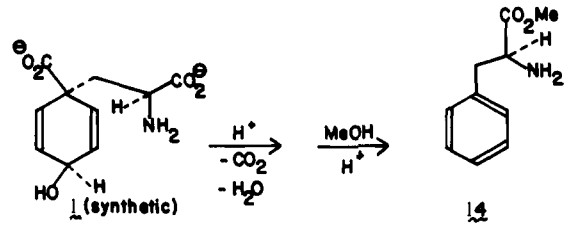

The total synthesis of optically pure arogenate from glutamate has thus been achieved. Furthermore, it appears that in this case, synthesis surpasses isolation in providing access to reasonable amounts of homogeneous material. It is hoped and expected that this synthesis will be helpful in designing experiments addressed to understanding the arogenate biosynthetic pathway.

Acknowledgment. This research was supported by P.H.S. Grant AI 16943-01. NMR measurements at 250 MHz were obtained on facilities supported by P.H.S. Grant RR-00296-11 for the Mellon Institute, Pitt, Carnegie (M.P.C.) Corporation. Those at 270 MHz were obtained through the auspices of the Northeast Regional N.S.F/N.M.R. Facility at Yale University supported by the N.S.F. Chemistry Division Grant C.H.F. 7916210. Additional support was forthcoming through an Andrew Mellon Predoctorial Fellowship to J.M. and an N.I.H. Postdoctoral Fellowship 06196-02 to L.A.C. The advice and encouragement of Professor Lolita Zamir of the State University of New York at Binghamton and the receipt from her of an authentic specimen sample of arogenate are gratefully acknowledged. We also acknowledge the valuable advice of Professor John Gerlt of Yale University in dealing with the chromatographic purification of synthetic arogenate.

(Trimethylsilyl)cyclopentene Annulation: A Regiocontrolled Approach to the Synthesis of Five-Membered Rings

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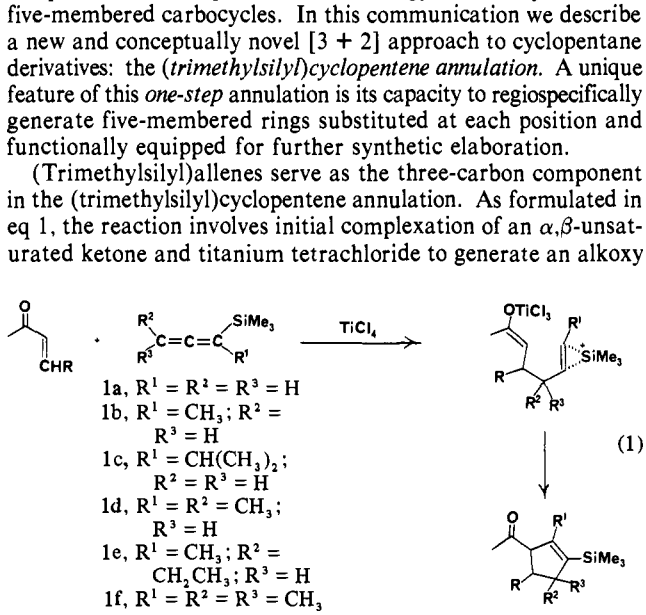
The identification of the prostaglandins and polyquinane natural products as important synthetic targets has stimulated the development of an impressive methodology for the synthesis of five-membered carbocycles. In this communication we describe a new and conceptually novel [3 + 2] approach to cyclopentane derivatives: the *(trimethylsilyl)cyclopentene annulation.* A unique feature of this *one-step* annulation is its capacity to regiospecifically generate five-membered rings substituted at each position and functionally equipped for further synthetic elaboration.

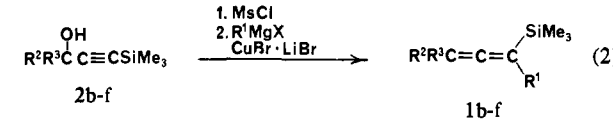
(Trimethylsilyl)allenes serve as the three-carbon component in the (trimethylsilyl)cyclopentene annulation. As formulated in eq 1, the reaction involves initial complexation of an α,β-unsaturated ketone and titanium tetrachloride to generate an alkoxy allylic carbocation. Regiospecific electrophilic substitution[1,2] of this cation at C_3 of the (trimethylsilyl)allene[3] provides a vinyl cation stabilized by interaction with the adjacent carbon–silicon bond. A 1,2 shift of the trimethylsilyl group[4,5] then affords an isomeric vinyl cation which is intercepted by the titanium enolate to produce a new five-membered ring.



1a, $R^1 = R^2 = R^3 = H$
1b, $R^1 = CH_3$; $R^2 = R^3 = H$
1c, $R^1 = CH(CH_3)_2$; $R^2 = R^3 = H$
1d, $R^1 = R^2 = CH_3$; $R^3 = H$
1e, $R^1 = CH_3$; $R^2 = CH_2CH_3$; $R^3 = H$
1f, $R^1 = R^2 = R^3 = CH_3$

(1)

The requisite 1-substituted (trimethylsilyl)allenes **1b–f** are easily obtained with a variety of substitution patterns employing the method of Westmijze and Vermeer (eq 2).[6,7] (Trimethylsilyl)-



(2)

allene itself is most conveniently prepared with the use of our previously reported procedure.[2a]

Table I delineates the scope of the (trimethylsilyl)cyclopentene annulation. In a typical reaction, 1.5 equiv of distilled titanium tetrachloride was rapidly added to a solution of methyl vinyl ketone and 1.0 equiv of allene **1b** in methylene chloride at −78 °C. The resulting red solution was stirred at −78 °C for 1 h, and the reaction was then quenched by addition of water and ether. Ether extraction furnished the (trimethylsilyl)cyclopentene **3**, obtained in 68–75% yield after chromatographic purification. The structure of the annulation product was established by spectral characterization[8] and conversion to 1-acetyl-2-methylcyclopentene.[9]

This last reaction illustrates the useful transformation of the annulation products to α,β-unsaturated ketones. Exposure of the (trimethylsilyl)cyclopentenes to either potassium carbonate in methanol or a dilute solution of hydrofluoric acid in acetonitrile at 25 °C results in isomerization followed by desilylation of the intermediate γ-trimethylsilyl α,β-unsaturated ketones. The vinylsilane moiety should serve as the basis for a variety of other interesting synthetic transformations of the initial annulation products.[1,10]

Both cyclic and acyclic enones participate in the (trimethylsilyl)cyclopentene annulation. α-Methylene ketones react to form spiro-fused systems. Molecular models indicate that the intermediates derived from acetylcyclohexene, cyclohexenone, and cyclopentenone are constrained to cyclize to cis-fused adducts.[11,12]

(1) For a review of electrophilic substitution of organosilicon compounds, see: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

(2) For previous examples of electrophilic substitution of (trimethylsilyl)allenes, see: (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. (b) Bourgeois, P.; Calas, R.; Merault, G. *J. Organomet. Chem.* **1977**, *141*, 23. Bourgeois, P. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1974**, *278*, 969. (c) Jellal, A.; Santelli, M. *Tetrahedron Lett.* **1980**, 4487.

(3) The C–Si bond in (trimethylsilyl)allenes is oriented cis coplanar to only the *allylic* π bond and thus can only afford direct stabilization to the transition state resulting from electrophilic substitution at C_3.

(4) For a review of 1,2-cationic rearrangements in organosilicon compounds, see: Brook, A. G.; Bassindale, A. R. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. II, pp 190–192.

(5) For a review of migration across the double bond of vinyl cations, see: Stang, P. J.; Rappaport, Z.; Hanack, M.; Subramanian, L. R. "Vinyl Cations"; Academic Press: New York, 1979; pp 459–483.

(6) Westmijze, H.; Vermeer, P. *Synthesis* **1979**, 390. We thank James T. Kadonaga for assistance in the preparation of these allenes.

(7) (Trimethylsilyl)propargylic alcohols **2d–f** were prepared by addition of (trimethylsilyl)acetylide to the requisite aldehydes and ketones.

(8) IR (film) 2957, 2910, 2850, 1708, 1615, 1350, 1250, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.06 (s, 9 H), 1.67 (m, 3 H), 2.00 (s, 3 H), 1.79–2.08 (m, 2 H), 2.33–2.58 (m, 2 H), 3.39 (t, 1 H, J = 7 Hz); mass spectrum *m/e* 196.1284 (M^+).

(9) Semicarbazone mp 220–220.5 °C, lit. mp 220–221 °C: Tabushi, I.; Fujita, K.; Oda, R. *Tetrahedron Lett.* **1968**, 4247.

(10) For a review of the chemistry of vinylsilanes, see: Fleming, I. In "Comprehensive Organic Chemistry"; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, pp 608–662.

(11) The coupling constants for the ring fusion protons in hydrindanes **4**, **13**, **16**, and **17** (J = 6.2–7.3 Hz) and bicyclo[3.3.0]octanes **7**, **19**, and **20** (J = 7.3–8.1 Hz) support the assignment of cis ring fusion stereochemistry in these compounds.[13]

(12) Epimerization of the kinetic products would not be expected to occur without significant isomerization to conjugated enones.[13]

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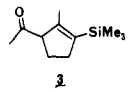
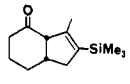
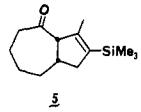
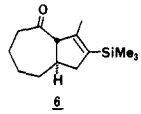
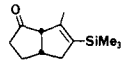
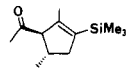
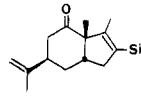
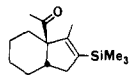
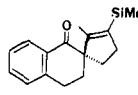
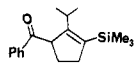
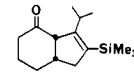
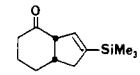
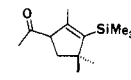
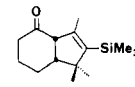
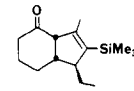
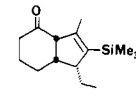
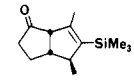
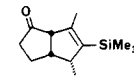
Table I. (Trimethylsilyl)cyclopentene Annulations

entry	α,β-unsaturated ketone	allene	(trimethylsilyl)-cyclopentene product[a]	yield,[b] %
1	methyl vinyl ketone	1b	 **3**	68–75
2	cyclohexenone	1b	 **4**	85
3	cycloheptenone	1b	 **5**	90–94
			 **6**	5:6 = 83:17
4	cyclopentenone	1b	 **7**	48
5	*trans*-3-penten-2-one	1b	 **8**	79
6	carvone	1b	 **9**	87
7	1-acetylcyclohexene	1b	 **10**	91
8	2-methylene-α-tetralone	1b	 **11**	80–84
9	phenyl vinyl ketone	1c	 **12**	69–73
10	cyclohexenone	1c	 **13**	81–85
11	cyclohexenone	1a	 **14**	17–19
12	methyl vinyl ketone	1f	 **15**	80
13	cyclohexenone	1f	 **16**	61–63
14	cyclohexenone	1e	 **17**	79
			 **18**	17:18 = 95:5
15	cyclopentenone	1d	 **19**	68
			 **20**	19:20 = 75:25

[a] Annulations were carried out with the use of 1.0–1.5 equiv of allene and 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 1 h (−20 °C, 2 h for entry 4). Reactions were quenched by rapid addition of ether and water. In the case of entries 12–15 this procedure resulted in partial conversion to enones, and an alternate procedure was consequently employed involving transfer of the reaction mixture by cannula to a rapidly stirred mixture of ether–water. [b] Isolated yields of purified products. IR, 250-MHz ^1H NMR, ^{13}C NMR (for most compounds), and mass spectral data were fully consistent with the assigned structures. High-resolution mass spectra were obtained for all new compounds.

Annulation with carvone afforded a single product (**9**);[13] the orientation of the isopropenyl group in this adduct was assigned by analogy with related conjugate additions to carvone.[14] Annulation with *trans*-3-penten-2-one also gave a single cycloadduct, tentatively identified as the trans isomer **8** on the basis of its ^1H NMR spectrum.[15] In contrast to the facile reaction of less hindered enones, β,β-disubstituted α,β-unsaturated ketones failed to combine with (trimethylsilyl)allenes under the usual annulation conditions.[16]

The (trimethylsilyl)cyclopentene annulation proceeds most efficiently with the use of 1-substituted (trimethylsilyl)allenes. The disappointing yield attending the reaction of (trimethylsilyl)allene itself (Table I, entry 11) is attributable to the relative instability of the terminal vinyl cation required in this case according to the mechanism proposed in eq 1. Fully substituted five-membered rings result from annulations employing allenes **1d-f**; reactions with **1f** proceed regiospecifically[17] to afford (trimethylsilyl)cyclopentenes containing quaternary centers. Also noteworthy is the stereoselectivity observed in reactions of allenes **1d–e** (Table I, entries 14 and 15).[18] Further studies are under

(13) Isomeric products were not detected in purified and crude reaction products by IR, ^1H NMR, or ^{13}C NMR (with the exception of entries, 3, 14, and 15).

(14) This assignment assumes antiparallel approach of allene from the less hindered face of the alkoxy allylic carbocation; Siscovic, E.; Rao, A. S. *Curr. Sci.* **1968**, *37*, 286.

(15) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; pp 287–289. Cyclopentene **8** exhibited ^1H NMR ($CDCl_3$, 250 MHz) δ 0.07 (s, 9 H), 0.99 (d, 3 H, J = 7.0 Hz), 1.65 (m, 3 H), 2.02 (s, 3 H), 1.95–2.06 (m, 1 H), 2.26–2.41 (m, 1 H), 2.70 (ddquint, 1 H, J = 2.2, 8.1, 16.1 Hz), 3.02 (d, 1 H, J = 4.6 Hz).

(16) No reaction occurred upon exposure of mesityl oxide and isophorone to excess allene **1b** at room temperature.

(17) Simple 1,1-disubstituted allenes undergo electrophilic substitution predominately at C_2; for a review, see ref 9, pp 153–167.

way in our laboratory to elucidate the mechanistic basis of this stereoselectivity and demonstrate the utility of the (trimethylsilyl)cyclopentene annulation in the synthesis of polyquinane natural products.

Acknowledgment. We thank the National Science Foundation for generous financial support.

(18) The stereochemistry of bicyclo[3.3.0]octanes **19** and **20** was assigned by analysis of carbon-13 spectral data.[19] ^{13}C NMR ($CDCl_3$) δ **19**: 21.7 (exo CH_3), 27.8 (C_3); **20**: 15.4 (endo CH_3), 21.8 (C_3).

(19) Whitesell, J. K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.

In Vitro Reactivity of the Meso and *dl* Dimers of the 3,5,5-Trimethyl-2-oxomorpholin-3-yl Radical with Adriamycin and Daunomycin

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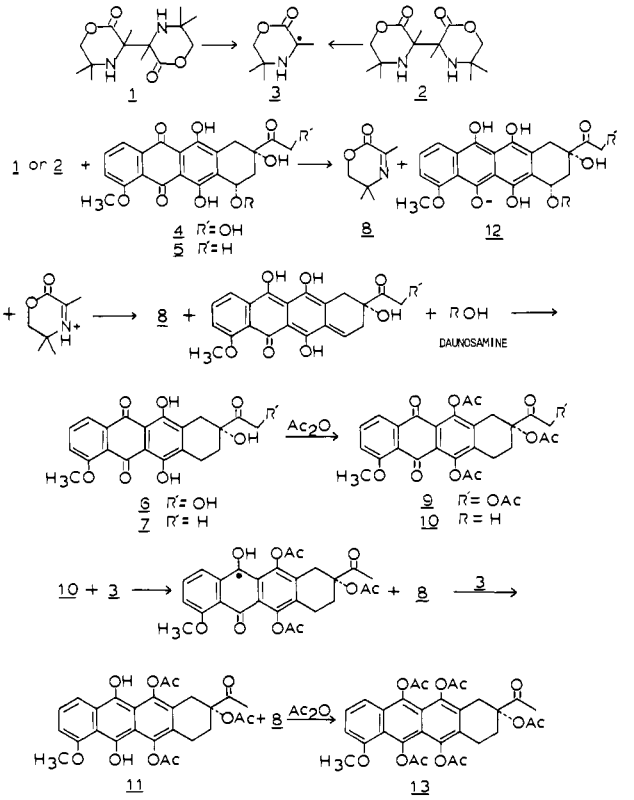
Received September 29, 1980

We have recently noted that the meso and *dl* dimers (**1** and **2**) of the 3,5,5-trimethyl-2-oxomorpholin-3-yl radical (**3**) dramatically reduce the toxicity in mice of the anthracycline, antitumor drug adriamycin hydrochloride (**4**).[1] This observation coupled with our recent report that **3**, which results from homolytic cleavage of **1** and **2**, reacts as a mild one-electron reducing agent[2] prompted us to study the in vitro reactivity of **1** and **2** with both adriamycin hydrochloride and daunomycin hydrochloride (**5**).

We now report that a mixture of the stereoisomeric radical dimers (**1** and **2**) react with adriamycin and daunomycin hydrochlorides in near quantitative yield to give the corresponding 7-deoxyaglycons (**6** and **7**) characterized as their tetraacetate and triacetate derivatives, respectively (**9** and **10**). The triacetate of **7** reacts further with **1** and **2** to give the hydroquinone **11** characterized as the pentaacetate **13**. This reactivity parallels the reactivity of adriamycin and daunomycin with nicotinamide adenine dinucleotide phosphate (NADPH) in rat liver microsomes and heart sarcosomes under anerobic conditions as proposed by Bachur and co-workers.[3,4] The reduction of daunomycin hydrochloride by the *dl* dimer **2** occurs faster than the rate of bond homolysis of **2** and is at least predominantly bimolecular.

A mixture of **1** and **2** in a freeze–pump–thaw degassed methanol solution reduced the anthracyclines **4** and **5** to their 7-deoxyaglycons **6** and **7** in excellent yields. In a typical experiment 2 equiv of the radical dimers and 1 equiv of anthracycline in absolute methanol were reacted in the dark at ambient temperature for 1 h. The 7-deoxyaglycons precipitated as red crystalline solids and were collected in greater than 90% yield. The only product observed by ^1H NMR spectroscopy from the dimers was 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**8**).[5] The 7-deoxyaglycons were characterized as their tetraacetate and triacetate derivatives, respectively (**9** and **10**). The derivatives were prepared in greater than 87% yield by reaction of the 7-deoxyaglycons with acetic anhydride in dry pyridine. The tetraacetate and triacetate were identical in all respects with those prepared by catalytic hydrogenation of adriamycin (**4**) followed by acetylation[6] and sodium dithionite reduction of daunomycin (**5**) followed by acetylation.[7]

Scheme I



The 7-deoxyaglycons appeared to react further with the dimers **1** and **2** in methanol solvent. The reaction was slow due in part to the low solubility of **6** and **7**. Consequently, this reactivity was examined further by using the triacetate of the 7-deoxyaglycon of daunomycin (**10**) which is soluble in organic solvents. An NMR sample tube was charged with a deuteriochloroform solution of **1**, **2**, and **10**, freeze–pump–thaw degassed, and sealed. When the solution was left in the dark for several hours at 25 °C it became visibly fluorescent. The ^1H NMR spectrum indicated that the dimer had oxidized to **8** and that **10** had disappeared. When the sample was exposed to air, the fluorescence rapidly disappeared and the 7-deoxyaglycon triacetate reappeared as indicated by ^1H NMR spectroscopy. When the reaction of **10** with **1** and **2** was allowed to occur in the presence of acetic anhydride and a catalytic amount of dry pyridine, the pentaacetate **11** was formed, isolated in 53% yield as a stable yellow crystalline material (mp 148 °C dec), and characterized from spectral data.[8]

The hydrogenolysis of adriamycin and daunomycin most likely proceeds via formation of the anion **12** as shown in Scheme I. Elimination followed by tautomerization gives the 7-deoxyaglycons and an amino sugar, daunosamine, which was not isolated or characterized. Initially we presumed that anion **12** was formed by electron transfer followed by proton transfer from two oxomorpholinyl radicals **3**, analogous to the mechanism for reaction of **3** with other substrates as proposed earlier.[2,9] We also presumed that the rate-controlling step would be homolysis of the radical dimer (Scheme I) as observed in the reaction between the radical dimers and *N*-methylisatin.[9]

The hydrogenolysis of daunomycin hydrochloride (**5**) by the *dl* dimer **2**, however, proceeds at least eight times faster than the

(1) Banks, A.; Jones, T.; Koch, T. *Cancer Treat. Rep.*, submitted for publication.

(2) Burns, J. M.; Wharry, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1979**, *101*, 2750.

(3) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Mol. Pharmacol.* **1977**, *13*, 901.

(4) Bachur, N. R.; Gordon, S. L.; Gee, M. V. *Cancer Res.* **1978**, *38*, 1745.

(5) Koch, T. H.; Olesen, J. A.; DeNiro, J. *J. Org. Chem.* **1975**, *40*, 14.

(6) Arcamone, F.; Franceschi, G.; Penco, S. *Tetrahedron Lett.* **1969**, 1007.

(7) Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653.

(8) The pentaacetate **13** gave the following spectral absorptions: IR ($CHCl_3$) 5.66 (br) and 5.76 (br) μm; UV (CH_3OH) (log ϵ) 266 (5.6), 356 (4.2), 375 (4.4), 395 (4.4), and 417 nm (4.3); ^1H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.16 (s, 3 H), 2.36–2.46 (overlapping s, 12 H), 2.56–3.30 (m, 4 H), 6.63–7.53 (m, 3 H); mass spectrum (70 eV), *m/e* (relative intensity) 594.9 (12), 553.0 (9), 512.0 (8), 511.0 (25), 468.8 (24), 408.8 (16), 366.8 (27), 365.7 (35), 324.6 (12), 323.6 (39), 43 (100).

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