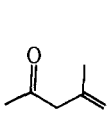

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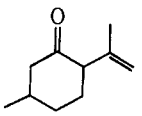

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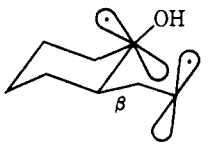
containing α-diketones, which undergo exclusive cyclobutanol formation upon irradiation.

It is interesting to speculate on the reason for the total absence of photoelimination products from photolysis of adamantylacetone (**3**). The most obvious explanation is the high energy of the unstable olefin, adamantene (**2**), which would result from the type II photoelimination reaction. Given the choice of forming adamantene or the much less strained and lower energy cyclobutanols **7** and **8**, the adamantyl excited state (or the 1,4 biradical resulting from intramolecular γ-hydrogen abstraction) may prefer the (presumably) lower energy reaction pathway yielding the cyclobutanols. This rationale could also serve to explain the absence of type II photoelimination products from the β,γ-unsaturated ketones **13** and **14**, as well as α-diketones, since photoelimination in these compounds would result in high-energy olefins, allenes, and ketenes, respectively. This would imply that the ratio of cyclobutanol:type II products resulting from intramolecular γ-hydrogen abstraction is sensitive to the relative stabilities of the products and the strength of the bond to be cleaved in going to products.

We have recently suggested[8] that the most favorable transition state for β cleavage of the 1,4 biradical resulting from intramolecular γ-hydrogen abstraction by alkyl ketone excited states is one in which both the radical center carbon 2p orbitals are approximately parallel to the β bond. This transition state allows the maximum development of the double-bond character of both the enol and the olefin as the β bond cleaves. The low efficiency of β cleavage from the 1,4 biradical generated by intramolecular γ-hydrogen abstraction from α-alkyl cyclohexanones has been partially attributed to an inability to easily achieve this transition state. In the lower energy chair conformation with the α substituent equatorial, the β bond is nearly orthogonal to the carbonyl carbon 2p orbital (**15**). Clearly this same effect could be operating in



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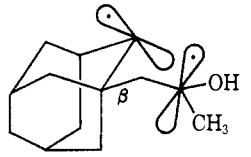

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the 1,4 biradical generated from adamantylacetone (**3**). In this case, moreover, the β bond is rigidly held in a position nearly orthogonal to the carbon 2p orbital at the 2 position (**16**).

(8) D. S. Weiss, N. J. Turro, and J. C. Dalton, *Mol. Photochem.*, **2**, 91 (1970).
(9) Ferguson Teaching Fellow.
(10) National Institutes of Health Predoctoral Fellow.
(11) Alfred P. Sloan Fellow.

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Received May 9, 1970

A Convenient, Stereoselective Synthesis of 9,10-Dimethyl-*trans*-1-decalones through the Protolysis of Fused Methoxycyclopropanes[1]

Sir:

Synthetic methods for the efficient, stereoselective angular methylation[2] of polycyclic systems are especially important for such logistically demanding synthetic programs as those directed toward the total synthesis of steroids and triterpenes. Our particular concern for this problem stems from the interest in the synthesis of such pentacyclic triterpenes as alnusenone and friedelin. Early results[3] from this effort focused our attention on methods for the stereoselective generation of synthetically useful intermediates that contain the *trans*-13,14-dimethyl C/D ring system present in these molecules.[4] Two such intermediates are the keto olefin **9** and the hydroxy ketone **10**, which not only possess the required carbon skeletons but also suitably situated unlike functional groupings for further synthetic elaboration. The successful syntheses of these substances reported here serve to demonstrate an approach of potential general utility for the angular methylation of polycyclic systems in the trans manner.

We were attracted to the current effort by the recent report[5] of Wenkert and Berges that protolysis of fused, polycyclic methoxycyclopropanes provided an efficient stereoselective route to the 9,10-dimethyl-*cis*-1-decalone system. Since the stereochemistry of the angular methylated 1-decalones formed by this method depends on that of the intermediate cyclopropyl ether, the success of such a plan for our purposes is related to the availability of suitable cyclopropyl derivatives of the *trans*-decalin series. The location and type of functionality desired in the ketones **9** and **10** suggested that such stereochemical control of the cyclopropylation process could be expected by application of the Simmons–Smith reaction[6] to the hydroxy enol ethers **5** and **6**. The facilitation and orientation[7] of this reaction by neighboring hydroxyl groups is well appreciated, and a similar approach provided the Wenkert group[5] entry into the *cis*-decalin series through cyclopropylation of a related C-2 equatorial hydroxy enol ether. The present situation, however, presents a problem of no minor proportions, for to orient the cyclopropyl grouping in the desired fashion the C-5 hydroxyl function must be axial.

This problem was approached through the keto enol ether **4**[8] (oil, evap dist 50° (0.025 mm)), which itself was prepared in 45% overall yield from 2-methyldihydroresorcinol (**2**). Condensation of the dione **2** with methoxymethyl vinyl ketone (**1**)[5,9] in the presence

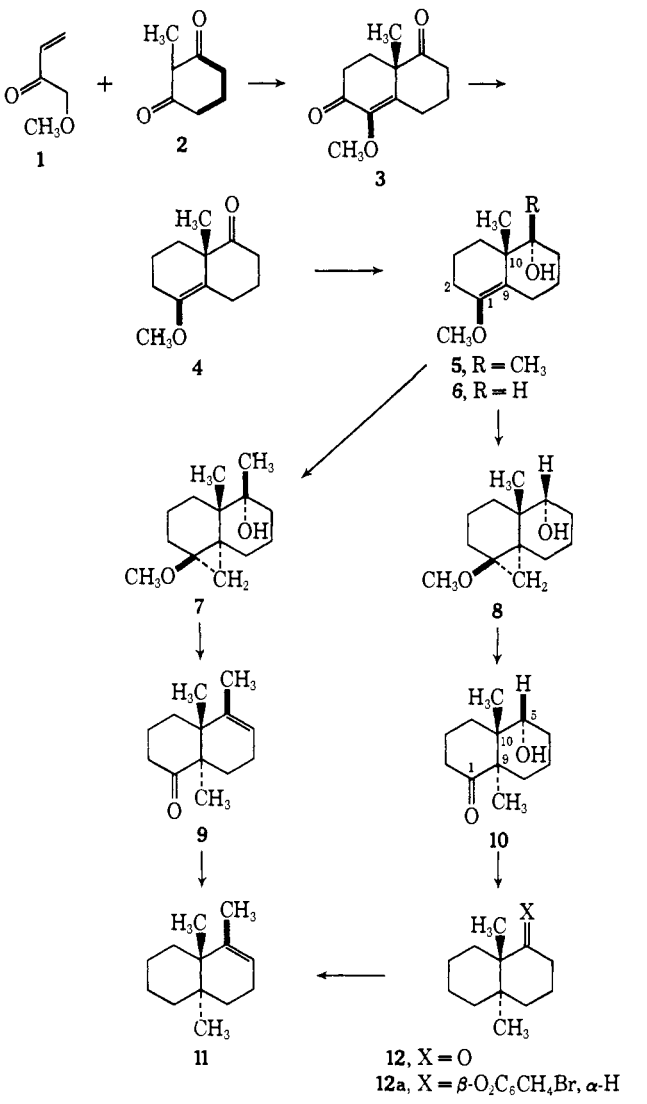
(1) Acknowledgment is made for support of this work by a grant (GP7810) from the National Science Foundation.
(2) G. Stork and P. L. Stotter, *J. Amer. Chem. Soc.*, **91**, 7780 (1969).
(3) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, **34**, 3717 (1969).
(4) Direct methylation of suitable 1-decalone derivatives has led to low yields and predominantly cis-fused products in our hands[3] and those of others: J. A. Marshall, G. L. Bundy, and W. I. Fanta, *ibid.*, **33**, 3913 (1968); H. W. Whitlock, Jr., and L. E. Overman, *ibid.*, **34**, 1962 (1969).
(5) E. Wenkert and D. A. Berges, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).
(6) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).
(7) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); W. G. Dauben and A. C. Ashcraft, *ibid.*, **85**, 3673 (1963).
(8) Spectral data and combustion analyses consistent with the structures of all new compounds reported were obtained.
(9) Prepared from 1,4-dimethoxy-2-butanone [G. F. Hennion and

of potassium hydroxide in methanol, and then aldolization and dehydration of the crude product by sodium benzoate in refluxing xylene, afforded the methoxydione **3**[8] (mp 76–78°) in 70% yield. The allylic C-2 carbonyl group was then removed in 64% overall yield in a manner similar to that reported by Marshall and coworkers[10] in the case of the desmethoxy material.

Treatment of the keto enol ether **4** with dimethylsulfoxonium methylide in dimethyl sulfoxide[11] and then lithium aluminum hydride reduction of the resulting crude epoxide afforded an 86% yield of an epimeric mixture of tertiary alcohols. Analysis[12] of the nmr spectrum of this mixture revealed that the desired axial alcohol **5** made up greater than 90% of this material. Inasmuch as this isomer proved to be quite labile, the mixture was not extensively purified but used directly in the Simmons–Smith reaction.[6] The resulting cyclopropyl ether **7**[8] [mp 60–61.5°; nmr ($CDCl_3$) δ 0.52 and 0.82 (2, two d, J = 5.5 Hz, cyclopropyl methylene), 1.03 (3, s, C-1, OCH_3), 1.15 (3, s, C-5, CH_3), and 3.23 ppm (3, s, C-10, CH_3)] formed rapidly at room temperature and was isolated in 61% overall yield from the keto enol ether **4**. Cleavage of the methoxycyclopropane with concomitant dehydration of the tertiary alcohol occurred when this material was heated under reflux for 2 hr in 7% methanolic hydrochloric acid. The unsaturated ketone **9**[8] [nmr 68–69°; ($CDCl_3$) δ 1.00 (s, 3, C-9, CH_3), 1.17 (s, 3, C-10, CH_3), 1.65 (d, J = 1.5 Hz, 3, C-5, CH_3), and 5.20 ppm (1, m, C-6, H)] was formed in 87% yield by this treatment and culminated a very satisfactory scheme for the C-9 methylation of a 10-methyl-1-octalone system.

Conclusive proof that introduction of the new angular methyl group has resulted in the formation of a trans-fused system was provided by correlation of the unsaturated ketone **9** with the saturated ketone **12**. The structure and stereochemistry of this latter molecule has recently been conclusively established[13] by single-crystal X-ray analysis of the derived *p*-bromobenzoate **12a**. Thus, Wolff–Kishner reduction of the unsaturated ketone **9** afforded the olefin **11**[8] (mp 52–55°) in 50% yield, and the identical olefin (mp and mmp 52–55°) was obtained in 76% yield from the ketone **12** after addition of methyllithium and dehydration with thionyl chloride in pyridine (see Scheme I).

Scheme I



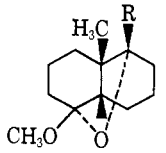
In order to modify this scheme so as to provide for the formation of the keto alcohol **10** and hence increase the potential generality of the suquence, we had need of a reagent for the conversion of the methoxy ketone **4** to the α (axial) hydroxy enol ether **6**. The recent report of Brown and coworkers[14] on the use of lithium perhydro-9b-boraphenalylhydride for the reduction of several cyclic ketones in just this fashion was quite timely. Application of this new reduction procedure to the methoxy ketone **4** resulted in a 70:30 mixture of the corresponding α (axial) **6** and β (equatorial) alcohols in quantitative yield, whereas the standard hydride reducing agents afforded only the β (equatorial) epimer. Again the axial alcohol **6** was very labile and extensive purification of this reduction product was avoided. Use of the crude alcohol mixture in the Simmons–Smith reaction allowed the isolation of the more stable cyclopropyl ether **8**[8] [oil, evap dist at 120° (0.65 mm); nmr ($CDCl_3$) δ 0.38 and 0.78 (2, two d, J = 5.5 Hz, cyclopropyl methy-

F. P. Kupiecki, *J. Org. Chem.*, **18**, 1601 (1953)] by the method of S. Archer, W. B. Dickinson, and M. J. Unser, *ibid.*, **22**, 92 (1957).

(10) J. A. Marshall and G. L. Bundy, *J. Amer. Chem. Soc.*, **88**, 4291 (1966).

(11) C. E. Cook, R. C. Corky, and M. E. Wall, *J. Org. Chem.*, **33**, 2789 (1968); E. J. Corey and M. Chaykorsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(12) The procedures described for the preparation of the axial alcohols **5** and **6** were developed after initial extensive experimentation in the more stable desmethoxy series. In this latter series it was possible to prepare and characterize fully both of the C-5 axial and equatorial alcohols in their pure state. In contrast, both of the hydroxy enol ethers **5** and **6** were particularly labile toward even mild acidic media and were quantitatively converted to the corresponding ketals i[8] and ii[8] after standing overnight at 25° in chloroform solution. After the



i, R = CH_3
ii, R = H

addition of several drops of pyridine, the chloroform solutions of these ethers **5** and **6** are stable to normal storage.

(13) R. E. Ireland, M. I. Dawson, J. Bordner, and R. E. Dickerson, *J. Amer. Chem. Soc.*, **92**, 2568 (1970).

(14) H. C. Brown and W. C. Dickason, *ibid.*, **92**, 709 (1970).

lene), 1.11 (3, s, C-1, OCH_3), 3.17 (3, s, C-1, OCH_3), and 3.14–3.37 ppm (1, m, C-5, H)], in 60% overall yield from the methoxy ketone **4**. Under the same acidic conditions employed above for protolysis and dehydration of the methoxycyclopropane **7**, the present cyclopropyl ether **8** was converted to the desired hydroxy ketone **10**[8] [mp 158–159°; nmr ($CDCl_3$) δ 0.83 (3, s, C-10,CH_3), 1.46 (3, s, C-9,CH_3), and 3.50–3.65 ppm (1, m, C-5,H)] in 80% yield without any evidence of dehydration of the secondary alcohol. Again conclusive proof for the structure and stereochemistry of this hydroxy ketone **10** was readily provided when Wolff–Kishner reduction and then oxidation of the resulting alcohol afforded the known ketone **12**[13] [mp and mmp 108–110° (sealed capillary)] in 50% overall yield. Aside from the utility of these intermediates for further synthetic exploration, the described approach toward angular methylation of polycyclic systems in the trans manner, together with the earlier results of Wenkert[5] that lead to the corresponding cis-fused systems, makes this methoxycyclopropane scheme a versatile method.

(15) Predoctoral Fellow of the National Science Foundation, 1968–present.

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Racemization During Peptide Couplings Using the Mixed Anhydride, *N*-Hydroxysuccinimide Ester, 8-Hydroxyquinoline Ester, and Acyl Azide Methods

Sir:

We have recently described a[1] method for assessing racemization with sensitivity in the 1–0.001% range. We wish to report results of applying this assay to four peptide coupling procedures.

The Mixed Anhydride Method. Though long regarded as racemization prone, this procedure has been found recently by Anderson and coworkers[2] to maintain optical integrity when used under defined conditions. Our observations confirm their findings in every detail.

When a THF solution, 0.2 *M* in *Z*-[1-^{14}C]-Gly-L-PheOH and triethylamine, was treated at −15° with 1 equiv of isobutyl chloroformate, followed 1 min later by 1 equiv of ethyl glycinate, then allowed to stand for 3 min and warmed to 22°, tripeptide was obtained in 30% yield, 1.5% of which was racemic. Use of *N*-methylmorpholine as base gave 98% yield, 0.20% DL, and with very carefully weighed equivalents of acid and methylmorpholine, 0.01% DL was observed. A Young coupling of [7-^{14}C]benzoyl-L-leucine with ethyl glycinate under the above conditions gave 1.4% DL with 1 equiv of triethylamine, and 39% DL with 2 equiv of base. Young couplings with 1.0, 1.1, and 2.0 equiv of *N*-methylmorpholine gave, respectively, 0.38, 2.4, and 15.7% DL.

The *N*-Hydroxysuccinimide (NHS) Ester Method. First studied by Anderson and coworkers,[3] these esters appear to couple without racemization and, owing to the high nucleophilicity of NHS toward acyl carbon, appear to be formed in optically pure state when NHS is combined with racemization prone peptide activated species.[4] We sought to test both these assertions quantitatively.

When *Z*-[1-^{14}C]-Gly-L-PheOH (0.5 *M*) and 1.1 equiv of NHS in DMF were combined at −10° with 1.1 equiv of dicyclohexylcarbodiimide, allowed to remain 4 hr at −10° and 12 hr at 2°, and then treated for 48 hr with 1.5 equiv of ethyl glycinate, tripeptide was obtained which was 3–7% racemic. When NHS was added in THF solution 1 min after the addition of chloroformate, under the mixed anhydride conditions of the preceding section, then followed 1 min later by ethyl glycinate, no reduction in racemization level was observed. For the coupling using *Z*-Gly-L-PheOH and triethylamine, addition of NHS changed the racemate level from 1.6 to 1.5%; for couplings with *N*-methylmorpholine, the figures were 0.19% without NHS, 0.14% with.

The optically pure NHS ester of *Z*-[1-^{14}C]-Gly-L-PheOH can best be prepared by reaction in chloroform of triethylamine and the HBr salt of the NHS ester of L-Phe[5] with the mixed anhydride derived from *Z*-[1-^{14}C]-GlyOH and isobutyl chloroformate. The resulting glass was identified by spectroscopic comparison with the characterized DL ester, mp 90–92°. When a chloroform solution of L ester, prepared without isolation, was combined at 22° with ethyl glycinate, tripeptide was obtained which contained 0.86% racemate. When any labeled D ester was selectively removed[1] by addition and recovery of unlabeled DL ester from the initial chloroform solution of L ester, coupling with ethyl glycinate again yielded 0.6–1.0% racemate.

8-Hydroxyquinoline Esters. Although available in optically pure form only by a Goodman inverse synthesis,[6,7] peptide esters of 8-hydroxyquinoline are of theoretical interest for their racemization-free coupling behavior.[7] Using D-labeled racemate[1] we have established the clean recovery of the DL 8-HQ ester of *Z*-Gly-PheOH (mp 125–128°) from excess L ester (mp 78–80°). By racemate recovery[1] we have prepared labeled L ester containing less than 0.001% of its activity as labeled D and have coupled it with ethyl glycinate in DMF, 40 hr, at either 0 or 20°. In either case, the isolated tripeptide contained 0.16% racemate.

Acyl Azides. Subsequent to our earlier azide results,[1] we have observed that the bicarbonate extraction which usually follows diazotization in an azide procedure has a substantial affect on the racemization level.

An ethereal solution of [7-^{14}C]benzoyl-L-leucyl azide, freshly extracted from an aqueous acetic–

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(2) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *ibid.*, **89**, 5012 (1967).

(3) J. E. Zimmerman and G. W. Anderson, *ibid.*, **89**, 7151 (1967); G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *ibid.*, **85**, 3039 (1963); G. W. Anderson, F. M. Callahan, and J. E. Zimmerman, *ibid.*, **89**, 178 (1967).

(4) M. Goodman and C. Glaser in "Peptides: Chemistry and Biology," Marcel Dekker, New York, N. Y., 1970.

(5) Satisfactory elemental analyses were obtained for new compounds, excepting the NHS ester of *Z*-Gly-L-PheOH.

(6) M. Goodman and K. G. Steuben, *J. Org. Chem.*, **27**, 3409 (1962); *J. Amer. Chem. Soc.*, **81**, 3980 (1959).

(7) H. D. Jakubke and A. Voigt, *Chem. Ber.*, **99**, 2419 (1966).