Table I. Reactions[a,b] of 3 with Several Base–Solvent Combinations

base–solvent	time for complete reaction, h	% yield of 4[c]
0.24 M MeONa–MeOH	32	91
0.27 M EtONa–EtOH	24	95
0.09 M *t*-BuOK–*t*-BuOH	32	94
0.13 M *t*-BuOK–hexane[d]	2	95

[a] All reactions were conducted at room temperature. [b] [Chloramine] = 0.07–0.08 M. [c] Yields determined by gas chromatography using an internal standard. Estimated error is ±2%. [d] Heterogeneous reaction mixture.

situ preparation of **3**.

The rates at which the four base–solvent combinations induced elimination from **3** were estimated by periodic sampling of the reaction mixture and analysis by gas chromatography. The time required for complete reaction is listed in Table I. As may be seen, *t*-BuOK–hexane gave considerably more rapid dehydrochlorination than did any alkoxide–alcohol combination.

Control experiments demonstrated the stability of **4** and **5** and the absence of solvolysis of **3** under the reaction conditions. Since imine-forming reactions of *N*-chlorobenzylmethylamine with alkoxide bases have been found to exhibit substantial primary deuterium isotope effects,[11] an E2 mechanism seems most reasonable for the dehydrohalogenation of **3**.

In base-promoted eliminations from 1-aryl-2-halopropanes, exclusive or highly predominate formation of 1-arylpropenes is observed.[12-14] Preferential elimination toward the aryl group is considered to result from a combination of two factors: (1) conjugation of the aryl group with the developing double bond in the transition state and (2) acidification of the β hydrogens by the aryl group.[15]

In comparing eliminations from 1-aryl-2-halopropanes and **3**, acidification of the β hydrogen by the β-aryl group should be a relatively constant factor.[16] On the other hand, if the imine-forming eliminations pass through transition states with little double-bond character, there would be less stabilization by phenyl group conjugation. This would result in a reduced propensity for production of the conjugated elimination product. In contrast to this prediction, eliminations from **3** exhibit the same positional orientation as that observed in dehydrohalogenations of 1-aryl-2-halopropanes. These findings are consistent with considerable carbon–nitrogen double-bond development in transition states for base-promoted imine formation.

A carbon–carbon double bond is about 60 kcal mol^{-1} stronger than the corresponding single bond, whereas a carbon–nitrogen double bond is approximately 80 kcal mol^{-1} stronger than the single bond.[18] With significant double bond character in transition states for dehydrohalogenations forming both carbon–carbon and carbon–nitrogen double bonds, an important factor in the greater facility of the latter must be the greater strength of the resultant double bond relative to the corresponding single bond.

Experimental Section

Materials. *N*-Benzylidene-*n*-butylamine (**4**) and *N*-*n*-butylidenebenzylamine (**5**) were prepared by the method of Campbell, Sommers, and Campbell.[19] Catalytic hydrogenation[19] of **4** gave benzyl-*n*-butylamine.

Base–solvent combinations of MeONa–MeOH and EtONa–EtOH were prepared by reacting freshly cut sodium metal with the dry alcohols under nitrogen. Combinations of *t*-BuOK–*t*-BuOH and *t*-BuOK–hexane were prepared by adding *t*-BuOK (Aldrich) to dried *t*-BuOH and hexane, respectively.

Chlorination of Benzyl-*n*-butylamine. Benzyl-*n*-butylamine (1.0 mmol) and *N*-chlorosuccinimide (1.3–1.5 mmol) (Parish Chemical) were magnetically stirred in 10 mL of pentane for 30 min at room temperature. The mixture was filtered and 10 mL of MeOH, EtOH, *t*-BuOH, or hexane was added to the pentane solution. Evaporation of the pentane in vacuo at room temperature gave solutions of **3** in the desired solvent.

In a proton magnetic resonance spectrum of **3** in pentane taken prior to solvent exchange, no absorptions due to N–H of the starting amine could be detected.

Elimination from 3. A reaction solution or mixture (15 mL total volume) containing 1.0 mmol of **3**, 1.0 mmol of cyclohexylbenzene (internal standard for gas chromatography), and 1.3–3.6 mmol of the base was magnetically stirred in a closed vessel at room temperature. Periodically samples were removed and analyzed by gas chromatography on a 4 ft × $\frac{1}{8}$ in. column of 20% Carbowax 400 on Chromosorb P at 130 °C (retention times: cyclohexylbenzene, 24 min; **4**, 38 min; **5**, 47 min).

Reactions of **3** with MeONa–MeOH and *t*-BuOK–hexane were also conducted in the absence of cyclohexylbenzene. Proton magnetic resonance spectra of the isolated reaction products were identical with that of **4**.

Control Experiments. The chloramine **3** was recovered unchanged after treatment with methanol and with hexane under conditions more forcing than those of the reactions with base. Mixtures of **4** and **5** were unaffected by treatment with the base–solvent combinations under conditions used for eliminations from **3**.

Registry No.—**3**, 68185-83-1; **4**, 1077-18-5; **5**, 56249-61-7; benzyl-*n*-butylamine, 2403-22-7; *N*-chlorosuccinimide, 128-09-6.

References and Notes

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The C(15) Configuration of Naturally Occurring Pimaren-15,16-diols[1]

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Among natural substances of the pimarane skeletal type there exist a limited number containing a vicinal glycol unit in the form of a 13-dihydroxyethyl group, i.e., the 15,16-diol moiety, in place of the more common 13-vinyl function.[2]

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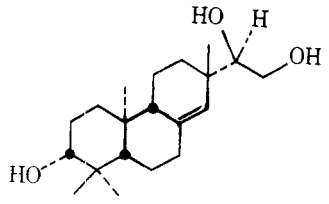
Whereas the stereochemistry of the rigidly held centers of these compounds is known, the configuration of their 15-hydroxy group has remained unsolved. This note describes the C(15) stereochemistry of darutigenol (1) and kirenol (2).



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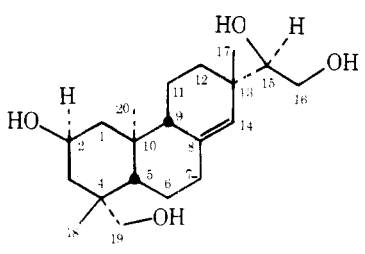

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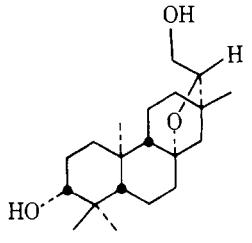

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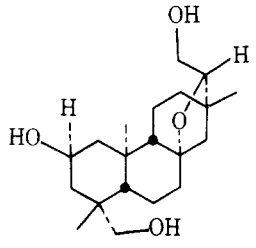
Darutigenol (1) is the product of enzymic hydrolysis of darutoside, a glucoside constituent isolated from the Madagascan plant *Siegesbeckia orientalis*.[2a] The C(15) configuration of the aglycone is difficult to ascertain in the case of a freely rotating, dioxygenated, two-carbon unit at C(13).[3] Contrastingly, isodarutigenol B (3), a rigid, tetracyclic product of acid-catalyzed hydrolysis of darutoside,[2a] appears to be a more attractive candidate for stereochemical analysis and NMR spectroscopy the analytical method of choice. Thus tetrahydrofuran 3 was reprepared[2a] and kirenol (2), a constituent of the Japanese folkmedicine kiren, *Siegesbeckia pubescens* Makino,[2c] was transformed into tetrahydrofuran 4 on treatment with hydrogen chloride. Furthermore, the tetrahydrofurans 8 and 9 were constructed as models for the spectral study by conversion of pimarol (5) into an inseparable mixture of triol isomers 6 and 7 on oxidation with osmium tetroxide[2a,c] and treatment of the triols with hydrogen chloride.

Inspection of the ^{1}H-NMR spectra of the pimarol-derived tetrahydrofuran models revealed them to be differentiated readily by the appearance of the oxymethine hydrogen region. In the spectrum of isomer 8 the C(15) and C(16) hydrogen signals overlapped and the hydrogen set appeared to be coupled strongly. The second isomer (9) revealed separated oxymethine and oxymethylene signals and weak coupling. The darutoside- and kirenol-derived tetrahydrofurans (3 and 4, respectively) exhibited a C(15) and C(16) hydrogen region identical with that of the first model tetrahydrofuran.

A ^{13}C-NMR spectral analysis of the tetracycles 3, 4, 8, and 9 led to the needed stereochemical information. The carbon shifts were assigned on the basis of previous data on pimaranic compounds[4] and are listed in Table I. Comparison of the C(12), C(14), and C(17) shifts of one of the C(15) epimers of the pimarol-based tetrahydrofurans with those of the other distinguish the two compounds easily and reveal their C(15) configurations as depicted in stereostructures 8 and 9, since the γ effects of C(16) exerted on C(12) in 8 and to a lower extent on C(14) and C(17) in 9 are pronounced. The three diagnostic carbon shifts also reveal the darutigenol- and kirenol-based tetracycles to possess stereostructures 3 and 4, respectively.

The above observations show darutigenol (1) and kirenol (2) to possess a C(15) *R* configuration. The pimaratriol model



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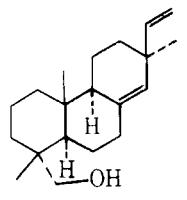

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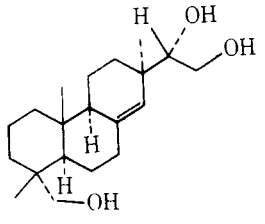

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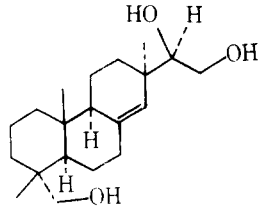

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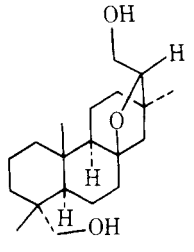

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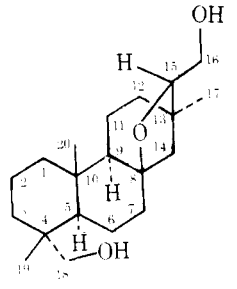

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of like stereochemistry thus is as shown in structure 6 and its C(15) epimer as in 7. As the ^{13}C NMR data of the pimaratriol models (Table I) indicate, the C(15) shift of 8(14)-pimarene-15,16-diols is a diagnostic constant for revealing the C(15) configuration of such natural products.[5]

Experimental Section

Melting points were determined on a Reichert microhotstage and are uncorrected. ^{1}H NMR spectra of $CDCl_3$ solutions (Me_4Si, $\delta = 0$ ppm) were recorded on a Varian EM-390 spectrometer and ^{13}C NMR spectra were run on a Varian XL-100-15 spectrometer operating at 25.02 MHz in the Fourier transform mode.

8,15-Oxidopimara-16,18-diols 8 and 9. A solution of 400 mg of pimaratriols[2a,c] 7 and 6 in 100 mL of chloroform saturated with hydrogen chloride gas was kept at 0 °C for 12 h. It then was poured in 200 mL of ice water and the organic solution washed with saturated sodium bicarbonate solution and with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel and elution with 30:1 chloroform–methanol yielded 250 mg of a solid whose crystallization from ethyl acetate produced crystalline 8: mp 98–100 °C; ^{1}H NMR δ 0.78, 0.93, 1.00 (s, 3 each, Me_3), 3.04, 3.37 (dd, 2, J = 11 Hz, H_2-18), 3.49, 3.59, 3.66, 3.76, 3.81, 3.89, 3.96 (7 lines, 3, H-15, H_2-16).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.30; H, 10.75.

Further elution with the same solvent mixture yielded 150 mg of a solid whose crystallization from ethyl acetate led to crystalline 9: mp 134–135 °C; ^{1}H NMR δ 0.80, 0.90, 1.03 (s, 3 each, Me_3), 3.05, 3.38 (dd, 2, J = 11 Hz, H_2-18), 3.43 (s, 2, H_2-16), 3.63, 3.68, 3.71, 3.76 (4 lines, 1, H-15).

Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.21; H, 10.72.

Table I. ^{13}C Chemical Shifts of Darutigenol, Kirenol, and Related Compounds[a]

	3[d]	4[e]	8[f]	9[g]	1[b,h]	2[b,i]	6[b,j]	7[b,k]
C(1)	37.8	48.2	37.8	38.0	37.0	47.3	38.2	38.3
C(2)	26.9	63.8	17.5	17.6	27.2	64.1	17.8	17.8
C(3)	78.8	44.1	35.1	35.2	78.7	43.6	35.3	35.4
C(4)	38.7	40.2	37.3	37.4	38.8	40.2	37.2	37.2
C(5)	54.5	54.6	47.8	47.9	54.1	54.9	47.2	47.2
C(6)	19.4[c]	19.6	19.4[c]	19.1[c]	22.1	21.8	22.0	22.0
C(7)	38.1	38.3	39.2	39.5	35.8	36.0	34.9	34.9
C(8)	81.5	81.9	81.9	82.4	138.9	138.0	138.6	137.1
C(9)	54.5	55.3	54.6	54.9	50.4	50.6	50.3	50.3
C(10)	36.8	38.6	36.8	36.7	37.9	39.2	36.6	36.5
C(11)	19.1[c]	18.9	19.0[c]	19.2[c]	18.2	18.3	17.8	17.8
C(12)	32.9	32.8	33.0	39.1	31.7	31.6	31.5	30.7
C(13)	40.4	40.4	40.4	40.9	37.0	37.0	37.4	36.6
C(14)	54.8	54.7	55.0	52.0	127.4	128.1	127.0	127.7
C(15)	88.0	88.3	88.0	84.7	75.6	76.0	75.5	78.2
C(16)	61.2	61.0	61.2	64.2	63.1	63.0	62.7	62.7
C(17)	22.3	22.4	22.6	19.9	22.8	22.4	21.8	22.9
C(18)	28.5	27.2	71.6	71.7	28.3	27.3	70.8	70.8
C(19)	15.8	65.2	18.0	18.0	15.6	64.6	17.3	18.3
C(20)	14.8	16.7	15.4	15.4	14.6	16.4	14.7	15.1

[a] In ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] In 20:1 $CDCl_3$–CD_3OD (by volume). [c] Assignments in any vertical column may be interchanged. [d] Registry no. 5975-40-6. [e] Registry no. 68152-04-5. [f] Registry no. 68152-05-6. [g] Registry no. 68199-26-8. [h] Registry no. 5940-00-1. [i] Registry no. 52659-56-0. [j] Registry no. 68152-06-7. [k] Registry no. 68199-27-9.

Isokirenol (4). A solution of 110 mg of kirenol in 20 mL of dioxane and 50 mL of chloroform saturated with hydrogen chloride gas was kept at room temperature for 48 h. Workup as above and chromatography of the crude product, 100 mg, on silica gel, followed by elution with 12:1 chloroform–methanol, yielded 55 mg of solid and subsequently 25 mg of another solid which was not characterized. Crystallization of the first product from ethyl acetate afforded crystalline 4: mp 156–157 °C; ^1H NMR δ 0.93, 1.00, 1.03 (s, 3 each, Me_3), 3.3–4.0 (m, 3, H-2, H_2-19), 3.49, 3.59, 3.66, 3.76, 3.81, 3.89, 3.96 (7 lines, 3, H-15, H_2-16).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 80.10; H, 10.20.

Acknowledgment. The authors are indebted to Dr. A. Diara and Professor Takao Murakami for generous samples of darutigenol and kirenol, to Dr. I. R. Burfitt for early ^{13}C NMR determinations, to Professor H. Kagan for the Horeau test,[3] and to Mme. Z. Varon for technical assistance. P.C. acknowledges with gratitude receipt of a travel grant under the Senior Fulbright-Hays Program.

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(3) Application of Horeau's method of determination of the absolute configuration of chiral alcohols to the 3-keto derivative of darutigenol (1), kindly prepared by Mme. Z. Varon, under conditions of exhaustive acylation led to (−)-α-phenylbutyric acid in 6.1% optical yield. Whereas this implies an *S* configuration for C(15), the result is only tenuous in the absence of any knowledge regarding the effect of the neighboring hydroxymethyl group.
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(5) The fact of the triacetates of the pimaratriol epimers **6** and **7** also showing a distinct C(15) shift difference ($\Delta\delta$ = 2.2 ppm) indicates that the dissimilarity of rotamer preferences is not a consequence of the 15,16-diols existing in intramolecularly hydrogen-bonded ($\Delta^{8(14)} \rightarrow$ OH) form.

An Approach to 2,3-Disubstituted Cyclopentanones

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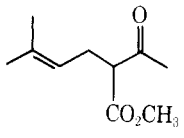
The general importance of cyclopentanones in natural products has led to the development of various methodology for such systems—especially based upon the conjugate addition of cuprates to enones.[1-3] We were specifically interested in the availability of 3-substituted-2-(carboalkoxy)cyclopentanones as a versatile building block for which such conjugate addition reactions are impractical—in part due to the lability of 2-(carboalkoxy)cyclopent-2-en-1-one.[4] We wish to report a new approach to such systems[5] and their utility on constructing 2,3-disubstituted cyclopentanones.

Scheme I summarizes the approach. The initial carbomethoxylation[6a] proceeds with high regioselectivity to give keto ester **1** producing only a very small amount (<5%) of alternate **2.** Separation of these positional isomers was unnecessary since the subsequent diazo transfer reaction[7] gave only diazo compound **3,** the product of reaction of **1.** The intramolecular cyclopropanations[8] to bicyclo[3.1.0]hexane **4** proceeded best with copper–bronze.



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The key step is the thermolytic opening of the cyclopropyl ketone which is suggested to be a concerted proton transfer with cleavage of the cyclopropyl C–C bond.[9] Two possible pathways invoke participation of the ketone oxygen (path a) or the ester oxygen (path b). While the product is superficially the same, it does lead to a differentiation of the methyl carbons. Geometrically, path b appears better aligned; furthermore, if the initial proton–oxygen interaction involves the lone pairs on oxygen, only path b is feasible.

In this event, passing a hexane solution of cyclopropyl ketone **4** through a hot column heated at 350 °C smoothly gave keto ester **5.** The crude product was purified by extraction from the organic phase as the potassium enolate salt followed

Scheme I. Synthesis of 3-Isopropenyl-2-(carbomethoxy)-cyclopentanone