Acknowledgment. We thank the National Cancer Institute of the National Institutes of Health for their generous support of our programs. Dr. P. Buhlmayer performed some of the model studies associated with this route.

Registry No. (±)-**2**, 87037-55-6; (±)-**9**, 65861-37-2; **10**, 86971-73-5; (±)-**11**, 86971-74-6; (±)-**12**, 82517-60-0; (±)-**13**, 87037-56-7; (±)-**14**, 86993-52-4; **15**, 86971-75-7; **16**, 86971-76-8; **17**, 86971-77-9; **18**, 86971-78-0; (±)-**20**, 86971-79-1; (±)-**20** acetate, 86971-80-4; (±)-**21**, 83124-70-3; **23**, 83124-87-2; **24**, 86971-82-6; **25**, 86971-83-7; (±)-**26**, 86993-53-5; **27**, 86971-84-8; **28**, 86971-85-9; CH_3CHO, 75-07-0; CCl_3COCl, 76-02-8; cyclopropyldiphenylsulfonium fluoroborate, 33462-81-6; dihydropyran, 110-87-2.

Supplementary Material Available: Structures and experimental data for **13**, **17**, **20**, **21**, **26**, and **2** (2 pages). Ordering information is given on any current masthead page.

An Umpolung of Allyl Bis(silanes). Tandem [6.5] Annulations via a Biallyl Equivalent

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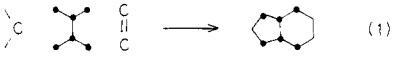
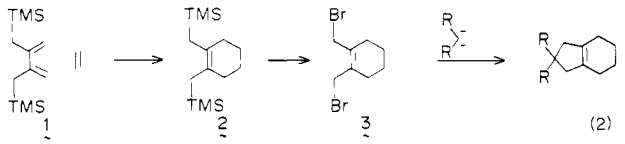
The widespread occurrence of [6.5] ring systems in natural products stimulates the development of new strategies.[1] A potentially very flexible approach envisions a two-stage "cycloaddition" methodology of a two and subsequently a one carbon fragment to a biallyl skeleton as outlined in eq 1. The convenience



(1)

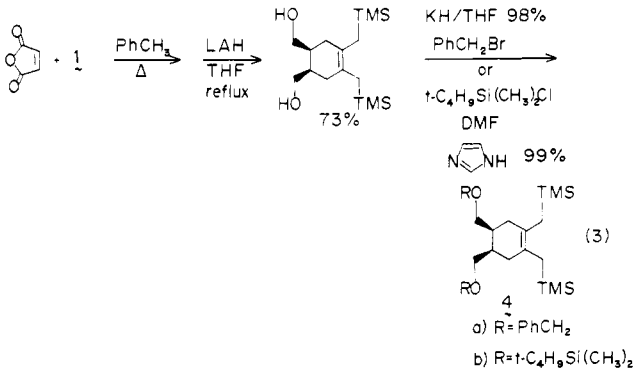
and ease of handling of 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene (**1**)[2] and the ability to manipulate the intermediate **2** prior to creation of the reactive dibromide **3**[3] suggested the sequence outlined in eq. 2. The key to this sequence was to devise a method



(2)

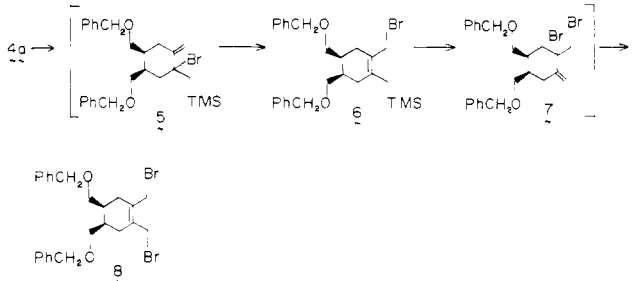
to effect an umpolung of the allylbis(silane) **2** *without allyl inversion.* We wish to record a simple solution to this problem and its utility in forming [6.5] ring systems especially with respect to the use of bis(phenylsulfonyl)methane in cycloalkylations.

We chose the dibenzyl ether **4**, which derives from the adduct of **1** and maleic anhydride according to eq 3, as a model in which the key was envisioned to be the rearrangement of allyl bromides



(3)

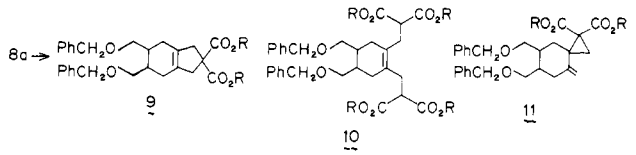
5 and **7** to the thermodynamically more stable isomers **6** and **8**.



Reacting 2 equiv of freshly recrystallized NBS with **4** in THF in the presence of propylene oxide at -78 to 0 °C indeed gave a 47% yield of **8**. Believing the presence of trimethylsilyl bromide may improve the rearrangement of **5** to **6** and/or **7** to **8** led us to use bromine with the result of a slight improvement in yield to 57%. The ability of cupric bromide to serve as a brominating agent[4] led us to explore the possibility that allylsilanes might also be brominated by this reagent. If an allylcopper species is involved, the regioselectivity of the bromination might be independent of the structure of the allysilane. Indeed, addition of a catalytic amount of cupric bromide to the bromination reaction dramatically improved the yield of **8** to 82%.

Experimentally, 1 equiv of bromine in carbon tetrachloride is added to a solution of 1 equiv of the bis(silane), 10 equiv of propylene oxide, and 1 mol % cupric bromide in THF at -78 °C (15 min). After warming to 0 °C (15 min) and recooling to -78 °C, an additional 1 equiv of bromine in carbon tetrachloride is added (15 min) and the mixture warmed to 0 °C (15 min). The reaction is quenched with sodium sulfite and worked up in standard fashion. Table I summarizes the results. The chemoselectivity is noteworthy in that ester, ketone, amide, and *tert*-butyldimethylsilyl ether groupings all are compatible. Most remarkably, the dihydro aromatic ring of entry 7 does not aromatize under the reaction conditions.

The use of such dibromides in cycloalkylation with malonic esters[5] showed a surprising dependence on the choice of the ester of the malonate. In all cases, to minimize or avoid the dialkylation product **10**, the malonate was added dropwise to a mixture of NaH and the dibromide **8a** in DMF. With dimethyl malonate, a



mixture of the cyclopentene **9** and the cyclopropanes **11** was

(1) Outside the obvious natural products such as steroids, which provided much of the stimulus in this field, a few recent cases of terpenes illustrate the widespread occurrence of such structural fragments and the need for new methodology. Stearylvelutinal: Favre-Bonvin, J.; Gluchoff-Fiasson, K.; Bernillon, J. *Tetrahedron Lett.* **1982**, *23*, 1907. Melleolide: Midland, S. L.; Izac, R. R.; Wing, R. M.; Zaki, A. I.; Mannecke, D. E.; Sims, J. *Ibid.* **1982**, *23*, 2515. Sterpuric acid: Ayer, W. A.; Saeedi-Ghomi, M. H.; van Engen, D.; Tagle, B.; Clardy, J. *Tetrahedron Suppl.* **1981**, *No. 9*, 379. Alliacolide and dihydrobotrydial: Hanson, J. R. *Pure Appl. Chem.* **1981**, *53*, 1155. Broderol: Ayer, W. A.; McCaskill, R. H. *Can. J. Chem.* **1981**, *59*, 2150. Merulidial: Quack, W.; Anke, T.; Oberwinkler, F.; Giannetti, B. M.; Steglich, W. *J. Antibiot.* **1978**, *31*, 737. Calomelanolactone: Bardouille, V.; Mootoo, B. S.; Hirotsu, K.; Clardy, J. *Phytochem.* **1978**, *17*, 275. Isolactarorufin: Daniewski, W. M.; Kocor, M.; Thoren, S. *Pol. J. Chem.* **1978**, *52*, 561.

(2) Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 4299.

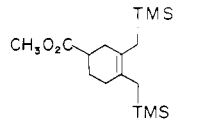
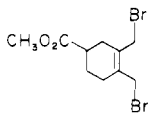
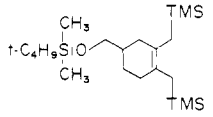
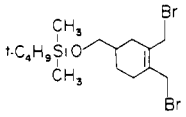
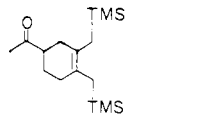
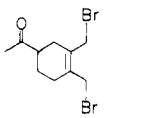
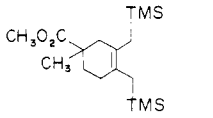
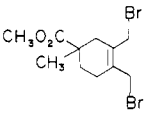
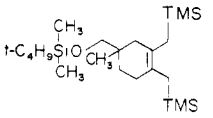
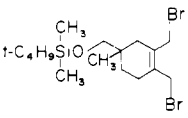
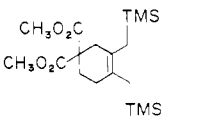
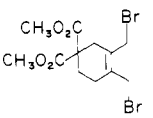
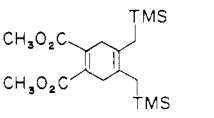
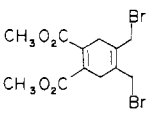
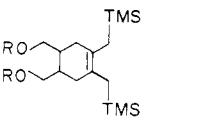
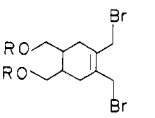
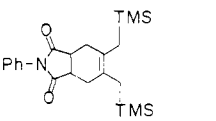
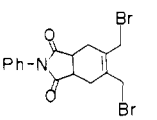
(3) Cf: Gaoni, Y.; Sadeh, S. *J. Org. Chem.* **1980**, *45*, 870. Hamon, D. P. G.; Spurr, P. R. *Synthesis* **1981**, 878. Bellus, D.; von Bredaw, K.; Sauter, M.; Weiss, C. D. *Helv. Chim. Acta* **1973**, *56*, 3004. Zahierezhy, V.-I.; Musso, H. *Justus Liebigs Ann. Chem.* **1973**, 1777. Butler, G. B.: Ottenbride, R. M. *Tetrahedron Lett.* **1967**, 4873.

(4) For example, see: Haruta, A. M.; Satoh, J. Y. *Chem. Lett.* **1980**, 473. Kojima, Y.; Usui, K.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3127. Kosower, E. M.; Cole, W. J.; Wu, G.-S.; Cardy, D. E.; Meisters, G. *J. Org. Chem.* **1963**, *28*, 630. Nonhebel, D. C.; Russell, J. A. *Tetrahedron* **1970**, *26*, 2781.

(5) For a recent study of this type of reaction and its problems see: Oediger, H.; Moller, F. *Justis Liebigs Ann. Chem.* **1976**, 348.

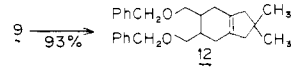
0002-7863/83/1505-6757$01.50/0

Table I. Conversion of Bis(silanes) to Dibromides[a]

entry	bis(silane)	dibromide	yield
1			35
2			86
3			41
4			66
5			80
6			83
7			73[b]
8	 4a, R = CH_2Ph	 8a, R = $PhCH_2$	82
9	4b, R = $Si(CH_3)_2C_4H_9$-*t*	8b, R = $Si(CH_3)_2C_4H_9$-*t*	80
10			81[c]

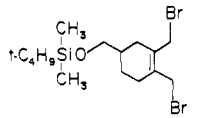
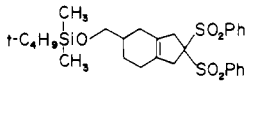
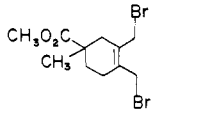
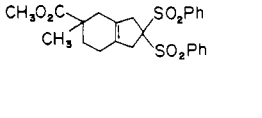
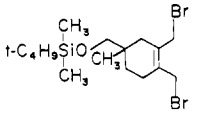
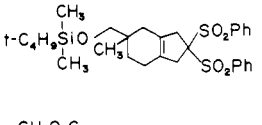
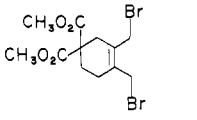
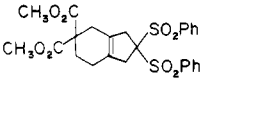
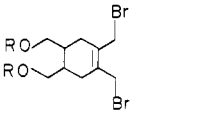
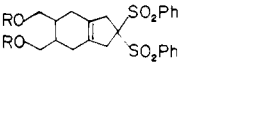
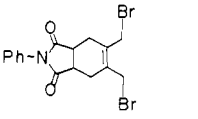
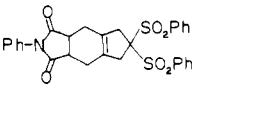
[a] All new compounds have been fully characterized by spectral means and elemental composition determined by high-resolution mass spectrometry and/or combustion analysis. [b] Mp 74–75 °C (hexane) (lit.[11] mp 76–76 °C). [c] Mp 166–167.5 °C (C_2H_5OH).

produced. With diisopropyl or di-*tert*-butyl malonate, the dialkylation product **10** formed in yields up to 30% regardless of variation of experimental conditions. On the other hand, diethyl malonate gave the desired cyclopentene in 64% yield. This dependence on the ester correlates with the steric demands of the ester. The common occurrence of a *gem*-dimethyl group in many natural products led us to perform the conversion of **9** to **12**, which proceeded, via standard methods,[6] in excellent overall yield.



In contrast to the malonates, bis(phenylsulfonyl)methane (**13**) smoothly led to cyclopentene products by simply mixing the dibromide with **13** in DMF in the presence of sodium hydride as summarized in Table II. Dialkylation and cyclopropane formation

Table II. Cycloalkylation with Bis(phenylsulfonyl)methane[a]

entry	dibromide	cyclopentene	yield, %
1			84[b]
2			75[c]
3			96
4			69[d]
5	 8a, R = CH_2Ph	 13a, R = CH_2Ph	85[e]
6	8b, R = *t*-$C_4H_9Si(CH_3)_2$	13b, R = *t*-$C_4H_9Si(CH_3)_2$	80[f]
7			88[g]

[a] All new compounds have been fully characterized by spectral means including determination of elemental composition by high-resolution mass spectroscopy and/or combustion analysis. [b] Mp 156.5–157 °C (hexane). [c] Mp 47–49 °C (hexane). [d] Mp 205–206.5 °C (CH_3OH-$CHCl_3$). [e] Mp 45–47 °C (C_2H_5OAc-hexane). [f] Mp 163–163.5 °C (hexane). [g] Mp 233–234.5 °C (C_2H_5OH-$CHCl_3$).

were not observed. The unexpected and extraordinary efficiency of bis(phenylsulfonyl)methane to participate in cycloalkylation reactions points to the need for a more detailed study of the use of a sulfone group to facilitate cyclizations.[7,8] In the present case, while the steric bulk of the phenylsulfonyl group might account for the formation of the cyclopentene ring over the cyclopropane ring, it would not seem to account for the absence of any dialkylation. The results with the malonates suggest that increasing steric bulk favors dialkylation over cyclo-monoalkylation–a seeming incongruity. While the explanation is not yet apparent, the synthetic efficiency and utility of the geminal phenylsulfonyl group for cyclizations is proven.

The utility of the bis(phenylsulfonyl) group for further structural elaboration was specifically demonstrated with **13a**. Limited quantities of Na(Hg) in the absence of buffer smoothly monodesulfonylated **13a** to give **14**; whereas, excess Na(Hg) in the presence of disodium acid phosphate converted the bis(sulfonyl) carbon directly to a methylene group to produce the simple cyclopentene **15**.[9] In addition, oxidation of the anion derived from **14** produces the cyclopentenone **16**.[10]

The ability to invert the reactivity of an allyl bis(silane) combined with cycloalkylation offers a new dimension to annulations. As summarized in eq 4, tandem formation of a bicyclo[6.5]nonene,

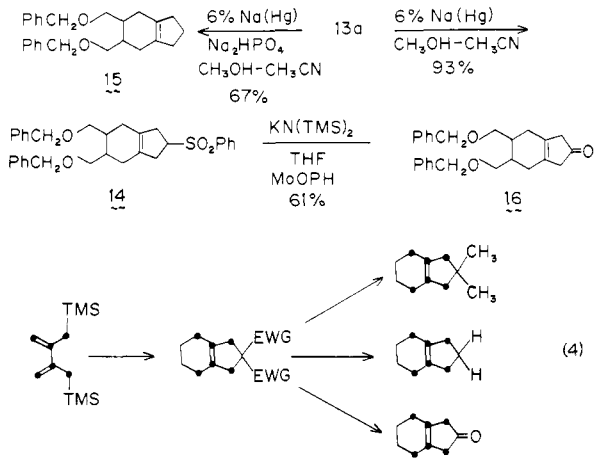
(6) The sequence involved (i) LAH, THF 0–50 °C; (ii) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2; (iii) $NaBH_4$, sulfolane, 100 °C. For the last reaction, see: Hutchins, R. O. *J. Org. Chem.* **1978**, *43*, 2259.

(7) For reviews on sulfone chemistry, see: Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. Durst, T. *Compr. Org. Chem.* **1979**, *2*, 171.

(8) For an unusual effect of the bis(phenylsulfonyl) group for Pd-catalyzed cyclizations see: Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940.

(9) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(10) Little, R. D.; Myong, E. O. *Tetrahedron Lett.* **1980**, 3339.



which has the flexibility of creating a diverse array of important substitution patterns, was developed. Other ring sizes may also be generated by simple modification of the conjunctive reagents. Thus, the [6 + *m* + *n*] bicycloannulation [(6 + 2 + 1) for the case of equ 4] may offer useful strategies toward important synthetic targets.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health–General Medical Sciences for their generous support of our programs.

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Allosteric Effects: Structural and Thermodynamic Origins of Binding Cooperativity in a Subunit Model

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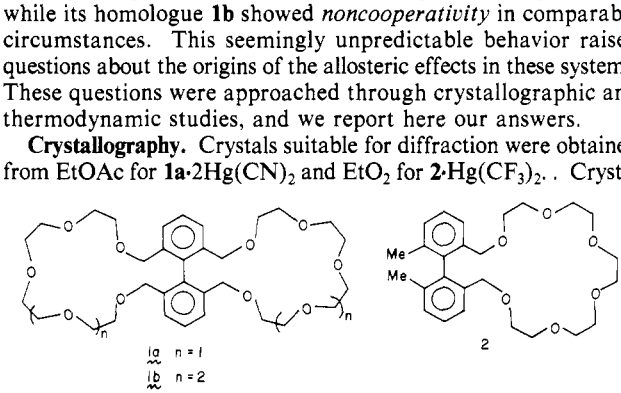
We recently introduced the macrobicyclic ethers **1** as models for the allosteric effects shown by subunit enzyme systems.[1] The binding of organomercurials to **1a** showed *positive cooperativity*, while its homologue **1b** showed *noncooperativity* in comparable circumstances. This seemingly unpredictable behavior raised questions about the origins of the allosteric effects in these systems. These questions were approached through crystallographic and thermodynamic studies, and we report here our answers.

Crystallography. Crystals suitable for diffraction were obtained from EtOAc for **1a**·2Hg(CN)$_2$ and Et$_2$O for **2**·Hg(CF$_3$)$_2$. . Crystal



data for **1a**·2Hg(CN)$_2$: $C_{36}H_{46}Hg_2N_4O_{10}$, M_r 1096.0, space group $P2_1/c$, a = 10.283 (1) Å, b = 25.263 (3) Å, c = 16.753 (2) Å, β = 110.10 (1)°, Z = 4. For **2**·Hg(CF$_3$)$_2$: $C_{28}H_{36}HgF_6O_6$, M_r 783.2, space group $P\bar{1}$, a = 11.532 (2) Å, b = 17.497 (3) Å, c = 8.245 (2) Å, α = 98.4 (2)°, β = 107.0 (2)°, γ = 98.1 (2)°, Z = 2. Data for both were collected with a Syntex $P2_1$ diffractometer with CuKα radiation, and unique reflections with $I > 2\sigma(I)$ [3500 for **1a**·2Hg(CN)$_2$, 4275 for **2**·Hg(CF$_3$)$_2$] were used in the structure solutions (heavy atom method) and least-squares refinement (ultimately with anisotropic thermal parameters for all non-hydrogen atoms).[2] Convergence was reached at R = 0.067 for **1a**·2Hg(CN)$_2$ and 0.073 for **2**·Hg(CF$_3$)$_2$. Positional and thermal parameters for all atoms are in Tables I–VI (supplementary material).

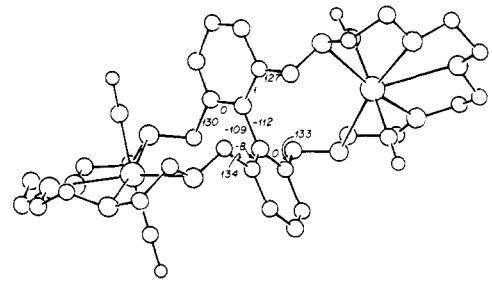


Figure 1. **1a**·2Hg(CN)$_2$.

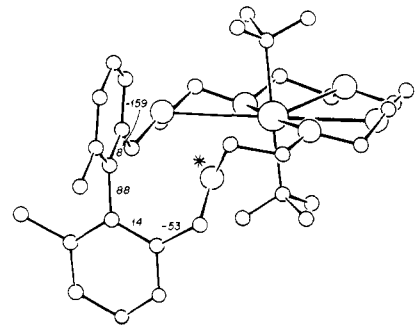


Figure 2. **2**·Hg(CF$_3$)$_2$. Computer-generated perspective drawings of the complexes; hydrogen atoms have been omitted for clarity. The uncoordinated benzyl oxygen in **2** is marked with an asterisk and selected endocyclic torsion angles are indicated on the figure.

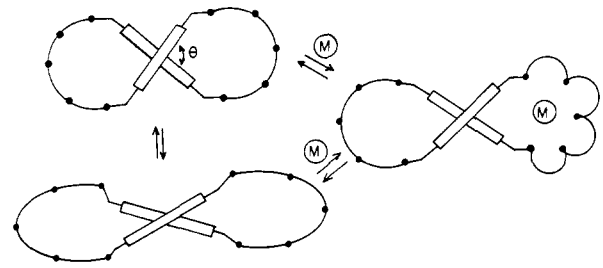


Figure 3.

Figures 1 and 2 reveal that while *all* of the ethereal oxygens are involved in binding Hg(CN)$_2$ to **1a**, only five of the six oxygens are involved in binding the Hg(CF$_3$)$_2$ to the 22-membered **2**. The uncoordinated benzyl oxygen atom in **2** lies significantly out of the plane of the other oxygen atoms and at a distance of 3.45 Å from the Hg atom (as compared to the other Hg–O distances of 2.84–3.12 Å).

Thermodynamic Origins. In order to determine whether the cooperativity shown by **1a** to Hg(CN)$_2$ arises from entropic or enthalpic effects, we examined the binding as a function of temperature. The question reduces to the temperature dependence of the *ratio* K_1/K_2, a value that can be obtained directly from the NMR spectra as previously described.[1] This ratio was determined

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(2) All crystallographic calculations were carried out on a VAX 11/780 computer. The principal programs used were FMLS, anisotropic full-matrix least-squares refinement (Ganzel, P. L., Sparks, R. A.; Trueblood, K. N., UCLA; modified by McPhail, A. T., Duke University), and ORTEP, crystallographic illustration programs (Johnson, C. K., Oak Ridge, ORNL-3794).

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