

Figure 1. Dependence of the NOE, T_1 , and T_2 ^{15}N relaxation parameters on the effective correlation time (τ_s) for internal motions for a spectral density function with a single internal motion ($S_f^2 = 1$; dashed lines) and two internal motions ($S_f^2 < 1$; solid lines). The curves are calculated by using the spectral density function given by eq 4, a rotational correlation time of 8.3 ns, a ^{15}N frequency of 60.8 MHz, and a ^1H frequency of 600 MHz. When $S_f^2 = 1$, the spectral density function (eq 4) reduces to the single internal motion spectral density function (eq 1) of the Lipari and Szabo treatment.²

with $\tau_i' = \tau_i \tau_R / (\tau_R + \tau_i)$, $i = f, s$. Note that eq 2 reduces to eq 1 when $S_f^2 = 1$ or $S^2 = S_f^2$. If it is assumed that the fast internal motions are axially symmetric (in which case $S_f^2 = S_f^2$ where S_f is the usual order parameter) and independent of the slow motions, then one can decompose the total generalized order parameter as

$$S^2 = S_f^2 S_s^2 \quad (3)$$

where S_s is the generalized order parameter describing the slow motions.

To find the simplest description consistent with the available data, we assume that τ_f is sufficiently small so as to make a negligible contribution to the relaxation parameters and hence use the spectral density

$$J(\omega) = \frac{S^2 \tau_R}{1 + (\omega \tau_R)^2} + \frac{(S_f^2 - S^2) \tau_s'}{1 + (\omega \tau_s')^2} \quad (4)$$

to fit the data. The best-fit values of S^2 , S_f^2 , and τ_s together with the calculated T_1 , T_2 , and NOE values are given in Table I. It will be noted that the generalized order parameters extracted by using eq 1 and eq 4 are essentially the same.

The values of the generalized order parameters for slow motions can be obtained by using eq 3 and interpreted within the framework of some model to get a physical picture of the amplitude of the motions. For example, if the fast motions occur in a cone of semiangle θ_0 , $S_f = (\cos \theta_0)(1 + \cos \theta_0)/2$, and, if the slow motions are described by a two site jump model, $S_s^2 = (1$

$+ 3 \cos^2 \varphi)/4$ where φ is the angle between the two orientations of the N-H bond.

The effect of using spectral density function eq 4 compared to eq 1 is easily understood by noting that the calculated values of τ_e (0.2–0.3 ns) are 1 order of magnitude smaller than those of τ_s (1–3 ns). For $\tau_R \sim 8$ ns and $\omega_N = 2\pi \times 60.8$ MHz, the NOE reaches a minimum value at an internal correlation time of ~ 0.25 ns. Thus the shift in internal correlation time to larger values which occurs in the two internal correlation time formulation results in larger values of the NOE, while the values of T_1 and T_2 are unaffected. This is illustrated in Figure 1.

These results clearly indicate that the ^{15}N relaxation data reflect the existence of internal motions of significant amplitude both on the very fast (extreme narrowing) and on the relatively slow time scales in certain regions of these proteins. Hence the correlation function for the internal motions of these residues can no longer be approximated to a single exponential of the Lipari and Szabo treatment,² but rather requires at least two exponentials. The slow correlation time, of the order of 1–3 ns, is somewhat faster than the overall rotational correlation time (8–9 ns) and can have a significant amplitude. The very fast motions may reflect the fast random thermal motions that are manifested in molecular dynamics calculations.^{11–13}

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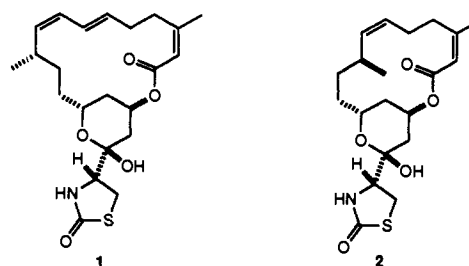
Total Synthesis of (+)-Latrunculin A

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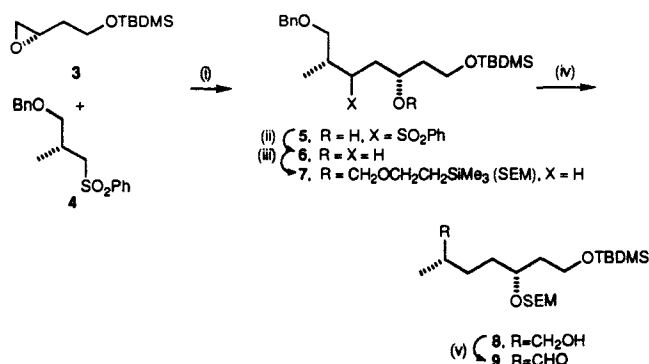
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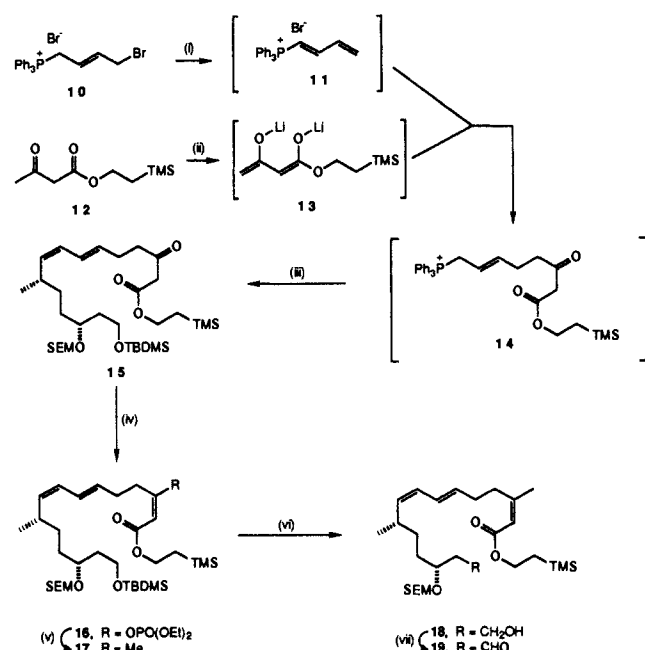
The ichthyotoxin latrunculin A (**1**), originally isolated from the Red Sea sponge *Latrunculia magnifica* (Keller),¹ has also been found in the Pacific nudibranch *Chromodoris elisabethina*² and in the Fijian sponge *Spongia mycofijiensis*.³ Its biological properties, particularly its powerful effect on the cytoskeletal protein actin⁴ and its ability to reversibly disrupt microfilament organization,⁵ have been compared to those of cytochalasin D.⁶ Synthesis of the structurally related, companion metabolite latrunculin B (**2**) was reported in 1986 by Smith et al.;⁷ we now describe the synthesis of **1** by a pathway that is significantly different from the published route to **2**.⁸



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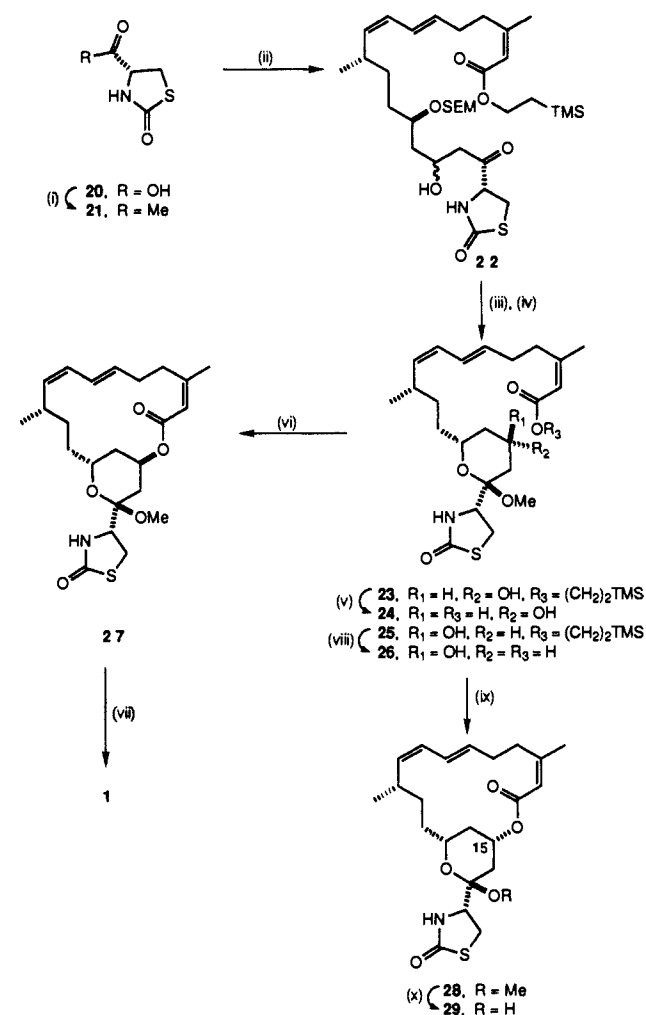
Scheme I^a

^a (i) *n*-BuLi, THF-HMPA, then 3, THF, 0 °C, 74%; (ii) Na(Hg), EtOH, 71%; (iii) Me₃SiCH₂CH₂OCH₂Cl (SEMCl), *i*-Pr₂NEt, CH₂Cl₂, 91%; (iv) H₂, 10% Pd/C, EtOAc, HCl (cat.), 95%; (v) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, 93%.

Scheme II^a

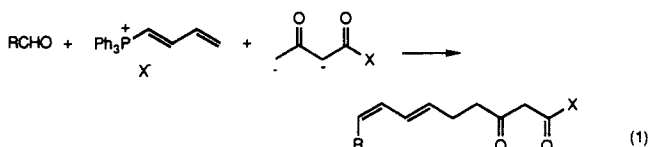
^a (i) LDA (1 equiv), THF, -50 °C, 0.5 h; (ii) LDA (2 equiv), THF, 0 °C; (iii) 9, THF, 0 °C, 60%; (iv) (EtO)₂POCl, *i*-Pr₂NEt, HMPA, DMAP, 0 °C, 96%; (v) MeLi, CuI, MeMgCl, THF, 87%; (vi) MeOH, PPTS, 25 °C, 86%; (vii) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -50 °C → -30 °C, 90%.

Specifically, our approach to 1 was designed to exemplify a novel synthesis of (*E,Z*)-1,3-dienes that involves tandem addition of an enolate dianion to a dienylphosphonium salt followed by a Wittig reaction of the derived ylide with an aldehyde (eq 1).⁹ This strategy assembles a large segment of the perimeter of la-trunculin A in a single step.

Scheme III^a

^a (i) MeLi, MeMgCl, THF, 25 °C, 2 h, 50%; (ii) LDA (2 equiv), THF, -78 °C, then CeCl₃ (1 equiv), THF, -78 °C, then 19, THF, -78 °C → -30 °C, 60% based on 19; (iii) HF (concentrated), CH₃CN, 20 °C; (iv) MeOH, CSA (cat.), 36% of 23, 30% of 25; (v) *n*-Bu₄NF, DMSO, 25 °C, 71%; (vi) Ph₃P, EtO₂CN=NCO₂Et, C₆H₆, 25 °C, 67%; (vii) AcOH-H₂O, 60 °C, 2 h, 72%; (viii) *n*-Bu₄NF, DMSO, 25 °C, 58%; (ix) Ph₃P, EtO₂CN=NCO₂Et, C₆H₆, 25 °C, 44%; (x) AcOH-H₂O, 60 °C, 2 h, 69%.

The aldehyde 9 employed in the three-component coupling process expressed in eq 1 was prepared from (*S*)-epoxide 3, obtained from (*S*)-malic acid by the method of Mori and Ikunaka,¹⁰ and the sulfone 4¹¹ (Scheme I). Alkylation of the lithio anion



of 4 with 3 gave hydroxy sulfone 5,¹² from which the sulfone moiety was removed reductively to yield 6. This alcohol was protected as its [2-(trimethylsilyl)ethoxy]methyl (SEM) ether 7, and the primary alcohol 8 resulting from hydrogenolysis of 7 was oxidized under Swern conditions to 9.

For elaboration of the C(1)-C(15) segment of 1 a brown solution of butadienyltriphenylphosphonium bromide (11),¹³ pre-

(10) Mori, K.; Ikunaka, M. *Tetrahedron* 1984, 40, 3471.

(11) Prepared from methyl (*R*)-3-hydroxy-2-methylpropionate by (a) benzylation with methyl trichloroacetimidate (White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* 1988, 110, 1624), (b) reduction with LiAlH₄, (c) tosylation, and (d) displacement with iodide and then with sodium benzenesulfinate.

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 (8) A different route to 1 has been completed recently by Smith et al. We thank Professor Amos B. Smith, III, for details of his work prior to publication.
 (9) The practical aspects of this reaction as a general stereoselective route to conjugated dienes of *E,Z* configuration will be described in due course (White, J. D.; Jensen, M. S., unpublished work).

pared by treatment of the phosphonium bromide **10**¹⁴ with strong base, was reacted at low temperature with a solution of the dilithio dianion **13**, prepared from 2-(trimethylsilyl)ethyl acetoacetate (**12**) (Scheme II). The resulting red solution of ylide **14** was then allowed to couple with **9** to furnish (*E,Z*)-**15** as the sole diene isomer. The (*E*)-enolate of this β -keto ester was generated with high stereoselectivity by the method of Weiler¹⁶ and was trapped with diethyl phosphorochloridate to give enol phosphate **16**. The latter underwent methylation via the magnesio cuprate¹⁷ to produce *Z* α,β -unsaturated ester **17**. The primary silyl ether was removed from **17**, and the resulting alcohol **18** was oxidized to **19**.

Condensation of **19** with (*R*)-4-acetyl-2-oxothiazolidine (**21**) was carried out without protection of the nitrogen atom under conditions that resulted solely in crossed aldol coupling. Thus, ketone **21**, prepared directly from carboxylic acid **20**,¹⁸ was converted to a mixed lithio cerio dianion which, upon reaction with

19, afforded an inseparable 1:1 mixture of epimeric alcohols **22** (Scheme III). Selective unmasking of the SEM ether and exposure of the resulting diol to acidic methanol gave easily separable ketals **23** and **25**. Cleavage of the ester from **23** and a Mitsunobu reaction of seco acid **24** afforded lactone **27** (mp 142–147 °C, $[\alpha]_D^{20} +302^\circ$), identical with the substance (mp 145–150 °C, $[\alpha]_D^{20} +308^\circ$) obtained by exposure of natural latrunculin A to acidic methanol. Finally, hydrolysis of **27** produced latrunculin A ($[\alpha]_D +143^\circ$) identical in all respects with the natural material. A parallel sequence from alcohol **25** led via seco acid **26** and lactone **28** to 15-epilatrunculin A (**29**, $[\alpha]_D^{20} +333^\circ$).

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Supplementary Material Available: IR, ¹H and ¹³C NMR, MS, $[\alpha]_D^{20}$, and analytical data for **1**, **5–9**, **12**, **15–19**, and **21–29** (6 pages). Ordering information is given on any current masthead page.

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Additions and Corrections

Enzymes in Organic Synthesis: Use of Subtilisin and a Highly Stable Mutant Derived from Multiple Site-Specific Mutations [*J. Am. Chem. Soc.* **1990**, *112*, 945–953]. CHI-HUEY WONG,* S.-T. CHEN, WILLIAM J. HENNEN, JEFFREY A. BIBBS, Y.-F. WANG, JENNIFER L.-C. LIU, MICHAEL W. PANTOLIANO, MARC WHITLOW, and PHILIP N. BRYAN

Page 950: Table VI should have reaction time (min) (placed above the number 40 of entry 1), % conversion (placed above the number 49 of entry 1), and products ee (%) included.

Deoxyribose-5-phosphate Aldolase as a Synthetic Catalyst [*J. Am. Chem. Soc.* **1990**, *112*, 2013–2014]. CARLOS F. BARBAS, III, YI-FONG WANG, and CHI-HUEY WONG*

The kinetic parameters for the enzyme should be as follows: $k_{cat} = 52.1 \text{ s}^{-1}$; $K_m = 0.193 \text{ mM}$; and $V_{max} = 55 \text{ U/mg}$.

Page 2014: (*S*)-1-Fluoro-3-hydroxy-4-methylhexan-2-one should read (*S*)-1-Fluoro-4-hydroxy-5-methylhexan-2-one.

Computer Software Reviews

KaleidaGraph, Version 2.0.2. Synergy Software (PCS Inc.): 2457 Perkiomen Avenue, Reading, PA 19606. List price \$249.00; educational and multicopy discounts available.

KaleidaGraph (KG) is a data analysis and graphics presentation program for the Macintosh family of computers. It requires a MacPlus or later model and System 4.1 (or later). The application itself uses 640K of memory, so 1 MB is the bare minimum RAM requirement but 2 MB seems more realistic. It claims to work with any color printer that has a Chooser print driver. For this review, it worked perfectly on an SE, a Mac II, and a Mac IIcx (all with ≥ 4 MB RAM); with a color monitor and a portrait monitor; and with Imagewriter II (color or black), Im-

ewriter LQ, and Laserwriter NT printers. The program comes in two versions, for Macs with or without a floating point math coprocessor. Both versions tested ran equally well under Multifinder. The programs are not copy protected and are easily transferred to a hard disk.

KG was reviewed very favorably in the February 1990 issue of *MacUser* magazine and in the April 1990 issue of *MacWorld*. Both reviews looked at it solely as another business application, since it is loaded with facilities for making pie charts, bar graphs, and a variety of other statistical formats that rarely appear in the pages of chemical journals. I shall stress the utility of KG as a scientific application.

The program has standard, very easy to use data entry features similar