* (rel intensity) 140 (10), 97 (10), 73 (100)] and Diels–Alder adduct **20a**/**21a** (75% based on amount of diene present) [bp 150 °C (20 Torr); IR 3.3–3.55, 5.78 μ; NMR δ 5.2 (1 H, bs), 3.55 (3 H, s), 1.2–2.2 (9 H, m), 0 (9 H, s); MS *m/e* (rel intensity) 226 (9), 159 (35), 94 (25), 73 (100). Calcd for $C_{12}H_{22}O_2Si$: 226.138 90. Found: 226.137 04]. GC analysis indicated an 80/20 radio of para/meta Diels–Alder products.

4-Carbomethoxycyclohexene (22a). Method A. Into a clean, dry 25-mL two-necked flask fitted with an argon bubbler were placed 10 mL of anhydrous methanol and 0.5 mL of acetyl chloride and 217 mg of **20a** was added at 0 °C. After 5 min the reaction mixture was quenched with water and extracted with ether. The ether layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation yielded 131 mg (88%) of **22a**: IR 3.2–3.5, 5.78, 6.05 μ (w); NMR δ 4.61 (2 H, s), 1.2–2.2 (9 H, m), 0 (9 H, s); MS *m/e* (rel intensity) 154 (9), 123 (14), 122 (24), 95 (75), 94 (100), 87 (46). Calcd for $C_9H_{14}O_2$: 154.0995. Found: 154.1001.

Method B. Compound **20b** gave **22a** under conditions identical with the above.

Trimethylstannylisoprene (19b). 10b/11b (300 mg) was placed in a clean, dry 15-mL cone-shaped flask and the flask attached to a horizontal oven-heated Vycor column packed with 4-mm Pyrex beads. After the column was a dry ice/acetone cooled 15-mL receiver connected to a vacuum pump. The system was evacuated and the column heated to 350 °C. The cone-shaped flask was warmed with a heat gun to drive the material through the column. The reaction was over in 15 min, yielding 180 mg (60%) of a colorless liquid: IR (neat) 3.4 μ; NMR δ 6.35 (1 H, dd, J = 18, 10 Hz), 4.7–5.15 (3 H, m), 1.85 (2 H, s), 0 (9 H, s); MS *m/e* (rel intensity) 232 (3), 230 (1), 217 (11), 187 (12), 185 (13), 169 (16), 167 (12), 165 (93), 164 (31), 163 (87), 162 (28), 161 (53), 150 (12), 135 (40), 134 (11), 133 (29), 131 (15), 113 (15), 85 (53), 75 (22), 69 (50), 55 (60), 43 (53), 41 (100). Calcd for $C_8H_{16}Sn$: 230.026 81. Found: 230.023 85.

1-Trimethylstannylmethyl-4-carbomethoxycyclohexane (20b). 19b (180 mg) and 0.2 mL of methyl acrylate were heated to 100 °C for 12 h. The excess methyl acrylate was removed and the product distilled bulb to bulb, yielding 230 mg of **20b** (93%). GC showed the isomer ratio **20b**/**21b** to be 91/9: IR 3.2–3.5, 5.73 μ; NMR δ 5.15 (1 H, s), 3.6 (3 H, s), 1.6–2.4 (9 H, m), 0 (9 H, s); MS *m/e* (rel intensity) 318 (1.9), 316 (1.1), 303 (24), 301 (20), 169 (15), 167 (13), 165 (88), 164 (72), 163 (22), 161 (40), 135 (20), 133 (15), 93 (18), 85 (39), 55 (100). Calcd for $C_{12}H_{22}O_2Sn$: 318.064 21, 316.063 60. Found: 318.063 35, 316.061 22.

Compound 23. 20a (222 mg, 1 mmol) in 3 mL of ether was treated with 2 mmol of methyllithium in ether at 0 °C under argon. After 2.5 h the reaction mixture was quenched with water and extracted with ether. The ether layer was washed twice with water, dried under $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation gave 215 mg of **23** (95%): IR (neat) 3.03, 2.9 μ; NMR ($CDCl_3$) δ 5.2 (1 H, broad singlet), 1.2 (6 H, s), 1.4 (2 H, s), 1.6–2.4 (7 H, m), 0 (9 H, s); MS 265 (0.42), 73 (100). Calcd for $C_{13}H_{26}OSi$: 226.175 29. Found: 226.173 83.

δ-Terpineol (22b). Method A. Compound **22a** was treated with 2 mol of CH_3Li in ether to give **22b** (100%).

Method B. 23 (160 mg, 0.6 mmol) was added to a cold (0 °C) solution of HCl in 10 mL of CH_3OH (from 0.5 mL of acetyl chloride). After 15 min, water was added and the reaction mixture extracted with ether. The ether layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation gave 100 mg of **22b** (92%):[27] bp 80 °C (2.5 mm); NMR ($CDCl_3$) δ 4.7 (2 H, s), 1.2 (6 H, s), 1.2–2.4 (10 H, m); IR (neat) 2.9, 6.06 μ; MS *m/e* (rel intensity) 154 (0.6), 59 (100).

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Structure of Ionomycin—a Novel Diacidic Polyether Antibiotic Having High Affinity for Calcium Ions

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Abstract: The structure and absolute configuration of ionomycin, $C_{41}H_{72}O_9$, a novel diacidic polyether antibiotic having high affinity for calcium ions, have been determined by X-ray and spectroscopic methods. X-ray analyses of orthorhombic forms ($P2_12_12$, $Z = 4$) of the isomorphous Cd and Ca salts and of a monoclinic form of the Cd salt containing two molecules per asymmetric unit ($P2_1$, $Z = 4$) indicate that the complexed ionophore adopts virtually identical conformations in the three independent solid-state environments. In both crystal forms, the ionophores are joined in pairs by two hydrogen bonds so as to form a "dimeric" globular structure having primarily lipophilic surfaces. Heptane and hexane molecules of crystallization are packed between the lipophilic "dimers" in the orthorhombic and monoclinic forms, respectively. The molecular structure of the salts of ionomycin contains a cisoid enolized β-diketone anion that, together with a carboxylate group and three other oxygen atoms, is octahedrally coordinated to the central divalent cation.

Introduction

The polyether antibiotics[2] display a range of interesting biological properties including antimicrobial activity, growth promotion in ruminants, and cardiovascular effects. These properties are related to the ability of the polyethers to form lipid-soluble complexes with inorganic cations and so transport them across hydrophobic barriers.

Ionomycin (**1**) is a new and especially interesting member of the polyether ionophores in that it chelates calcium (and

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