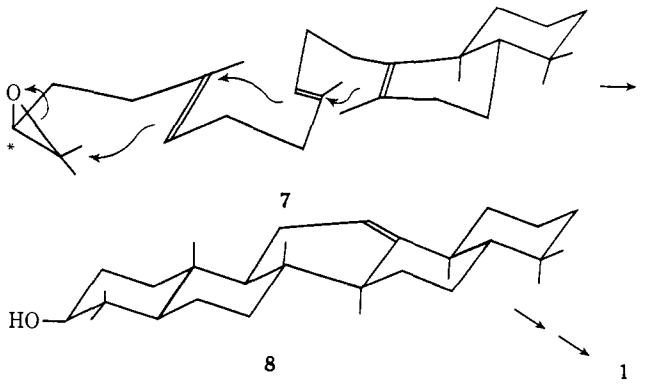
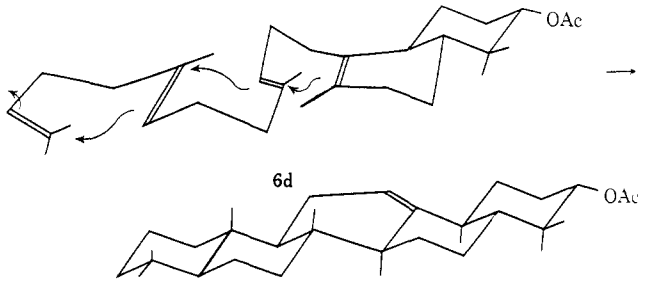


7

8 1

could be achieved, providing epoxide **7**, believed to be a 50:50 mixture of C-3(*) epimers [nmr (CCl_4) δ 5.15 (2, m), 2.53 (1, t, J = 6 Hz), 1.23 (3 s), 1.20 (3, s)]. Cyclization of **7**, carried out by means of $SnCl_4$ in CH_3NO_2 for 0.5 hr at 0°, yielded, after thin layer chromatographic separation, *dl*-Δ^{12}-dehydrotetrahymanol (**8**), mp 252–254°, [M^+ *m/e* 426.3896 (calcd, 426.3861); ir 3330 (br), 2920, 1701, 1254, 1084 cm^{-1}; nmr ($CDCl_3$) δ 5.25 (1, m), 3.25 (1, m), 1.13, 1.10, 0.97, 0.90, 0.87, 0.82, 0.78 (aliphatic methyl)] (yield 20%, based on the utilizability of one C-3 epimer).

In an alternative approach which more nearly approximates the established biological pathway,[6] the bicyclic polyene acetate **6d** was synthesized and cyclized. Under conditions similar to those described above, the known[7] bicyclic bromo ether **4b** was coupled with thioether **5**, providing thioether **6c** [nmr (CCl_4) δ 7.17 (10, s), 4.98 (3, m), 4.45 (2, q, J = 11 Hz), 3.95 (1, m), 2.82 (1, m), 0.97 (6, s), 0.83 (3, s)], which on reduction (Li–$C_2H_5NH_2$) and acetylation afforded tetraene **6d** [nmr (CCl_4) δ 5.05 (3, m), 3.11 (1, m), 0.98 (3, s), 0.93 (3, s), 0.77 (3, s)]. Although H_3PO_4 or $SnCl_4$ was ineffectual, CH_3CO_2H–H_2SO_4 or $BF_3 \cdot (C_2H_5)_2O$ served to convert (2%) **6d** to *dl*-$\Delta^{9(11)}$-dehydrotetrahymanyl acetate (**9**), identified at the microgram level by its nmr, ir, gc, and tlc properties, which were essentially identical with those of *dl*-Δ^{12}-dehydrotetrahymanyl acetate, and by its characteristic mass spectrum [*m/e* 468 (2%), 276 (33%), 216 (55%), 201 (67%), 191 (100%)].



6d

9

Conversion of synthetic *dl*-Δ^{12}-dehydrotetrahymanyl acetate, mp 249–251°, [M^+ *m/e* 468.3994 (calcd 468.3969 (7%), 249 (5%), 218 (100%), 203 (67%), 189 (55%)] to *dl*-tetrahymanol, patterned after a published relay,[8] involved initial CF_3CO_3H oxidation (80%), carried out in CH_2Cl_2 in the presence of Na_2CO_3,[9] to the acetate of *dl*-tetrahymanol-12-one, mp 290–292° [ir 1723, 1694 cm^{-1}; nmr (CCl_4) δ 2.05 (3, m), 1.95 (3, s); M^+ *m/e* 484.4010 (calcd 484.3916)]. On Wolff–Kishner reduction,[10] the ketone afforded (85%) *dl*-tetrahymanol, mp 271–274° [M^+ *m/e* 428.4048 (calcd 428.4018)] identical, except for melting point and optical properties, with naturally occurring tetrahymanol (mass spectral, nmr, ir, gc, and tlc comparison).[11]

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(6) J. M. Zander, J. B. Greig, and E. Caspi, *J. Biol. Chem.*, **245**, 1247 (1970).

(7) E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(8) Y. Tsuda and coworkers (ref 2) have reported the conversion of α-onocerin diacetate to tetrahymanol.

(9) R. A. Micheli, *J. Org. Chem.*, **27**, 666 (1962).

(10) Satisfactory results were achieved only by carrying out the reaction at 130° for 48 hr in the presence of anhydrous diethylene glycol, anhydrous hydrazine, and hydrazine hydrochloride, then adding sodium diethylene glycolate–diethylene glycol and warming to 210° for 24 hr; see W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964); K. Schaffner, L. Cagliotti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **41**, 152 (1958).

(11) All new compounds gave satisfactory elemental analyses.

(12) National Science Foundation fellow.

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Received June 12, 1972

Biogenetic-Type Total Synthesis. δ-Amyrin, β-Amyrin, and Germanicol

Sir:

We wish to announce the total biogenetic-type synthesis[1] of the pentacyclic triterpenoids δ-amyrin (**2**),[2] β-amyrin (**3**),[3] and germanicol (**4**),[4] all produced in nature presumably from squalene 2,3-oxide (**1**).[5] The laboratory reaction sequence features two separate polyolefin cyclization operations: in one, five asymmetric centers are generated during intramolecular annulation of the tetraene epoxide **5**, and in the second, a key intermediate **8a** is built up by means of a Linstead-type reaction carried out on triene **7**.

To initiate the synthesis of the D–E component, the Michael addition of ethyl 1-methallylmalonate to 3-chloro-2,5,5-trimethylcyclohex-2-one[6] was carried out

(1) Treatise on biogenetic-type synthesis: E. E. van Tamelen, *Fortschr. Chem. Org. Naturst.*, **19**, 242 (1961).

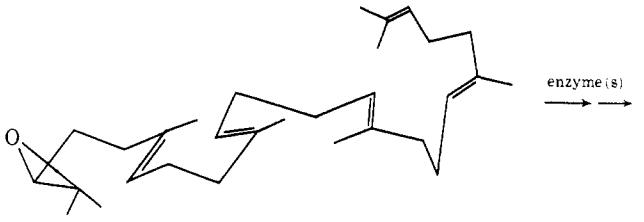
(2) Natural occurrence: O. C. Musgrave, J. Stark, and F. S. Spring, *J. Chem. Soc.*, 4393 (1952).

(3) Previous synthetic accomplishments in the β-amyrin area: (a) production of δ-amyrene–iso-β-amyrin from (+)-ambreinolide, J. A. Barltrop, J. D. Littlehailes, J. D. Rushton, and N. A. J. Rogers, *Tetrahedron Lett.*, 429 (1962); E. J. Corey, H. J. Hess, and S. Proskow, *J. Amer. Chem Soc.*, **81**, 5258 (1959); **85**, 3979 (1963); E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964); (b) conversion of δ-amyrene to β-amyrin, D. H. R. Barton, E. F. Lier, and J. F. McGhie, *J. Chem. Soc. C*, 1031 (1968).

(4) Synthesis of *dl*-germanicol: R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, *J. Amer. Chem. Soc.*, **92**, 5743 (1970).

(5) The oxide has been established as a progenitor of β-amyrin in pea seedlings: E. J. Corey and P. R. Ortiz de Montellano, *ibid.*, **89**, 3362 (1967)

(6) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).



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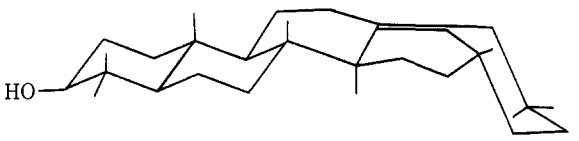

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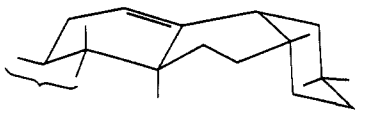

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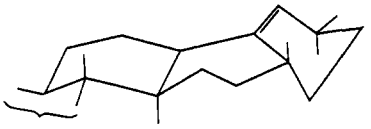

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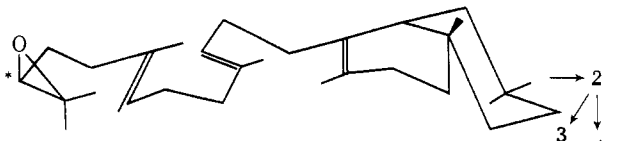

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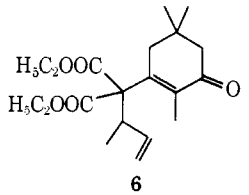
(potassium *tert*-butoxide in *t*-BuOH for 2 hr at 80°), resulting in the formation, after *in situ* β elimination, of chloride ion of the diene keto diester **6** (80%, bp 170° (0.1 mm)) [ir 1725, 1670, 915 cm^{-1}; nmr δ 6.02 (1, m), 5.05 (2, m), 4.18 (4, q, J = 7 Hz), 3.44 (1, m), 1.76 (3, t, J = 1.5 Hz), 0.96 (6, s)]. After $NaBH_4$ reduction of **6**, acidification, and work-up,



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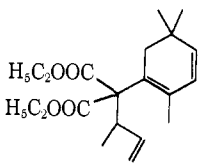

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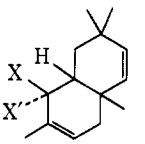
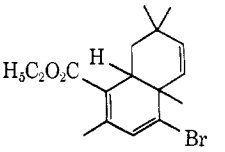
distillation of crude intermediate alcohol **6a** afforded directly (80–85%) the triene diester **7** (bp 160° (0.1 mm)) [ir 1640, 742 cm^{-1}; nmr δ 5.61 (1, d, J_{AB} = 9 Hz), 5.50 (1, d, J_{AB} = 9 H); λ_{max}^{EtOH} 270 mμ]. On exposure to a large excess of $BF_3 \cdot (C_2H_5)_2O$ in benzene at room temperature for 24 hr, **6a** or **7** was transformed (60%) to the cis bicyclic diene diester **8a** [nmr δ 5.61 (1, m), 1.8 (3, m), 0.81 (3, s)]. Decarboethoxylation of **8a**, carried out by heating at 160° in DMSO with NaCN for 6 hr,[7] provided (70%) a *ca.* 8:1 mixture of α- and β-diene esters (**8b** and **8c**, respectively), separated by preparative tlc on silica gel [β, nmr δ 2.70 (1, d, J = 12 Hz); *m/e* M^+ 262, 189 (33%), 173 (69%), 122 (100%) 107 (60%), α, nmr δ 2.59 (1, d, J = 6 Hz)].[8] Since the



8a, X = X′ = $CO_2C_2H_5$
b, X′ = H; X = $CO_2C_2H_5$
c, X′ = $CO_2C_2H_5$; X = H



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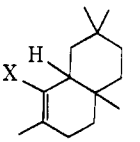
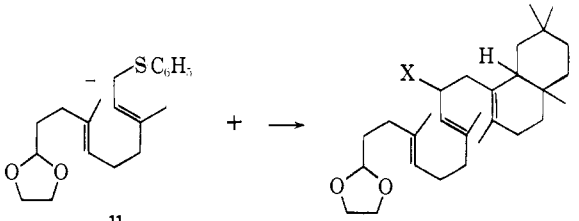


10a, X = $CO_2C_2H_5$
b, X = CH_2Br

β,γ-unsaturated ester could not be converted by base or acid to the α,β isomer, the latter, required system had to be secured by indirect means. The crude bromination product which resulted from heating of **8a,b** with 2.5 equiv of *N*-bromosuccinimide in refluxing CCl_4 (benzoyl peroxide initiator) was subjected to DBN[9] elimination (room temperature in benzene), yielding the bromotriene ester **9** after multiple elution thick layer chromatography [nmr δ 6.00 (1, s), 2.20 (3, s); λ_{max}^{EtOH} 295 mμ; *m/e* M^+ 340–338, 259 (52%)]. Catalytic hydrogenation (10% Pd/C) in C_2H_5OH provided (10% overall from **8**) the monounsaturated ester **10a** [ir 1711 cm^{-1}; nmr δ 2.3 (1, m), 2.1 (2, m), 1.92 (3, s); λ_{max}^{EtOH} 225 mμ; *m/e* M^+ 264, 203 (30%), 191 (100%), 175 (60%)]. Reduction (95%) of ester **10a** with AlH_3 in $(C_2H_5)_2O$, followed by treatment of the resulting allyl alcohol with 48% hydrobromic acid–petroleum ether, gave rise (100%) to the bicyclic allyl bromide **10b** [nmr δ 3.9 (1, d, J_{AB} = 11 Hz), 3.8 (1, d, J_{AB} = 11 Hz)].[10]

In order to complete the synthesis of epoxide **5**, the carboacyclic moiety was introduced through alkylation of the phenyl thioether anion **11** with bromide **10b**,

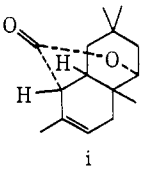


11

12a, X = SC_6H_5
b, X = H

carried out in dry THF at −78° for 1 hr with gradual warming to room temperature. The resulting product **12a** (45%) [nmr δ 7.2 (5, m), 5.2 (2, m), 4.80 (1, t, J = 5 Hz), 1.56 (9, s), 0.86 (6, s), 0.80 (3, s)], on treat-

acid corresponding to **8c** to a lactone, the chemical and spectral (ir, nmr) properties of which revealed it to possess structure i.



i

(7) A. P. Krapcho, G. A. Glynn, and B. J. Grenon, *Tetrahedron Lett.*, 215 (1967).

(8) That bicycles **8a–c**, **9**, and **10** are indeed *cis*-hydronaphthalenes was indicated by the thermally (160° (30 mm)) induced conversion of

(9) C. W. Spangler, R. Euchen, K. Silver, and B. Butzlaff, *J. Org. Chem.*, **36**, 1695 (1971).

(10) Another approach to the bicyclic moiety **10** was recently published by C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971).

ment with Li–$C_2H_2NH_2$ at −78°,[11a] was converted to acetal **12b** (95%) [nmr δ 5.2 (2, m); *m/e* M+ 428, 205 (31%), 109 (97%), 95 (100%)]. The experimental sequence acetal → aldehyde → terminal epoxide, as described elsewhere,[11b] was applied here, providing (55% overall from **12b**) epoxide **5** [nmr δ 2.70 (1, t, J = 6 Hz), 1.20 and 1.17 (6, s,); *m/e* M+ 426.385010 (calcd 426.385986)], unquestionably a *ca.* 50:50 mixture of racemates differing stereochemically at C-3(*). Alternatively and more expeditiously, similar reductive coupling of bromide **10b** with *trans,trans*-farnesyl phenyl thioether furnished (53%) the expected bicyclic tetraene (**5**, with Δ^2 double bond instead of 2,3-epoxide) [nmr δ 5.1 (3, m); *m/e* M+ 410, 205 (46%), 109 (100%), 95 (82%)], which was terminally oxidized[12] (55%) to epoxide **5**.

Stannic chloride–CH_3NO_2 at 0° for 2 hr effected transformation of epoxide **5** to *dl*-δ-amyrin (8%, based on the consumption of one of the two epoxide racemates) (mp 185–188°), isolated and purified by multiple elution tlc[13] and indistinguishable by mass spectra, nmr, and vpc from δ-amyrin produced by acid isomerization of β-amyrin benzoate.[14] Resolution of *dl*-δ-amyrin was accomplished by means of the (*R*)-α-methoxy α-trifluoromethylphenylacetate (MTPA),[15] which, after three crystallizations from $CHCl_3$–MeOH (1:10), yielded ester (mp 233–234.5°), identical (mmp 232.5–234.5°) with the MTPA ester of authentic δ-amyrin (mp 233–234.5°). (−)-δ-Amyrin was regenerated from the ester by $LiAlH_4$ reduction. In view of the prior conversion of δ-amyrin from natural sources to δ-amyrene,[14] and the transformation of the latter to β-amyrin,[3b] the δ-amyrin synthesis described herein also constitutes a formal synthesis of β-amyrin (**3**). Finally, the laboratory production of **2** also embraces germanicol (**4**), since the latter is isolated as the predominant product when δ-amyrin in *t*-BuOH–H_2O (10:1) is photolyzed in the presence of *p*-xylene (quartz tube at 2537 Å in Rayonet reactor) for 48 hr at 30°[16] under nitrogen, followed by preparative vpc.[17]

Acknowledgment. Financial support was provided by the National Science Foundation (GP 23019), while nmr and mass spectral contributions were made by Dr. L. Durham and Dr. J. Trudell (Stanford Medical Center). Authentic triterpene samples were donated by Professors R. Ireland (California Institute of Technology) and C. Djerassi (Stanford University), and MTPA-Cl was furnished by H. Mosher (Stanford University).

(11) (a) J F. Biellman and J. B. Ducep, *Tetrahedron Lett.*, 3701 (1969); (b) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C R. Chauvin, R. J. Anderson, and R. S. Achini, *J. Amer. Chem Soc.*, 92, 7202 (1970).

(12) E. E. van Tamelen and T. J Curphey, *Tetrahedron Lett.*, 121 (1962).

(13) After tlc, the product was composed (vpc) of 95% *dl*-δ-amyrin and 5% *dl*-β-isoamyrin.[14]

(14) G Brownlie, M. B. E. Fayez, F. S. Spring, R. Stevenson, and W. S. Strachen, *J. Chem. Soc.*, 1377 (1956).

(15) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 34, 2543 (1969).

(16) J. A. Marshall, *Accounts Chem. Res.*, 2, 33 (1969), and references cited therein.

(17) Elemental analyses on all intermediates were satisfactory. All nmr spectra were recorded in $CDCl_3$ + 1% TMS.

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Preferential Stabilization of σ-Delocalized Ions by Methyl Substituents Compared to Phenyl Substituents[1,2]

Sir:

The solvolytic rate ratio between a secondary halide or ester and the related α-methyl substituted tertiary derivative is[3,4] 10^5–10^8. The particular value found depends on the leaving group, the solvent, and any special structural features present. Under those conditions leading to the 10^5 value[3] the rate enhancement due to phenyl substitution in place of methyl was found to be 10^8, in approximate conformity to the rule of thumb that "one phenyl is worth two methyls."[5]

Substitution of methyl groups for hydrogen on a cyclopropylcarbinyl residue produces solvolytic rate enhancements that depend on the position of attachment.[6] The pattern of rate response to methyl substitution can be interpreted in terms of transition state charge delocalization corresponding to that calculated for the free cation.[7]

Interestingly, the pattern for phenyl substitution is strikingly different with little or none of the expected rate enhancement for a phenyl in the 2 position.[8] This has been ascribed to the absence of charge,[8a] steric inhibition of resonance,[8b] and to a fortuitously balanced blend of conjugative stabilization and retarding inductive effect.[9]

In a recent numerical exploration of symmetrical σ-bridged ions using an extended Hückel model[10] a remarkable insensitivity to resonance stabilizing substitutents was noted[11] which provided an alternative explanation for many of the seemingly anomalous results observed in studies of neighboring σ participation.[12] It seemed of interest to determine if this result also provided an explanation for the different response patterns of methyl and phenyl substitution of cyclopropylcarbinyl molecules. Toward this end we report here some new experimental results that probe this question by determining the substituent effect on the homoallylic route to cyclopropylcarbinyl intermediates.

(1) Taken largely from the Ph.D. Dissertation of H. D. Banks, Cornell University, 1970.

(2) Supported, in part, by the National Science Foundation.

(3) H. C. Brown, *Chem. Ind. (London)*, 2, 199 (1966); H. C. Brown and M.-H. Rei, *J. Amer. Chem. Soc.*, 86, 5008 (1964). (Note that limiting secondary rates are estimated from acetolyses of tosylates.)

(4) See P. v. R. Schleyer, *et al.*, *J. Amer. Chem. Soc.*, 92, 2538 (1970), for a detailed discussion and further references.

(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 325.

(6) P. v. R. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, 88, 2321 (1966).

(7) K. B. Wiberg, *Tetrahedron*, 24, 1083 (1968); H. S Tremper and D. D. Shillady, *J. Amer. Chem. Soc.*, 91, 6341 (1969)

(8) (a) R. A. Sneen, K. M. Lewandowski, I. A. I. Taha, and B. R. Smith, *J. Amer. Chem. Soc.*, 83, 4843 (1961); (b) M. Nikoletic, S. Borcic, and D. E. Sunko, *Tetrahedron*, 23, 648 (1967); (c) T. Shono, I. Nishiguchi, and R. Oda, *J. Org. Chem.*, 35, 42 (1970).

(9) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, 87, 1331 (1965); G. D. Sargent has proposed a fortuitous blend of conjugative stabilization and inductive retardation to explain the lack of stabilization of several proposed nonclassical transition states by phenyl groups, *Quart. Rev., Chem. Soc.*, 20, 301 (1966).

(10) R. Hoffmann, *J. Chem. Phys.*, 40, 2480 (1964).

(11) C. F. Wilcox, Jr., R. G. Jesaitis, and S. Belin, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, No. ORGN 8.

(12) (a) E. J. Corey and H. Uda, *J. Amer. Chem. Soc.*, 85, 1788 (1963); (b) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *ibid.*, 86, 1246 (1964); (c) C. F. Wilcox, Jr., and R. G. Jesaitis, *Tetrahedron Lett.*, 2567 (1967); (d) J. A. Berson, D. Wege, G. M. Clarke, and R. G. Bergman, *J. Amer. Chem. Soc.*, 90, 3240 (1968); (e) T. Takino and Y. E. Rhodes, *ibid.*, 92, 5270 (1970).