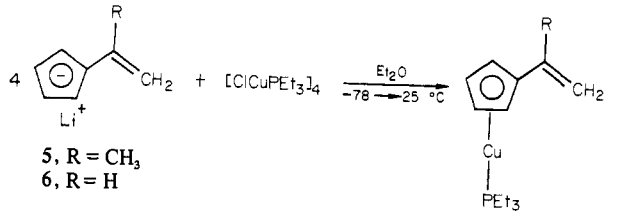

5, R = CH_3
6, R = H

16, R = CH_3 (66%)
17, R = H (90%)

and polymers. Polymerization studies of these monomers under free-radical or cationic conditions are leading to a better understanding of how the organometallic moiety affects vinyl polymerization. Further investigations along these lines are in progress in our laboratories.

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Registry No. 5, 77060-52-7; **6**, 80339-97-5; **7**, 80339-98-6; **8**, 80339-99-7; **9**, 80340-00-7; **10**, 80340-01-8; **11**, 80340-02-9; **12**, 73231-00-2; **13**, 12145-96-9; **14**, 80340-03-0; **15**, 80340-04-1; **16**, 80340-05-2; **17**, 80340-06-3; (η^5-CH_2=CHC_5H_4)-η^5-$C_5H_5Ti(CO)_2$, 80340-07-4; 6,6-dimethylfulvene, 2175-91-9; lithium diisopropylamide, 4111-54-0; η^5-cyclopentadienyltrichlorotitanium, 1270-98-0; molybdenum hexacarbonyl, 13939-06-5; tris(dimethylformamide)tricarbonyltungsten, 59561-69-2; $Co_2(CO)_8$, 10-210-68-1; $[Rh(CO)_2Cl]_2$, 14523-22-9; $[ClCuPEt_3]_4$, 55606-52-5; 6-methylfulvene, 3839-50-7.

Ion Pair Effects in an Intercalation Process. An Approach to the Bicyclo[5.3.1]undecyl System of Taxane

Barry M. Trost* and Henk Hiemstra

McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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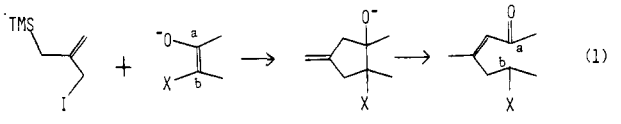
Bifunctional reagents such as **1** containing electrophilic and nucleophilic reaction centers which do not self-annihilate offer a unique approach to ring formation.[1,2] The presence of an

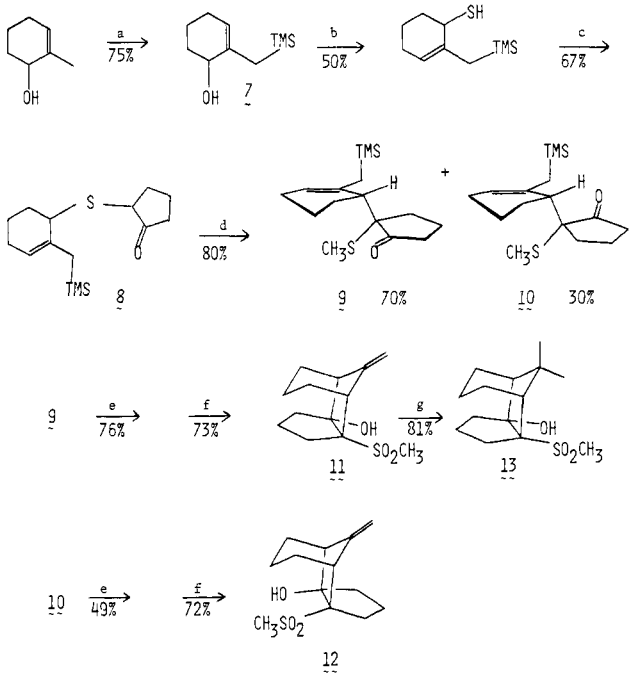


(1)

1 **2** **3**

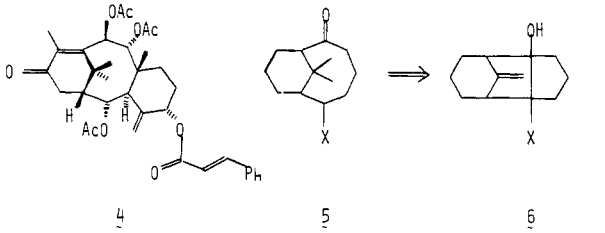
electron-withdrawing group in **2** (i.e., X = EWG) induces fragmentation of the initial adduct **3** and thus constitutes a three-carbon intercalation[3] between C(a) and C(b) (see eq 1).[2] In conjunction with a synthesis of the taxane system[4,5] (e.g., taxinine

Scheme I. Synthesis of Fragmentation Substrates[a]



[a] (a) (i) n-C_4H_9Li, TMEDA, hexane, room temperature. (ii) Me_3SiCl, 0 °C. (iii) 1% H_2SO_4, H_2O, THF, room temperature. (b) (i) n-C_4H_9Li, ether, CS_2, CH_3I, room temperature, then warm to 60 °C neat. (ii) LAH, ether, reflux. (c) NaH, 2-chlorocyclopentanone, DMF, 0 °C, room temperature. (d) KH, DME, reflux, 1.5 min, then room temperature, CH_3I. (e) m-CPBA, CH_2Cl_2, $NaHCO_3$, H_2O, 0 °C. (f) $C_2H_5AlCl_2$, $PhCH_3$, room temperature. (g) (i) CH_2I_2, $(C_2H_5)_2Zn$, $PhCH_3$, dry air, 50-55 °C. (ii) H_2, PtO_2, HOAc.

4), we envisioned application of this strategy in which the critical step is the fragmentation of **6** to create the very sterically congested 11,11-dimethylbicyclo[5.3.1]undecyl system **5**. The factors that govern this type of fragmentation reaction remain to be established. We wish to report an unusual ion pair effect on this fragmentation, the utilization of the ability to invert thermodynamic acidities and thereby control the course of a reaction and the successful realization of the synthesis of the critical bridged bicyclic ring system of the taxane nucleus.



4 **5** **6**

Scheme I outlines the synthesis of the fragmentation substrates **11-13**. The bifunctional conjunctive reagent **7**[6] smoothly formed by the direct metalation approach.[1a] Since attempts to effect direct displacement of leaving groups derived from alcohol **7** failed, the requisite C-C bond was formed via sigmatropic rearrangements—initially an O → S conversion via a [3.3] rearrangement of the xanthate[7] and then a S → C conversion via a [2.3] rearrangement of a sulfur stabilized carbanion derived from **8**.[6,8] The great facility of these rearrangements should be noted

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(3) As suggested by a referee, in order to avoid confusion with the use of the term intercalation in nucleic acid chemistry, we are using intercalation to mean insertion of atoms *in a covalent manner* into an existing ring or chain.

(4) For a review, see: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(5) For formation of a bicyclo[5.3.1]undecanyl system, see: Prelog, V.; Barman, P.; Zimmermann, M. *Helv. Chim. Acta* **1949**, *32*, 1284. Roth, W. R.; Erker, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 503. Levine, S. G.; McDaniel, R. L., Jr. *J. Org. Chem.* **1981**, *46*, 2199. Kahn, M. *Tetrahedron Lett.* **1980**, 4547.

(6) This compound has been fully characterized by spectral means and has a satisfactory elemental composition determined by either high-resolution mass spectroscopy or combustion analysis.

(7) Taguchi, T.; Kawazoe, Y.; Yoshihira, K.; Kanayama, H.; Mori, M.; Tabata, K.; Harano, K. *Tetrahedron Lett.* **1965**, 2717. Ferrier, R. J.; Vethaviyasar, N. *Chem. Commun.* **1970**, 1385. Also see: Hackler, R. E.; Balko, T. W. *J. Org. Chem.* **1973**, *38*, 2106. Nakai, T.; Mimura, T.; Kurokawa, T. *Tetrahedron Lett.* **1978**, 2895.

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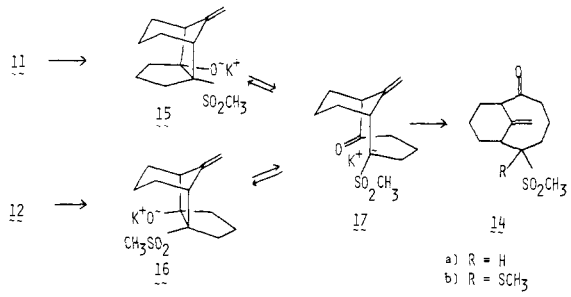
and may reflect the propensity of the substituents to be axial as a result of A strain[9] with the trimethylsilylmethyl substituent. Consideration of the steric interactions in these rearrangements led to the assignment of the *S*,R** configuration to **9**. Subsequent reactions support this assignment (vide infra). While attempts to effect cyclization of the sulfones related to **9** and **10**[6] with fluoride ion were unsatisfactory,[2] Lewis acid initiated cyclization proceeded smoothly to generate **11**[6] (mp 179–180 °C) from **9** and **12**[6] (mp 104–106 °C) from **10**. Subsequent base-catalyzed equilibration showed that **12** is thermodynamically more stable than **11** in accord with the cyclopentane ring being endo in **11** and exo in **12**, further evidence for the stereochemical assignments of **9** and **10**. Conversion of the exocyclic methylene group of **11** to a gem-dimethyl group employed the Furukawa modification of the Simmons–Smith reaction[10] to give a crystalline cyclopropane,[6] mp 104–107 °C, followed by hydrogenolysis of the least hindered cyclopropyl bond[11] to give **13**[6] as beautiful needles, mp 119–120 °C. The facility of cyclopropanation of **11** relative to **12** as a result of participation of the hydroxyl group in **19** provides further evidence for the stereochemical assignments.[12] Thus, this strategy permits creation of the gem-dimethyl group in the sterically less crowded environment offered by the tricyclic skeleton before embedding it in the subsequent cyclooctyl ring.

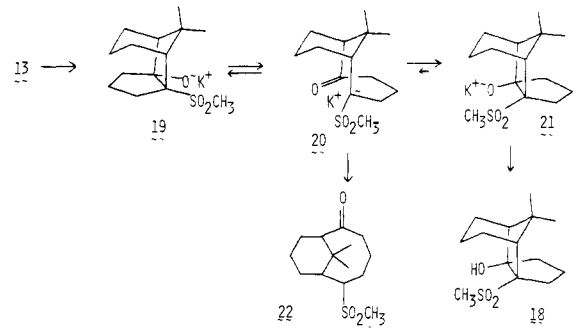
With the requisite substrates **11**, **12**, and **13** in hand, their fragmentation was examined. Treatment of **11** or **12** with KH in DME followed by protonation led to a mixture of **12** and **14a**[6] in a ratio 4:1. This ratio showed remarkable sensitivity to the



presence of cation complexing agents—changing to 1:1 by the addition of 1 equiv of 18-crown-6[13] and reversing to 1:9 by the addition of [2.2.2]-cryptand.[14] These results are nicely accommodated by correlating the product ratio with the thermodynamic stability of the intermediates **15**–**17**. Of the two closed forms **15** and **16**, the latter is greatly preferred since it minimizes nonbonded interactions. In the absence of crown or cryptand, the tight ion pair is more stable in the closed form **16** than in the open form **17** due to the stronger O–K bonding compared to C–K bonding. As one goes from a tight ion pair to a solvent separated ion pair by addition of crown or cryptand, the equilibrium shifts toward **17** due to the greater polarizability of the sulfone group compared to oxygen and thus its ability to stabilize the negative charge. This reordering of anion stability as a function of "solvation" effects correlates nicely with the differential response of the thermodynamic acidity of weak oxygen acids and weak carbon acids to solvation effects.[15]

Support for this interpretation derives from two experiments. Selective reaction of **17** would shift the equilibrium toward the open product. Indeed, addition of dimethyl disulfide to the reaction of **11** or **12** with KH in DME led to **14b**[6] (mp 137–139 °C) in addition to a small amount of **14a** which appeared to derive from the presence of adventitious amounts of water in the disulfide. More dramatic was the effect of only a catalytic amount of base. With 0.2 equiv of KOC_4H_9-*t* in Me_2SO, **11** or **12** fragmented to a single isomer of **14a** in 95% yield. Under these conditions, one is equilibrating the neutral molecules which apparently cleanly favors the open form. *Thus, by equilibrating ion pairs or neutral compounds, complementary results pertain and control to either the closed or open forms can be exercised.*

Changing to the dimethyl series **13** causes a dramatic effect on the equilibrium ratio of the ion pairs. KH, in the absence or presence of 18-crown-6 or [2.2.2]-cryptand, led only to endo–exo equilibration. Employment of 2.0 equiv of KOC_4H_9-*t* in Me_2SO



also only isomerized **13** to **18**,[6] mp 136–137 °C. The steric congestion created by inserting a gem-dimethyl group into the center of the eight-membered ring in **20** appears sufficient to shift the equilibria among **19**, **20**, and **21** completely to **21**. Nevertheless, a *catalytic* amount of KOC_4H_9-*t* in Me_2SO quantitatively converted **13** into the fragmented product **22**[6] (mp 156–158 °C). While the equilibrium among the ion pairs favors the closed form, equilibration of the neutral molecules still strongly favors the open form.

These results indicate the utility of the delicate balance that exists among the factors affecting the relative stability of ion pairs.[16,17] In the first series (**15**, **16**, **17**), the degree of association of the cation with the alkoxide dominates—the tighter the association the more the charge wants to localize on oxygen. While this effect must also operate in the latter series (**19**–**21**), a steric effect is superimposed and dominates. In both cases, the factors which dominate the equilibria in the ions are decoupled from those which dominate the equilibria in the neutral compounds.

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Registry No. **7**, 80359-70-2; **8**, 80359-71-3; **9**, 80359-72-4; **10**, 80359-73-5; **11**, 80359-74-6; **12**, 80408-19-1; **13**, 80359-75-7; **14a**, 80359-76-8; **14b**, 80359-77-9; **18**, 80408-20-4; **22**, 80359-78-0; 2-methyl-2-cyclohexen-1-ol, 20461-30-7; 2-(trimethylsilylmethyl)-2-cyclohexen-1-thiol, 80359-79-1.

Supplementary Material Available: Spectral data of compounds **11**–**14**, **18**, and **22** (2 pages). Ordering information is given on any current masthead page.

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