Communications to the Editor

Cyclization Terminators. Vinylcyclopropanol as a Composite Functional Group

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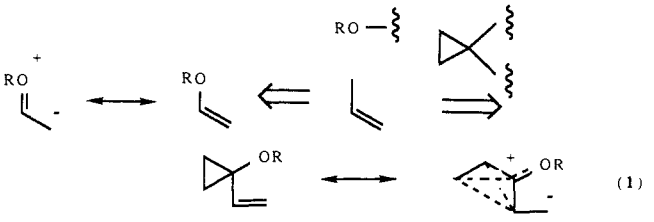
Received March 14, 1988

The efficacy of cyclizations depends critically on the choice of initiator and terminator. The magnitude of the success of such processes by proper choice of these groups is highlighted by the polyolefin cyclization to polycycles.[1] We wish to report that utilizing vinylcyclopropanols as cyclization terminators permits an unexpected facility in ring construction highlighted by efficient formation of eight-membered rings.

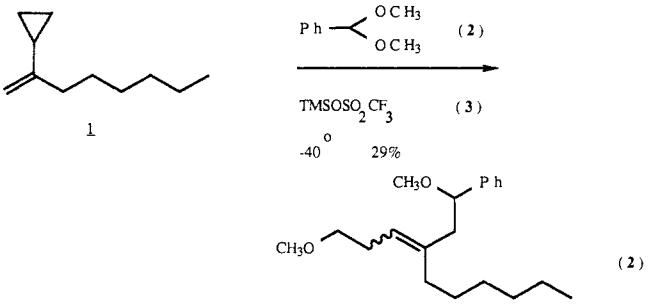
The composite of an olefin and a hydroxyl group which generates an enol creates a special reactivity associated with the strong electron donation from oxygen to carbon in spite of the electronegativity of oxygen (eq 1). It can be imagined that the composite



(1)

of an olefin and a hydroxyl group mediated through a cyclopropane in the form of a 1-vinylcyclopropanol[2,3] may still permit polarization of the double bond to enhance its nucleophilicity as depicted in eq 1.

The susceptibility of the double bond toward electrophilic attack tests such a concept. Qualitative observations support this notion. For example, whereas, the vinylcyclopropane **1** reacts with benzaldehyde dimethyl acetal (**2**) in the presence of trimethylsilyl trifluoromethanesulfonate (**3**) only at temperatures of −40 °C or higher (eq 2), the vinylcyclopropyl silyl ether **4** participates smoothly in such a reaction at −78 °C (eq 3).[4] In the absence of electron donation by oxygen at the transition state, the addition of this electronegative substituent should have resulted in a rate retardation. Furthermore, the nature of the group on oxygen also plays a role. Replacing trimethylsilyl by acetyl does retard the reaction as expected for a transition state requiring electron donation by oxygen.



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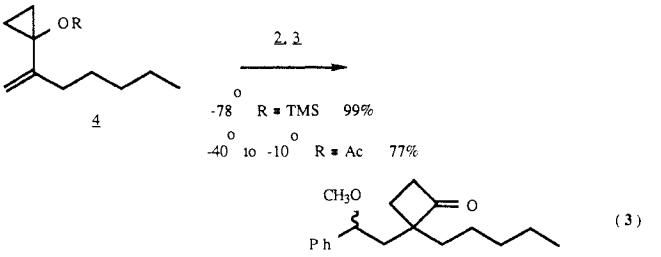
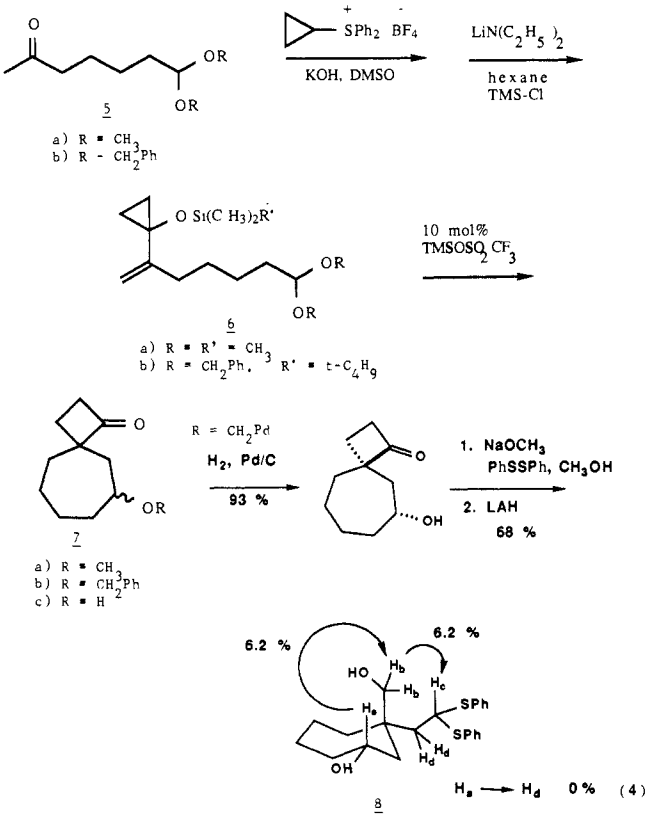


(3)

Such enhanced nucleophilicity of the olefin combined with the utility of a cyclobutanone for further structural manipulation[5] led us to explore the use of the trimethylsilyl ethers of vinylcyclopropanols as terminators in cationic initiated cyclizations. The requisite vinylcyclopropanol substrates can be readily synthesized in two steps from appropriate ketoacetals (eq 4). Treatment of **5a** or **5b** with cyclopropyldiphenylsulfonium fluoroborate[6] and powdered potassium hydroxide provides an oxaspiropentane which



(4)

is converted to the vinylcyclopropyl silyl ether **6a** or **6b** by

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(1) For a recent innovation in terminators see: Johnson, W. S.; Telfer, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2517. For reviews see: Johnson, W. S. *Angew. Chem.* **1976**, *15*, 9; *Biorg. Chem.* **1976**, *5*, 51.

(2) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311. Trost, B. M.; Kurozumi, S. *Tetrahedron Lett.* **1974**, 1929. Salaun, J.; Ollivier, J. *Nouv. J. Chem.* **1981**, *5*, 587. Girard, C.; Amice, P.; Barnier, J. P.; Conia, J. M. *Tetrahedron Lett.* **1974**, 3329.

(3) Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980**, *45*, 2874 and references therein. Salaun, J.; Garnier, B.; Conia, J. *Tetrahedron* **1974**, *30*, 1413. Bourelli-Wargnier, F. *Tetrahedron Lett.* **1974**, *1589*. Trost, B. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1983**, *105*, 6755. Trost, B. M.; Mao, M. K. T.; Balkovec, J. M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965. Also see: Salaun, J. *Chem. Rev.* **1983**, *83*, 619; Trost, B. M. *Acc. Chem. Res.* **1974**, *7*, 85; *Pure Appl. Chem.* **1975**, *43*, 563. Brady, W. T. *Tetrahedron* **1981**, *37*, 2649.

(4) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041.

(5) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3.

(6) Bogdanowicz, M. J.; Trost, B. M. *Org. Synth.* **1974**, *54*, 27.

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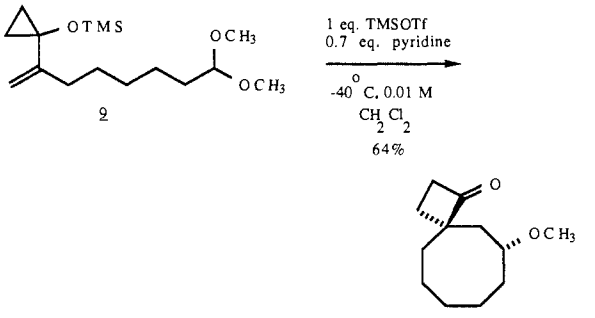
treatment with lithium diethylamide in hexane followed by trimethylsilyl chloride (49–97%).[2] Exposure to 10 mol % of silyl triflate **3** at −40 °C (for **7a**) or boron trifluoride etherate and pyridine at −20 °C (for **7b**) provides a 60–93% yield of the seven-membered-ring **7a**[7] or **7b**[7] as a 2:1 mixture of diastereomers. The stereochemical assignment of the major isomer is based on an NOE study of **8**[7] available from the major isomer of **7b** via debenzylation, secosulfenylation,[8] and reduction as shown in eq 4.

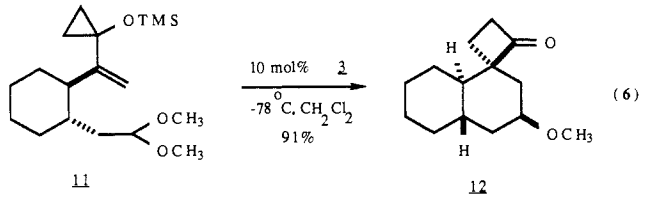
Astonishingly, ready formation of an eight-membered ring (**10**)[7] can be accomplished by treating the silyl ether **9** with 1 equiv of catalyst **3** and 0.7 equiv of pyridine at −40 °C without resorting to high dilution (0.01 M in methylene chloride) in 64% yield (eq 5).[9,10] The major diastereomer (9:1 ratio) is tentatively assigned



9 10 (5)

as depicted based upon mechanistic considerations and analogy to other cyclizations.

The possibility for relay of stereochemistry from preexisting asymmetric centers to two newly created asymmetric centers was explored by using vinylcyclopropyl silyl ether terminators to create fused-ring systems. Cyclization of **11** upon treatment with catalytic TMSOTf at −78 °C afforded 91% of a 7:1 mixture of the bicyclo[4.4.0]decane **12**[7] epimeric at the methoxy group as depicted in eq 6. The stereochemistry of the major isomer was assigned on the basis of an analysis of the ^1H and ^{13}C NMR spectra.[11,12]



11 12 (6)

Equation 7 illustrates the application of this methodology to a synthesis of the commonly occurring perhydroazulene skeleton.

(7) All new compounds have been fully characterized by spectral means including combustion analysis and/or high-resolution mass spectroscopy.

(8) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1976**, *41*, 3217.

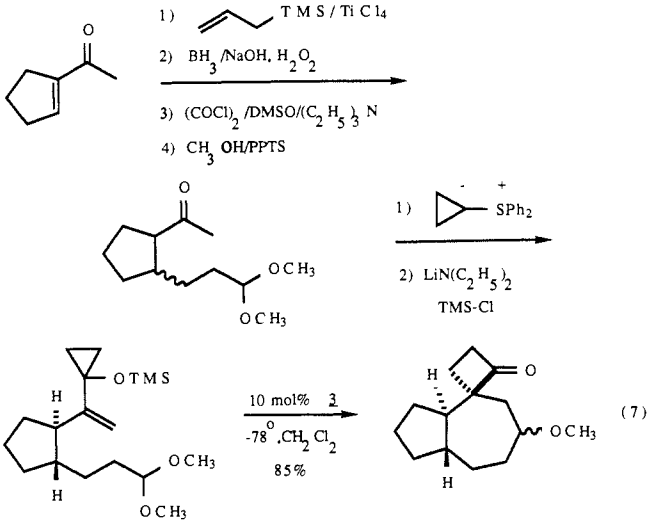
(9) For some recent work on the formation of eight-member carbocyclic rings by direct cyclization see: McMurray, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255. Krishnappa, S. *Indian J. Chem.* **1984**, *23B*, 412. Bertram, H. J.; Winterfeldt, E. *Annalen* **1986**, 456. Berthiaume, G.; Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5451. Kende, A. S.; Johnson, S.; SanFilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. Kato, N.; Nakinishi, K.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1109. Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. Cambie, R. C.; Clark, G. R.; Craw, P. A.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1984**, *37*, 1775. Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303. Taafrout, M.; Landais, T.; Robin, J.-P. *Tetrahedron Lett.* **1986**, *27*, 1781. Robin, J.-P.; Dhal, R.; Brown, E. *Tetrahedron* **1984**, *40*, 3509. Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446. Majetich, G.; Behnke, M.; Hull, K. *J. Org. Chem.* **1985**, *50*, 3615. Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. I* **1985**, 2101. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.

(10) For some recent work on eight-membered-ring oxygen heterocycles see: Cockerill, G. S.; Kocienski, P. C. *J. Chem. Soc., Perkin Trans. I* **1985**, 2093. Nicolaou, K. C.; Duggan, M. E.; Hwan, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516.

(11) Structural assignment discussed in the Appendix.

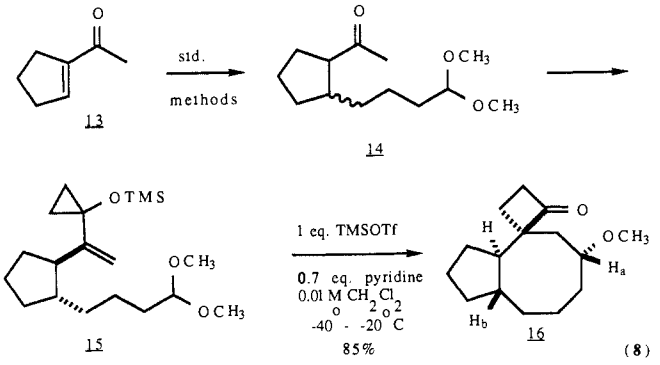
(12) Trost, B. M.; Scudder, P. *J. Am. Chem. Soc.* **1977**, *99*, 7601.

This example illustrates the source of the requisite keto acetal from 1-acetylcyclopentene by a Sakurai conjugate allylation,[13] hydroboration—oxidation, and acetal formation. The stereochemistry depicted is based upon spectral considerations and analogy.



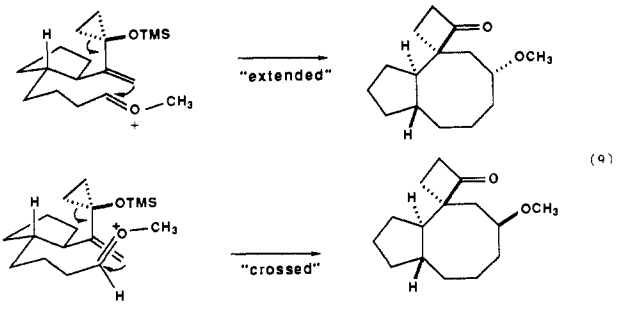
(7)

The facility with which an eight-membered ring can be generated is once again demonstrated by the formation of a trans-fused bicyclo[6.3.0]undecane ring system in 96% yield upon treatment of **15** with 1 equiv of silyl triflate **3** and 0.7 equiv of pyridine at 0.01 M in methylene chloride at −50 to −20 °C as shown in eq 8. An 11.5:1:1 mixture of three isomers was obtained. The major isomer assigned as depicted in **16**[7] could be obtained in 85% yield by flash chromatography.



(8)

Analogous to an enol silyl ether, the vinylcyclopropanol composite functional group should react with acetals in an extended type of orientation[14] with the more favorable equatorial oxonium ion through a crown type conformation as depicted in eq 9 for the formation of the bicyclo[6.3.0]undecane system. The stereochemistry predicted by this type of transition-state model is in accord with the stereochemistry assigned to the bicyclo[6.3.0]-undecane system (vide supra).



(9)

(13) Sakurai, H. *Pure Appl. Chem.* **1982**, 54, 1. Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(14) Murata, S.; Suzuke, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

Equation 7 illustrates several useful features of this novel annulation strategy. The methyl ketone **14** need not be stereohomogeneous since using the potassium hydroxide conditions for the ylide condensation effects epimerization faster than sulfur ylide addition to the carbonyl group.[5] The trans diastereomer which possesses the sterically more accessible carbonyl group assures the trans stereochemistry of **15** and consequently the annulation product **16**. Conjugate addition methodology makes the keto acetal **14** easily available from 1-acetylcyclopentene. The efficiency with which the vinylcyclopropanol composite functional group acts as a terminator in electrophilic cyclizations forming six-to-eight-membered rings, the possibility for further structural elaboration of the spirocyclobutanone products, and the high diastereoselectivity observed in the generation of quaternary carbons in the form of a spirocyclobutanone in compounds **10**, **12**, and **16** make this methodology especially useful for the synthesis of complex natural products containing these rings.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs. We thank Dr. Bruce Adams and Rebecca Braslau for high-field NMR spectra (SPT difference, NOE, COSY, and CH correlation).

Registry No. 5a, 36727-64-7; **5b**, 115756-88-2; **6a**, 115796-54-8; **6b**, 115756-89-3; *trans*-**7a**, 115756-90-6; *cis*-**7a**, 115756-95-1; *trans*-**7b**, 115756-91-7; *cis*-**7b**, 115756-94-0; *trans*-**7c**, 115756-92-8; **8**, 115756-93-9; **9**, 115756-96-2; *trans*-**10**, 115756-97-3; *cis*-**10**, 115756-98-4; **11**, 115756-99-5; **12**, 115757-00-1; **12** (methoxy epimer), 115887-53-1; **13**, 16112-10-0; *trans*-**14**, 115757-05-6; *cis*-**14**, 115757-06-7; **15**, 115757-07-8; **16**, 115757-08-9; **16** (methoxy epimer), 115887-55-3; cyclopropyldiphenylsulfonium fluoroborate, 33462-81-6; *trans*-1-acetyl-2-(3,3-dimethoxypropyl)cyclopentane, 115757-01-2; *cis*-1-acetyl-2-(3,3-dimethoxypropyl)cyclopentane, 115757-02-3; *trans*-1-[1-[1-(trimethylsilyloxy)cyclopropyl]vinyl]-2-(3,3-dimethoxypropyl)cyclopentane, 115757-03-4; (3aα,4β,6β,8aβ)-6-methoxyperhydrospiro[azulene-4,1'-cyclobutane]-2-one, 115757-04-5; (3aα,4β,6α,8aβ)-6-methoxyperhydrospiro[azulene-4,1'-cyclobutane]-2-one, 115887-54-2.

Supplementary Material Available: Characterization data for **7a**, **7b**, **8**, **10**, **12**, **16**, and 4-methoxybicyclo[6.3.0]undecane-2-spiro-1'-cyclobutan-2'-one (3 pages). Ordering information is given on any current masthead page.

A Synthesis of Taxusin

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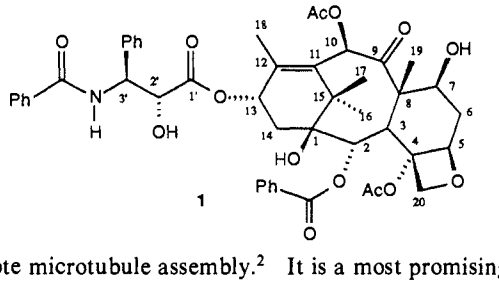
Received April 8, 1988

The compound taxol (**1**)[1] has been the subject of extraordinary interest. It exhibits unique biological activity through its ability

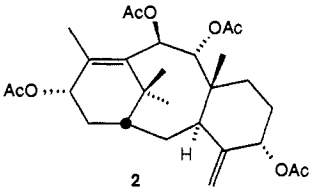


1

to promote microtubule assembly.[2] It is a most promising antitumor agent,[1,3] now in phase II clinical trials, obtained by isolation from the bark of the pacific yew tree.[1,4] The most recent harvest, which requires sacrifice of ca. 12 000 trees to obtain ca. 60 000 pounds of bark and 2.5 kg of taxol, threatens the survival of the pacific yew and its habitat, the virgin rainforest, and is a subject of considerable environmental concern.[5]

These factors combine with the skeletal and stereochemical complexity of the taxanes[6] to provide an enormous synthetic challenge. Although a number of synthetic approaches have been reported,[7] none of the natural products have heretofore been synthesized.

We now describe the first synthesis of taxusin (**2**).[8] The cornerstone of this work, like that of our taxane skeleton synthesis,[9] is the fragmentation of a bicyclic epoxy alcohol.[10]



2

The synthesis proceeds from the commodity chemical patchino (**3**),[11] which, upon treatment with *tert*-butyllithium (hexane, reflux, 5 h) gave rise to the sensitive tertiary allylic alcohol **4**, which typically was epoxidized (*t*-BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, 2 h) without purification to give **5**,[12] mp 97-99 °C $[\alpha]^{25}_{Hg}$ -5° (CH_3OH, *c* 11.91), in 98% yield from **3**. Epoxy alcohol **5** rearranged ($BF_3{\cdot}Et_2O$, CF_3SO_3H, CH_2Cl_2, -80 °C, 22 h) to diol **6**,[12] mp 100-101 °C $[\alpha]^{25}_{Hg}$ +67° ($CHCl_3$, *c* 0.50), in 93% yield at 75% conversion.[13] Oxidation of diol **6** (PDC, DMF; 94%) furnished ketone **7**,[12] mp 71-72 °C $[\alpha]^{25}_{Hg}$ +57° ($CHCl_3$, *c* 4.76),

(1) (a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggan, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. (b) Miller, R. W.; Powell, R. G.; Smith, C. R., Jr. *J. Org. Chem.* **1981**, *46*, 1469 and references contained therein.

(2) For leading references, see: (a) Manfredi, J. J.; Fant, J.; Horwitz, S. B. *Eur. J. Cell Biol.* **1986**, *42*, 126. (b) Solari, A. J.; Duschak, V. G. *Micro Sc. Electron. Biol. Cel.* **1985**, *9*, 163. (c) Bhattacharyya, B.; Ghoschaudhuri, G.; Maity, S.; Biswas, B. B. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 791. (d) Horwitz, S. B.; Lothstein, L.; Manfredi, J. J.; Melcado, W.; Parness, J.; Roy, S. N.; Schiff, P. B.; Sorbara, L.; Zeheb, R. *Ann. N.Y. Acad. Sci.* **1986**, *466*, 733. (e) Wallin, M.; Nordh, J.; Deinum, J. *Biochim. Biophys. Acta* **1986**, *880*, 189.

(3) For leading references, see: (a) Riondel, J.; Jacrot, M.; Picot, F.; Beriel, H.; Mouriquand, C.; Potier, P. *Cancer Chemother. Pharmacol.* **1986**, *17*, 137. (b) Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83. (c) Hamel, E.; Lin, C. M.; Johns, D. G. *Cancer Treat. Rep.* **1982**, *66*, 1381. (d) Suffness, M.; Douros, J. D. *Methods Cancer Res.* **1979**, *16*, 73. (e) Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219. (f) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(4) Large scale isolation: Boettner, F.; Williams, M.; Boyd, R.; Halpern, B. D., preparation Report 9 on Contract N01-CM-77070, N.C.I.

(5) A large number of articles describing this situation have appeared in U. S. and Canadian newspapers and magazines. For leading references, see: (a) *The New York Times*, **1987**, May 3, I, 29:1. (b) Strycker, L. *The Register-Guard* (Eugene, OR), **1987**, *120* (*166*), 1B. (c) Brooks, B. *Tallahassee Democrat* (FL) **1987**, *82* (*270*), 1E. (d) *Audubon*, 9/87. (e) Boling, R. *Equinox* **1988**, *37*, 7:1, 107.

(6) Review: Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

(7) Synthetic studies from over 20 different laboratories have been described. See: (a) Swindell, C. S.; Patel, B. P. *Tetrahedron Lett.* **1987**, *28*, 5275. (b) Kraus, G.; Thomas, P. J.; Hon, Y. S. *J. Chem. Soc., Chem. Commun.* **1987**, 1849. (c) Pettersson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753. (d) Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221. (e) Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 3513. (f) Winkler, J. D.; Hey, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6425 and references cited therein.

(8) (a) Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Liu, C. L.; Lin, Y. C.; Lin, Y. M.; Chen, F. C. *T'ai-wan K'o Hsueh* **1984**, *38*, 119. (c) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931. (d) Lee, C. L.; Hirose, Y. *Nakatsuka Mokuzai Gakkaishi* **1975**, *21*, 249. (e) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923.

(9) Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 5731.

(10) Holton, R. A.; Kennedy, R. M. *Tetrahedron Lett.* **1984**, *25*, 4455.

(11) Patchino (**3**) is the International Flavors and Fragrances, Inc. trade name for β-patchoulene oxide, $[\alpha]^{25}_{Hg}$ -10°; $[\alpha]^{25}_{Na}$ -8° ($CHCl_3$, *c* 1.12).[21]

(12) Characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS or elemental analysis.

(13) Diol **6** is the kinetic product of this rearrangement: Holton, R. A.; Juo, R. R.; Lowenthal, R. E.; Goedken, V., manuscript in preparation.

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