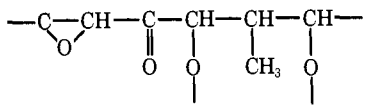
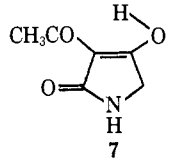


for C(7)–C(12). If the oxygen at C-7 or that at C-9 were attached to C-12, a hemiketal would be generated in the reduction of **2** and **3** and that would have been further reduced rather than giving **5**. Thus, the extra CH_3C unit must be attached to both O-7 and O-9, and at C-12 as well, along with the remaining methyl group. The structure of tirandamycic acid is then **2**. It is of interest that the carbon skeletons of **2** and streptolic acid[5] are identical, the two acids differing only in functional groups on the tetrahydropyran ring. As expected,[11] **2** and all its degradation products, as well as **1**, show facile mass spectral fragmentations along line a···a to give intense peaks (at *m/e* 197 for **1** and **2**, at *m/e* 199 for **3**, at *m/e* 241 for **4**, at *m/e* 201 for **5**, and at *m/e* 243 for **6**).

Subtraction of the acyl group ($C_{18}H_{23}O_5$) from the molecular formula of tirandamycin ($C_{22}H_{27}NO_7$) leaves $C_4H_4NO_2$ for the tetramic acid portion of the molecule, *i.e.*, the tetramic acid must be unsubstituted except for the 3-acyl group. In agreement with this assignment is a mass spectral peak due to cleavage between C-1 and C-2 of the acyl group (calcd for $C_5H_4NO_3$, 126.0191; found, 126.0193). Moreover, the nmr spectrum ($CDCl_3$) of **1** contains an amide NH at δ 6.95 and an isolated methylene group at 3.76, as well as an enolic OH at 13.16; synthetic 3-acetyltetramic acid, **7**, exhibits nmr absorptions[12] for the amide NH at δ 6.82 and the isolated methylene at 3.72 (as well as the enolic OH at 11.8, reflecting the difference in the functions of **1** and **7** α to the enolic carbon).



7

Acknowledgment. This work was supported in part by Public Health Service Grants AI 01278 and AI 04769 from the National Institute of Allergy and Infectious Diseases and CA 11388 from the National Cancer Institute.

(11) K. L. Rinehart, Jr., *Carygraph*, 3 (2), 1 (1964).
(12) A. Aebi, H. U. Daeniker, and J. Druey, *Pharm. Acta Helv.*, 38 (1963).

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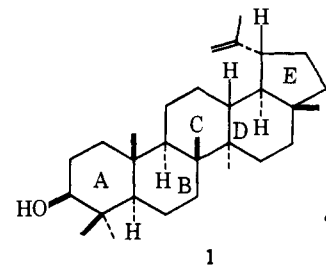
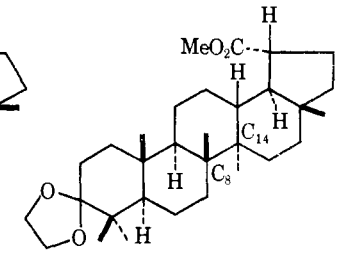
The Total Synthesis of Lupeol

Sir:

Lupeol (**1**), said to be the most abundant of the pentacyclic triterpenes,[1] became of interest to us, not only because of the stereochemical challenge of its ten asymmetric centers, but also because this rather complex structural problem presented us with the opportunity of using and extending the enolate trapping method.[2]

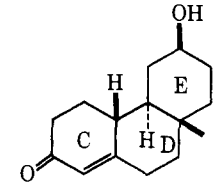


1



2

The goal of the synthesis was the pentacyclic ketal ester **2** which embodies essentially all the asymmetry of lupeol into which it presumably should be easily convertible. The correctness of this assumption was checked by demonstrating that **2**, mp 204–206°, made from natural lupeol,[3] could, indeed, be reconverted to lupeol by (a) treatment with excess lithium methyl in refluxing dioxan, followed by phosphorus oxychloride–pyridine dehydration, to establish the isopropenyl group and (b) deketalization and sodium borohydride reduction. The identity of the lupeol thus formed was established by comparison of its benzoate, mp 250–252°, with that of an authentic sample (mixture melting point, tlc, ir, and nmr spectra).

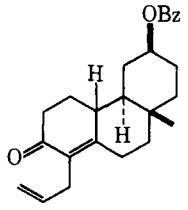


3

We now report the synthesis of **2** from the previously described[4] tricyclic enone **3**. The first major problem in the elaboration of **3** toward **2** involves the critical introduction of the two vicinal *trans*-methyl groups at C_8 and C_{14}, together with a substituent at C_8 to serve as a precursor of ring **B**. The goal at this stage thus became **9**, the construction of which, starting with the benzoate, mp 143–144°, of **3**,[5] was initiated by thermal rearrangement (refluxing pyridine, 20 hr) of its allyl enol ether (allyl orthoformate–allyl alcohol in tetrahydrofuran–*p*-toluenesulfonic acid, room temperature 1 hr) to **4**, mp 134–135° (70% from **3**). Addition of diethylaluminum cyanide[6] to the enone **4** (4:1 benzene–toluene, 0°, followed by 1 hr at 45°) gave the cyano

(1) J. Simonsen and W. C. J. Ross, "The Terpenes," Vol. IV, Cambridge University Press, Cambridge, 1957, p 329. In all structural formulas heavy and dotted lines stand for methyl groups unless otherwise labeled.
(2) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, **87**, 275 (1965). For a different approach to pentacyclic triterpene synthesis, *cf.* the total synthesis of germanicol: R. E. Ireland, *et al.*, *Ibid.*, **92**, 5743 (1970).
(3) Starting from the known 3β-hydroxy ester corresponding to **2** (L. Ruzicka and G. Rosenkranz, *Helv. Chim. Acta*, **23**, 1311 (1940); E. R. H. Jones and R. J. Meakins, *J. Chem. Soc.*, 1335 (1940)) by Jones' oxidation and ketalization. We thank Professors K. Nakanishi and R. Stevens for samples of natural lupeol.
(4) G. Stork, H. J. E. Loewenthal, and P. C. Mukharji, *J. Amer. Chem. Soc.*, **78**, 501 (1956).
(5) All intermediates had mass nmr and ir spectra in accord with their expected structures. Some were further characterized by carbon and hydrogen analyses or (as indicated in the text) by exact masses.
(6) *Cf.* W. Nagata, *Nippon Kagaku Zasshi*, **90**, 837 (1969).

ketone **5**, mp 171–172°, in 90% yield. The latter, by transformation to its ketal, mp 203–204°, reduction to the imine alcohol (large excess of lithium aluminum hydride, 5 hr in refluxing tetrahydrofuran under N_2), followed by hydrolysis (5% acetic acid–tetrahydrofuran–methanol (1:1:1), buffered with sodium acetate, room temperature overnight), and rebenzoylation to the aldehyde **6**, mp 162–163° (*m/e* 452.2566), and, finally, reduction with sodium borohydride gave the ketal alcohol **7**, mp 166–167° (*m/e* 454.2715), in 52% overall yield from **5**.



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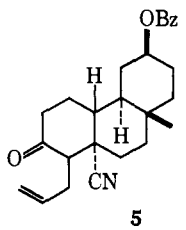

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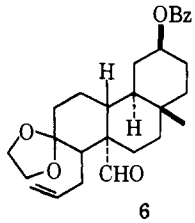

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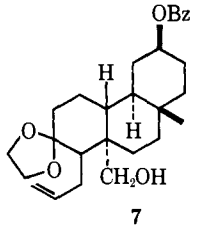
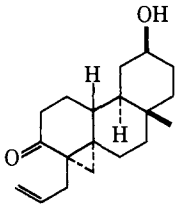


7

The cyclopropyl ketone **8**, the crucial precursor of the 8,14-dimethyl system of **9**, was then constructed by formation of the mesylate of **7** which underwent simultaneous deketalization and solvolytic closure of the cyclopropyl ring on treatment with 3% hydrochloric acid–tetrahydrofuran at 45° overnight. Saponification of the benzoate then gave **8**, mp 132–133° (*m/e* 288.2088), in 85% overall yield from **7**.



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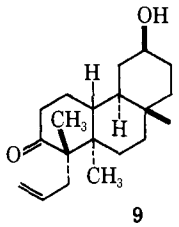
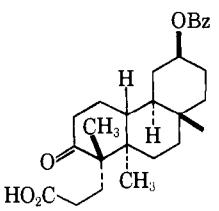


9

Reductive alkylation of **8**[7] was the last step to **9**; a solution of 4 g of **8** in 80 ml of glyme and 2.2 ml of *tert*-butyl alcohol was added to 350 mg of lithium in 250 ml of liquid ammonia. Addition of hexamethylphosphoramide, after 1 hr, and warming to 0° (allowing ammonia to escape) was followed by rapid addition of 18 ml of methyl iodide and 1 hr of stirring at room temperature. The desired keto alcohol **9**, mp 150–152° (*m/e* 304.2401), was thus obtained in 60% yield.



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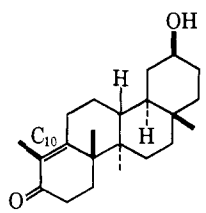
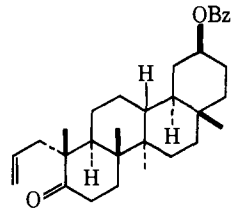


11

(7) This is an extension to cyclopropyl ketones of the enolate trapping method of ref 2; *cf.* W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

Completion of ring **B** was carried out *via* the propionic acid **10**, mp 214–215°, made by treatment of the benzoate, mp 153°, of **9** with disiamylborane, followed by Jones' oxidation of the intermediate organoborane. The enone ring of **11** was then established unexceptionally[8] (formation of enol lactone, mp 147–149°, addition of ethyl magnesium bromide in ether–tetrahydrofuran at −30°, and aqueous methanolic base cyclization). The tetracyclic hydroxyenone **11**, mp 226–227° (*m/e* 330.2554), was thus obtained in 56% overall yield from **9**.

The regio- and stereospecific problems attending the establishment of ring A were efficiently solved *via* the enolate trapping sequence[2] which led to the desired trans B/C junction and the correct side-chain attachment at C_{10}. Trapping of the enolate from **11** with allyl bromide by the usual procedure, followed by benzoylation, gave the allyl ketoalcohol benzoate (**12**), as an oil, in 80% yield. The latter was converted to the pentacyclic enone **13** by the sequence described above for **9** → **11**, with the exception that the ring **B** ketone was protected as the dioxolane prior to hydroboration (with 9-**BBN**[9] in this case). The pentacyclic hydroxyenone **13**, mp 289–290° (*m/e* 398.3179), was thus obtained in about 50% overall yield from **12** *via* the intermediate enol lactone benzoate, mp 255–256°. Reductive alkylation[2] with methyl iodide was once more employed, this time to introduce the *gem*-dimethyl group at C_4 and establish the A/B trans junction.[10]



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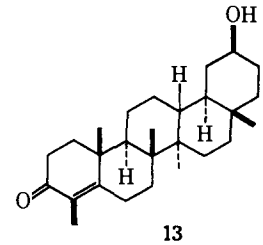

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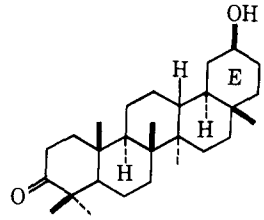
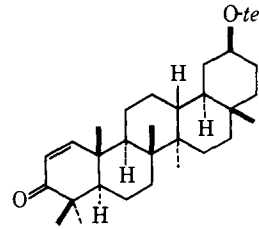


14

(8) (a) *Cf.* R. B. Turner, *J. Amer. Chem. Soc.*, **72**, 579 (1950); (b) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951).

(9) E. F. Knights and H. C. Brown, *ibid.*, **90**, 5280 (1968).

(10) This reductive alkylation gave yields up to ~65%, but occasionally gave difficultly separable mixtures of **14** with the simple reduction product of **13**. We therefore devised an alternative route starting with **13**, *via* the following sequence: reduction (Li–NH_3); acetylation and introduction of Δ^1 unsaturation (Br_2–AcOH; Li_2CO_3–LiBr–DMF); deacetylation, and *tert*-butyl ether formation to i; methylation (sodium hexamethyldisilazane in benzene) and hydrogenation (Pd/C) to ii, mp 225–227°, finally transformed by loss of isobutylene into **14**, identical with the product of the direct reductive alkylation of **13**.



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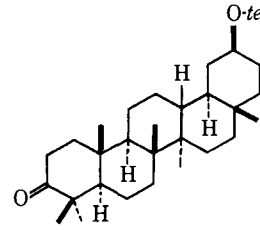
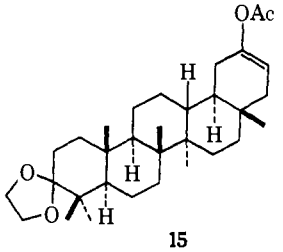


ii

The resulting pentacyclic ketol **14**, mp 269–271° (*m/e* 414.3493), differs from our goal, the ester **2**, only in ring E. We now describe the steps which served to transform **14** into **2**. Ketalization of **14** gave the dioxolane alcohol, mp 188–190°, oxidized to the ring E ketone, mp 230–232°, which was smoothly converted to its enol acetate **15**, mp 198–199°, by quenching the enolate (2.5-hr reflux with excess sodium hexamethyldisalazane in tetrahydrofuran) with acetic anhydride. Ozonolysis of **15** (methylene chloride–methanol (2:1), −70°, followed by sodium borohydride–sodium hydroxide at 0°), acidification (10% acetic acid), esterification (diazomethane), and tosylation led to the isolation of the crude tosylate ester **16** (silica gel–benzene ether, 10:1) which we expected to cyclize readily to the (±)-pentacyclic ketal ester **2**. This proved to be the case. Upon heating for 30 min with an excess of sodium hexamethyldisilazane in benzene, cyclization of **16** gave an 80% yield of (±)-**2**, mp 200–202° from ether–hexane. (*Anal.* Found: C, 76.31; H, 10.39). The ir, nmr, and mass spectra of (±)-**2** were identical with those of the methyl ester **2** derived from natural lupeol (*vide supra*).[11]



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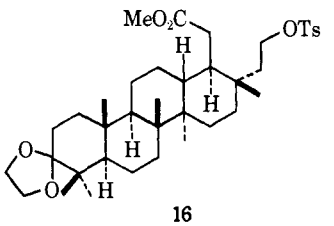

16

Since the path from **2** to lupeol had already been delineated (*vide supra*) the route was now complete between β-naphthol (the precursor of our starting material, the tricyclic enone **3**) and lupeol.

Acknowledgments. We wish to thank the National Science Foundation and the National Institutes of Health for the support of this work.

(11) Although formally unnecessary, we also converted our (±)-**2** to (±)-lupeol, but because of the small scale on which we carried out this transformation, the melting point (202–204°) of our material may be low.

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Determination of Various Hydrogen–Deuterium Isotope Effects in Carbanion Reactions Using Electron Transfer as a Reference Reaction

Sir:

We wish to report a convenient method for measuring isotope effects on carbanion protonation at steady-state concentrations and to draw some general conclusions regarding such reactions. It has been suggested[1] that observation of a substantial hydrogen isotope effect on the ionization of a carbon acid requires that the protonation of the resultant carbanion show a similar isotope effect and that this is only possible in cases where the reprotonation is not diffusion controlled. Other approaches to the assessment of reprotonation rates include the association of linear Brønsted plots of log k (isotopic exchange) *vs.* pK_a[2] and the occurrence of internal return[3] with diffusion-controlled reprotonation.

Experimentally, the situation is highly contradictory. Substituted triphenylmethane systems in *tert*-butyl alcohol show both internal return[4,5] and primary isotope effects.[6] Substituted fluorenes in methanol not only exhibit isotope effects[7] and internal return[8] but also give linear Brønsted plots.[9]

Electron-transfer trapping of such carbanions[10] adds a new dimension to the problem and, in our opinion, demonstrates a relatively slow reprotonation for those anions which can be trapped. This category has previously been shown to include potassium triphenylmethide in *tert*-butyl alcohol[10] and in this paper is extended to 9-methoxyfluorenide ion in methanol. Electron transfer trapping can also be used to demonstrate isotope effects. We have determined not only the primary isotope effect for proton removal from the carbon acid, following the method of Russell,[11] but have extended the technique to determination of solvent isotope effects. Most importantly, we have been able to measure the primary isotope effect for proton removal by the carbanion from solvent molecules. The data on which these determinations are based are listed in Table I. These results can be analyzed in terms of

Table I. Rate Constants for Exchange and Loss of 9-Methoxyfluorene Catalyzed by Potassium Methoxide (0.47 *N*) in Methanol at 30.0°

Run	Substrate	Solvent	Acceptor[c]	k_{ex},[a] M^{-1} sec^{-1}	k_{loss},[b] M^{-1} sec^{-1}
1	RH	MeOD	None	5.97×10^{-4}	
2	RH	MeOD	3,5-$Cl_2C_6H_3NO_2$		6.12×10^{-4}
3	RD	MeOH	None	4.40×10^{-5}	
4	RD	MeOH	3,5-$Cl_2C_6H_3NO_2$		4.45×10^{-5}
5	RH	MeOH	3,5-$Cl_2C_6H_3NO_2$		2.53×10^{-4}
6	RH	MeOH	$C_6H_5NO_2$		1.22×10^{-5}
7	RD	MeOD	3,5-$Cl_2C_6H_3NO_2$		1.15×10^{-4}
8	RD	MeOD	$C_6H_5NO_2$		2.41×10^{-5}

[a] Exchange was followed by isolation of substrate and mass spectral analysis. At least five points were taken per kinetic run and rate constants determined by the least-squares method. The correlation coefficient was greater than 0.99 and reproducibility in duplicate runs was within 2%. [b] Loss was followed by gas chromatography, relating unreacted substrate to internal hexadecane. Excellent first-order kinetics were again obtained with reproducibility within 3%. The product of the reaction was almost exclusively (80% recovery) 9,9′-dimethoxy-9,9′-bifluorene from deoxygenated reaction mixtures under purified nitrogen. This is indisputably the product of an electron transfer reaction. Unreacted substrate in run 2 contained no D. [c] 0.2 *M*.

(1) G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, *Advan. Chem. Ser.*, No. 75, 174 (1968).

(2) D. J. Cram in "Fundamentals of Carbanion Chemistry," A. T. Blomquist, Ed., Academic Press, New York, N. Y., 1965, p 14.

(3) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **90**, 2821 (1968).

(4) D. J. Cram, F. Wiley, H. P. Fischer, and D. A. Scott, *ibid.*, **86**, 5370 (1964).

(5) R. D. Guthrie and G. R. Weisman, *Chem. Commun.*, 1316 (1969).

(6) R. D. Guthrie, *J. Amer. Chem. Soc.*, **92**, 7219 (1970).

(7) A. Streitwieser, Jr., and F. Mares, *ibid.*, **90**, 2444 (1968).

(8) W. T. Ford, E. W. Graham, and D. J. Cram, *ibid.*, **89**, 689 (1967). The authors observe about 5% isoinversion. Isoretention, an invisible process, might well be larger.

(9) A. Streitwieser, J. I. Brauman, J. H. Hammons, and A. H. Pudjaatmaka, *ibid.*, **87**, 386 (1965).

(10) R. D. Guthrie, *ibid.*, **91**, 6201 (1969).

(11) G. A. Russell and A. G. Bemis, *ibid.*, **88**, 5491 (1966).