BMS Reduction of Tertiary and Secondary Amides in the Presence of BF_3·OEt_2. Reduction of *N*,*N*-Dimethylbenzamide. Procedure H. The experimental setup was as described in procedure D. The flask was charged with 4.48 g (30 mmol) of *N*,*N*-dimethylbenzamide and 3.91 mL of THF. Then BF_3·OEt_2 (3.69 mL, 30 mmol) was added and the mixture heated to reflux. To the clear solution was added 2.32 mL (22 mmol) of BMS in drops over a period of 10 min. Dimethyl sulfide and ether distilled off and were collected and measured (3.6 mL). The reaction was monitored as described earlier. After 0.25 h, the product was isolated either with HCl/NaOH (procedure D) or TMEDA (procedure E).

The results are summarized in Table VII.

Reduction of *N*-Methylbenzamide. The above procedure was folllowed, except that 33 mmol of BMS was added instead of 22 mmol. The amine was isolated by following procedure D.

Registry No. Benzyl alcohol, 100-51-6; 1-hexanol, 111-27-3; 2-phenylethanol, 60-12-8; (hydroxymethyl)cyclohexane, 100-49-2; (hydroxymethyl)adamantane, 770-71-8; 3-bromopropanol, 627-18-9; *m*-bromobenzyl alcohol, 15852-73-0; *p*-chlorobenzyl alcohol, 873-76-7; *p*-nitrobenzyl alcohol, 619-73-8; *m*-methoxybenzyl alcohol, 6971-51-3; *p*-methoxybenzyl alcohol, 105-13-5; 1,4-butanediol, 29733-86-6; phthalyl alcohol, 612-14-6; phthalan, 496-14-0; *n*-hexylamine, 111-26-2; cyclopropanemethylamine hydrochloride, 7252-53-1; benzylamine, 100-46-9; neopentylamine hydrochloride, 15925-18-5; 2,2-diphenylethylamine, 3963-62-0; *p*-chlorobenzylamine, 104-86-9; *m*-nitrobenzylamine hydrochloride, 26177-43-5; *o*-xylylamine, 89-93-0; *p*-methoxybenzylamine, 2393-23-9; 1,6-diaminohexane, 124-09-4; *N*,*N*-dimethylhexylamine, 4385-04-0; *N*,*N*-dimethyloctadecylamine, 124-28-7; [(dimethylamino)methyl]cyclohexane, 16607-80-0; *N*,*N*-dimethylbenzylamine, 103-83-3; *N*,*N*-dimethyl-2-phenylethylamine, 1126-71-2; *N*,*N*-dimethylneopentylamine, 10076-31-0; *N*,*N*-diisopropylbutylamine, 41781-44-6; [(diisopropylamino)methyl]cyclohexane, 80934-61-8; *N*,*N*-diisopropylbenzylamine, 34636-09-4; *N*,*N*-dimethyl-*p*-chlorobenzylamine, 15184-98-2; *N*,*N*-dimethyl-*p*-nitrobenzylamine, 15184-96-0; *N*,*N*-dimethyl-*o*-methoxybenzylamine, 58774-83-7; *N*,*N*-dimethyl-*p*-methoxybenzylamine, 15175-54-9; *n*-hexylpiperidine, 7335-01-5; *N*-ethylphenothiazine, 1637-16-7; *N*-hexylmorpholine, 31866-75-8; *N*-ethylisoindoline, 36139-84-1; *N*-methylbutylamine hydrochloride, 6973-82-6; cyclohexylmethylamine, 100-60-7; *N*-methylbenzylamine, 103-67-3; 2,4-dimethyl-*N*-ethylaniline, 1742-94-5; homopiperidine, 111-49-9; *n*-hexylamine hydrochloride, 142-81-4; octadecylamine hydrochloride, 1838-08-0; (aminomethyl)cyclohexane, 3218-02-8; 2-methylbenzylamine hydrochloride, 14865-38-4; 2-methoxybenzylamine, 6850-57-3; 4-chlorobenzylamine hydrochloride, 42365-43-5; 4-nitrobenzylamine hydrochloride, 18600-42-5; neopentanediamine dihydrochloride, 29082-53-9; ethyl benzoate, 93-89-0; ethyl hexanoate, 123-66-0; ethyl phenylacetate, 101-97-3; ethyl cyclohexanecarboxylate, 3289-28-9; ethyl adamantane-1-carboxylate, 2094-73-7; ethyl 3-bromopropionate, 539-74-2; ethyl *m*-bromobenzoate, 24398-88-7; ethyl *p*-chlorobenzoate, 7335-27-5; ethyl *p*-nitrobenzoate, 99-77-4; ethyl *m*-methoxybenzoate, 10259-22-0; ethyl *p*-methoxybenzoate, 94-30-4; diethyl succinate, 123-25-1; γ-butyrolactone, 96-48-0; phthalide, 87-41-2; capronitrile, 628-73-9; cyclopropyl cyanide, 5500-21-0; benzonitrile, 100-47-0; pivalonitrile, 630-18-2; diphenylacetonitrile, 86-29-3; *p*-chlorobenzonitrile, 623-03-0; *m*-nitrobenzonitrile, 619-24-9; *o*-tolunitrile, 529-19-1; *p*-methoxybenzonitrile, 874-90-8; adiponitrile, 111-69-3; *N*,*N*-dimethylhexanamide, 5830-30-8; *N*,*N*-dimethyloctadecanamide, 3886-90-6; *N*,*N*-dimethylcyclohexanecarboxamide, 17566-51-7; *N*,*N*-dimethylbenzylamide, 611-74-5; *N*,*N*-dimethylphenylacetamide, 18925-69-4; *N*,*N*-dimethylpivalamide, 24331-71-3; *N*,*N*-diisopropylbutyramide, 38161-09-0; *N*,*N*-diisopropylcyclohexanecarboxamide, 61259-25-4; *N*,*N*-diisopropylbenzamide, 20383-28-2; *N*,*N*-dimethyl-*p*-chlorobenzamide, 14062-80-7; *N*,*N*-dimethyl-*o*-methoxybenzamide, 7291-34-1; *N*,*N*-dimethyl-*p*-methoxybenzamide, 7291-00-1; *N*-acetylphenothiazine, 1628-29-1; *N*-(2-bromoethyl)phthalimide, 574-98-1; *N*-methylbutyramide, 17794-44-4; *N*-cyclohexylformamide, 766-93-8; *N*-methylbenzamide, 613-93-4; 2,4-dimethylacetanilide, 2050-43-3; caprolactam, 105-60-2; hexanamide, 628-02-4; *n*-octadecanamide, 124-26-5; cyclohexanecarboxamide, 1122-56-1; benzamide, 55-21-0; pivalamide, 754-10-9; 2-methylbenzamide, 527-85-5; 2-methoxybenzamide, 2439-77-2; 4-chlorobenzamide, 619-56-7; 4-nitrobenzamide, 619-80-7; 2,2-dimethylmalonamide, 41882-44-4; *N*,*N*-dimethylbenzamide, 611-74-5; *N*,*N*-dimethyl-*p*-nitrobenzamide, 7291-01-2.

Notes

Benzoannelation of Ketones

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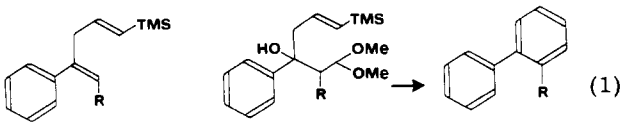
Received December 7, 1981

Aromatic annelation, the elaboration of aromatic rings from nonaromatic precursors, is not always a general or a preparatively useful process. This gap in current synthetic methodology has resulted in a renewal of interest in aromatic chemistry.[1] Our early contribution to this area was a general method for the synthesis of unsymmetrical biphenyls from alkyl aryl ketones.[2] Our method relied upon an intramolecular cationic cyclization, followed by loss of methanol and water as depicted in eq 1. This was the first example of a cationic ketone benzoannelation, and certain problems were evident. Although the preparation of the starting materials was straightforward, it was tedious

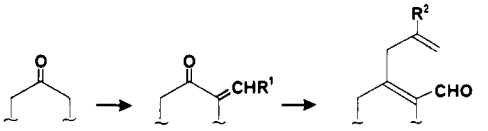


(1)

1

to perform on a large scale. Also, the method did not appear well suited for the more general preparation of benzoannelated aliphatic ketones. Furthermore, the isolation of byproduct 1 showed that a delicate balance existed between cyclization and other competing processes. Additional work was clearly necessary in order to develop a more useful benzoannelation.

The first problem was the conversion, in one or two operations, of an α-methylene ketone to a β-allylic unsaturated aldehyde or its equivalent (eq 2). The presence



(2)

2

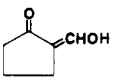
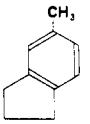
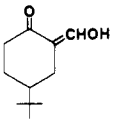
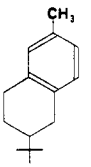
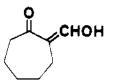
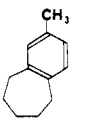
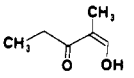
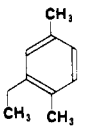
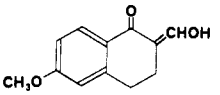
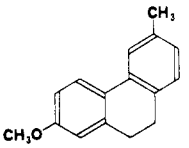
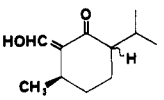
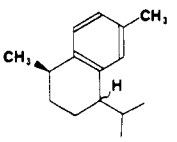
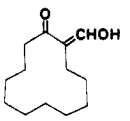
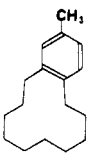
of the α,β-double bond is crucial to the success of the

(1) (a) Paquette, L. A.; Melega, W. P.; Kramer, J. D. *Tetrahedron Lett.* **1976**, 4033. (b) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002. (c) Boger, D. L., Panek, J. S. *Ibid.* **1981**, *46*, 2179. (d) Sukumaram, K. B.; Harvey, R. G. *Ibid.* **1981**, *46*, 2740 and references cited therein.

(2) Tius, M. A. *Tetrahedron Lett.* **1981**, 3335.

0022-3263/82/1947-3163$01.25/0

Table I. Ketone Benzoannelation

entry	starting matl[a]	product (yield, %)[b,c]	bp or mp, °C
1		 (58)	
2		 (77)	bp 270-271
3		 (81)[d]	bp 236
4		 (87)	
5		 (72)	mp 58-59
6		 (76)[e]	bp 266-267
7		 (84)	

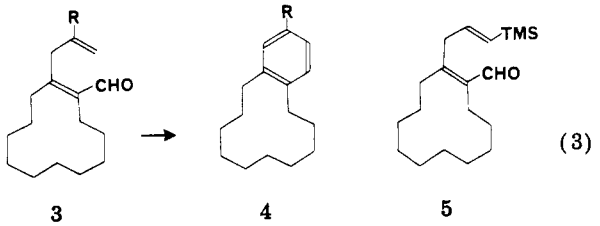
[a] Prepared according to ref 5. [b] Overall yield from 2-hydroxymethylene ketone. [c] All compounds gave satisfactory IR, NMR, and mass spectra. [d] Reference 19. [e] Yield refers to cyclization of purified enal.

aromatic cyclization because it blocks the formation of 1. Thiomethylene compounds 2 (R^1 = SPh and S-*n*-Bu) were prepared according to known procedures.[3] Further reaction with (allyltrimethylsilyl)lithium[4] took place at the carbonyl carbon in high yield; however, treatment with a variety of protic and Lewis acids failed to produce benzoannelated compounds. Rather, it appeared that mixtures of labile cyclohexadienes had been formed, and this approach was abandoned.

The addition of Grignard and alkyllithium reagents to 2-hydroxymethylene ketones 2 (R^1 = OH)[5] and the derived alkyl ethers takes place indiscriminately at both the α- and γ-carbons of the unsaturated system.[6] The silyl analogue of this reaction (2, R^1 = $OSiR_3$) was, to our knowledge, unknown. Consequently, a series of experiments was undertaken. 2-(Hydroxymethylene)cyclododecanone was converted to the *tert*-butyldimethylsilyl ether by treatment in anhydrous dichloromethane at 23 °C with a small excess of each of trimethylamine and *tert*-butylchlorodimethylsilane. The reaction of the *O*-trialkylsilyl compound with methallylmagnesium chloride at 0 °C in ether followed by immediate hydrolysis with aqueous hydrochloric acid produced aldehyde 3 (R = CH_3).[7] The cheaper trimethylsilyl ether also gave 3 (R = CH_3) in high yield.[8] The observed preference for 1,2-attack of the Grignard reagent on the unsaturated system is kinetic.[9] Indeed, longer reaction times and higher temperatures produced mixtures containing the product of 1,4-attack.[10] The selectivity for 1,2-attack in the trialkylsilyl series is in contrast to the results reported for the *O*-alkyl compounds.[5] This may be a consequence of the lower electronegativity of silicon vs. carbon and of the attending change in the polarization of the enone.[11,12]

(3) (a) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620. (b) Bernstein, P. R. *Tetrahedron Lett.* **1979**, 1015.
(4) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004 and references cited therein.
(5) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1971**, *36*, 3070.
(6) Dreiding, A. S.; Nickel, S. N. *J. Am. Chem. Soc.* **1954**, *76*, 3965.
(7) (a) O'Brien, S.; Fishwick, M.; McDermott, B.; Wallbridge, M. G. H.; Wright, G. A. *Inorg. Synth.* **1970**, *13*, 72. (b) Halstead, G. W.; Baker, E. C.; Raymond, K. N. *J. Am. Chem. Soc.* **1975**, *97*, 3049. (c) Mandell, L.; Brodmann, J. M. *J. Org. Chem.* **1966**, *31*, 591.
(8) The *tert*-butyldimethylsilyl ethers were labile compounds which slowly reverted to the 2-hydroxymethylene ketones on standing. The trimethylsilyl ethers could not be isolated.
(9) See also: Stork, G.; Maldonado, L. *J. Am. Soc.* **1974**, *96*, 5272.
(10) This observation was made in our laboratory by Mr. Andrew Thurkauf.
(11) A comparison of the ^{13}C NMR chemical shifts of the β-carbon atom between the *O*-alkyl and the *O*-silyl series will clarify this point. The observed preference for 1,4-attack on conjugated enaminones is consistent with the hypothesis. Abdulla, R. F., Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248. Simons, G.; Zandler, M. E.; Talaty, E. R. *J. Am. Chem. Soc.* **1976**, *98*, 7869.

The crucial step, the acid-catalyzed cyclization of **3** to methyl aromatic **4** (R = CH_3) (eq 3) caused difficulty at

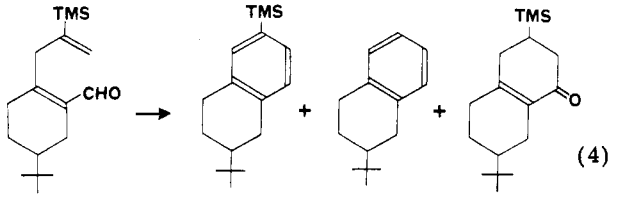


(3)

3 4 5

first. Lewis acids in a number of different solvents gave only poor yields of **4** (R = CH_3). Treatment of **3** (R = CH_3) in refluxing benzene containing *p*-toluenesulfonic acid for 15 min, however, produced **4** (R = CH_3) in 91% yield. To demonstrate the usefulness of this procedure, we prepared the aromatic compounds shown in Table I. The reaction tolerates a number of common ring sizes. The synthesis of 2-ethyl-*p*-xylene from 3-pentanone (entry 4) shows that the benzoannelation is applicable to acyclic systems and that both *E* and *Z* isomers of the aldehyde undergo cyclization to the aromatic. *l*-Menthone was converted to (+)-calamenene and 7-isocalamenene (entry 6).[13] Steric encumbrance of the carbonyl carbon due to the α-isopropyl led to an increase of byproducts derived from 1,4-addition in this case. By performance the Grignard addition at −40 °C instead of at 0 °C these competing processes were largely suppressed.

We next turned our attention to the preparation of unsubstituted benzoannelated compounds. The cyclization of allyl compound **3** (R = H) took place under the same conditions which were successful in the methallyl case, but the yield of **4** (R = H) could not be improved beyond 12%. The acid catalyst, solvent, and temperature were all varied in a futile attempt to improve the yield. Much to our surprise, aldehyde **5** derived from (allyltrimethylsilyl)-lithium[4] produced only 10% of **4** (R = H).[14] Because the stabilization of β positive charge by silicon is weak and appears to be easily perturbed by small steric effects, another experiment suggested itself.[15] Aldehyde **6** was prepared from 2-(hydroxymethylene)-4-*tert*-butylcyclohexanone by following the same sequence of reactions as with [2-(trimethylsilyl)-2-propenyl]magnesium chloride.[16] The cyclization of **6** with *p*-toluenesulfonic acid in refluxing benzene gave a mixture of aromatic compounds **7** and **8**[1a] (eq 4) in 53% yield along the ca. 15% of enone **9**, the



(4)

6 7 8 9

product derived from hydride transfer. It appears that acceptable yields of the unsubstituted benzoannelated compounds can be prepared by this route. It may be possible to intercept trimethylsilyl aromatic **7** with electrophiles other than a proton.[17]

In summary then, a general method for the direct benzoannelation of ketones has been found. Preliminary results indicate that similar methodology can be used for the preparation of substituted phenols and pyridines. A description of this work and its application to the total synthesis of representative natural products will be disclosed in due course.

Experimental Section

Ether was distilled from sodium benzophenone ketyl immediately prior to use. Dry benzene was degassed with a stream of argon gas. A 1/1 (v/v) solution of chlorotrimethylsilane and triethylamine was centrifuged to remove the precipitate of hydrochloride salt. The supernatant was used to silylate the 2-hydroxymethylene ketones.[18] Nuclear magnetic resonance (NMR) spectra were recorded either at 100 MHz (Varian XL-100 spectrometer) or at 60 MHz (Varian EM 360). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Infrared (IR) spectra were recorded either on a Beckman IR 10 or a Perkin Elmer 410A. Mass spectra were recorded on a Varian MAT-311 instrument.

General Procedure for Ketone Benzoannelation. A solution of methallylmagnesium chloride was prepared by dropwise addition of 1.4 mL (14.35 mmol) of distilled methallyl chloride at 0 °C over 30 min to 1.04 g (42.79 mmol) of magnesium turnings in 10 mL of ether. Stirring was continued for 1 h at 0 °C at which time the cooling bath was removed. The mixture was stirred for an additional 1.5 h at 23 °C. In a separate flask a solution of 276 mg (1.31 mmol) of 2-(hydroxymethylene)cyclododecanone in 12 mL of anhydrous ether was treated with 0.72 mL of a chlorotrimethylsilane–triethylamine mixture (ca. 2 equiv). An immediate reaction took place with deposition of a white precipitate. The Grignard solution was cooled to 0 °C, and the crude solution of silyl ether was added via cannula. After 10 min the reaction mixture was poured into 1 N aqueous HCl. The two-phase mixture was stirred for 3 h, extracted with ether, and washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford crude aldehyde **3** (R = CH_3) which needed no purification.

A solution of 75 mg (0.4 mmol) of *p*-toluenesulfonic acid in 13 mL of dry, degassed benzene was heated to reflux. Aldehyde **3** (R = CH_3), dissolved in a small amount of the same solvent, was added to the refluxing mixture. After 20 min the solution was allowed to cool and was then partitioned between ether and water. Washing with saturated aqueous sodium bicarbonate solution and brine was followed by drying ($MgSO_4$) and concentration. The crude material was filtered through silica gel, rinsing with hexane, to produce 254 mg of 2-methylbenzocyclododecene **4** (R = CH_3): 1.10 mmol (84% overall yield); IR (neat) 2950, 2850, 1600, 1505, 1470, 1450, 890, 820, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.97 (3 H, m), 2.61 (4 H, t, J = 7.5 Hz), 2.27 (3 H, s), 1.42 (18 H, br m); mass spectrum (70 eV), m/e 230 (p), 229 (p − 1), 190, 148, 136, 124, 122, 100, 98, 84, 82, 70.

2-Methylbenzocyclopentene: IR (neat) 3000, 2870, 1620, 1500, 1450, 1250, 1070, 870, 840, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.96 (3 H, m), 2.75 (4 H, t, J = 7.2 Hz), 2.20 (3 H, s), 1.93 (2 H, q, J = 7.2 Hz); mass spectrum (70 eV), m/e 132 (p), 131 (p − 1), 117 (p − CH_3), 91.

2-*tert*-Butyl-6-methyl-1,2,3,4-tetrahydronaphthalene: IR (neat) 3000, 1470, 1370, 900, 800, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (3 H, m), 2.83 (4 H, m), 2.27 (3 H, s), 0.94 (3 H, s); mass spectrum (70 eV), m/e 202 (p), 201 (p − 1), 159, 158, 144 (p − $(CH_3)_3C$), 57 ($(CH_3)_3C$).

2-Methylbenzocycloheptene: IR (neat) 2950, 2870, 1660, 1610, 1500, 1450, 800, cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.94 (3 H, m), 2.72 (4 H, m), 2.31 (3 H, s), 1.74 (6 H, br m); mass spectrum (70 eV),

(12) We thank Dr. Larry C. Blaszczak for helpful discussions.
(13) Ladwa, P. H.; Joshi, G. D.; Kulkarni, S. N. *Chem. Ind. (London)* **1968**, 1601.
(14) Treatment of aldehyde **5** with potassium *tert*-butoxide in tetrahydrofuran–*tert*-butyl alcohol at reflux also produced a small amount of **4** (R = H). This appears to be an example of an electrocyclic annelation: Magnus, P. *Nouv. J. Chim.* **1978**, *2*, 555.
(15) (a) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046. (b) Soderquist, J. A.; Brown, H. C. *Ibid. J. Org. Chem.* **1980**, *45*, 3571.
(16) Lai, Y.-H. *Synthesis* **1981**, 585.
(17) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.
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m/e 160 (p), 159 (p - 1), 144, 130, 118, 117, 116, 114, 104.

2-Ethyl-p-xylene: IR (neat) 2970, 2900, 1500, 1460, 1380, 1060, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (3 H, m), 2.59 (2 H, q, J = 7.5 Hz), 2.29 (3 H, s), 2.25 (3 H, s), 1.19 (3 H, t, 7.5 Hz); mass spectrum (70 eV), m/e 134 (p), 119 (p - CH_3), 105 (p - CH_2CH_3), 95, 91.

2-Methoxy-6-methyl-9,10-dihydrophenanthrene: IR (neat) 3000, 2850, 1600, 1490, 1460, 1425, 1300, 1270, 1230, 1150, 1100, 1030, 900, 840, 790, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.99 (6 H, br m), 3.75 (3 H, s), 2.74 (4 H, s), 2.30 (3 H, s); mass spectrum (70 eV), m/e 224 (p) 223 (p - 1), 208 (p - 1 - CH_3), 193, 192, 178, 177, 165, 164.

(+)-Calamenene: IR (neat) 2960, 2880, 1440, 1370, 1370, 800 cm^{-1}; ^1H NMR ($CDCl_3$) 6.93 (3 H, br s), 2.23 (3 H, s), 1.23–0.60 (9 H); mass spectrum (70 eV), m/e 202 (p), 201 (p - 1), 158, 145, 144, 143, 142, 141, 130, 128, 127, 105.

Benzocyclododecene: IR (neat) 2920, 2850, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) 7.13 (4 H, br s), 2.64 (4 H, t, J = 7.6 Hz), 1.52 (16 H, m).

Compound 6: ^1H NMR ($CDCl_3$) δ 9.95 (1 H, s), 5.43 (2 H, br s), 3.33 (2 H, br s), 0.87 (3 H, s), 0.07 (9 H, s); mass spectrum (70 eV), m/e 278 (p), 277 (p - 1), 263 (p - CH_3), 249, 221 (p - $(CH_3)_3C$), 205 (p - $(CH_3)_3Si$), 193, 191, 179, 130, 91, 75, 73 ($(CH_3)_3Si$).

Compound 7: ^1H NMR ($CDCl_3$) δ 7.07 (3 H, s), 2.78 (4 H, br m), 0.94 (9 H, s), 0.24 (9 H, s); mass spectrum (70 eV), m/e 260 (p), 245 (p - CH_3), 203 (p - $(CH_3)_3C$), 189 (p - $(CH_3)_3Si$), 132, 73 ($(CH_3)_3Si$).

Compound 9: IR (CH_2Cl_2) 2960, 1660, 1370, 830 cm^{-1}; ^1H NMR ($CDCl_3$) 2.17 (8 H, br m), 0.87 (9 H, s), 0.01 (9H, s); mass spectrum (70 eV), m/e 278 (p), 263 (p - CH_3), 221 (p - $(CH_3)_3C$), 195, 194, 193, 181, 180, 179, 147, 131, 91, 73 ($(CH_3)_3Si$).

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Registry No. 3 (R = H), 81857-26-3; **3** (R = Me), 81857-27-4; **4** (R = Me), 81857-28-5; **5**, 81857-29-6; **6**, 81857-30-9; **7**, 81857-31-0; **8**, 42044-22-4; **9**, 81857-32-1; 7-isocalamenene, 483-77-2; methallyl chloride, 563-47-3; 2-(hydroxymethylene)cyclododecanone, 949-07-5; 2-[[(trimethylsilyl)oxy]methylene]cyclododecanone, 81857-33-2; 2-methylbenzocyclopentene, 874-35-1; 2-*tert*-butyl-6-methyl-1,2,3,4-tetrahydronaphthalene, 81857-34-3; 2-methylbenzocycloheptene, 827-40-7; 2-ethyl-*p*-xylene, 1758-88-9; 2-methoxy-6-methyl-9,10-dihydrophenanthrene, 81857-35-4; (+)-calamenene, 22339-23-7; benzocyclododecene, 7125-10-2; 2-(hydroxymethylene)cyclopentanone, 2-(hydroxymethylene)cyclopentanone; 4-*tert*-butyl-2-(hydroxymethylene)cyclohexanone, 22252-96-6; 2-(hydroxymethylene)cycloheptanone, 934-20-3; 1-hydroxy-2-methyl-1-penten-3-one, 50421-81-3; 6-methoxy-2-(hydroxymethylene)-1,2,3,4-tetrahydronaphthalenone, 16252-53-2; *cis*-2-(hydroxymethylene)-3-methyl-6-isopropylcyclohexanone, 59123-00-1; 2-[[(*tert*-butyldimethylsilyl)oxy]methylene]-cyclododecanone, 81857-36-5; *trans*-2-(hydroxymethylene)-3-methyl-6-isopropylcyclohexanone, 59122-99-5.

Biomimetic Synthesis of (±)-Pallescensin 1

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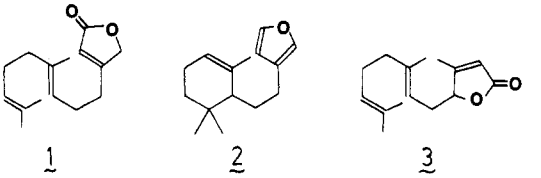
During an investigation of a biomimetic approach to the synthesis of the pallescensins[1] and the drimane sesquiterpenes,[2] we considered that butenolide 1 or its derivatives might serve as a common precursor to both classes of compounds. Cationic cyclization of the A ring would lead to (±)-pallescensin 1 (2) whereas bicyclization would furnish drimenin.[3] A recently published preparation of starting material 1 by oxidation of farnesal *O*-trimethylsilyl cyanohydrin appeared well suited to our purpose.[4] Farnesol,[5] available as a mixture of *E* and *Z* isomers at C-2, was oxidized to a mixture (ca. 1:1) of *E* and *Z* aldehydes. Conversion to the unstable *O*-trimethylsilyl cyanohydrins was accomplished by the use of trimethylsilyl cyanide and potassium cyanide/18-crown-6 complex.[6] Oxidation with pyridinium dichromate[4,7] in dry *N,N*-dimethylformamide gave a mixture of butenolides 1 and 3 in 62% overall yield from the aldehyde mixture. Proton NMR spectroscopy at 100 MHz gave no indication of the presence of butenolide isomers. Multiple TLC elutions failed to effect separation, but suggested the presence of two compounds. This was confirmed by reduction to a mixture of furans. Chromatographic separation of 1 and 3 was not practical on a preparative scale, so the separation was effected at the aldehyde stage.[8] Whereas the *E* aldehyde was oxidized to butenolide 1 regiospecifically, as shown by reduction with diisobutylaluminum hydride[9] to pure dendrolasin 4[10] (54% yield), treatment of the *Z* aldehyde under identical conditions furnished a reproducible 60:40 mixture of 4 and sesquirosefuran 5[11] (57% yield). The ratio of 4 to 5 in the product mixture was easily determined by integration of the signals for the furan β protons in the NMR spectrum. It is thus shown that the butenolide synthesis is regiospecific only for the *E* aldehyde.



1 2 3

The reaction of 1 with Lewis acids was subsequently examined. Treatment of 1 with 2 equiv of stannic chloride in dry dichloromethane at −30 °C for 1 h gave in 60% isolated yield the desired monocyclic butenolide 6,[12] ac-

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