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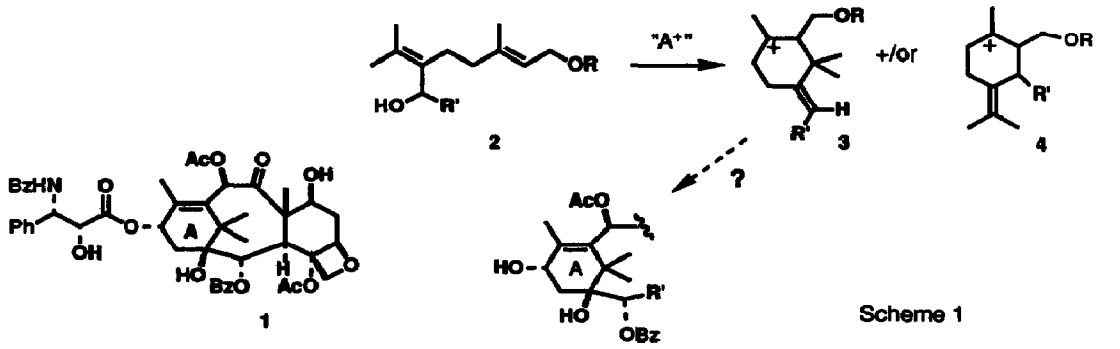
Regiospecificity in the Cyclization of 6-(1-Hydroxyalkyl) Geraniol Derivatives. A Simple Route to the Taxol A-Ring System.

Takayuki Doi[1a], Jeremy Robertson[1b], Gilbert Stork,* and A. Yamashita[1c]
Department of Chemistry, Columbia University, New York, NY10027

Abstract: *Readily available derivatives of geraniol bearing a 1-hydroxyalkyl side chain in the 6-position undergo acid-catalyzed regiospecific cyclization to form cyclogeraniol derivatives which have an interesting relation to ring A of taxol.*

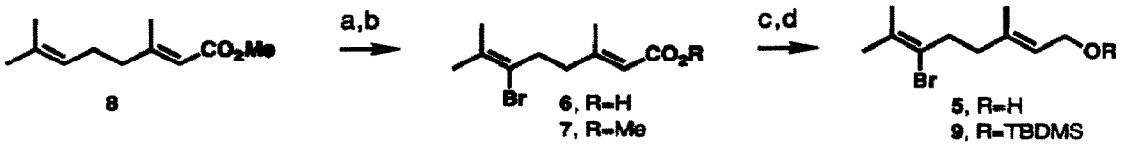
The relationship of the structure of ring A of taxol (**1**)[2] to that of geraniol strongly suggests the desirability of the latter as a starting material for its construction. We now report that 6-(1-hydroxyalkyl) derivatives of geraniol (**2**, scheme 1) undergo cationic cyclization, readily and in good yield, and that the regiochemistry of these cyclizations can be controlled to form **3** rather than **4**. This result is of special interest in the context of those approaches to taxol which start with the construction of ringA.[3]



Scheme 1

An obvious starting material for allylic alcohols of type **2** would be 6-bromogeraniol (**5**), but, surprisingly, neither that simple substance nor the related 6-bromogeranic acid (**6**), or its esters (cf **7**), appear to have been described in the literature. The route we followed to the *tert*-butyldimethylsilyl ether of 6-bromogeraniol (**9**) is shown in Scheme 2, starting with the regiospecific addition of bromine to the 6,7 double bond of methyl geranate (**8**).[4,5]

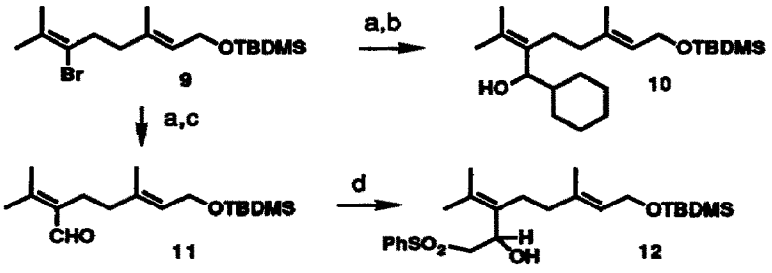
The ether **9** was used in two different constructions of the desired allylic alcohols. In the first, formation of the vinyl lithium derivative was followed by addition of cyclohexanecarboxaldehyde to give the carbinol **10** in quantitative yield. The high yield (82%) of unsaturated aldehyde **11**



a) Br_2, CH_2Cl_2, -20 °C to room temperature; b) DBU, CH_2Cl_2, reflux, 1h; c) AlH_3[6], THF, 0 °C,1h; 62% from **8**; d) TBDMS-Cl, Imidazole, CH_2Cl_2, 0 °C, 12h; 80%.

Scheme 2

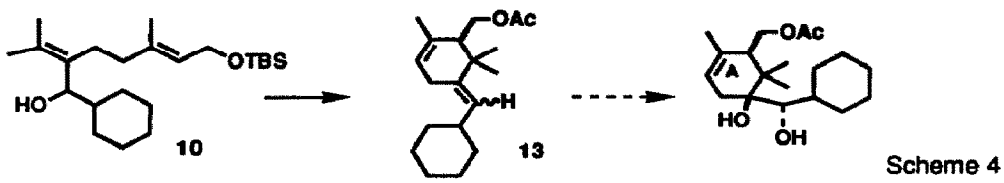
obtained by reaction of the lithium derivative from **9** with dimethylformamide provides another route to those allylic alcohols not easily obtainable by the method used to make **10.** For example, reaction of **11** with phenylsulfonylmethylmagnesium bromide[7] produced the allylic carbinol **12** in quantitative yield.



Scheme 3

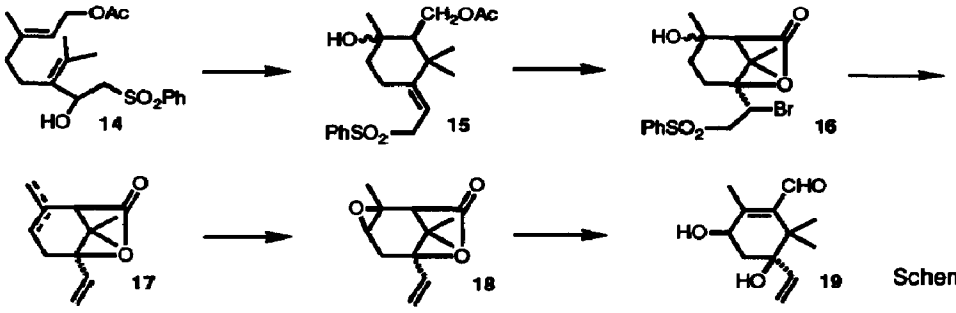
a) t-BuLi, THF, -78 °C, 1h; b) cyclohexanecarboxaldehyde, -78 °C, 10 min; quantitative from**9**; c) DMF, -78 °C; 82%; d) see text.

We could now explore the regiochemistry of the cationic cyclization of **2**. We anticipated that the interplay of the usual two effects, electron distribution and steric crowding, might be adjusted to favor the course **2** to **3**, but we were surprised by the ease with which cyclization took place in the direction we had hoped.[8] For instance, when allylic alcohol **10** was dissolved in acetic anhydride, followed , at 0° C, by a catalytic amount (0.25 equiv) of ferric chloride, TLC analysis indicated complete disappearance of the starting material after 1.5h. The ^1H nmr spectrum of the product, however, showed not only the expected complete conversion of the siloxy group to the acetate,[9] but also that *cyclization had taken place* to yield (65%, unoptimized) the, *predominantly E*, diene **13.** It will be realized that even this simple case has some conceptual connection to taxol when the structure of the latter is compared to that of one of the cis glycols derivable from **13** (Scheme 4).



Scheme 4

The success of the simple model cyclization above prompted us to examine the cyclization reaction in a case more obviously related to the taxol A ring problem. Cyclization of **14** (3 equiv 0.5 % BF_3·Et_2O[10] in CH_2Cl_2 at -30 ~ -15 °C; quenched with saturated $NaHCO_3$) proceeded, again regioselectively at the tertiary site, to give **15** (72%; 3:1 mixture of tertiary alcohol epimers [11,12]). We believe that, in this case, the electronic and steric effects of the sulfonyl group are both involved in inhibiting cyclization at the secondary center (Scheme 5).



Scheme 5

Hydrolysis of the acetate of **15** and oxidation of the resulting alcohol with Jones reagent to the corresponding acid was followed by treatment with NBS in THF to give the anticipated bromolactone **16** (52% from **15**). The latter could be transformed into the dienic lactone **17** by reductive elimination with tributylstannane[13] in refluxing benzene (92%), followed by dehydration of the tertiary alcohol function with 1.1 equiv of BF_3·Et_2O[14] in refluxing CH_2Cl_2. Lactone **17** was thus obtained (90%) as a 3:1 endo - exo mixture,[15] the endo component of which reacted selectively with 1.2 equiv of *m*CPBA at room temperature to give monoepoxide **18** (68%).[16] Reduction of the lactone system of **18** with 1.2 equiv of DIBAL, followed by treatment with DBU at 40-50 °C, gave the usefully functionalized γ–hydroxy-α,β-unsaturated aldehyde **19** (40%).[17,18] Aside from any taxol related interest, the regiospecific cyclization described here should expand the already large area of usefulness of cationic polyene cyclizations.[19]

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References and Notes.

(1) Current Addresses: (a) Dept. of chem. engineering, Tokyo Institute of Technology, Tokyo 152, Japan. (b) The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K. (c) Lederle Laboratories, Pearl River, NY 10965.

(2) For a recent review, see Kingston, D.G.I; Molinero, A.A.; Rinaldi, J.M., *Progress in the Chemistry of Organic Natural Products*, vol. 61, Springer Verlag: New York, 1993, pp. 1ff.

(3) For recent examples of other approaches to the taxol ring A substructure: (a) Lu, Y. F.; Fallis, A. G. *Tetrahedron Lett.* 1993 *34*, 3367. (b) Wang, Z.; Warder, S. E.; Perrier, H ; Grimm, E. L.; Bernstein, M. A.;Bell, R. G. *J. Org. Chem.* 1993, *58*,

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(4) Cf Kato, T.; Ichinose, I. *J. Chem. Soc. Perkin Trans. 1* **1980**, 1051.

(5) Spectral data in agreement with the reported structures were obtained for all compounds in this paper.

(6) The use of AlH_3 was necessary to avoid the partial reduction of the vinylic halide which was observed with $LiAlH_4$.

(7) (a) Kohler, E. P.; Potter, H. *J. Am. Chem. Soc.* **1935**, *57*, 1316. (b) Field, L. *J. Am. Chem. Soc.* **1952**, *74*, 3919.

(8) In contrast, a similar competition in a *cyclohexyl system* led entirely to bond formation at the *secondary* center: Johnson, W. S.; Neustaedter, P. J.; Schmiegel, K. K. *J. Am. Chem. Soc.* **1965**, *87*, 5148.

(9) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728.

(10) Cf Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. Cyclization of **14** with ferric chloride was unsuccessful in this case.

(11) For the origin of the tertiary hydroxyl, see Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581.

(12) ^{1}H NMR **15** (200 MHz, $CDCl_3$) δ, major isomer, 0.95 (s, 3H), 1.1-1.3 (m, 1H), 1.16 (s, 3H), 1.20 (s, 3H), 1.4-1.6 (m, 2H), 1.7-2.0 (m, 1H), 2.0-2.2 (m, 1H), 2.04 (s, 3H), 3.86 (d, 2H, J=8.0 Hz), 4.13 (dd, 1H, J=5.1, 12.0 Hz), 4.25 (dd, 1H, J=4.6, 12.0 Hz), 5.27 (t, 1H, J=8.0 Hz), 7.5-7.7 (m, 3H), 7.8-7.9 (m, 2H); minor isomer: 0.8-1.3 (m, 2H), 1.03 (s, 3H), 1.08 (s, 3H), 1.15 (s, 3H), 1.4-1.6 (m, 1H), 1.9-2.2 (m, 2H), 2.04 (s, 3H), 3.83 (dd, 1H, J=8.0, 15.0 Hz), 3.87 (dd, 1H, J=8.0, 15.0 Hz), 4.25 (dd, 1H, J=3.2, 12.7 Hz), 4.44 (d, 1H, J=4.8, 12.7 Hz), 5.27 (t, 1H, J=8.0 Hz), 7.5-7.7 (m, 3H), 7.83 (d, 2H, J=9.0 Hz).

(13) Cf Lythgoe, B.; Waterhouse, I. *Tetrahedron Lett.* **1977**, 4223.

(14) Posner, G. H.; Shulman-Roskes, E. M.; Oh, C. H.; Carry, J.-C.; Green, J. V.; Clark, A. B.; Dai, H.; Anjeh, T. E. N. *Tetrahedron Lett.* **1991**, *32*, 6489, and references therein.

(15) The exo olefin component of the dienic lactone mixture could be isomerized to the endo olefin by treatment with trifluoromethanesulfonic acid in methylene chloride at room temperature.

(16) The stereochemistry of the epoxide was assigned by relating the coupling constant of the epoxide proton to the corresponding dihedral angles of the two possible diastereomers. **18**: ^{1}H NMR (400 MHz, $CDCl_3$) d 0.99 (s, 3H), 1.15 (s, 3H), 1.51 (s, 3H), 2.21 (dd, 1H, J=16.4, 4.0 Hz), 2.26 (d, 1H, J=16.4 Hz), 2.61 (s, 1H), 3.21 (d, 1H, J=4.0 Hz), 5.30 (dd, 1H, J=11.1, 1.0 Hz), 5.40 (dd, 1H, J=17.4, 1.0 Hz), 5.73 (dd, 1H, J=17.4, 11.1 Hz).

(17) **19**: ^{1}H NMR (400 MHz, $CDCl_3$) d 1.17 (s, 3H), 1.25 (s, 3H), 2.03 (dd, 1H, J=15.0, 1.45 Hz), 2.21 (dd, 1H, J=15.0, 5.37 Hz), 2.30 (s, 3H), 3.93 (dd, 1H, J=5.37, 1.45 Hz), 5.29 (dd, 1H, J=10.7, 0.9 Hz), 5.33 (dd, 1H, J=17.3, 0.9 Hz), 6.08 (dd, 1H, J=17.3 10.7 Hz), 10.22 (s, 1H).

(18) The secondary hydroxyl group in **19** has the opposite relative configuration from that in the corresponding position of taxol. We believe that the difficulties attending the eventual closing of the eight-membered ring B should be less with that epimer. In any case, this stereochemistry is readily invertable.

(19) (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (b) Sutherland, J. K. in *Comprehensive Organic Synthesis*, Trost, B. M., Ed., Pergamon Press: New York, 1992, vol. 3, pp.341ff.

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