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BICYCLOOCTANES: *CIS*-BICYCLO[3.3.0]OCTA-2,6 AND 2,7-DIENE-2-CARBOXYLIC ACIDS

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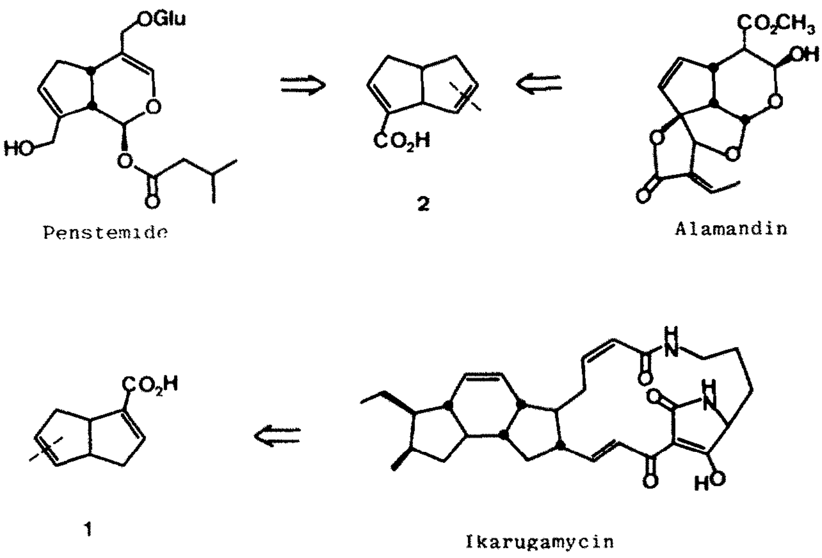
Abstract—Two independent routes to each of the title acids, useful in the synthesis of natural products, are presented. The sequences commence with readily available materials which are amenable to the preparation of multigram quantities. Complete ^{13}C spectral data is supplied for intermediates and products.

We have been involved for some time in exploiting the structural and stereochemical features of bicyclo[3.3.0]octanes for the synthesis of natural products that either contain[1-3] or are devoid[4,5] of a 5-membered, carbocyclic ring. Our current interests are directed at the synthesis of the sesquiterpenes of the plumeride class[6] and of the intriguing and unique structural array found in ikarugamycin.[7] Each of these natural products exhibits a cyclopentane ring bearing two adjacent, *cis* related substituents. The *cis*-bicyclo[3.3.0]octane frame of acids **1** and **2** would provide, after cleavage of one of the rings, just such a *cis*-disubstituted cyclopentane subunit for elaboration to the natural compounds. We describe here to independent routes to each of these acids.

RESULTS AND DISCUSSION

The readily available bicyclo[4.3.0]nonadiene **3**[8] seemed an attractive source of the nine carbon atoms that, through contraction of the six membered ring, could be converted to the desired bicyclo[3.3.0]octane ring system. To this end we examined an extensive array of reagents for the selective oxidation of the cyclohexenyl over the cyclopentenyl double bond. Among the reagents bromine, chlorine, osmium tetroxide, ozone, and permanganate, none were found to exhibit selectivity of greater than 2:1, and the most selective in the series (OsO_4, $KMNO_4$, O_3) showed a greater propensity for oxidation of the 5-membered ring. On the other hand, Woodward oxidation[9] (iodine acetate followed by silver acetate-wet acetic acid) was found to effect preferential oxidation (>4.5:1) of the six-membered ring with essentially complete stereoselectivity for the formation of the *endo* diols **4** and **5**. The regiochemical identity of these two isomers was established by comparison of the ^{13}C spectral data with that for diene **3**. The 6-membered ring sp^2 centers are superimposed in the diene and nearly so in **4**, as these carbons are identically substituted out to the γ-carbons. On the other hand, the vinyl carbons in the 5-membered ring are separated by 6.5 and 6.7 in the diene **3** and diol **5**, respectively, where the carbon atoms closer to the bridgeheads bear one additional β-substituent. The assignment of the *endo* stereochemistry for **4** and **5** is based on analogy with the usual course of the Woodward oxidation as well as the formation of two stereochemically different diols (**18** and **19**) from the oxidation of **3** with osmium tetraoxide.

Oxidative cleavage of **5** was carried out with periodate and the resulting dialdehyde (**7**) was converted to a 1:1 mixture of the bicyclic aldehydes **8** and **9**. Each of these



Penstemide

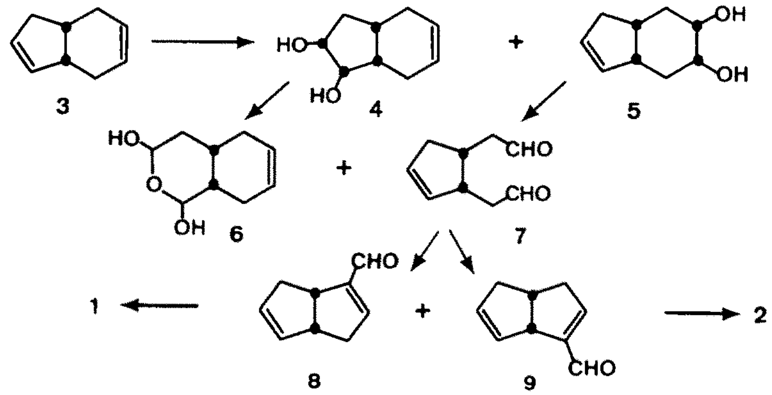
2

Alamandin

1

Ikarugamycin

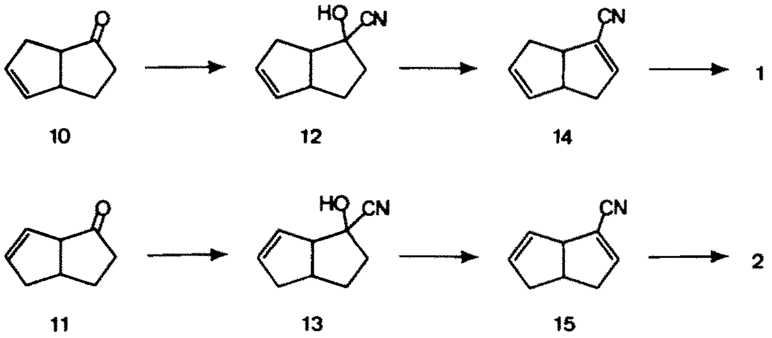
Fig. 1.



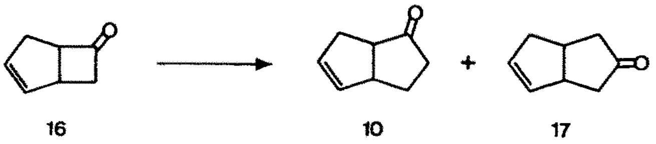
Scheme 1.

aldehydes could be isolated from the mixture in a reasonable state of purity using hplc. In practice, the minor diol (**4**) from the *cis*-hydroxylation was not removed at the point of its formation but carried through the periodate cleavage. The resulting dialdehyde, as the bishemiacetal **6**, was relatively inert to base and could be removed from the desired aldehydes **8** and **9** by simple filtration through silica-gel. Clean oxidation of the aldehydes to acids **1** and **2** was achieved with sliver oxide. This route to the acids was devised and executed at a time when silver was less than $40/mole. During the course of 1980, certain financial events[10] in this state led to an over ten fold increase in the price of this material which was an essential part of the selective oxidation of **3**. We were thus forced to develop the alternate synthesis described below.

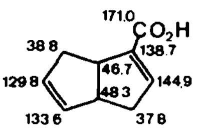
Our second approach is based on the conversion of the isomeric ketones **10** and **11** to **1** and **2** through cyanohydrin formation, dehydration, and hydrolysis of the resulting nitrile. While the ketone **11** was readily available from 1,5-cyclooctadiene in four, high yield steps[11], the catercorner functionalized isomer **10** was not. While it had previously been prepared by ring expansion of the bicyclo[3.2.0]heptenone **16**,[12] the expected preference for migration of the more substituted carbon led to low yields with significant contamination by the isomeric ketone **17**. However, while not well known, diazomethane ring expansions of ketones will show profoundly altered regioselectivity of methylene insertion when carried out in the presence of Lewis acids.[13] In the present case, ring expansion of **16** with diazomethane in the presence of lithium perchlorate afforded the regioisomeric ketones **10** and **17** in a ratio of 4:1 from which a 44% yield of the desired isomer **10** could be obtained by large scale, routine hplc separation. In the absence of Lewis acids, the observed ratio was approximately 3:2. Accurate assessments of regioselectivity in the ring expansion are not possible from these ratios as both with and without Lewis acids the product ketones are further ring expanded, and with somewhat greater facility in the case of **17**. The sequence from the ketones **10** and **11** through to the acids **1** and **2** was carried out as depicted below in Scheme 2. Recrystallization of the crude hydrolysis products removed a relativley minor amount of the corresponding deconjugated acid in each case and provided the desired acids in respectable yield from the ketones (65% for **1**, 49% for **2**) and in a high state of purity.



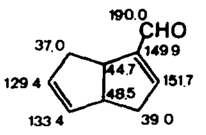
Scheme 2.



Scheme 3.



1



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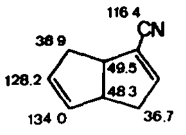

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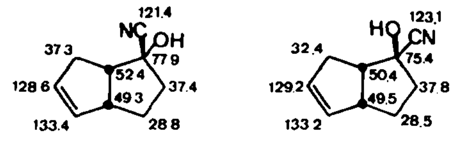

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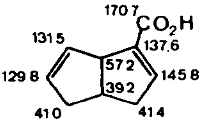

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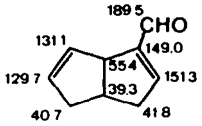

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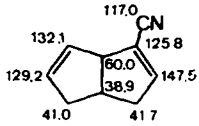

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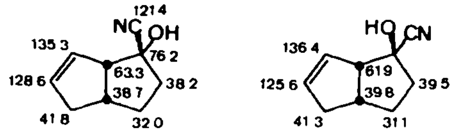

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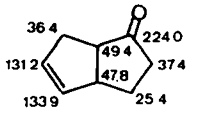

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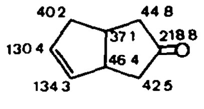

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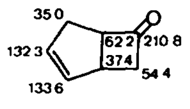

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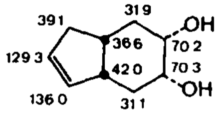

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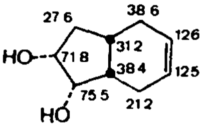

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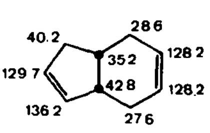

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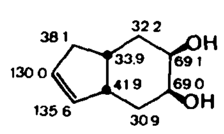

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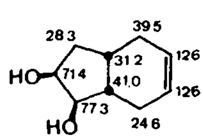

19

Assignments were made using established α, β and γ effects, our previous observations,[15] and continuous wave decoupling techniques (to distinguish between methylene and methine carbons). Assignments between like carbons (CH, CH_2, CH_3) differing by less than 3 δ may be reversed. The stereoisomers of cyanohydrins **12** and **13** with the cyano group *exo* were formed in preponderance over the *endo isomers*. In the case of **13**, too little of the *endo* isomer was formed to permit a ready assignment of the quaternary carbons.

EXPERIMENTAL

Materials. All reagents and solvents were obtained from commercial sources and used without further purification except for ether solvents which were dried with sodiumbenzophenone and distilled before use.

Procedures. Reactions were routinely effected under a dry nitrogen atmosphere and with magnetic stirring. Crude reaction products were purified by "column filtration" through silica gel using an appropriate mixture of hexane and ethyl acetate. Samples thus treated were often homogeneous by thin layer chromatographic analysis (Merck precoated glass plates, sulfuric acid charring visualization). Further purification of samples in large quantities was effected using a Waters System 500 liquid chromatograph. Nuclear magnetic resonance spectra were obtained using a Varian HA-100 or a Perkin–Elmer R-12 spectrometer for ^1H NMR and a Varian FT-80 spectrometer for ^{13}C NMR (off resonance, continuous wave decoupling techniques were used to assess multiplicities). Chloroform-*d* was universally used as solvent except for the carbon spectra of **12** and **14** where acetone-d_6 was employed. Infrared spectra were recorded on a Perkin–Elmer 237B or a Beckman AccuLab 7. Mass spectra were obtained using a Dupont 21-491 for low resolution and a Dupont 21-110B instrument for high resolution analysis. Combustion analyses were performed by Chemalytics, Inc., Tempe, Arizona and Galbraith Laboratories, Inc., Knoxville, Tennessee.

cis-*Bicyclo*[3.3.0]*octa*-2,6-*diene*-2-*carboxylic acid* (1)

Method A. To a stirred solution of 1.36 g (34.0 mmol, 2.1 equiv) of sodium hydroxide in 6 mL of water was added a solution of 2.96 g (17.4 mmol, 1.1 equiv) of silver nitrate in 6 mL of water. The resulting thick brown mixture was stirred for 5 min at room temperature and then cooled to 0°. Aldehyde **8** (1.11 g, 8.27 mmol) was then added dropwise over 5 min followed by 5 mL of ethanol. After 15 min of continued stirring at 0° the black mixture was filtered and the precipitate was washed with hot water. Ethanol was removed *in vacuo* and the resulting aqueous mixture was washed with ether, acidified with concentrated hydrochloric acid, and extracted three times with dichloromethane. The organic extracts were combined, filtered, and concentrated to give 1.09 g (88%) of crystalline acid. Purification and spectral properties are given below under Method B.

Method B. A mixture of 35.7 g (0.26 mol) of crude nitrile **14** and 400 mL (0.78 mol, 1.5 equiv) of 10% w/w aqueous potassium hydroxide was refluxed with stirring for 16 hr, during which time the mixture became homogeneous. The cooled solution was washed with dichloromethane, acidified with concentrated hydrochloric acid, and then extracted three times with dichloromethane. These extracts were combined, filtered through cotton, and concentrated *in vacuo*, leaving 39.3 g (97%) of crude acid as a viscous oil that slowly crystallized. Purification was achieved by either preparative hplc with 3.5:1 hexane:ethyl acetate or by recrystallization from ethyl acetate, m.p. 106–107.5. IR (CH_2Cl_2): 3050 (br), 2920, 1723, 1687, 1631, 1430, 1353, 1270, 1197, 1165, 1102. ^1H NMR δ 6.82 (m, 1H), 5.60 (m, 2H), 3.60 (m, 2H), 2.18–2.94 (m, 4H). HRMS: M^+ *m/e* calc. for $C_9H_{10}O_2$: 150.0681; found: 150.0682. Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; found: C, 71.89; H, 6.83%.

cis-*Bicyclo*[3.3.0]*octa*-2,7-*diene*-2-*carboxylic acid* (2)

Method A. Oxidation of aldehyde **9** using the same procedure described above for the conversion of **8** to **1** provided acid **2** in 77% yield, m.p. 90–91.5° (ethyl acetate).

Method B. The ketone **11** was converted to acid **2** via **11**, **13**, and **15** using the same procedures as described for the preparations of **10**, **12**, and **14**. The overall yield of material identical to that prepared by Method A was 49%. IR (CH_2Cl_2): 3050 (br), 2900, 1722, 1688, 1630, 1340, 1270 (br), 1197, 1165. ^1H NMR δ

6.83 (q, $J = 2$ Hz, 1 H), 5.93 (m, 1 H), 5.68 (m, 1 H), 4.01 (m, 1 H), 2.01–3.31 (m, 5 H). Calc. for $C_9H_{10}O_2$: C, 71.98; H, 6.71; found: C, 71.89; H, 6.82%.

cis - *bicyclo*[4.3.0]*non* - 7 - *ene* - cis,endo - 3,4 - *diol* (**5**), *and* cis - *bicyclo*[4.3.0]*non* - 3 - *ene* - cis,endo - 7,8 - *diol* (**4**)

A 500 mL flask protected from light was charged with 450 mL of glacial acetic acid, 35.5 mL (0.275 mol) of *cis*-bicyclo[4.3.0]nona-3,7-diene, and 91.8 g (0.55 mol) of anhydrous silver acetate. Withe good stirring under a nitrogen atmosphere, 63.4 g (0.25 mol) of iodine was added in ten portions over 45 min. After an additional 30 min, 50 mL (2.75 mol, 10 equiv) of water was added and the yellow mixture was left stirring overnight. The mixture was then heated at 50° for 2 hr. The acetic acid was removed *in vacuo* and the residue was diluted with 15 mL of ether and filtered. The precipitate was washed well with ether and the combined filtrate and washings were extracted with 1 N aqueous sodium bicarbonate. The aqueous layer was separated and back extracted once, then the combined organic layers were washed with brine, dried over molecular sieves, and concentrated *in vacuo*. The resulting crude diol monoacetate mixture (48.5 g, 90%) was stirred overnight with 210 mL (0.32 mol, 30% excess) of 10% w/w methanolic potassium hydroxide. The methanol was then removed *in vacuo* and the residue was partitioned between brine and ethyl acetate. The organic extract was dried over molecular sieves and concentrated *in vacuo* leaving 34.3 g (90%) of a mixture of **4** and **5** which could be separated by preparative hplc (ethyl acetate) but which was generally used without purification or separation. Samples for analysis were prepared by recrystallization from ethyl acetate–hexane.

5: m.p. 52.5–54°. ^{1}H NMR δ 5.70 (m, 2H), 3.78 (m, 4 H), 1.40–2.54 (m, 8 H). HRMS: M$^+$ *m*/*e* calc. for $C_9H_{14}O_2$: 154.0994; found: 154.0996.

4: m.p. 74–75.5°. ^{1}H NMR δ 5.72 (m, 2 H), 3.86–4.36 (m, 4 H), 1.36–2.44 (m, 8 H). HRMS: M$^+$ *m*/*e* calc. for $C_9H_{14}O_2$: 154.0994; found: 154.0998.

cis - *Bicyclo*[3.3.0]*octa* - 2,6 - *diene* - 2 - *carboxaldehyde* (**8**), *and* cis - *bicyclo*[3.3.0]*octa* - 2,7 - *diene* - 2 - *carboxaldehyde* (**9**)

To a stirred solution of 34.3 g (0.22 mol) of crude diol mixture obtained above in 750 mL of water under nitrogen and with a room temp. water cooling bath was added in one portion a solution of 52.2 g (0.24 mol) of sodium metaperiodate in 1200 mL of water. After 15 min, 69 mL of 20% w/w aqueous potassium hydroxide was added to the thick white mixture. After an additional 15 min, the reaction mixture was saturated with solid sodium chloride and then extracted with ether three times. The combined extracts were dried over molecular sieves and concentrated *in vacuo* leaving 26.8 g (90%) of a 1:1 mixture of crude aldehydes. Separation was effected using the Prep 500 system with 30:1 hexane:ethyl acetate and recycle techniques. Typically, separation of 10 g of material prepared as above would afford 3.5 g of each aldehyde with 85 to 95% purity and 3 g of a mixed fraction.

8: ^{1}H NMR δ 9.73 (s, 1 H), 6.78 (m, 1 H), 5.60 (m, 2 H), 3.58 (m, 2 H), 2.1–2.9 (m, 4 H). HRMS: M$^+$ *m*/*e* calc. for $C_9H_{10}O$: 134.0732; found: 134.0728.

9: ^{1}H NMR δ 9.76 (s, 1 H), 6.77 (m, 1 H), 5.87 (m, 1 H), 5.65 (m, 1 H), 3.99 (m, 1 H), 2.0–3.3 (m, 5 H). HRMS: M$^+$ *m*/*e* calc. for $C_9H_{10}O$: 134.0732; found: 134.0735.

cis-*Bicyclo*[3.3.0]*oct-6-en-2-one* (**10**)

To a solution of 27.7 g (0.256 mol) of bicyclo[3.2.0]hept-5-en-2-one[14] in 400 mL of ether was added with stirring under a nitrogen atmosphere 13.6 g (0.128 mol, 0.5 equiv) of anhydrous lithium perchlorate. This solution was cooled to −78° and then 0.256 mol (by titration) of diazomethane in 500 mL of ether (precooled to −78°) was added all at once. The cooling bath was removed after 10 min and the reaction was allowed to proceed for 1 hr after reaching room temperature. Half of the solvent was removed *in vacuo* and the resulting organic material was washed twice with water. The combined aqueous layers were back extracted once and then the combined organic layers were washed with brine and dried over molecular sieves. Concentration afforded 34.0 g of an approximately 1:4:1:1 mixture of starting ketone, the desired ketone **10** the isomeric ketone **17** and over ring expanded ketones derived from **17**. Preparative hplc (15:1) afforded 14 g (44%) of essentially pure **10**, identical with material prepared by ring expansion in the absence of Lewis acid.[12]

exo- *and* endo - 2 - *hydroxy* - cis - *bicyclo*[3.3.0]*oct* - 6 - *ene* - 2 - *carbonitrile* (**12**)

Freshly prepared, liquid hydrogen cyanide (from 78 g, 1.2 mol, 4 equiv, of potassium cyanide in 160 mL of water and 150 mL of 50% aqueous sulfuric acid) was added dropwise to a mixture made from 0.1 g of potassium hydroxide, 3 drops of water, and 37 g (0.3 mol) of ketone **10** cooled in an ice bath. The reaction was stirred for 4 hr after the addition was complete and then 3 drops of 50% aqueous sulfuric acid was added. Removal of volatile material afforded 37.5 g of crude cyanohydrin. Short path distillation gave 33.3 g (74%) of a 4.5:1 stereoisomeric mixture of cyanohydrines, b.p. 80–82° (0.07 mm), as a viscous pale yellow oil. IR (CH_2Cl_2): 3580, 3450 (br), 2949, 2870, 2860, 1450, 1352, 1197, 1150, 1108, 1066, 1006, 1000, 942 cm^{-1}. ^{1}H NMR δ 5.57 (m, 2 H), 4.29 (s, 1 H), 3.36 (m, 1 H), 1.45–3.2 (m, 7 H). HRMS: M$^+$ *m*/*e* calc. for $C_9H_{11}NO$: 149.0841; found: 149.0837.

cis-*Bicyclo*[3.3.0]*octa*-2,6-*diene*-2-*carbonitrile* (**14**)

To a mechanically stirred solution of 38.8 g (0.26 mol) of cyanohydrines **12** in 100 mL of pyridine cooled in an ice bath was added 24.3 mL (0.26 mol) of phosphorus oxychloride dropwise over 45 min. The reaction was stirred for 45 min with cooling, warmed to room temp., and then heated at 55° for 1 hr. The ice-cooled reaction was quenched by dropwise addition of 100 mL of 6 N aqueous hydrochloric acid. The solution was extracted with ether which was then washed with 2 N aqueous hydrochloric acid. The combined aqueous layers were extracted with ether and the combined organic layers were washed with water, 1 N aqueous sodium bicarbonate, and brine, and then dried with molecular sieves. Concentration *in vacuo* afforded 35.7 g (>100%) of crude nitrile that was hydrolyzed to the acid without further purification.

cis - *Bicyclo*[4.3.0]*non* - 7 - *ene* - cis,exo - 3,4 - *diol* (**18**), *and* cis - *bicyclo*[4.3.0]*non* - 3 - *ene* - cis, exo - 7,8 - *diol* (**19**)

The procedure of VanRheenen[16] using catalytic osmium tetraoxide whth N-methylmorpholine-N-oxide was followed, affording a 1:2 mixture of diols **18** and **19** in a combined yield of 41%. Analysis by ^{13}C was carried out on the mixture by dividing the adsorptions into two sets based on relative intensities.

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