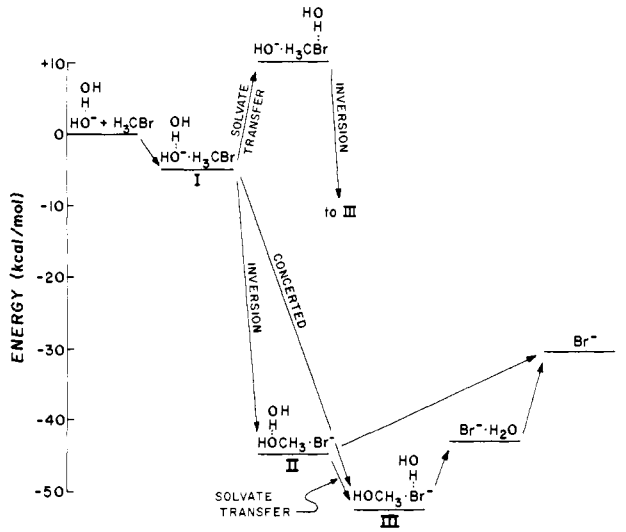

Figure 2. Energies of the reaction intermediates and products, relative to that of the reactants. Thermochemistry from ref 6 and estimates based thereon. Pathways are indicated without showing potential energy barriers.

transfer from nucleophile to leaving group must be inefficient and must couple ineffectively with the Walden inversion[15] of the methyl group.

How can Br^- be formed without involving $Br^-\cdot H_2O$ as an intermediate? Figure 2 shows three possible reactive pathways open to the intermediate I, formed from the reactants:[16] sequential solvate transfer and inversion (upper pathway), concerted solvate transfer/inversion (middle), and sequential inversion and solvate transfer (lower). Since at 300 K the upper pathway is inaccessible energetically, the choice for the intermediate I is between the steps I → II and I → III. We argue that both these steps will show comparable potential energy barriers,[17] but that the concerted process will show the greater "free energy" barrier, resulting from the entropic contribution of the tight transition state for solvate transfer.[3c,18] This argument channels I to II, which is a bromide ion, solvated with a water molecule and a methanol molecule. II contains considerable vibrational energy (~45 kcal/mol), and it has only to desolvate (+~14 kcal/mol) to give Br^-, the principal product observed.[19]

Contrast what happens in the gas phase (reaction 2a) with what happens in solution (reaction 2b). In the gas phase, solvate transfer is inefficient and the product is not solvated.[13] In solution, the product *is* solvated, without the need for the solvate to be transferred. As the displacement proceeds in solution, there is a *concerted* desolvation of the nucleophile and solvation of the leaving group, with different solvent molecules.[20] In solution the role of the bulk solvent, all pervasive, is crucial.

What trends may be identified for these solvated-ion reactions, with increasing solvation number n? (1) The rate constants do *not* decrease monotonically, extrapolating to the limiting value for the reaction in solution.[5] Instead, reaction is only possible for that limited range of n for which reaction 2a is exothermic. (Here $0 \leq n \leq 2$,[21] as seen in Table I.) (2) The reaction-coordinate diagrams do *not* transform systematically toward that for the reaction in solution.[5,22] The reaction is not reaction 2b but reaction 2a.

What distinguishes these solvated-ion reactions in the gas phase from reactions in solution is the kinetic role of the bulk solvent. What such solvated-ion reactions can reveal is the kinetic participation of the solvate in the absence of bulk solvent.

Acknowledgment. M.H. acknowledges support from AFOSR (80-0116) and NIH (BRSG S07 RR07044).

Registry No. H_2O, 7732-18-5; OH^-, 14280-30-9; $OH^-\cdot H_2O$, 23138-14-9; $OH^-\cdot(H_2O)_2$, 34118-36-0; $OH^-\cdot(H_2O)_3$, 34118-37-1; CH_3Br, 74-83-9; CH_3Cl, 74-87-3.

(15) Lieder, C. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1974**, *96*, 4028. Lieder, C. A.; Brauman, J. I. *Int. J. Mass Spectrom. Ion Phys.* **1975**, *16*, 307.
(16) Morokuma, K. *J. Am. Chem. Soc.* **1982**, *104*, 3732.
(17) The intrinsic energy barriers (ref 3b) for the two steps are comparable (ref 16), and these are then scaled according to the exothermicities, which are comparable (Figure 2). The existence of a barrier for the process I → II or III follows from the reaction efficiency (ref 3a) being ~50% (Table I).
(18) Where the solvate water must bridge the nucleophile and leaving group (ref 16).
(19) The alternative pathway (II → III) involves solvate transfer. While admittedly exothermic (~−8 kcal/mol), it has an energy barrier (ref 16) and requires another tight transition state (ref 18).
(20) Dewar, M. J. S.; Dougherty, R. C. "The PMO Theory of Organic Chemistry"; Plenum Press: New York, **1975**; p 231.
(21) See footnote *e* in Table I.
(22) Wolfe, S.; Mitchell, D. J.; Schlegel, H. B.; Minot, C.; Eisenstein, O. *Tetrahedron Lett.* **1982**, *23*, 615.

A Simplified Total Synthesis of Cytochalasins via an Intramolecular Diels–Alder Reaction

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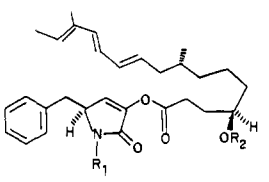
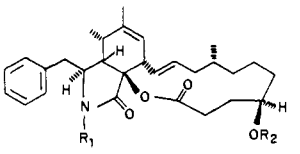
Received October 12, 1982

The macrocyclic lactone ring is one of the challenging problems in the synthesis of cytochalasin B and its congeners.[1] We present here a simplification of our original synthesis[1a] that (a) uses an intramolecular version of the Diels–Alder construction from the tetraene **1**[2] and (b) introduces the proper oxidation state in the cyclohexane ring at the end of the synthesis (**2** → **3** → **4**).[3]



1



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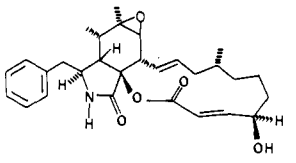
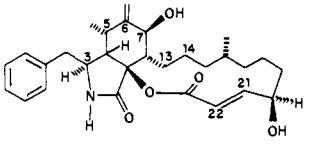


3



4

Reduction of *N*-carbobenzoxy-(L)phenylalanine methyl ester (2 equiv of DIBAL, −78 °C; 2 N HCl) gave aldehyde **5**,[4,5]

(1) (a) For a total synthesis of cytochalasin B and leading references, see: Stork, G.; Nakahara, Y; Nakahara, Y; Greenlee, W. G. *J. Am. Chem. Soc.* **1978**, *100*, 7775. (b) For the lactone ring formation see: Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
(2) See Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, 2537, for an earlier example of the use of the internal Diels–Alder reaction in the construction of large rings.
(3) The numbering system is taken from: Graf, W.; Robert, J.-L.; Vederas, J. C.; Tamm, Ch.; Solomon, P. H.; Miura, I.; Nakanishi, K. *Helv. Chim. Acta* **1974**, *57*, 1801.
(4) Purification of this readily racemizable aldehyde could be achieved by "flash" chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. The aldehyde was considered to be optically pure as judged by the corresponding phenylalaninol ($NaBH_4$): Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.
(5) All compounds gave spectral data, in particular ^1H NMR ($CDCl_3$) spectra, in agreement with the postulated structures. Mass spectra were taken in a CI mode using methane as reagent gas. Rotations are for pure chloroform solutions and refer to the sodium D line.

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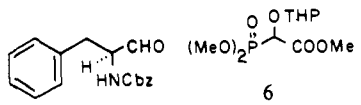
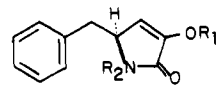


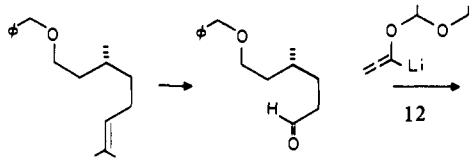
5 6



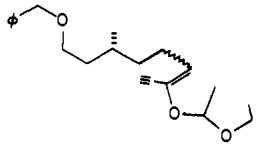
7, R_1 = TPH; R_2 = Cbz
8, R_1 = H, R_2 = Ac
9, R_1 = R_2 = Ac

(63–73%), phosphonate **6**[6] to give the unsaturated lactam **7**, which was then transformed to the *N*-acetylhydroxypyrrolone **8** (70% yield from **5**) by appropriate exchange of protective groups. The optical purity of **8** (80% ee from ^{1}H NMR of its MTPA ester) was confirmed by the rotation of its diacetate **9**: $[\alpha]^{21}$ +90.9° (*c* 3.23).[1a]

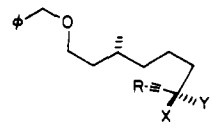
The synthesis of the chiral triene moiety of **1** started from citronellol. Optically pure citronellol (from (+)-pulegone) was benzylated to **10** (benzyl bromide, sodium hydride, THF), which was then cleaved (OsO_4/*N*-methylmorpholine *N*-oxide, H_5IO_6) to the aldehyde **11** (85%). The elaboration of **11** to the required acetylenic ketone **14** now required a method for the transformation RCHO → $RCH_2C(=O)C{\equiv}CH$. This was achieved by reaction of **11** with the lithio allene **12** (−78 °C, THF) followed by chlorotrimethylsilane (−78 → 0 °C) and 2 equiv of *n*-BuLi (−78 °C → room temperature). The resulting enyne **13**, was then hydrolyzed to the acetylenic ketone **14** $[\alpha]^{21}$ +3.20° (*c* 8.82), in an overall yield of 60–65% from **11**.[7] Reduction of the ketonic group (91%) with (−)-*N*-methylephedrine-complexed lithium aluminum hydride (0.08 M ether solution; −15 ± 5 °C) gave the (*R*) ethynyl carbinol **15**, $[\alpha]^{24}$ +4.40° (*c* 3.88) (90% optical purity).[8] The derived silyl ether **16** was then carbethoxylated by reaction of its lithium salt with excess ethyl chloroformate (5 equiv, −78 °C, THF) to **17** thus obtained in 92% yield. Saturation of the triple bond (5% Rh on alumina, ethanol) and debenzylation (10% Pd–charcoal, ethanol) quantitatively afforded the hydroxy ester **18**, which was then oxidized with pyridinium chlorochromate (80% yield) to the aldehyde **19**.



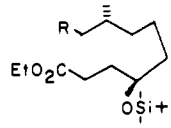
10 11 12



13



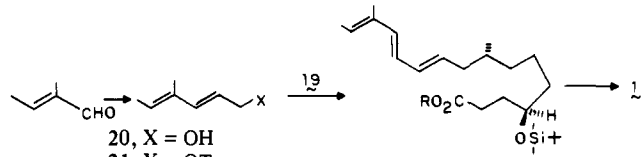
14, R = H; X, Y = O
15, R = H; X = OH; Y = H
16, R = H; X = OSi+; Y = H
17, R = CO_2Et; X = OSi+; Y = H



18, R = CH_2OH
19, R = CH=O

(6) Nakamura, E. *Tetrahedron Lett.* **1981**, *22*, 663.
(7) For an earlier variant of this sequence, see: Hoff, S.; Steenstra, G. H.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1284.
(8) Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683. Reduction of **14** with *R*-selective reagent, (+)-Darvon alcohol/LAH, also gave the same compound in slightly diminished optical purity (Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339).

The phosphonate reagent required for the construction of triene **23** was then prepared from the tosylate **21** of dienyl alcohol **20**.[1a] Reaction of the lithium salt of **22** with aldehyde **19** (−78 °C in THF, followed by 1.4 equiv of HMPA at room temperature for 3 h) gave the acid-sensitive triene ester **23** in 69% yield ("flash" chromatography on silica gel prewashed with 5% $KHCO_3$ in methanol): IR (neat) 1742 cm-1; CIMS, *m/e* 453 (M + 17), 451 (M + 15), 411 (M + 1 − 26). Hydrolysis of **23** (NaOH/aqueous ethanol, followed by 10 equiv of tartaric acid) quantitatively afforded the trienic acid **24**, which was finally transformed by

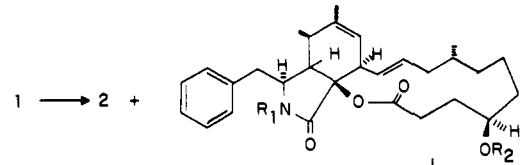


20, X = OH
21, X = OTs
22, X = O=P(OEt)$_2$

23, R = Et
24, R = H

esterification with the hydroxypyrrolone **8** by Mukaiyama's method[9] (2-chloropyridine methiodide, 20 mol % DMAP, triethylamine, room temperature, CH_2Cl_2) to the required tetraene **1** (R_1 = Ac, R_2 = *t*-BuMe_2Si) in 69% yield.

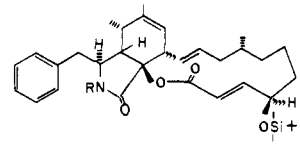
The acid-sensitive tetraene (0.005 M in degassed mesitylene) was heated at 180–190 °C in a base-washed, silylated, sealed tube for 6 days to give the product of cycloaddition in 30% yield. This was raised to 35% after one recycling of the recovered starting material.[10] The adduct appeared homogeneous on HPLC analysis (10% THF in hexane, μporasil), but was actually a mixture of **2** and **25** (R_1 = Ac, R_2 = *t*-BuMe_2Si; 4:1 ratio) separable on silica



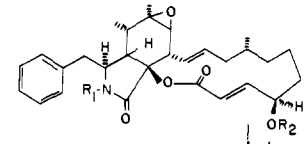
25, R_1 = Ac; R_2 = Si+

after deacetylation (K_2CO_3, MeOH; 99%). The faster moving major isomer **2** (R_1 = H, R_2 = *t*-BuMe_2Si) was homogeneous by TLC analysis: $[\alpha]^{22}$ −32.1° (*c* 2.10); IR 3420, 1720 cm^{-1}; CIMS, *m/e* 580 (M + 1). The required, and expected, endo structure of **2** was confirmed by the shift of the C-11 methyl at δ 0.8 to δ 0.24 after reacetylation of the NH group (CIMS, *m/e* 622). ^{1}H NMR comparison with suitable models indicated that the minor product was the exo adduct.

Two operations, introduction of the C_{21}–C_{22} unsaturation and of the C_6–C_7 functionality, remained to be done. Lithiation (3 equiv of LDA, −78 °C, THF), addition of PhSeCl (3 equiv), and oxidation (H_2O_2/pyridine/CH_2Cl_2) transformed **2** (R_1 = H, R_2 = *t*-BuMe_2Si) into  , $[\alpha]^{21}$ −64.8° (*c* 2.00), in 70–76% yield.



26, R = H
27, R = Ac



28, R_1 = Ac; R_2 = Si+

The reaction was highly trans selective: ^{1}H NMR δ 7.02 (dd, *J* = 6, 15 Hz), 5.84 (dd, *J* = 2, 15 Hz). The trans geometry of the previously introduced C_{13}–C_{14} double bond was confirmed at this stage by NMR decoupling (δ 5.95 (dd, *J* = 10, 15 Hz for H at C_{13})).

The necessary regio- and stereoselective epoxidation of the cyclohexene bond of **26** was achieved by using the *N*-acetyl derivative **27** (Ac_2O/DMAP/triethylamine, 88%). Epoxidation was

(9) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863.

unselective with MCPBA, but conditions were finally found (1.0 equiv of *t*-BuOOH/2.5 mol% of $Mo(CO)_6$, 0.7 M benzene solution, 75 °C, 1.5 h) that gave **28** in 89% yield (44% conversion). The ^1H NMR of **28** clearly showed the C_{13}–C_{14} olefin (δ 5.93 (ddd, J = 1.5, 10, 15 Hz) and 5.28 (ddd, J = 3.5, 9.5, 15 Hz)), and the ^{13}C NMR showed the required 32 signals. Deacetylation (K_2CO_3 in methanol; 86%) and desilylation (tetrabutylammonium fluoride, THF; 75%) gave cytochalasin F (**3**) as an amorphous solid, $[\alpha]^{23}$ −33.1° (*c* 0.90), which was homogeneous on HPLC analysis, and showed a ^1H NMR spectrum in satisfactory agreement with that reported for the natural product.

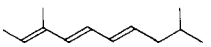
The identity of our synthetic material was confirmed, and the synthetic route to cytochalasin B was completed by the conversion, in 74% overall yield, of its immediate precursor **28** into cytochalasin B (**4**) upon refluxing with aluminum isopropoxide in xylene for 8 h,[11] followed by deacetylation and desilylation. The synthetic cytochalasin B, thus obtained as fine needles, was shown to correspond to the natural product by ^1H NMR, IR, and EI/MS. The melting point of the natural substance was not depressed after admixture with the synthetic material.

The reasonably simple construction of the cytochalasin system that we are reporting here should especially be valuable for the synthesis of simple analogues.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial support of this work. We also thank Dr. W. G. Greenlee of Merck Sharp and Dohme for the high-pressure experiment (ref 10), Dr. M. Nakatani for some HPLC analyses, and Dr. W. B. Turner of ICI for making available to us the spectra of cytochalasin F and of the endocyclic olefinic isomer of cytochalasin B.

Supplementary Material Available: Experimental details and spectra (33 pages). Ordering information is given on any current masthead page.

(10) The yield in the earlier[1a] intermolecular cycloaddition was somewhat higher (~40%) than that from the present intramolecular process, but the latter avoids the rather inefficient lactonization of our earlier route. An attempt to improve the endo–exo ratio by carrying out the *intermolecular* cycloaddition between **8** and the model triene i at very high pressure (9.2 ×



i

10^3 bars) led to the observation of a much faster reaction (30% yield after 20 h at 80 °C) than at ordinary pressure,[1a] but the endo–exo ratio remained unchanged (4:1). The minor exo isomer was incorrectly stated to be a regioisomer in our earlier report.

(11) Cf.: Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *J. Org. Chem.* **1979**, *44*, 1979.

*Book Reviews**

Progress in Analytical Atomic Spectroscopy. Volume 2. Edited by C. L. Chakrabarti. Pergamon Press, New York. 1981. 386 pp. $60.00.

The first section of this book, by N. Omenetto and J. D. Winefordner, covers the basic principles and applications of atomic fluorescence spectroscopy. The authors' stated intent, "...to cover in an exhaustive manner the theory and practice of atomic fluorescence spectroscopy..." is indeed accomplished in eight chapters and two Appendices covering 184 pages. The material ranges from highly mathematical treatments of the fundamental processes to a candid assessment of the future of AFS. They feel that diagnostic studies of flames and plasmas will be the principal use and that atomic emission and absorption methods will continue to dominate in practical analysis.

The next section is on Trace Element Analysis of Food and Beverages by Atomic Absorption Spectroscopy, by F. L. Fricke, W. B. Robbins, and J. A. Caruso. Each element (Al, SB, As, B, Cd, Ca, Cr, Co, C, Fe, Pb, Mg, Mn, Hg, Ni, K, Se, Na, Sn, and Zn) is treated separately with a rapid overview of methods, references for that element, and a table of reported values in various foods. The approach leads to considerable redundancy which is hardly justified when only one analytical method is considered. Grouping similar elements would have been better. Methods descriptions are too brief to be followed but ready access to the original literature is provided.

A section on Determination of Trace Metals in Ultrapure Water, by K. S. Subramanian and C. L. Chakrabarti, covers contamination and its control, techniques and methodology, data reliability evaluation, and definitions of purity and ultrapurity. Problems associated with the various steps of water analyses are identified and references to detailed solutions provided. A general Comparison of Methods is given which presents atomic spectroscopic methods too favorably in comparison to other techniques. For example, proponents of neutron activation analysis and spark source mass spectrometry are unlikely to agree that their method may be 100 000 times poorer in absolute sensitivity than furnace atomic absorption.

In the next section, I. Rubeska and J. Musil discuss interferences in flame spectrometry from the perspective of the underlying processes which lead to inaccurate analytical results as opposed to a tabulation of observed effects and solutions. The coverage is thorough and in sufficient depth to be of great value to the serious student of flame spectroscopy.

The last section is on emission spectroscopy of cool flames by E. Henden, N. Pourreza, and A. Townshend. Emphasis is on molecular cavity emission analysis using methods in which analyte vapor is generated externally and transported to a metal cavity held in a hydrogen diffusion flame. Methods are given for the analysis of boron (BO_2 emission from methyl borate), arsenic, antimony, tin selenium, tellurium, sulfur, and carbon compounds.

The contributing authors are among the world's leading authorities in atomic spectroscopy; yet, this reviewer must question what was accomplished by publishing the book. It lacks coherence, depth of coverage ranges from very thorough (atomic fluorescence) to quite superficial, and much of the material is too old to truly represent "Progress". With the possible exception of atomic fluorescence, better reference sources exist for each of the topics.

S. R. Koirtyohann, *University of Missouri*

Computer Calculations for Multicomponent Vapor-Liquid and Liquid-Liquid Equilibria. By J. M. Prausnitz (University of California), T. F. Anderson (University of California), E. A. Grens (University of California), C. A. Eckert (University of Illinois), R. Hsieh (University of Illinois), and J. P. O'Connell (University of Florida). Prentice Hall, Inc., Englewood Cliffs, New Jersey. XIII + 353 pp.

This book is aimed primarily at design engineers and scientists in the chemical process industries. It provides a detailed approach to the estimation of multicomponent vapor–liquid and liquid–liquid equilibria at low or moderate pressures using computerized iterative techniques based on experimental data. It supersedes an earlier (1967) book "Computer Calculations for Multicomponent Vapor-Liquid Equilibria". However, it not only updates this earlier work but also extends it to liquid–liquid equilibria and expands it to include generalized iterative techniques for equilibrium calculations. The focus is on nonelectrolytes and some inorganic fluids (e.g., water and carbon dioxide). The main text consists of seven chapters and is about one-third of the length of the book. The rest of the book is comprised of ten appendices providing details on the computer programs involved.

The set of simultaneous thermodynamic equations on which the calculation of vapor and liquid fugacities in multicomponent systems is based is presented in the first two chapters which go briefly through activity coefficients, symmetric and unsymmetric conventions for normalization, the Gibbs-Duhem equation, and standard state fugacities for condensable and noncondensable components.

The third chapter discusses the calculation of fugacity coefficients for the vapor phase, the virial equation, and strongly interacting substances. The fourth chapter discusses the methods for calculating the fugacity of a component in a liquid mixture, data reduction, adjusted activity coefficients for noncondensable components, fugacity of the pure liquid, Henry's constant, and ternary and quaternary systems. The fifth chapter is devoted to the calculation of enthalpies in vapor-phase and liquid-phase

*Unsigned book reviews are by the Book Review Editor.