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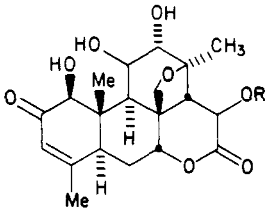
Communications

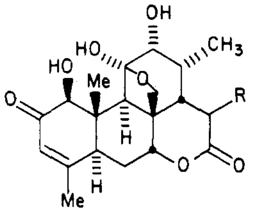
Advances in the Chemistry of 2,3-Epoxy Alcohols. New Methodology for Contra-Trans-Diaxial Opening and Selective Enediol Oxidation

Summary: A selenoaluminum-mediated, contra-trans-diaxial epoxide opening and a selective enediol-to-hydroxy enone oxidation have been developed for the total synthesis of bioactive quassinoids.

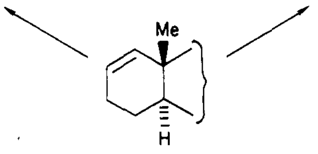
Sir: Interest in the antileukemic and antineoplastic properties of pentacyclic quassinoids has prompted several research groups to undertake their total synthesis.[1,2] Many of these medicinally important substances exhibit A-ring 1β-hydroxy-4-methyl-$\Delta^{3,4}$ 2-one functionality which is apparently essential for biological activity [cf. inter alia. C13-bridged structures quassimarin (1) and simalikalactone D (2); C11-bridged structures chaparrinone (3) and glaucarubinone (4)]. To date, however, the problem of stereoselectively assembling this sensitive hydroxy enone late in the synthesis from simple, relatively inert latent functionality (e.g., 5)[2a] has not been addressed. Here we report a mild and efficient construction which illustrates (1) a new regiocontrolled epoxy alcohol rearrangement and (2) a highly selective enediol oxidation.



1, R = COC(CH$_3$)(OAc)Et
2, R = COCH(CH$_3$)Et



3, R = H
4, R = OCOC(CH$_3$)(OH)Et



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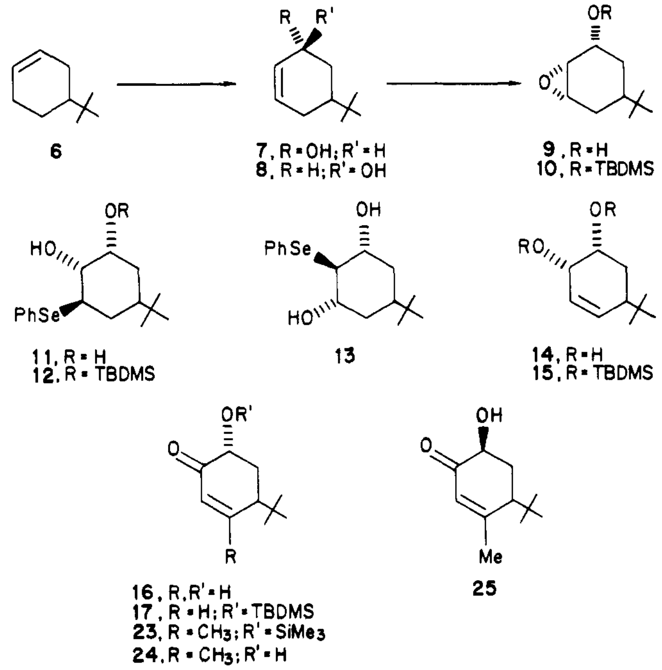
Alkene 6 (Scheme I) was converted to axial allylic alcohol 7 by known methods[3] and then further oxidized by using t-BuOOH/VO(acac)$_2$ to syn-epoxy alcohol 9 in 55% yield after chromatography.[4] Attempts to rearrange 9 to enediol 14 directly with lithium dialkylamides in ether[3] gave the desired product in only modest yield. An alternative, two-step approach was considered, but nucleophilic attack on 9 by PhSeNa gave, predictably, the undesired 1,3-diol 13 in 90% yield.

We reasoned that dialkylaluminum selenides[5,6] might offer a viable route to 11 and hence 14, given that the corresponding aluminum alkynes react regioselectively at the 3-position of acyclic or conformationally mobile cyclic epoxy alcohols.[7,8] Success would require that the well-known chelation effects of trivalent aluminum reagents with epoxides[9] override the stereoelectronic preference for trans-diaxial opening. In fact, 9 reacted with diisobutylaluminum phenylselenide (DIBPS, 2.65 equiv in CH$_2$Cl$_2$, 0 °C–room temperature, 80%) to afford a 4:1 mixture of 11 and 13. *tert*-Butyldimethylsilyl (TBDMS) ether 10 behaved similarly, affording 12 as the major product (5:1 ratio).[10]

Scheme I



6; 7, R = OH; R' = H; 8, R = H; R' = OH; 9, R = H; 10, R = TBDMS; 11, R = H; 12, R = TBDMS; 13; 14, R = H; 15, R = TBDMS; 16, R,R' = H; 17, R = H; R' = TBDMS; 23, R = CH$_3$; R' = SiMe$_3$; 24, R = CH$_3$; R' = H; 25

Selenide 11 was smoothly oxidized with *m*-chloroperoxybenzoic acid (MCPBA; ClCH$_2$CH$_2$Cl, −10 °C) and then eliminated (3 equiv of Et$_3$N, ClCH$_2$CH$_2$Cl, 65 °C, 1–2 h) to afford 14 (77%). This *cis*-enediol proved very susceptible to overoxidation by the usual oxidants; with MnO$_2$ the corresponding catechol was formed (90%). However dichlorodicyanobenzoquinone[11] (DDQ) selectively converted 14 to hydroxy enone 16 in quantitative yield without cleavage or epimerization. The oxidation is general, as examples in Table I illustrate. Particularly noteworthy are the oxidation of *cis*-enediol 19 to 20, and of shikimic

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(1) Review: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.

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(4) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

(5) Dimethylaluminum methylselenolate has been used to make active acyl-transfer reagents: Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735.

(6) Diisobutylaluminum phenylselenide promotes the Beckmann rearrangement of oxime sulfonates: Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

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(9) (a) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. (b) See also ref 20 in: Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.

(10) Dimethylaluminum methylselenolate was less selective toward 9 (2:1 11–13). Use of titanium tetraisopropoxide as a cocatalyst with DIBPS considerably lowered the selectivity of epoxide opening.

(11) Review: Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153.

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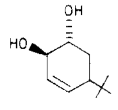
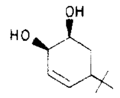
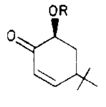
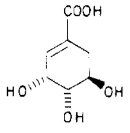
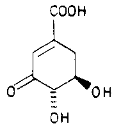
Table I. DDQ Oxidations of Enediols

reactant	DDQ equiv (solv)	time, h	temp, °C	product (yield,[a] %)
14	2.7 (C_6H_6)	12	60	**16** (100)
15	3.1 (C_6H_6)	26.5	60	**17** (64)
 18[b]	1.4 (C_6H_6)	16	70	**16** (70)
 19[c]	3 (C_6H_6)	 20, R = H (82)	70	#c
 21	3 (THF)	 22 (60)	65	#e

[a] All new compounds were completely characterized by IR, NMR, and MS. [b] Prepared from **7** in five steps: (i) TBDMS–Cl, imidazole; (ii) MCPBA–CH_2Cl_2, (iii) PhSeNa; (iv) MCPBA, –PhSeOH; (v) Bu_4NF. [c] Prepared from **8** in three steps: (i) MCPBA–CH_2Cl_2, (ii) PhSeNa; (iii) MCPBA, –PhSeOH.

acid (**21**) to 3-dehydroshikimic acid (**22**) in 60% yield, representing a major improvement over the rather capricious published procedure using Pt–O_2.[12]

To complete the model A-ring construction, enone **16** underwent one-pot cuprate addition [2.2 equiv of $Li(CH_3)_2Cu$, 5 equiv of Me_3SiCl, ether)] and oxidation [$Pd(OAc)_2$, CH_3CN] using the method of Saegusa[13] and furnished **23** (46%), which could be desilylated to the desired hydroxymethyl enone **24**. The same sequence on protected enones **17** and **20** (R = TBDMS) produced **24** and **25** in yields of 85% and 54%, respectively, without epimerization at the acidic α′-carbon. This short and efficient approach to highly functionalized A-rings should find application in several quassinoid total synthesis endeavors.

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Registry No. **7**, 17502-34-0; **8**, 26819-49-8; **9**, 26828-76-2; **10**, 99417-69-3; **11**, 99417-68-2; **12**, 99417-70-6; **13**, 99417-67-1; **13** mono-TBDMS ether, 99417-71-7; **14**, 99417-61-5; **15**, 99417-62-6; **16**, 99417-64-8; **17**, 99417-65-9; **18**, 99439-58-4; **19**, 99417-63-7; **20**, 99417-66-0; **20** (R = TBDMS), 99457-35-9; **21**, 138-59-0; **22**, 2922-42-1; **23**, 99417-72-8; **24**, 99417-73-9; **24** (R′ = TBDMS), 99417-74-0; **25** (R = TBDMS), 99417-75-1; **25** (R = H), 99417-76-2; DIBPS, 85028-55-3.

Supplementary Material Available: Representative experimental procedures for the major transformations shown and characterization data for all new substances (7 pages). Ordering information is given on any current masthead page.

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Stereochemistry of Intramolecular Cyclopropanation of an Organoiron Reagent[1]

Summary: Intramolecular cyclopropanation using an iron carbene precursor results in formation of a trans-fused methanodecalin system.

Sir: Cyclopropanation of alkenes is an important operation in synthetic organic chemistry.[3] Intramolecular versions of these reactions have also proven to be quite useful, especially in the construction of complex polycyclic, cyclopropane-containing systems.[4] In some cases, cyclopropanations are followed by cleavage of the three-membered rings leaving carbon skeletons bearing stereoselectively introduced alkyl substituents.[5]

In recent years, carbene complexes of several transition metals have been shown to have many applications,[6] and cationic carbene complexes of the general structure $[(\eta^5\text{-}C_5H_5)(CO)_2Fe{=}CR^1R^2]^+X^-$ have proven to be excellent reagents for alkene cyclopropanations.[7] However, there have been very few reports of carbene complexes undergoing intramolecular cyclopropanation reactions.[8]

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(1) Taken in part from the Ph.D. Dissertations of R. S. Iyer and G.-H. Kuo, State University of New York at Stony Brook, 1985.

(2) Address correspondence to this author at the Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

(3) For some reviews of the chemistry of cyclopropanes, see: (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* (*N. Y.*) **1973**, *20*, 1. (b) McQuillin, F. J.; Baird, M. S. "Alicyclic Chemistry", 2nd ed.; Cambridge University Press: Cambridge, 1983; pp 92–112. (c) Moody, C. J. In "Organic Reaction Mechanisms 1983"; Knipe, A. C., Watts, W. E., Eds.; Wiley: Chichester, England, 1985; Chapter 6 and the earlier volumes of this series.

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(5) For an elegant application of cyclopropane cleavage, see: Ireland, R. E.; Dawson, M. I.; Welch, S. C.; Hagenbach, A.; Bordner, J.; Trus, B. *J. Am. Chem. Soc.* **1973**, *95*, 7829.

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