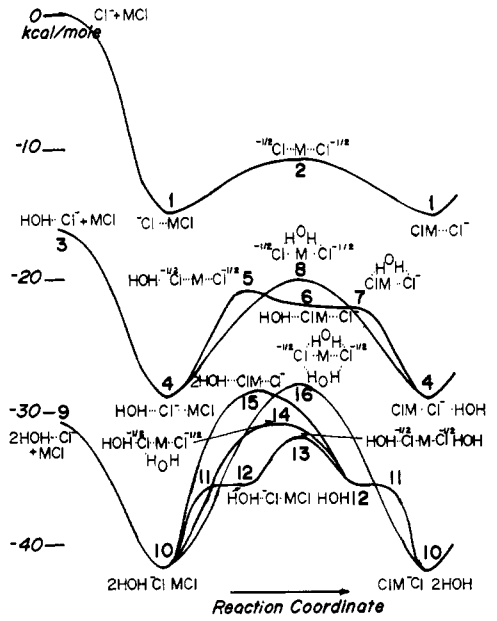

Figure 1. Profiles of the potential-energy surfaces. The energy is relative to isolated molecules and ions.

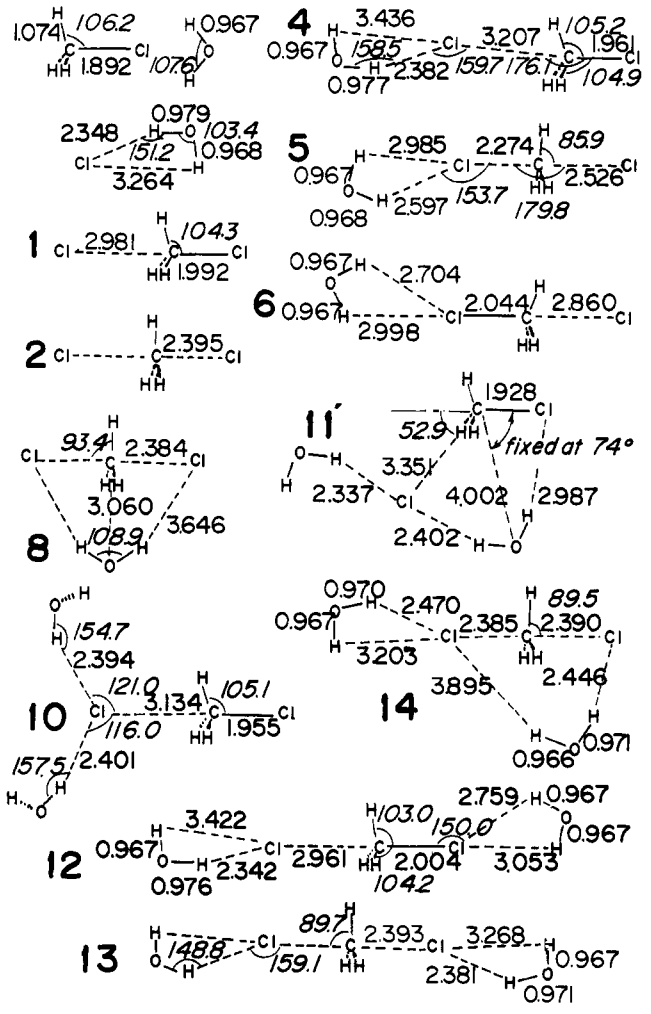

Figure 2. Optimized geometries of some important species.

from which H_2O migrates with little or no barrier 7[5b] to give the product **4**. Because of the symmetry of the system, the reverse sequence, **4** → **7** → **6** → **5** → **4**, namely H_2O migration followed by the CH_3 transfer (not shown in Figure 1 for clarity) is of course equally feasible. The simultaneous path leads directly to the symmetric transition state **8**. The energy difference between the two barriers is too small for the present level of calculation to exclude either possibility. Both barriers are higher than the barrier **2** without hydration.

In the reaction of the complex **10** with a dihydrated chloride **9**, two H_2O migrations and a CH_3 transfer–inversion can take place one by one, two by one, or all three simultaneously. We find that the most favorable path is the initial migration of one H_2O with little or no barrier (**11**)[5b] to form the intermediate complex **12**, followed by the CH_3 inversion through the transition state **13** and the final migration **12** → **11** → **10** of the other H_2O molecule. The first H_2O migration ensures that Cl^- is hydrated throughout the reaction and keeps the potential energy low. The initial simultaneous H_2O migration–CH_3 inversion, **10** → **14** → **12**, has a slightly larger barrier but cannot be excluded. The overall barriers **13** and **14** for $n = 2$ are higher in energy than the corresponding barriers for $n = 1$, which in turn is higher than the barrier for $n = 0$.

One notes that H_2O migrations, **6** → **7** → **4** and **12** → **11** → **10**, proceed with little or no barrier. The geometry of **11′** in Figure 2,[5b] which is on the path connecting **12** and **10**, reveals an important role of Cl^- in the H_2O migration; Cl^- moves away from the C_{3v} axis to accompany the migrating H_2O until H_2O is delivered to the opposite Cl atom, and then it flips back onto the C_{3v} axis. This close association of Cl^- keeps the potential energy low for the process.

From the above results, we can suggest even for larger clusters that the first and the last steps are the H_2O migration possibility simultaneously with the CH_3 inversion. When n is large and the first solvation shell of halide is completed, the initial interaction involves dehydration and a new feature of the potential surface is expected to appear.

Further studies are in progress and will be published elsewhere.[7]

Acknowledgment. I am grateful to Drs. S. Kato, K. Kitaura, and S. Obara for much advice and discussion. Numerical calculations have been carried out at the IMS Computer Center.

Registry No. Cl^-, 16887-00-6; CH_3Cl, 74-87-3; H_2O, 7732-18-5.

(7) Morokuma, K., to be submitted for publication.

Intramolecular Carbocyclic [3 + 2] Cycloaddition via Organopalladium Intermediates

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The intramolecular Diels–Alder reaction offers a powerful solution to many problems in complex natural products synthesis.[1] Converting olefin geometry into the stereochemistry of saturated carbon combined with forming two rings simultaneously from acyclic precursors accounts for the popularity of this approach. With the increasing importance of cyclopentanoid natural products, an intramolecular cycloaddition-like process that focuses on five-membered ring formation would complement the Diels–Alder reaction in some cases (e.g., toward perhydroindanes) and offer a unique approach in other cases (e.g., toward pentalenes, hirsutanes, etc.). As in eq 1 diyls generated from azo precursors

(1)

represent such an approach.[2,3] We wished to examine an approach

(1) For recent reviews see: Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, *37*, 3.

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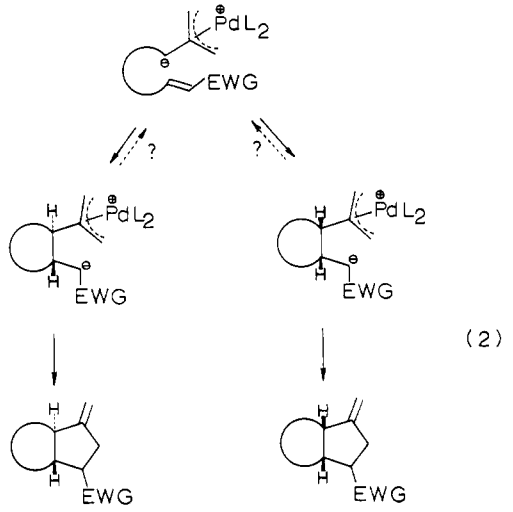
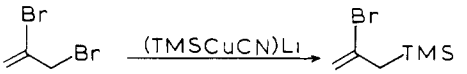
based upon the cycloadditions of trimethylenemethanepalladium complexes (TMM–Pd).[4,5] Considering that such a reaction has been shown to be a two-step process,[4] i.e., conjugate addition followed by S_N2-like displacement, its success in an intramolecular process can critically depend upon the stereochemistry of the initial addition step (see eq 2). For example, in a bicycloannulation



(2)

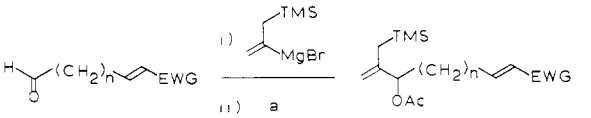
to a bicyclo[3.3.0]octane, formation of the trans stereochemistry in the first step would seem to preclude the second ring closure.[6] Thus, either this step must be reversible (an unprecedented type of cleavage of a C–C bond) or the initial stereochemistry must be preferentially cis. While neither prospect was particularly bright, the importance of such a process warranted investigation. In this communication, we record our observations and the utility of a new conjunctive reagent, 2-bromo-3-(trimethylsilyl)propene (**1**).



1

The key reagent **1**[7] (bp 82–85 °C, 58–60 mmHg) forms in 63% yield upon reacting lithium (trimethylsilyl)cyanocuprate[8,9] in a 3:1 THF–HMPA mixture at 0 °C with 2,3-dibromopropene. The corresponding magnesium derivative is generated either by metal–halogen exchange with *tert*-butyllithium (ether, −78 °C) followed by addition of anhydrous magnesium bromide or by direct reaction with magnesium turnings in THF. The bifunctional aldehyde partners are formed by standard olefination and oxidation routes from the appropriate diols in the cases of **2**,[7] **3**,[7] and **4**[7] and from 10-undecenal in the case of **5**.[7]

The cyclization experiments show a sensitivity toward the purity of substrates **6–9**.[7] To ensure dryness, either pretreatment with

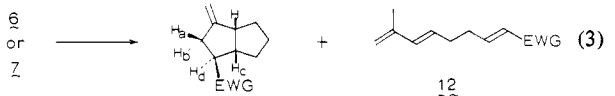


2	$n = 3$, EWG = $CO_2C_2H_5$	**6**
3	$n = 3$, EWG = SO_2Ph	**7**
4	$n = 4$, EWG = SO_2Ph	**8**
5	$n = 8$, EWG = SO_2Ph	**9**

[a] AcCl, catalyst DMAP, C_5H_5N, CH_2Cl_2.

O,N-bis(trimethylsilyl)acetamide and/or its addition to the reaction mixture is performed. Freshly purified substrate is also preferable.

Treatment of **6** with 9 mol % of $(Ph_3P)_4Pd$ (**10**) in the presence of 9 mol % of additional triphenylphosphine in refluxing THF produces a 30% yield of **11**[7] as well as a 40% yield of the triene

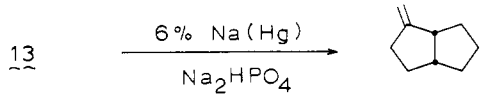


(3)

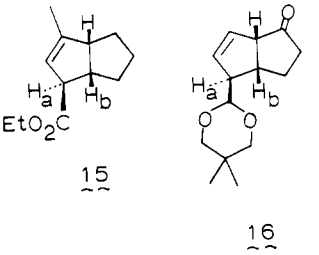
12

11, EWG = CO_2Et
13, EWG = SO_2Ph

12 (see eq 3).[7] Use of $(dppe)_2Pd$[10] and added dppe causes a drop in the yield of **11** to 18% and an increase of **12** to 54%. On the other hand, use of 8–9 mol % of **10** and 4–6 mol % of dppe increased the yield of the desired cyclization product to 51–52%. While in this case the triene **12** is isolated and characterized, in most preparative cyclizations addition of maleic anhydride to the crude reaction mixture in $CHCl_3$ (60 °C) followed by chromatographic purification conveniently removes the triene byproducts and permits easy isolation of the pure cyclization products.



Treatment of **7** with a similar catalyst system in refluxing DME gives the bicyclo[3.3.0]octyl ring system (i.e., **13**, mp 62–66 °C) in an astonishing 65% yield. A temperature dependence is observed. In THF at 46–48 °C, the yield is only 27%, whereas in refluxing THF it is 45%. That the cyclization product was indeed the cis-fused system **13** is easily demonstrated by desulfonylation[11] to **14**, whose spectral properties are identical with an authentic sample.[12] The stereochemistry of the EWG as exo is suggested by NMR data. For example, **11** isomerized to **15**[7] (TsOH, $CDCl_3$, 55 °C) in which J_{ab} = 3.6 Hz is in good agreement with the corresponding coupling of 2.5 Hz in **16**.[13] The cycloadduct **13**

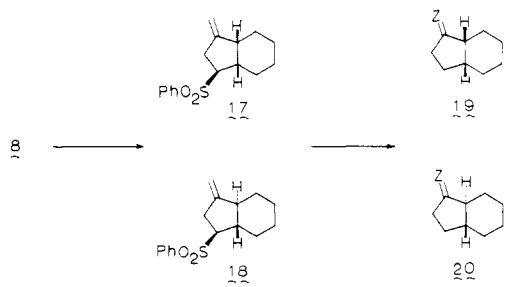


shows Eu(fod)$_3$-induced shifts of 356 Hz for H_c, about the same for H_a (362 Hz), but considerably larger than for H_b (221 Hz)—a pattern in agreement with the sulfone being syn to two vicinal protons as in **13**. The facts that the trans stereochemistry of **6** and **7** should translated into the *exo* products[4] and that attempts

(2) Intramolecular [3 + 2] cycloadditions of heteroatom 1,3-dipoles are well known. See: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(3) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744.
(4) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429, 6432; **1980**, *102*, 6359.
(5) For codimerizations of olefins with methylenecyclopropanes see: Binger, P.; Germer, A. *Chem. Ber.* **1981**, *114*, 3325. Binger, P.; Schuchardt, U. *Ibid.* **1981**, *114*, 3313; **1980**, *113*, 3334. Binger, P. *Synthesis* **1973**, 427.
(6) The trans-fused bicyclo[3.3.0]octane is 7 kcal/mol more strained than the cis. Baneth, J. W.; Linstead, R. P. *J. Chem. Soc.* **1935**, 436; Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
(7) This compound has been fully characterized by spectral means and satisfactory elemental composition determined by either combustion analysis and/or high-resolution mass spectroscopy. Selected spectral data for **1**, **6**, **7**, **8**, **11**, **13**, **17**, and **18** appear as supplementary material.
(8) Prepared by reacting 0.8 equiv of (trimethylsilyl)lithium [Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063] with 1.2 equiv of CuCN.
(9) Cf. Fleming, I.; Roessler, F. *J. Chem. Soc., Chem. Commun.* **1980**, 276. Fleming, I.; Ager, D. J. *Ibid.* **1978**, 178.
(10) dppe = 1,2-bis(diphenylphosphino)ethane.
(11) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(12) Gassman, P. G.; Valcho, J. J.; Proehl, G. S.; Copper, C. F. *J. Am. Chem. Soc.* **1980**, *102*, 6519.
(13) Mao, M. Ph.D. Thesis, University of Wisconsin, Madison, WI, 1980. A coupling of 7–9 Hz would be expected for the epimer. Cf. Takeuchi, S.; Ogawa, Y.; Yonehara, H. *Tetrahedron Lett.* **1969**, 2737.

to equilibrate **11** with base led to no change in stereochemistry support the assignments presented.

Subjection of **8** to the same reaction conditions leads to a 70%



yield of the bicyclo[4.3.0]nonanes **17**[7] and **18**[7] in a 2:1 ratio. That the mixture resulted from a mixture of ring-juncture isomers and not from the stereochemistry of the sulfone is demonstrated by desulfonylation (6% Na(Hg), Na_2HPO_4, CH_3OH)[11] to **19a**[7] and **20a**[7] in the same ratio. Ozonolysis (O_3, CH_3OH, CH_2Cl_2, −78 °C) and comparison (spectrally and chromatographically) of the resulting ketone mixture of **19b** and **20b** to an authentic sample[14] assign the major isomer to the cis-fused series and the minor isomer to the trans-fused series. Note that the stereochemistry of the sulfone group in both products faithfully reflects the stereochemistry of the starting olefin.

The reaction is best envisioned in the two-step manner depicted in eq 2. That nucleophilic attack must be initiated by the carbon atom of the TMM–Pd moiety bearing the electron-releasing alkyl substituent is in accord with our earlier work on the methyl-substituted series.[15] The surprising success of the process for formation of the bicyclo[3.3.0]octyl system raises the specter of the initial addition being reversible. Carbon leaving groups in retro-Michael reactions are rare—usually requiring release of strain energy or formation of an exceptionally stabilized anion. Unfortunately, the question of the relative stability of TMM–Pd cannot be addressed at the moment. A more probable explanation lies in the initial addition proceeding preferentially to give the cis adduct in the first step. While steric factors argue against such a proposal, this step does involve conversion of a β-zwitterion-like species (i.e., the TMM–Pd complex) to one with greater separation of charge. Initial formation of a cis five-membered ring minimizes this charge separation. The formation of both isomers in the bicyclo[4.3.0]nonyl system supports this view. Once again, the cis isomer dominates. However, the ability to place the two substituents in a diequatorial arrangement not only can minimize charge separation but also can relieve unfavorable skew interactions. Thus, formation of the trans-fused product begins to compete. Additional evidence favoring this interpretation arises from the failure of **9** to give a bicyclic product since the initial Michael addition requires formation of the unfavorable ten-membered ring. It is interesting to contrast this failure with the facility of palladium-initiated macrocyclizations of allylic acetates to form a very unfavorable ring size.[16] In these latter cases charge neutralization accompanying the cyclization accounts for their successes; in the former case, charge separation must occur and the reaction fails. Fortunately, it is clear that an intramolecular [3 + 2] strategy is feasible in appropriate cases. The facility of forming the desired substrates by utilizing **1** suggests the above may be a very useful strategy in synthesis of multicyclic compounds bearing at least one cyclopentanoid ring.

(14) Larock, R. C.; Dertte, K.; Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190. The equilibrium ratio of **19b** to **20b** is 3:1. See: House, H. O.; Rasmusson, A. H. *J. Org. Chem.* **1963**, *28*, 31.

(15) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *Ibid.* **1981**, *103*, 5974.

(16) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1977**, *99*, 3867; *Tetrahedron Lett.* **1978**, 2275; *J. Am. Chem. Soc.* **1979**, *101*, 1595; *Ibid.* **1980**, *102*, 4743.

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Registry No. 1, 81790-10-5; **2**, 59612-36-1; **3**, 81790-11-6; **4**, 81790-12-7; **5**, 81790-13-8; **6**, 81790-14-9; **7**, 81790-15-0; **8**, 81790-16-1; **9**, 81790-17-2; **11**, 81790-18-3; **12**, 81790-19-4; **13**, 81790-20-7; **14**, 70598-79-7; **15**, 81790-21-8; **17**, 81790-22-9; **18**, 81790-23-0; **19a**, 52775-75-4; **19b**, 2826-65-5; **20a**, 81790-24-1; **20b**, 16783-22-5; lithium (trimethylsilyl)cyanocuprate, 81802-36-0; 2,3-dibromopropene, 513-31-5.

Supplementary Material Available: Spectral data for **1**, **6**, **7**, **8**, **11**, **13**, **17**, and **18** (2 pages). Ordering information is given on any current masthead page.

Synthesis of Jaborosalactone A, B, and D[1]

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Received January 19, 1982

Withanolides, a group of naturally occurring steroids with an ergostane-type skeleton, have been isolated from the plants of the *Solanaceae* family.[2a] Several members possess interesting biological activities, mainly antitumor[2b] and insect antifeedant properties.[2c] Their novel structures, which include the highly oxygenated A:B rings and also include the side-chain lactone, have made them an attractive synthetic target. Although several synthetic approaches to the functionalities have been made,[3] a total synthesis has not yet been accomplished.

In this communication, we report the synthesis of jaborosalactone A (**1a**),[4a] B (**1b**),[4a] and D (**1c**)[4b] as a first synthesis of withanolides from a readily available steroid (Scheme I). The key strategy involves the side-chain synthesis in which the correct configuration at C_{22} is generated via the (22*S*)-22,23-epoxide **7**, and the hydroxymethyl unit at C_{25} is introduced into the C_{25} anion equivalent of **9**, the enolate of **11a**.

Commercially available 3β-hydroxy-22,23-bisnorchol-5-enoic acid (**2**) was transformed into the triol diacetate **4**.[5] In four steps **4** was converted to the 1,3-bis(methoxymethyl) (MOM) ether **5** of the 22-olefin in good yield. Generation of the *R* configuration at C_{22} was efficiently accomplished through the transformation of the chiral 22(*S*)-epoxide **7**, which was prepared from **5** by the

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(1) Synthetic Studies of Withanolides. 5. Part 4: Hirayama, M.; Gamoh, K.; Ikekawa, N. *Chem. Lett.* **1982**, 491.

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(4) (a) Tschesche, R.; Schwang, H.; Legler, G. *Tetrahedron* **1966**, *22*, 1121. Tschesche, R.; Schwang, H.; Fehlhaber, H. W.; Snatzke, G. *Ibid.* **1966**, *22*, 1129. (b) Tschesche, R.; Baumgarth, M.; Welzel, P. *Ibid.* **1968**, *24*, 5169. Acnistoferin, reported by Bukovits and Gros (Bukovits, G. J.; Gros, E. G. *Phytochemistry* **1979**, *18*, 1237) is identical with jaborosalactone D.

(5) Fuerst, A.; Labler, L.; Meier, W. Ger. Offen. 1978, 2,746,107; *Chem. Abstr.* **1978**, *89*, 60008f.

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