(d, 3 H, J = 7 Hz, C(2) CH_3), 1.39 (s, 3 H, C(10) CH_3), 1.43 and 1.52 (2 q, 6 H, J = 0.8 Hz, acetonide), 3.82 (dd, 1 H, J = J' = 7 Hz), 3.85 (dd, 1 H, J = 4.4 Hz, J' = 5.5 Hz), 6.42 (d, 1 H, J = 15.3 Hz, C(8) H), 6.77 (d, 1 H, J = 15.3 Hz, C(9) H).

[2*R*-(2*R,3*S**,4*S**,6*R**,8*E*,10*S**,11*R**)]-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-10,11-dihydroxy-2,4,6,10-tetramethyl-7-oxo-8-tridecenoic Acid (37).** To a stirred solution of 1.2 mg (0.0025 mmol) of the acetonide **36** in 0.10 mL of acetonitrile under an argon atmosphere was added 0.10 mL of 1 N aqueous HCl. After 60 min at room temperature, the reaction mixture was diluted with 1.5 mL of water, and 0.090 mL of 1 N aqueous NaOH was added, resulting in a pH 2 solution. This mixture was extracted with three 1-mL portions of ether, and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was separated by preparative TLC (10 × 10 cm precoated TLC plate, silica gel 60 F-254, layer thickness 0.5 mm, manufactured by E. Merck and Co.) with ethyl acetate as the eluant (single elution, visualized by ultraviolet light) and afforded three major fractions.

Fraction 1: R_f 0.55 (silica gel, ethyl acetate); 0.4 mg (30%) of recovered starting acetonide **36**.

Fraction 2: R_f 0.30 (silica gel, ethyl acetate); 0.2 mg (20%) of the desired diol **37** as a colorless oil; 500-MHz ^{1}H NMR δ 0.11 (s, 6 H, $SiCH_3$), 0.92 (s, 9 H, t-BuSi), 0.97 (d, 3 H, J = 6.8 Hz, C(4) CH_3), 1.02 (t, 3 H, J = 7.3 Hz, C(13) H_3), 1.12 (d, 3 H, J = 6.8 Hz, C(6) CH_3), 1.16 (d, 3 H, J = 7 Hz, C(2) CH_3, 1.37 (s, 3 H, C(10) CH_3), 2.61 (dq, 1 H, J = J' = 7.3 Hz, C(2) H), 2.76 (tq, 1 H, J = J' = 6.9 Hz, C(6) H), 3.49 (m, 1 H, C(11) H), 3.81 (dd, 1 H, J = 2 Hz, J' = 7.5 Hz, C(3) H), 6.49 (d, 1 H, J = 15.6 Hz, C(8) H), 6.88 (d, 1 H, J = 15.6 Hz, C(9) H); mass spectrum, calcd for $C_{23}H_{44}O_6Si$ ($M^+ - H_2O - C_4H_9$) m/e 369.2097, found ($M^+ - H_2O - C_4H_9$) m/e 369.2105.

Fraction 3: R_f 0.20 (silica gel, ethyl acetate); 0.1 mg (10%) of a compound lacking both the acetonide and the TBS.

Acknowledgment. We are very grateful to Professor P. A. Grieco for providing us with spectra of the seco-acid derivatives **36** and **37** for comparison purposes. Grateful acknowledgement is made for support of this investigation through the National Science Foundation (Grant CHE-78-21066). We also thank the Veterans Administration (Grant 5455-01P), the National Institutes of Health Grant AM30579), the Kroc Foundation for Medical Research, the National Arthritis Foundation, and the Wisconsin Arthritis Foundation for their support. Acknowledgement is also made for use of the Southern California Regional NMR Facility, Caltech, Pasadena, CA (National Science Foundation Grant No. 7916324), for all 500-MHz ^{1}H NMR spectra and for use of the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE (National Science Foundation Regional Instrumentation Facility), for all high-resolution mass spectra.

Supplementary Material Available: Atomic positional and thermal parameters (Table I), hydrogen atom positional and thermal parameters (Table II), bond distances (Table III), and bond angles (Table IV) (6 pages). Ordering information is given on any current masthead page.

Stereochemical Control of Reductions. 7.[1] Reagent Hinges: Cis Reduction of β-Octalones by Internal Delivery of Chromium(II)[2]

Hugh W. Thompson* and Nalini V. Shah

Carl A. Olson Memorial Laboratories, Department of Chemistry, Rutgers University, Newark, New Jersey 07102

Received August 3, 1982

$\Delta^{1,9}$-Octal-2-ones with angular substituents R have been synthesized and subjected to reduction conditions by employing the ethylenediamine complex of $CrSO_4$ in aqueous DMF at 25 °C. For R = Me, $CH_2OCH_2OCH_2CH_2OMe$, CH_2OTHP, and COOMe negligible reduction was observed within 60 h, and starting materials were recovered in 60% yields. For R = CH_2OH and COOH complete disappearance of starting material was achieved in 30–64 h, with isolation of ca. 40% of saturated ketone having exclusively cis stereochemistry. These results are interpreted in terms of precoordination of Cr(II) to the hydroxyl function, internal donation to yield a chelated organochromium intermediate, and stereoretentive hydrolysis to cis product.

In reduction of unsaturated ketones of the β-octalone (1) type by reactive metals in low oxidation states, stereochemistry is generated irreversibly at the β-position. In the best understood cases, those of metal–ammonia reductions,[3] this stereochemistry is thought to be the result of kinetic protonation of the most stereoelectronically stable of the various conformations available to the radical–anion intermediate.[3,4] The normal result in such reductions of **1** is trans stereochemistry in the products,[3-5] and external control over this stereochemistry is imperfect at best. Varying the metal and the solvent has produced a limited degree of control,[6] and placement of a proton-donating function within reach of the β-carbon has resulted in predominance of cis stereochemistry in a few instances,[7] but the generality of the latter method of control is problematic,[8] so *cis*-decalone systems are usually produced from octalones by other methods of reduction.[9]

Because of our interest in using hydroxylic functions as internal proton donors and reagent hinges,[1,10] we wished to explore the stereochemistry of reduction of **2a** and **3a** by use of chromium(II), which is known to operate by mechanisms bearing some similarity to those of alkali metal–ammonia systems.[11] We entertained two specific

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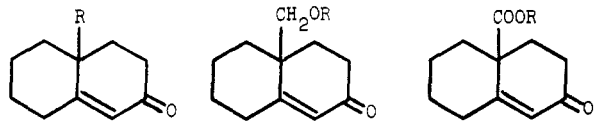
0022-3263/83/1948-1325$01.50/0



1a, R=H
1b, R=Me

2a, R=H
2b, R=MEM
2c, R=THP

3a, R=H
3b, R=Me

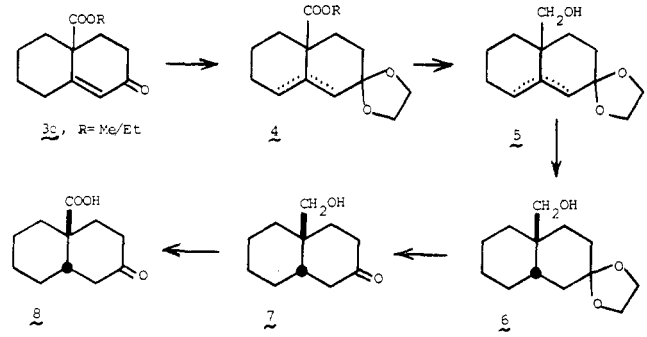
possibilities. One was that angular hydroxylic functions might selectively enhance the rate of protonolysis at the ring juncture for cis-fused anionic or organochromium reduction intermediates. The second was that they might serve as reagent hinges to promote cis addition of Cr species at the ring-juncture position and provide chelative stabilization for the resulting cis organochromium intermediates. Either of these general mechanisms could favor the formation of cis products. Anticipation of such internal assistance was encouraged by the results of Castro and Stephens,[12] who found that Cr(II) reduction of alkynes was accelerated by the presence of neighboring carboxyl and hydroxyl functions.

Reductions by Cr(II) have some properties which might be advantageous for particular compounds: they can be carried out at or near room temperature and in partially aqueous media. On the other hand, yields from enones have been mediocre,[11a] and the Cr(II) reagents are sensitive to air. Hence, they are much less studied and used for enones than their alkali metal–ammonia counterparts, and few reports have involved generation of stereochemistry.[11a,13] House and Kinloch[11a] reduced **1a** in poor yield but with a relatively high proportion of cis product (13%, vs. 19% trans), attributed to a covalent C–Cr ring-juncture bond which increased the importance of purely steric conformational factors relative to stereoelectronic ones. Addition of a radical-trapping H· donor dramatically improved the relative and absolute yield of trans product. Their mechanism for enone reduction, based partly on the above observations, depicts conversion of an enone first to a chromium enolate radical. This reacts with a second Cr(II) species to yield a chromium enolate with a β-carbon–chromium bond, and this is slowly hydrolyzed to saturated ketone.

Results and Discussion

Although the relationships of the various keto esters, ketols, diols, etc. of the general family of **2** and **3** have been thoroughly established,[14] the cis keto acid **8** had never been reported, and we synthesized this compound (Scheme I) along with cis ketol **7** and the corresponding trans epimers for comparison with our reduction products. The conditions which appeared to give the cleanest reaction mixtures with **2a** and **3a**, allowing us most easily to assess product ratios and residual starting material, utilized the ethylenediamine complex of $CrSO_4$ in aqueous DMF.[11a,15] Under these conditions **2a** and **3a** each gave a single isolated product, having cis stereochemistry. The yields were 41% and 40%, respectively, and no starting material was

Scheme I



detectable when the reactions were run at room temperature for 30 and 64 h, respectively.

This stereospecificity suggested that our angular functional groups had indeed acted either as proton donors or as reagent hinges. The first of these alternatives seemed less likely for compound **3a** because at the operating pH of our reductions (ca. 10) only about one carboxyl in 10^5 would be protonated, although solvation-shell water clustered about such a carboxylate or coordinated to chromium bound to such a carboxylate might still be involved. To gain information about these mechanisms and to ensure that cis stereochemistry was not simply the normal outcome of such a reduction of any angularly substituted octalone, we synthesized several alkylated derivatives of **2** and **3** for study, along with 10-methyl-2-octalone (**1b**).[16] Removal of the hydroxylic function should suppress intramolecular components of the mechanism, which lead to cis products. From compound **2a** were synthesized two ethers, the (β-methoxyethoxy)methyl (MEM) ether **2b** and the tetrahydropyranyl (THP) ether **2c**. The methyl ester (**3b**) of carboxylic acid **3a** was also prepared. Each of these derivatives, along with **1b**, was subjected to the reaction conditions previously established as adequate to ensure complete disappearance of **2a** and **3a**. Except for **2c**, which may have been reduced very slightly (see Experimental Section), the outcome in each case was recovery only of unchanged starting material in yields of 58–62%. These results are consistent with those from reduction of **2a** and **3a** in showing that essentially no trans products are generated from **2** or **3** under our reaction conditions.[17] They also imply that all of the products we did observe from **2a** and **3a** were due to an intramolecular mechanism.

Of the several steps in the general mechanism for this reaction,[11a] two stand out as candidates for the internal process we have evidently suppressed by removing the hydroxylic functions: C–Cr bond hydrolysis by intramolecular proton donation and internal Cr donation to the unsaturated system (or chelative capture of an externally added Cr). However, if only the hydrolytic step had been retarded in our nonhydroxylic substrates, we should still have been able to observe product formation. Several studies of Cr(II) reductions[15a,18] under basic conditions describe the observed buildup of intermediate organochromium species which hydrolyze slowly, and House and Kinloch found rapid hydrolysis of such an intermediate

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(17) Because of the normally poor yields in these reactions, attributed to formation of dimers and acid-soluble amine adducts,[11a] we have not been able to prove that production of trans materials in these reactions was nil. However, control reductions employing the trans ketol **9** and keto acid **10** returned the identical materials in ca. 60% yields, rendering it very likely that we would have been able to observe these materials had they been produced at all.
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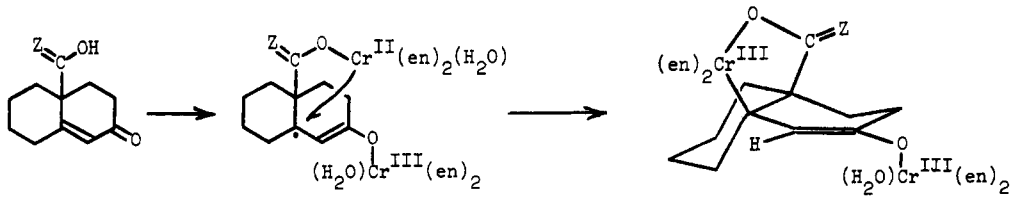
Scheme II



upon acidification of the basic medium.[11a] Our failure to observe reduced products even after acidic workup suggests a low or negligible concentration of such intermediates, for which an earlier slow step must have been responsible.

Acceleration of the reaction to yield reduced products with cis stereochemistry, unaccompanied by trans isomers, when angular hydroxylic functions were present clearly implies intervention of an internal process associated with formation of the organochromium intermediates. In our view the most favorable candidate for this step is an internal Cr donation similar to that shown in Scheme II. Although we cannot exclude chelative capture of an unstable species formed reversibly by external chromium, the existing literature does not appear to support facile reversibility for such additions.

We have observed negligible reduction of **1b**, **2b,c**, and **3b**, and thus normal addition of Cr(II) appears clearly more sluggish than under the conditions employed by House and Kinloch, who were able to reduce **1a** to both cis and trans product. The presence of angular hydroxylic functions in **2a** and **3a** accelerates the addition of Cr(II) by an internal mechanism to yield cis products, but external addition of Cr(II) leading to trans products remains unobservably slow. This rate differential may be exploited for cis control of stereochemistry when a hydroxylic function can be placed appropriately. Its chief drawback at present is mediocre yield.

Experimental Section[19]

10-(Hydroxymethyl)-$\Delta^{1,9}$-octal-2-one (2a) was prepared[14] from 10-carbalkoxy-$\Delta^{1,9}$-octal-2-one (**3c**) derived from carbalkoxycyclohexanone commercially available as a 2:3 mixture of Me and Et esters.

10-(Hydroxymethyl)-*cis*-decal-2-one (7), prepared as indicated in Scheme I,[14d] was isolated as an oil;[14d] GC indicated 85% purity, the balance consisting of at least four peaks with comparable areas.

10-(Hydroxymethyl)-*trans*-decal-2-one (9), prepared as described,[14] was isolated as an oil;[14d] GC indicated 67% purity, the balance consisting of at least three peaks with comparable areas.

The unsaturated ketol **2a** and its cis (**7**) and trans (**9**) reduction products could be resolved and distinguished by GC; typical retention times with the oven temperature rising 4 °C/min from 100 to 200 °C were 14, 15.9, and 24.2 min for **9**, **2a**, and **7**, respectively.

10-Carboxy-$\Delta^{1,9}$-octal-2-one (3a). This compound was previously reported[14c] as an unintentional byproduct (15%) of the Robinson annelation leading to **3**. In the present study, a solution of 2.88 g (72.0 mmol) of NaOH in 25 mL of water was added dropwise with stirring to a solution of 7.75 g (36.2 mmol) of **3c** in 25 mL of EtOH. After being stirred 60 h at 25 °C, the mixture was partitioned with 60 mL each of Et_2O and water. Addition of dilute HCl to the aqueous layer and filtration gave 5.27 g (75%) of crude **3a** as a yellow solid, mp 110–115 °C. Recrystallization from CH_2Cl_2 provided 2.97 g (42%) of light yellow needles: mp 128–130 °C (lit.[14c] mp 130–131 °C); IR 3500–2200, 1725, 1640[20] cm^{-1}; ^1H NMR δ 0.9–2.8 (12 H, complex), 5.95 (1 H, s), 10.5 (1 H, br s).

10-Carboxy-*cis*-decal-2-one (8). A mixture of 437 mg (2.4 mmol) of cis ketol **7**[14d] in 30 mL of acetone and 3 mL (8.0 mmol) of Jones reagent was prepared and stirred at 0 °C for 1 h. To this were added with stirring a solution of 30 g (365 mmol) of NaOAc in 50 mL of water and 50 mL of benzene. After the mixture was stirred 10 min, the benzene layer was separated, washed with water, and extracted with saturated $NaHCO_3$ (3 × 50 mL). Acidification of the extracts led to isolation of 312 mg (66%) of crude **8** as a viscous liquid. Chromatography (SiO_2, hexane–Et_2O) provided material melting at 95–99 °C, and recrystallization (Et_2O–hexane) gave 198 mg (42%) of white needles: mp 109–113 °C (raised to 113–114 °C by another recrystallization); IR 3600–2300, 1690 cm^{-1}; ^1H NMR δ 1.0–2.8 (15 H, complex), 9.9 (1 H, br s). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.21.

10-Carboxy-*trans*-decal-2-one (10)[14c,21] was prepared by catalytic hydrogenation of **3a** and also, in comparable yield and purity, by Li–NH_3 reduction of **3a** and reoxidation of the resulting hydroxy acid.

The cis (**8**) and trans (**10**) reduction products of **3a** could be resolved and distinguished by GC; typical retention times with an oven temperature of 196 °C were 3.5 and 3.8 min for **10** and **8**, respectively. Under these conditions the unsaturated keto acid **3a** was completely decarboxylated.

(β-Methoxyethoxy)methyl (MEM) Ether Derivative[22] (2b) of 10-(Hydroxymethyl)-$\Delta^{1,9}$-octal-2-one. To a solution of 250 mg (1.38 mmol) of **2a** in 2.5 mL of dry CH_2Cl_2 were added with stirring 514 mg (4.1 mmol) of MEM chloride and 776 mg (6.0 mmol) of EtN(*i*-Pr)$_2$. After 48 h of stirring at 25 °C the mixture was partitioned with 10 mL each of water and CH_2Cl_2. The washed, dried, and concentrated organic phase (97% crude yield) was chromatographed (Al_2O_3) and reconcentrated to give 286 mg (77%) of **2b** as a pale yellow oil, which was used without further purification; GC indicated no contaminants of comparable volatility: IR 1680, 1630 cm^{-1}, and no OH absorption in the 3-μm region; ^1H NMR δ 1.0–2.8 (12 H, complex), 3.4 (3 H, s), 3.6 (6 H, m), 4.7 (2 H, s), 5.85 (1 H, s).

Tetrahydropyranyl (THP) Ether Derivative (2c) of 10-(Hydroxymethyl)-$\Delta^{1,9}$-octal-2-one. To a solution of 502 mg (2.8 mmol) of **2a** in 25 mL of anhydrous Et_2O were added 349 mg (4.1 mmol) of dihydropyran and 53 mg (0.28 mmol) of *p*-toluenesulfonic acid. After the mixture was stirred 12 h at 25 °C, 1.0 g (7.2 mmol) of solid anhydrous K_2CO_3 was added. After being stirred another 2 h, this mixture, with 10 mL of CH_2Cl_2, was washed with aqueous $NaHCO_3$ and with water, partitioned, and dried. The crude oily concentrate (96%) was chromatographed (Al_2O_3) and reconcentrated to give 559 mg (76%) of **2c** as a pale

(19) Melting points were determined with a Laboratory Devices Mel-Temp apparatus and are uncorrected, as are boiling points. IR spectra were taken with a Beckman IR-10 or Acculab 6 spectrometer by using NaCl plates for liquids (neat) and KBr pellets for solids. ^1H NMR spectra were recorded with a Hitachi Perkin-Elmer R-24A (60 MHz) or a JEOL PSFT-100 (100 MHz) instrument with $CDCl_3$ (Me_4Si) as the solvent. Gas chromatographic (GC) analyses were carried out with a Hewlett-Packard 7610A instrument, equipped with flame-ionization detectors, by utilizing a 44 × 0.75 in. glass column packed with 3% OV-17 silicone rubber on 100–200-mesh Chromosorb. All reactions were run under N_2, and all solvents and reagents were used as supplied by Aldrich, Baker, Fisher, or Mallinkrodt unless otherwise specified. Microanalyses were kindly performed by F. Scheidl, through the courtesy of Hoffmann-La Roche, Inc.

(20) Such displacement of the ketone C=O band toward lower wavenumbers has been observed in other keto acids capable of internal H bonding. Cf.: Nakanishi, K.; Solomon, P. H. "Infrared Absorption Spectroscopy", 2nd ed.; Holden-Day: San Francisco, CA, 1977, p 38. Gula, M. H.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 805, footnote 18. Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Co.: Milwaukee, WI, 1975, No. 282A.

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(22) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

yellow oil, which was used without further purification; GC indicated no contaminants of comparable volatility: IR 1680, 1630 cm^{-1}, and no OH absorption in the 3-μm region; ^1H NMR δ 0.8–2.8 (18 H, complex), 3.2–4.1 (4 H, m), 4.8 (1 H, m), 5.88 (1 H, s).

10-Carbomethoxy-$\Delta^{1,9}$-octal-2-one (3b).[23] This compound was produced by transesterification of **3c** on a 1-g scale. Chromatography and distillation with an oil bath at 99–110 °C (0.1 mm) gave 68% of **3b** as a colorless oil; although GC and ^1H NMR indicated that the 96 h of reflux had increased the Me/Et ratio from the original 2:3 only to 2:1, this mixture was used for the attempted Cr(II) reduction: IR 1730, 1680, 1630 cm^{-1}; ^1H NMR δ 1.1–2.6 (12 H, complex), 3.75 (3 H, s), 5.92 (1 H, s).

Cr(II) Reduction of 10-(Hydroxymethyl)-$\Delta^{1,9}$-octal-2-one (2a). A mixture of 6.8 mL of deoxygenated DMF and 13.6 mL of deoxygenated water was flushed with N_2 for 30 min before addition by syringe, with stirring, of 12 mL (6.0 mmol) of 0.50 M $CrSO_4$ solution,[24] followed by 1.113 g (18.5 mmol) of ethylenediamine. Following addition of 300 mg (1.66 mmol) of **2a**, the mixture was stirred under N_2 for 30 h at 25 °C. It was worked up by dilution with 10 g each of water and ice, acidification to pH 2–3 with 10% HCl, saturation with NaCl, and extraction with Et_2O (5 × 7.5 mL). The combined, washed, dried, and concentrated extracts were freed of DMF at 0.4 mm by warming to 70–75 °C for 5 h. After passage through a short column of Al_2O_3 and reconcentration, the product consisted of 125 mg (41%) of pale yellow oil having IR and ^1H NMR spectra consistent with absence of **2a**. GC analysis under the conditions described for **2a**, **7**, and **9** showed only **7** to be present.

Cr(II) Reduction of 10-Carboxy-$\Delta^{1,9}$-octal-2-one (3a). A mixture of 8.7 mL of deoxygenated DMF and 17.8 mL of deoxygenated water was flushed with N_2 for 30 min. As described for **2a**, 15 mL (7.5 mmol) of 0.50 M $CrSO_4$, 1.35 g (22.4 mmol) of ethylenediamine, and 200 mg (1.0 mmol) of **3a** were added sequentially. After being stirred 64 h at 25 °C under N_2, the mixture was worked up as described to yield 81 mg (40%) of crude white solid, mp 108–110 °C. GC analysis under the conditions described for **8** and **10** showed the presence of **8** with no detectable **10**, and IR and ^1H NMR spectra were consistent with absence of **3a**. Recrystallization gave 49 mg (24%) of white needles (mp 111–112.5 °C) whose IR and ^1H NMR spectra were identical with those of authentic **8**.

Attempted Cr(II) Reduction of 1b, 2b,c, and 3b. For each of these materials reduction was attempted, on the scale described for **2a** and **3a**, under two sets of conditions: first, by utilizing 3.4–5.0 mmol of $CrSO_4$ and 10.8–14.9 mmol of ethylenediamine per millimole of enone for 35–36 h and then by increasing the amount of reagent and the time to 6.65–8.1 mmol of $CrSO_4$ and 21–25 mmol of ethylenediamine per millimole of enone for 60 h.

In each case unchanged starting material was recovered in 58–62% yield, and, except for the case of **2c**, no evidence for the presence of reduced materials could be found by GC, IR, or ^1H NMR, which displayed retention times and spectra essentially identical with those for starting materials. Although **2a** recovered from attempted reductions of **2c** had a melting point comparable to that of authentic **2a**, GC after 35 h showed an immeasurable peak corresponding to trans ketol **9**, which after 60 h amounted to ca. 6% of total area. Cis ketol **7** could not be detected.

Acknowledgment. Financial support from the National Institutes of Health through NIH Biomedical Research Support Grant No. RR-7059 is gratefully acknowledged. Gratitude is expressed to Gree L. Spoog for helpful consultations.

Registry No. **1b**, 826-56-2; **2a**, 18992-92-2; **2b**, 84987-89-3; **2c**, 84987-90-6; **3a**, 84987-91-7; **3b**, 29494-21-1; **3c** (R = Et), 7478-39-9; **7**, 24795-55-9; **8**, 84987-92-8; **10**, 23595-68-8; $CrSO_4$, 13825-86-0; MEM chloride, 3970-21-6; 10-carboxy-$\Delta^{1,9}$-octal-2-ol, 84987-93-9; ethylenediamine, 107-15-3; dihydropyran, 110-87-2.

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Aklavin-Type Anthracyclinones: Brief, Regiospecific Syntheses of Tetracyclic Intermediates

Frank M. Hauser,*[1] Subbarao Prasanna, and Donald W. Combs

Department of Chemistry and Biochemical Sciences, Oregon Graduate Center, Beaverton, Oregon 97006

Received June 15, 1982

A brief route for regiospecific synthesis of multigram quantities of diversely functionalized tetracyclic precursors to aklavin-type anthracyclinones is described.

The report that the aklavin-type anthracycline antibiotics 11-deoxydaunorubicin (**1a**), 11-deoxyadriamycin (**1b**),[2] and aklavamycin A_1 (**3**)[3] (Chart I) are less toxic[2,4] than the clinically important rhodomycins daunorubicin (**1c**) and adriamycin (**1d**)[5] has generated interest in their preparation. Elegant total syntheses of the aglycons **2a**[6] and **4**[7] of **1a** and **3**, respectively, as well as the aglycon **2e**[8]

(1) Recipient of a Career Development Award, 1978–1983, from the National Cancer Institute (Grant No. CA 00486).

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