From known pK_a and redox potential data,[1a,4b] the profile of the pH dependence of $\Delta G°$ for eq 1 and 2 is given in Figure 1. The change in ΔG with pH is complicated by the equilibria involving the HNO_2/NO_2^- and $(bpy)_2pyRu^{III}OH_2^{3+}/(bpy)_2pyRu^{III}OH^{2+}$ acid-base pairs. Except in extremely strong acid, the plot shows that eq 1 and 2 are both thermodynamically spontaneous in the reverse direction and predict that HNO_2 or NO_2^- should be capable of reducing $(bpy)_2pyRu^{IV}O^{2+}$ to $(bpy)_2pyRu^{II}(OH_2)^2$

In a $H_2PO_4^-/HPO_4^{2-}$ buffer at neutral pH, $(bpy)_2pyRu^{IV}O^{2+}$ is, in fact, reduced by NO_2^- to give $(bpy)_2pyRu^{II}(OH_2)^{2+}$. Since the reaction is slow, excess NO_2^- is required to achieve a reasonable rate, and a subsequent substitution of the aquo ligand by NO_2^- yields $(bpy)_2pyRu(NO_2)^+$ as the final ruthenium product. In acidic solution, the reaction between HNO_2 and $(bpy)_2pyRu^{IV}O^{2+}$ is rapid and gives rise to the nitrosyl complex $(bpy)_2pyRu(NO)^{3+}$ as shown by electrochemical and spectral experiments. The nitrosyl complex is the expected product in acidic solution since for the nitro-nitrosyl equilibrium in eq 11, $pK_a = 3.8$.[4a]

$$(bpy)_2pyRu(NO_2)^+ + 2H^+ \rightleftharpoons (bpy)_2pyRu(NO)^{3+} + H_2O \qquad (11)$$

We view the preliminary results reported here to be significant because (1) they suggest possible approaches to the catalytic use of HNO_3 as a chemical oxidant in synthesis or fuel cell applications, (2) combined with the earlier work on the reactivity of the $(bpy)_2pyRu^{IV}O^{2+}$ ion, they suggest the existence of a general type of multiple-electron, atom-transfer reactivity in this and related systems, and (3) detailed kinetic studies may give further insight into related processes in biological systems.

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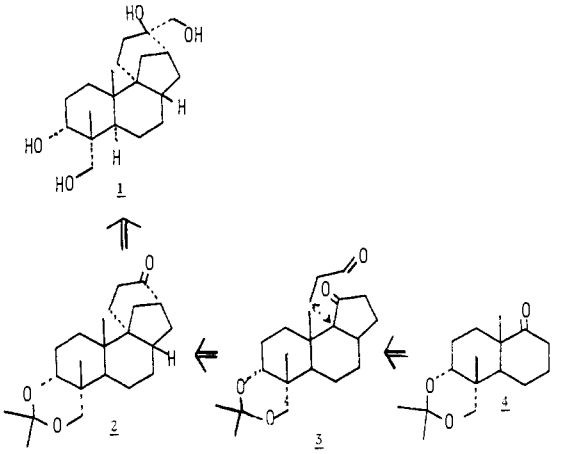
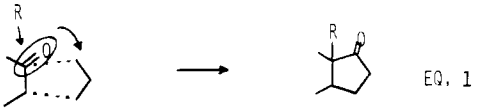
A Total Synthesis of Aphidicolin

Sir:

Aphidicolin (**1**), isolated from the fungus *Cephalosporium aphidicola* Petch, is an antibiotic that reduces the mitotic rate of mouse "L" cells and inhibits the growth of *Herpes simplex* type 1.[1] For a synthesis of this most unusual structure, some simplification in the target can be accomplished since the ketone **2**, which is obtained by degradation of **1**, has already been reconverted into aphidicolin. We analyzed the synthetic problem represented by **2** in terms of a regiocontrolled alkylation of a cyclopentanone as represented in formula **3**. Such



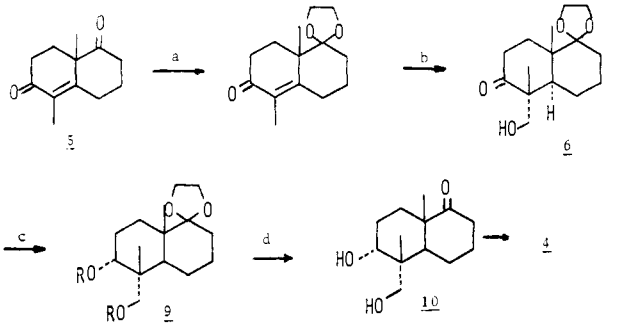
an analysis takes advantage of our recently described cyclopentanone annulation (eq 1) which allows adding a cyclopentanone ring onto a carbonyl compound with migration of the carbonyl group and with the ability of adding a new alkyl residue selectively at the carbon of the former carbonyl group.[2,3] Using such a strategy, the key intermediate becomes ketone **4**.



EQ. 1

The synthesis of ketone **4** (see Scheme I) begins with Δ^4-4,10-dimethyloctalin-3,9-dione (**5**)[4] which is chemoselectively ketalized. Reductive formylation[5] is best achieved by quenching the intermediate enolate in the dissolving metal reduction with chlorotrimethylsilane, regenerating the enolate in ether, and then bubbling in gaseous formaldehyde to give **6**,[6,7] mp 110–112 °C. Strikingly a single stereoisomer results

Scheme I. Synthesis of 4β,10β-Dimethyl-3α,11-isopropylidenedioxy-*trans*-decalin-9-one (**4**)[a]



[a] (a) $HOCH_2CH_2OH$, TsOH, PhH, reflux, Dean-Stark, 79%. (b) [i] Li, NH_3, THF, 0.8 equiv of t-C_4H_9OH, −78 °C, quench with isoprene and then $(C_2H_5)_3N$, $(CH_3)_3SiCl$; [ii] CH_3Li, ether, room temperature and then −78 °C, HCHO, 68%. (c) $(i\text{-}C_4H_9)_2(t\text{-}C_4H_9)AlH^-Li^+$, hexane, heptane, ether, −78 °C, 99%. (d) 3 N HCl, THF, room temperature, 100%. (e) CH_3COCH_3, TsOH, reflux, 92%.

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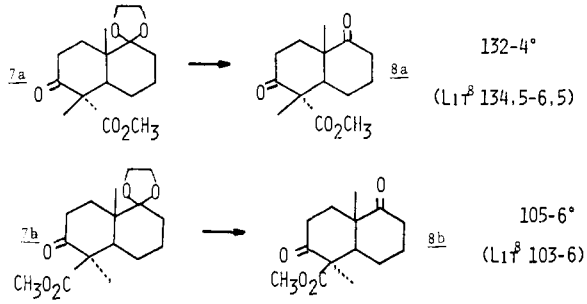
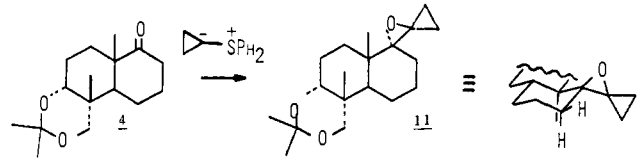
from this reaction, whereas quenching with carbon dioxide gives a mixture (**7a** and **7b**) epimeric at C(4) after esterification with diazomethane. We correlated **7a**[6] and **7b**[6] with the known[8] diketo esters **8a**[6] and **8b**.[6] Since **6** correlates to **7a**, the stereochemistry of C(4) and C(5) is established as shown.

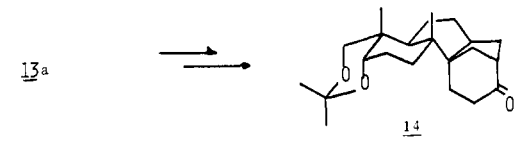


Reduction of the 3-keto group to the 3α alcohol proved troublesome until we discovered that the ate complex generated from fresh *tert*-butyllithium and fresh diisobutylaluminum hydride[9] gives the desired alcohol **9** (R = H),[6,7] mp 139-140°, quantitatively. The stereochemistry at C(3) is best assigned in diacetate **9**[6] (R = Ac) which shows the methine proton at δ 4.84 (br d, J = 2.5 Hz), clearly indicative of an equatorial hydrogen, whereas in the 3β-acetoxy compound this proton appears at δ 4.80 (dd, J = 11, 5 Hz), clearly indicative of an axial hydrogen. Hydrolysis to **10**,[6,7] mp 95-96 °C, and acetonide formation to give **4**,[6,7] mp 98-99 °C, are unexceptional.

Condensation of the ketone **4** with diphenylsulfonium cyclopropylide under reversible ylide generation conditions[10] proceeded smoothly to give the oxaspiropentane **11** (see Scheme II). A problem arises, however, since the epoxide opening with base requires the proton being abstracted to be cis axial to the cleaving C-O bond.[2] Since **11** should have the stereochemistry depicted, because the ylide always appears to

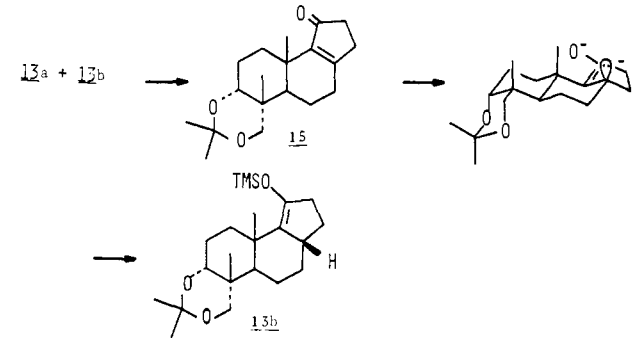


give the product of equatorial C-C bond formation, this oxaspiropentane does not possess such a proton. Indeed, treatment of the oxaspiropentane with lithium dialkylamides gives no discernible vinylcyclopropanol. An alternative method based upon a type of merged substitution-elimination process[11] was devised. Treatment of the oxaspiropentane with sodium phenylselenide,[12,13] generated in situ, gives a crystalline alkylidenecyclopropanol **12** (R = H),[6,7] mp 117-118 °C, which is silylated to **12** (R = $(CH_3)_3Si$)[6] quantitatively. Surprisingly, thermal rearrangement via flash vacuum pyrolysis[14] of **12** (R = $(CH_3)_3Si$) proceeded to give a 2:1 mixture of epimers at C(8), **13**, as determined by the ratio of signals for the methyl groups (major, δ 1.06 and 0.65; minor, δ 1.00 and 0.60).[15] By subsequent conversion[16] of the major product to **14**,[6,7] mp 150



°C, whose structure was verified by X-ray crystallography,[17] the major isomer is assigned the 8α configuration.

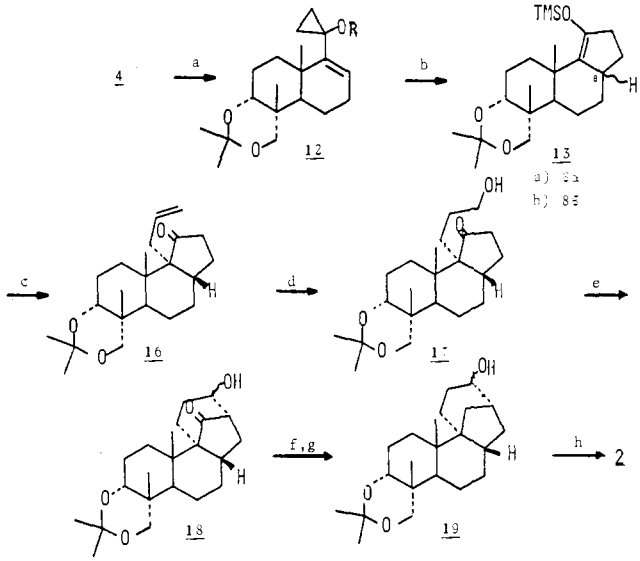
To circumvent this problem, the mixture was directly oxidized to the enone **15**[6,7] ($Pd(OAc)_2$,[18] CH_3CN, room temperature, 73%), mp 158.5-159 °C. Dissolving metal reduction (Li, NH_3, THF, 0.8 equiv of t-C_4H_9OH, 82%) re-formed a single enol silane corresponding to the minor product of the initial rearrangement, **13b**,[6,7] and thus the correct stereochemistry at C(8). Generation of the enolate in THF, addition



of an equal volume of HMPA, and inverse quenching of the resultant enolate solution into hot (85 °C) excess allyl iodide gives a major product **16**,[6,7] mp 141-142 °C, assigned as shown. The stereochemistry of the alkylation was anticipated to prefer to be trans to the angular methyl, but is verified only by the successful completion of the synthesis.

The remaining steps of the synthesis are rather straightforward as outlined in Scheme II. The aldehyde formed upon oxidation[20] of the alcohol **17**[21] is directly cyclized to the aldol product **18**[6,7] as an ~3:7 mixture of epimers at C(16). Wolf-Kishner reduction of **18** requires prior protection of the alcohol at C(16) via formation of the tetrahydropyranyl ether. Oxidation of the alcohol **19** gives crystalline (±)-3α,18-isopropylidenedioxy-17-noraphidicolan-16-one,[6,7] mp 139.0-139.5 °C. Comparison of IR, 270-MHz ^{1}H NMR, and ^{13}C NMR spectra with those of an authentic sample obtained from the natural product revealed their identity except for optical rotation. Since this ketone has already been converted back to the natural product in three steps, the synthesis of **2** completes

Scheme II. Synthesis of 3α,18-Isopropylidenedioxy-17-noraphidicolan-16-one[a]



[a] (a) [i] c-$C_3H_5S^+Ph_2BF_4^-$, KOH, Me_2SO; [ii] PhSeSePh, $NaBH_4$, DME, 60 °C; [iii] $CH_3C[OSi(CH_3)_3]{=}NSi(CH_3)_3$, $(C_2H_5)_3N$, PhH, 60 °C, 56%. (b) Flash vacuum pyrolysis at 610 °C, 97%. (c) C_4H_9Li, THF, room temperature; add HMPA; inverse addition to allyl iodide, 85 °C, 35%. (d) $(CH_3)_2CHC(CH_3)_2BH_2$, diglyme, 0 °C, and then NaOH, H_2O_2, 45 °C, 57%. (e) PCC,[19] NaOAc, CH_2Cl_2, room temperature, and then 2% KOH, CH_3OH, room temperature, 54%. (f) [i] DHP,[19] TsOH, $CHCl_3$, room temperature; [ii] 95% NH_2NH_2, KOH, $HO(CH_2CH_2O)_3H$, 140 °C, and then raise to 220 °C, 91%. (g) 0.5% TsOH, CH_3COCH_3, room temperature, 78%. (h) See e, 87%.

the task. The successful application of the cyclopentanone annulation using the cyclopropylide reagent illustrates the utility of this method for creation of complex molecular architecture.

Acknowledgment. We thank Dr. Barrie Hesp for a generous sample of aphidicolin and related compounds and Dr. J. Calabrese for a critical X-ray structure determination. We also thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health for their generous support of our programs.

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(6) This compound has been fully characterized by spectral means and elemental composition determined by either high resolution mass spectroscopy and/or elementary analysis.
(7) **6:** IR 3500, 1695 cm^{-1}; 100-MHz NMR δ 0.96 (3 H, s), 1.14 (3 H, s), 3.26 and 3.58 (2 H, AB, J = 12 Hz); ^{13}C NMR δ 16.3, 16.9, 21.3, 22.7, 29.8, 30.3, 35.2, 42.5, 43.1, 52.3, 64.9, 65.2, 66.7, 112.7, 180. **9** (R = H): IR 3400 cm^{-1}; 100-MHz NMR δ 0.76 (3 H, s), 1.12 (3 H, s), 3.2–4.0 (6 H, m). **10:** IR 3400, 1710 cm^{-1}; 100-MHz NMR δ 0.85 (3 H, s), 1.14 (3 H, s), 2.96 (2 H, s), 3.61 (2 H, s), 3.85 (1 H, d, J = 3 Hz). **4:** 100-MHz NMR δ 0.82 (3 H, s), 1.16 (3 H, s), 1.32 (3 H, s), 1.36 (3 H, s), 3.18 and 3.54 (2 H, AB, J = 12 Hz), 3.58 (1 H, d, J = 3 Hz). **12** (R = H): 100-MHz NMR δ 0.76 (3 H, s), 1.22 (3 H, s), 1.28 (3 H, s), 1.34 (3 H, s), 3.16 and 3.54 (2 H, AB, J = 12 Hz), 3.60 (1 H, bs), 5.50 (1 H, t, J = 3.5 Hz). **13b:** 100-MHz NMR δ 0.13 (9 H, s), 0.60 (3 H, s), 1.00 (3 H, s), 1.28 (6 H, s), 3.04 and 3.45 (2 H, AB, J = 12 Hz), 3.50 (1 H, d, J = 3 Hz). **14:** IR 1740 cm^{-1}; 270-MHz NMR δ 0.84 (3 H, s), 1.13 (3 H, s), 1.42 (3 H, s), 1.43 (3 H, s), 2.64 (1 H, t, J = 6 Hz), 3.30 and 3.56 (2 H, AB, J = 12 Hz), 3.69 (1 H, dd, J = 3.5, 2 Hz); ^{13}C NMR (C_4D_6) δ 211.7, 97.8, 73.6, 68.0, 51.4, 48.8, 40.1, 37.9, 37.1, 36.8, 35.7, 35.6, 34.8, 30.8, 30.4, 28.4, 28.2, 24.0, 21.9, 19.7, 18.9, 18.7. **15:** IR 1700, 1635 cm^{-1}; 100-MHz NMR δ 0.76 (3 H, s), 108 (3 H, s), 1.30 (3 H, s), 1.34 (3 H, s), 3.21 and 3.58 (2 H, AB, J = 12 Hz), 3.61 (1 H, dd, J = 3.5, 2 Hz). **16:** IR 1740 cm^{-1}; 100-MHz NMR δ 0.68 (3 H, s), 1.00 (3 H, s), 1.32 (6 H, s), 3.12 and 3.53 (2 H, AB, J = 12 Hz), 3.58 (1 H, dd, J = 3.5, 2 Hz), 4.6–6.2 (3 H, m). **18:** ir 3600, 3450, 1735 cm^{-1}; 270-MHz NMR δ 0.70 (3 H, s), 1.10 (3 H, 2s), 1.41 (6 H, s), 3.22 and 3.97 (2 H, AB, J = 12 Hz), 3.98 (1 H, bd, J = 3.5 Hz), 4.03 (0.7 H, m), 4.22 (0.3 H, m). **19:** IR 3620, 3400 cm^{-1}; 270-MHz NMR δ 0.77 (3 H, s), 1.05 (3 H, s), 1.51 (6 H, s), 2.72 (1 H, ddd, J = 11.8, 8, 3 Hz), 3.43 and 3.83 (2 H, AB, J = 12 Hz), 3.8–4.0 (2 H, m). **2:** IR 1730 cm^{-1}; 270-MHz NMR δ 0.74 (3 H, s), 1.08 (3 H, d, J = 1 Hz), 1.42 (6 H, s), 3.25 and 3.61 (2 H, AB, J = 12 Hz), 3.67 (1 H, t, J = 3 Hz); ^{13}C NMR (C_6D_6) δ 211.9, 98.0, 73.6, 68.7, 49.3, 48.4, 41.5, 39.5, 34.7, 34.4, 33.4, 33.2, 31.5, 30.1, 27.2, 26.2, 24.2, 22.3, 21.6, 19.0, 17.1, 16.1.
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(12) (a) For opening of epoxides to allyl alcohols by selenide followed oxidation, see Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973,** *95,* 2697. (b) For the case of oxaspiropentanes, see Trost, B. M.; Scudder, P. H. *ibid.* **1977,** *99,* 7601.
(13) A byproduct (~9%), presumably the hydroxy selenide, is isolated but has not been characterized; cf. ref 12b.
(14) For a description of the apparatus employed see Trost, B. M.; Godleski, S. A.; Ippen, J. *J. Org. Chem.* **1978,** *43,* 4559.
(15) The rearrangement was anticipated to provide the equatorial C–C bond because of a severe 1,3 interaction with the angular methyl group for an axial bond to form and because of related work. See Trost, B. M.; Keeley, D. E. *J. Am. Chem. Soc.* **1976,** *98,* 248.
(16) The procedure employed is exactly analogous to that detailed for the successful synthesis.
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(19) PCC = pyridinium chlorochromate. DHP = 2,3-dihydropyran.
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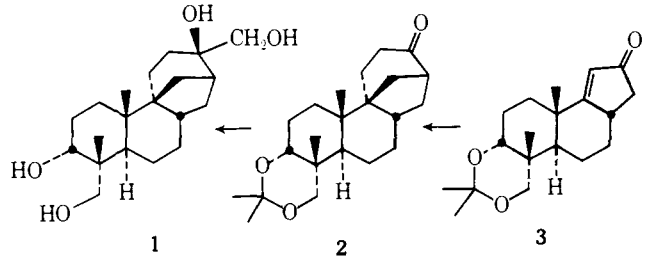
Stereospecific Total Synthesis of Aphidicolin

Sir:

The search for effective anti-viral agents has long been pursued, though with little success to date. It was therefore of interest when, in 1972, the isolation and structure determination of aphidicolin was announced.[1] Aphidicolin (**1**), a diterpenoid tetraol produced by the mold *Cephalosporium aphidicola* Petch, shows strong in vitro activity against herpesvirus, presumably through an inhibition of virus DNA synthesis.[2] We report here the stereospecific total synthesis of this interesting molecule.[3]

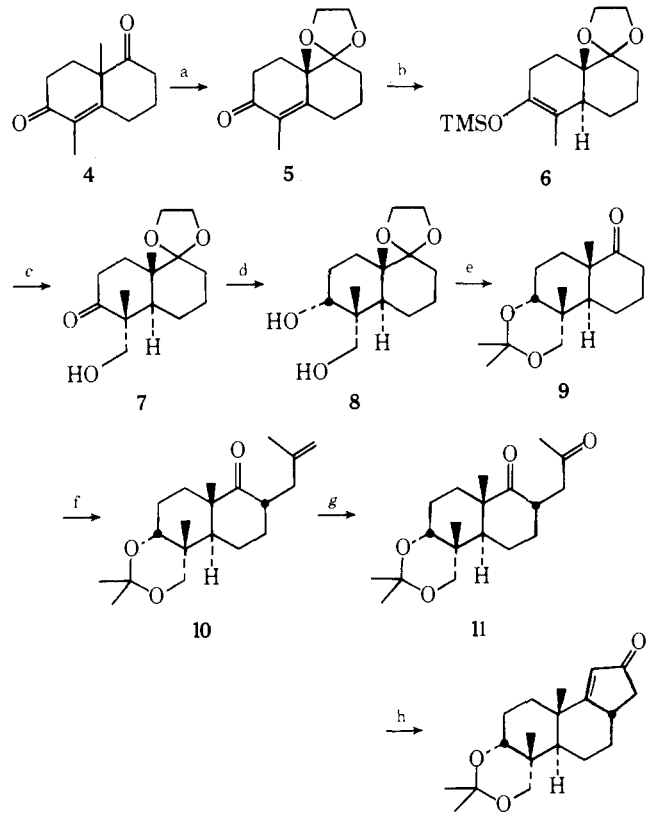
The synthetic problem is simplified to an extent by the fact that ketoacetonide **2** has been obtained from, and reconverted into, aphidicolin.[1] Compound **2** therefore became our actual synthetic goal.



1 2 3

After considering a number of possible synthetic paths to **2**, we settled on cyclopentenone **3** as our key intermediate. Addition of a three-carbon piece across the ends of the enone system of **3** would then construct the bicyclo[3.2.1]octane

Scheme I[a]



4 5 6 7 8 9 10 11 3

[a] (a) $HOCH_2CH_2OH$, *p*-TsA, benzene, 80%. (b) Li, NH_3, THF, and then $(CH_3)_3SiCl$, $(CH_3CH_2)_3N$, 97%. (c) CH_3Li, THF, and then CH_2O. (d) Li(*sec*-Bu)$_3$BH, THF. (e) CH_3COCH_3, *p*-TsA, CH_2Cl_2, 85% from **6**, (f) 1.2 equiv of LDA, THF, and then methallyl iodide, 89%. (g) Trace of OsO_4, $NaIO_4$, H_2O, dioxane, 86%. (h) NaH, trace of *tert*-amyl alcohol, benzene, reflux, 95%.

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