of great versatility. The presence of an electron-donating group like oxygen on the olefin substituent of the cyclization substrate **9** which destabilizes the first step of the catalytic sequence[6] does not appear to harm the macrocyclization significantly. The use of the carbonate[15] precludes the need for exogenous base. A role of the sulfone group to conformationally anchor the 11-membered ring, and ultimately control the diastereoselectivity of the hydroxylation, may be a more general one, i.e., the sulfone group serves as a stereorelay between the tetrahydroisoindolinone and the C(17) hydroxyl group. We believe that these features impart versatility to this approach for the construction of many other natural (and unnatural) macrocycles of biological interest.

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institutes, for their generous support of our programs. S.J.B. and S.A.B. were supported in part by an NIH fellowship. We especially appreciate the generosity of Professor W. Keller-Schierlein (ETH, Zurich) for a comparison sample of (−)-aspochalasin B. Mass spectra were gratefully provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: Characterization data for **4–10** and **13b**, X-ray data, ORTEP drawing, atomic coordinates, isotropic thermal parameters, and selected interatomic distances and angles for **11**, and ORTEP drawing for calculated conformation for **10** (9 pages). Ordering information is given on any current masthead page.

(15) The first use of vinyl carbonates as substrates for alkylations was performed by G. Masse in our laboratories and cited in the following: Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550. This area has been intensely investigated by Tsuji et al. See: Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140.

Synthetic Studies Directed toward Naturally Occurring Cyclooctanoids. 2. A Stereocontrolled Assembly of (±)-Pleuromutilin via a Remarkable Sterically Demanding Oxy-Cope Rearrangement

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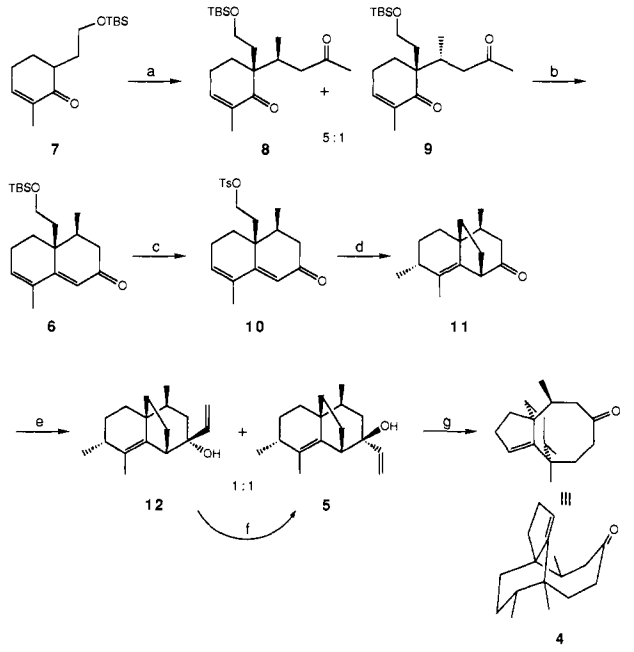
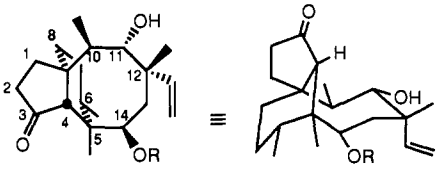
Pleuromutilin (**1**) represents a challenging vehicle to explore the development of methodology for the construction of eight-membered-ring systems and the direct installation of stereogenic centers in these ring systems based upon conformational analytical principles.[1-5] The complex stereostructure and chemistry of **1** (and mutilin (**2**)) and the practical utility of derivatives (e.g., tiamulin (**3**), used as an animal food additive to control dysentery in swine and poultry)[4] have stimulated other investigations, including the only successful synthetic approach to date, by Gibbons.[6,7]

Scheme I[a]



[a] Reagents: (a) 3-penten-2-one (1.4 equiv), LDA (1 equiv), THF, −23 °C, 2.25 h; (b) pyrrolidine (10 equiv), H^+ (catalytic), PhH, Δ, 48 h, then excess $HOAc/H_2O/NaOAc$ (2:2:1, w/w) added, Δ, 2 h; (c) $HOAc/H_2O/THF$ (2:1:1, v/v), 25 °C, 8 h, then *p*-TsCl (1.1 equiv), DMAP (catalytic), pyridine (8 equiv), CH_2Cl_2, 25 °C, 40 h; (d) $(CH_3)_2CuLi$ (1.05 equiv from CuBr–DMS (1.1 equiv)) and CH_3Li (2.1 equiv of 1.37 M solution in Et_2O), Et_2O, −78 °C, 1.33 h, then excess HMPA (20% v/v), 0 °C, 1 h; (e) **5** (dropwise) to $CH_2{=}CH$-MgBr (28 equiv), THF, 25 °C, 30 min; (f) PhSCl (1.4 equiv), THF, −20 °C → 25 °C, 30 min, then replace solvent with CH_3OH, $P(OEt)_3$ (3 equiv), Δ, 6 h; (g) KH (3.2 equiv), 18-crown-6 (1.5 equiv), diglyme (anhydrous), 25 °C → 110–115 °C, 1.5 h.



1 R = $C(O)CH_2OH$
2 R = H
3 R = $C(O)CH_2S(CH_2)_2N(C_2H_5)_2$

The two primary challenges reside in the efficient construction of the requisite substituted tricyclo[5.4.3.0^{1,8}]tetradecane nucleus and the stereocontrolled installation of the required eight stereogenic centers, all but one residing on the eight-membered ring. Two working hypotheses guided our selection of a strategy: (1) All the substituents (except the vinyl residue) on the eight-membered ring reside in equatorial-like environments in the most stable conformation (boat–chair (bc) from MM2 calculations). (2) The restrictions imposed on the conformations available to the eight-membered ring by the bridged bicyclic ring fusion (C_5–C_9) greatly reduce the conformational complexity of the system (only two unique low-energy conformations by MM2, bc and boat–boat (bb)). Thus, the target selected for ring-system construction was **4**, which is devoid of most of the stereogenic centers in the eight-membered ring. Construction of **4** (Scheme I) was envisioned via a key sterically demanding oxy-Cope rearrangement

(1) Isolation: Kavanaugh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1951**, *37*, 570.

(2) Arigoni, D. *Gazz. Chim. Ital.* **1962**, *92*, 884. Arigoni, D. *Pure Appl. Chem.* **1968**, *17*, 331.

(3) Birch, A. J.; Cameron, D. W.; Holzapfel, C. W.; Rickards, R. W. *Chem. Ind.* **1963**, 374. Birch, A. J.; Holzapfel, C. W.; Rickards, R. W. *Tetrahedron* **1966**, Suppl. 8, Part II, 359.

(4) Berner, H.; Vyplel, H.; Schulz, G. *Tetrahedron* **1987**, *43*, 765. Egger, H.; Reinshagen, H. *J. Antibiot.* **1976**, *29*, 915 and 923. Laber, G.; Schutze, E. *Antimicrob. Agents Chemother.* **1975**, *7*, 517.

(5) Dobler, M.; Durr, B. G. *Cryst. Struct. Commun.* **1975**, *4*, 259.

(6) Kahn, M. *Tetrahedron Lett.* **1980**, *21*, 4547. Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *J. Org. Chem.* **1988**, *53*, 1441. Paquette, L. A.; Bulman-Page, P. C.; Pansegrau, P. D.; Wiedeman, P. E. *J. Org. Chem.* **1988**, *53*, 1450. Paquette, L. A.; Wiedeman, P. E.; Pansegrau, P. D. *J. Org. Chem.* **1988**, *53*, 1461.

(7) Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767.

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of tricyclic vinyl carbinol **5** which could arise via a stereoelectronically controlled 1,6-addition/alkylation of a suitable derivative of dienone **6**.

The preparation of **5** (Scheme I) was initiated by condensation of the cross-conjugated enolate derived from enone **7** with 3-penten-2-one at −23 °C (temperature control required) to afford a chromatographically separable mixture of diketones **8** and **9** (5:1) in 73% yield.[8,9] Diketone **8** was cyclized via the pyrrolidine enamine, affording the required dienone **6** (98% yield). Desilylation of **6** ($HOAc/H_2O$) followed by tosylation of the resulting primary alcohol furnished dienone tosylate **10** for the key conjugate addition–alkylation sequence (74% overall from **6**).

Treatment of **10** with $LiCu(CH_3)_2$ in THF at −78 °C followed by addition of HMPA and warming to 0 °C over 1 h afforded the desired bicyclic enone **11** in 93% yield with complete axial stereoselectivity (the C_6 methyl was confirmed pseudoaxial (α) by NMR (J_{vic} = 6.0, 6.0 Hz, CH_2 at C_7 (see **1**))) resulting from stereoelectronic control in the cuprate addition.[10,11] Surprisingly, addition of $CH_2{=}CHMgBr$ to **11**, expected to proceed from the α face syn to the 1-carbon bridge, afforded a stereorandom addition, producing a readily separable mixture of alcohols **5** and **12** (1:1) in ~86% yield. Fortunately, **12** could be conveniently equilibrated to a mixture of **5** and **12** (~1:1) by treatment with $PhSCl/P(OEt)_3$ to produce **5** in 70% overall yield (after two cycles).[12]

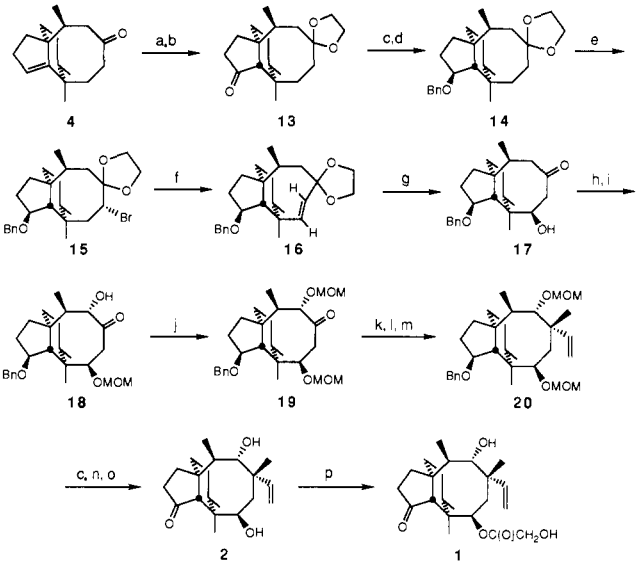
Few documented examples of the crucial oxy-Cope of a β,β-disubstituted system exist, and these generally proceed in low yield.[13] However, alcohol **5**, which possesses only one rotational degree of freedom, can readily assume the usually favored chair-like transition-state geometry. *Most gratifyingly, exposure of **5** to KH in diglyme at 110 °C in the presence of 18-crown-6 (2 equiv) for 1.5 h smoothly and exceedingly cleanly effected the desired rearrangement to afford ketone **4** in 99% yield.*[14] *The relative facility of the rearrangement in the present case may be due in part to the absence of side reactions such as retro ene processes owing to the presence of the allyl unit in a rigid framework.*[15]

Elaboration of **4** to (±)-**1** (Scheme II) was initiated by epoxidation of **4** (MCPBA) and rearrangement/selective ketalization of the resulting single diastereomeric epoxide with $BF_3{\cdot}Et_2O/(CH_2OH)_2$ producing the crystalline (mp 157–158 °C) keto ketal **13** (89% overall from **4**). This sequence avoids the intervention of transannular reactions, which are common in systems containing 1,5-functionalized eight-membered rings. The residual carbonyl group in **13** was converted to benzyl ether **14** (69% overall) using standard methods.

Introduction of the three remaining stereogenic centers on the eight-membered ring was envisioned to proceed via initial introduction of C_{13}–C_{14} unsaturation. Consideration of the two geometric isomers led to the conclusion that 1,4-addition at C_{14} appeared more feasible for the trans isomer.[16] Treatment of **14** with $PyH^+Br_3^-$ provided the equatorial bromo ketal **15** (≥8:1 regioselectivity), which underwent syn dehydrohalogenation (KO-*t*-Bu/DMSO) via the only stereoelectronically feasible pathway, to provide the trans ketal olefin **16** (67% overall from **14**). Since the trans olefin in **16** functions as an element of chirality, stereoselective 1,4-addition of the elements of H_2O (peripheral to the medium ring[17]) and hydrolysis of the ketal occurred upon exposure of **16** to *p*-TsOH (H_2O–acetone) at reflux, providing a single ketol **17** (67%). After protection of the C_{14} hydroxyl group (CH_3OCH_2Cl(MOMCl)/iPr_2NEt), the resulting MOM ketol (mp 122.5–124 °C) was converted regiospecifically to a single TMS enol ether (TMSI/HMDS), oxidized (MCPBA), and subjected to TBAF to afford the required C_{11} α ketol **18** (62% overall from **17**).[18,19] Protection of **18** as before (90%) produced bis-MOM ether **19**, whose spectroscopic data was indistinguishable from data for (±)-**19** reported by Gibbons and (+)-**19** obtained by degradation of natural (+)-mutilin (**2**).[7,20]

Introduction of the remaining C_{12} quaternary center proceeded from **19** in three steps by (1) addition of $CH_2{=}CHMgBr$, (2) conversion of the resulting tertiary carbinol to the primary allylic chloride ($SOCl_2$), and (3) S_N2' γ-alkylation with $CH_3CuB(CH_3)_3$,

Scheme II[a]



[a] Reagents: (a) MCPBA (1.3 equiv), hexanes, 0 °C → 25 °C, 12 h; (b) $BF_3{\cdot}Et_2O$ (3.15 equiv), PhH, 25 °C, 10 min, then $(CH_2OH)_2$ (7.2 equiv) added, 25 °C, 15 min; (c) Li (excess), anhydrous NH_3(l)–THF, −33 °C, 1 h, then NH_4Cl; (d) KH (8.6 equiv) THF, 0 °C → 25 °C, 1 h, then $PhCH_2Br$ (3 equiv), 25 °C, 20 min; (e) $PyH^+Br_3^-$ (1 equiv), THF, 0 °C, 10 min; (f) KO-*t*-Bu (5 equiv), DMSO, 110 °C, 1 h; (g) 1 M aqueous *p*-TsOH (2 equiv)/acetone (1:3 v/v, ~0.125 M in substrate), 65 °C (sealed system), 8 h; (h) CH_3OCH_2Cl (23 equiv), iPr_2NEt (23 equiv), CH_2Cl_2, 0 °C → 25 °C, 12 h; (i) TMSI (1.1 equiv), HMDS (3.1 equiv), CH_2Cl_2, −20 °C → 10 °C, 1.2 h, then aqueous $NaHCO_3$, 0 °C followed by MCPBA (1.2 equiv), $NaHCO_3$ (excess), CH_2Cl_2, 0 °C → 25 °C, 2 h, and then aqueous TBAF (1 M in H_2O–THF, 53 equiv), THF, 25 °C, 45 min; (j) CH_3OCH_2Cl (60 equiv in two portions), iPr_2NEt (60 equiv), CH_2Cl_2, 0 °C → 25 °C, 22 h; (k) $CH_2{=}CHMgBr$ (10 equiv), THF, 0 °C, 20 min; (l) $SOCl_2$ (5.9 equiv), THF, −30 °C → 0 °C, 20 min; (m) $CH_3CuB(CH_3)_3$ (from 10 equiv of CuBr–DMS, CH_3Li (7.9 equiv of 1.5 M solution), and $B(CH_3)_3$ (7.9 equiv of 0.16 M solution in hexane–ether–THF from BCl_3 and CH_3Li)), −40 °C, 15 min, then substrate, −40 °C → −20 to −15 °C, 4.5 h; (n) PCC (2.9 equiv), CH_2Cl_2, 25 °C, 4 h; (o) anhydrous HCl–EtOH (excess), 25 °C, 3 h; (p) $AcOCH_2COOMs$ (excess), DMAP (excess), THF, 25 °C, 12 h (two retreatments), then 5% aqueous KOH/CH_3OH, 25 °C, 8 h.

(8) McGuire, H. M.; Odom, H. C., Jr.; Pinder, A. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1879.

(9) All new substances exhibited spectroscopic data (IR, NMR (300 MHz), and MS) in accord with the assigned structure and provided acceptable combustion or high resolution mass spectral analytical data.

(10) Marshall, J. A.; Ruden, R. A.; Hirsch, L. K.; Phillipe, M. *Tetrahedron Lett.* **1971**, 587.

(11) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867. Boeckman, R. K., Jr. *J. Org. Chem.* **1973**, *38*, 4450. Posner, G. A.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(12) For a conceptually related case, see: Van Rheenan, V.; Shepard, K. P. *J. Org. Chem.* **1979**, *44*, 1582.

(13) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1. Swaninathan, S.; Srinivasan, R.; Venkataramani, P. S. *Tetrahedron* **1970**, *26*, 1453.

(14) Evans, D. A.; Golob, M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(15) Conversion to 4 fails in the absence of 18-crown-6, when the TBS ether of **5** is employed, and when rearrangement the epimeric vinylcarbinol is attempted (18-crown-6, 160 °C).

(16) In the course of his studies, Gibbons obtained a diene bearing a trans C_{13}–C_{14} double bond that exhibited a UV λ_{max} of 248 nm, indicating the presence of conjugation, where the corresponding cis isomer had no λ_{max} >215 nm.[23]

(17) For related applications of conformationally directed stereocontrol, see: Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(18) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(19) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

(20) Springer, D. M. Ph.D. Dissertation, University of Rochester, 1989. We thank Drs. Russell Buchman and Larry Powers and Fermenta USA for a generous gift of tiamulin (**3**), which was utilized for our degradative work.

providing **20** (5:1, γ/α) in 60% overall yield from **19**.[21] Conversion of **20** (Scheme II) to (±)-mutilin (**2**) proceeded uneventfully by standard methods (80% overall from **20**). (±)-**2** (mp 186.5–188 °C; lit.[7] mp 187.5–189 °C) was spectroscopically identical with both natural (+)-**2** and synthetic (±)-**2**.[7] (±)-**2** was converted to (±)-pleuromutilin (**1**) by the two-step procedure of Gibbons.[7] (±)-**1** (mp 167–169.5 °C) was also spectroscopically identical with natural (+)-**1**.[22]

The synthetic route described above makes use of novel approaches to the construction of the tricyclic framework and for introduction of the stereogenic centers present on the eight-membered ring, and provides (±)-pleuromutilin (**1**) in 25 steps from readily available materials.

Acknowledgment. We are extremely grateful to the Institute of General Medical Sciences (NIGMS) of the National Institutes of Health for a grant (GM-29290) in support of these studies.

Supplementary Material Available: NMR spectroscopic data for compounds **1**, **2**, **4–8**, and **10–20**, combustion analytical data for compounds **5**, **6**, **8**, **11**, **15**, **17**, **19**, and **20**, and HRMS data for compounds **4**, **13**, and **14** (21 pages). Ordering information is given on any current masthead page.

(21) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318.

(22) The melting point reported for (±)-**1** is the first reported determination since the Gibbons conversion of (±)-**2** to (±)-**1** was effected on a sample that had been admixed with authentic (+)-**2** as a relay.[23]

(23) Gibbons, E. G. Ph.D. Dissertation, Harvard University, 1982.

A New, Highly Efficient, Selective Methodology for Formation of Medium-Ring and Macrocyclic Lactones via Intramolecular Ketene Trapping: An Application to a Convergent Synthesis of (−)-Kromycin

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Over the past decade, there has been intense interest in the development of methodology for formation of macrocyclic and medium-ring lactones, since a number of these substances possess important and useful biological properties.[1] A number of ingenious methods have been developed and applied to the synthesis of an array of naturally occurring systems.[2–4] However, limitations on most of the methods exist due particularly to the incompatibility of the activated carbonyl derivative that is the common intermediate in most methods with a number of functional groups and reaction conditions. Thus, the development of a method incorporating a masked activated carbonyl derivative that would be compatible with a variety of types of transformations and that would permit generation of the reactive species under mild neutral conditions in the presence of the nucleophilic hydroxyl group might serve to overcome many of the limitations. We describe in this communication the use of dioxolenones as precursors of β-acyl ketenes,[5] which can be thermally generated under mild neutral conditions in the absence of other nucleophiles to afford good yields of medium- and large-ring lactones[6–8]

(1) *Macrolides*; Omura, S., Ed.; Academic Press: New York, 1984.

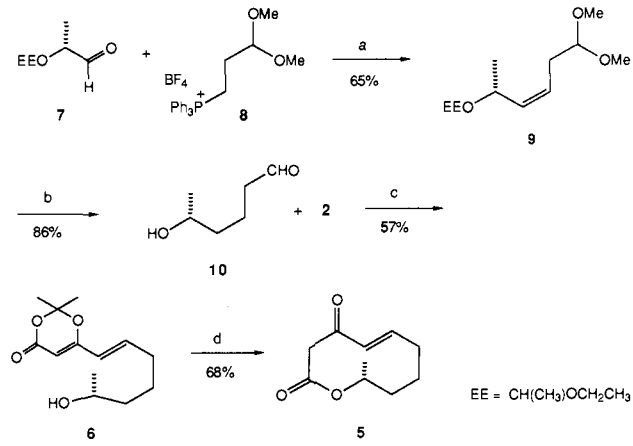
(2) Nicoloau, K. C. *Tetrahedron* **1977**, *33*, 683. Masamune, S.; Bates, G. S.; Corcoran, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(3) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(4) Boeckman, R. K., Jr.; Goldstein, S. W. *Total Synth. Nat. Prod.* **1988**, *7*, 1.

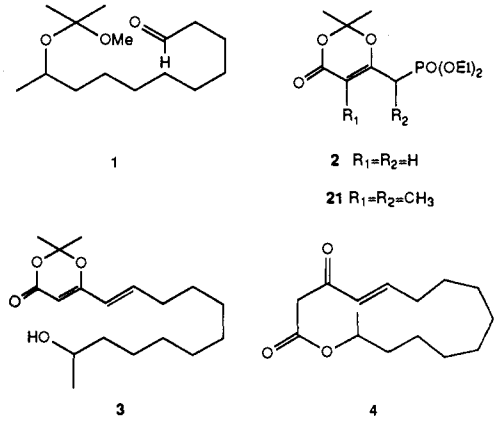
(5) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, *49*, 5105.

Scheme I[a]



[a]Reagents: (a) **8** (1.05 equiv), *t*-BuOK (1.05 equiv), THF, 0 °C, then **7** (1 equiv), −20 °C → 25 °C, 3 h; (b) H_2 (3 atm), PtO_2, EtOAc, 12 h, then Amberlyst-15 (catalytic), THF–H_2O (98:2, v/v); (c) **2** (2 equiv), *t*-BuOK (2 equiv), THF, −78 °C → 25 °C, 5 h; (d) **6** (~10^{-4} M), $PhCH_3$, Δ, 4 h.

We initiated our investigation by attempting formation of a 15-membered lactone. Treatment of the protected hydroxy aldehyde **1**[9] with dioxolenone phosphonate **2**[10] and *t*-BuOK in THF provided the required dioxolenone **3** after deprotection (Amberlyst-15/2% aqueous acetone) in ~80% overall yield.[11] Thermolysis of **3** in $PhCH_3$ at reflux (~10^{-4} M) for 2 h cleanly afforded the desired β-keto lactone **4** in 60% yield (unoptimized) after chromatographic purification.[12]



To investigate the limitations of the cyclization method and enable direct comparison of the efficiency with other known methods, we next chose to prepare (+)-diplodialide A (**5**) as shown in Scheme I.[13] The strained 10-membered ring in **5** bearing a

(6) For representative cases of bimolecular trapping, see: Sato, M.; Kanuma, N.; Sato, T. *Chem. Pharm. Bull.* **1984**, *32*, 106. Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177. Yamamoto, Y.; Morita, Y. *Chem. Pharm. Bull.* **1984**, *32*, 2555. Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848. See also ref 7.

(7) Boeckman, R. K., Jr.; Potenza, J. C.; Enholm, E. J. *J. Org. Chem.* **1987**, *52*, 469.

(8) For cases of intramolecular trapping, see: Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486 (by an amine). Quinkert, G.; Billhardt, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Durner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771 (by alcohols using photochemical ketene generation).

(9) Available in four steps from 10-undecenoic acid by standard methods.

(10) Boeckman, R. K., Jr.; Thomas, A. J. *J. Org. Chem.* **1982**, *47*, 2823. Boeckman, R. K., Jr.; Perni, R. B.; Macdonald, J. E.; Thomas, A. J. *Org. Synth.* **1988**, *66*, 194.

(11) All new substances exhibited satisfactory spectroscopic (NMR, IR, UV) and combustion or high resolution mass spectral analytical data.

(12) The cyclizations are conducted by addition of the substrate via syringe pump to refluxing $PhCH_3$ at such a rate as to maintain ~10^{-4} M in reacting substrate.

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