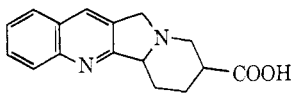
a 76% yield of the ketone **10**. Friedlander condensation between the keto ester–$\alpha$-methylene lactam **10** and *N*-(2-aminobenzylidene)-*p*-toluidine[8] gave a 75% yield of the tetracyclic $\alpha$-methylene lactam **11**,[9] containing the indolizino[1,2-*b*]quinoline ring system and having ultraviolet absorption typical for such a substituted quinoline (319, 312, 306, 298, 293, 288, 234 nm).

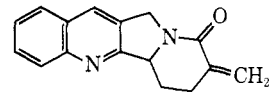
The remaining tasks were aromatization of ring D and formation of the $\alpha$-hydroxylactone ring E. Both aromatization and formation of the necessary primary allylic alcohol were accomplished in one step by $SeO_2$ oxidation of $\alpha$-methylene lactam **11** in glacial acetic acid (80°, 30 min) to the $\alpha$-acetoxymethylpyridone **12** (uv 370, 290, 253 nm). Hydrolysis–lactonization of **12** in 2 *N* $H_2SO_4$–glyme at 50° for 5 hr gave a 72% yield of deoxycamptothecin (**13**) from **11**: mp 262–264° dec; uv 370, 290, 253 nm. Oxidation of deoxycamptothecin ($CuCl_2$–DMF–$O_2$)[2d] is accomplished in quantitative yield to give *dl*-camptothecin (**1**) whose tlc, and uv, nmr, and high-resolution mass spectra are identical with those of the natural product.[10] Although a detailed development of the individual steps has not been made, we have thus obtained *dl*-camptothecin in an overall yield of 11% starting from pyridine-2,5-dicarboxylic acid.

(8) T. K. Liao, W. H. Nyberg, and C. C. Cheng, *J. Heterocycl. Chem.*, **8**, 373 (1971).

(9) The AB rings in camptothecin can be incorporated at earlier stages. Thus, *via* the Friedlander condensation, we have obtained compound i from keto acid **2** and compound ii from the keto-$\alpha$-methylenepiperidone **5** (prepared by hydrolysis of acetate **4** followed by DCC–DMSO oxidation[7]). These compounds may be further elaborated to camptothecin, and these processes will be reported in detail in the future.




i




ii

(10) Obtained from young (90 day) *C. acuminata* plants by Dr. G. Sheriha. These plants were grown from seeds kindly provided by Mr. R. L. Smith and Dr. R. Perdue of the U. S. Department of Agriculture.

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*Received August 30, 1972*

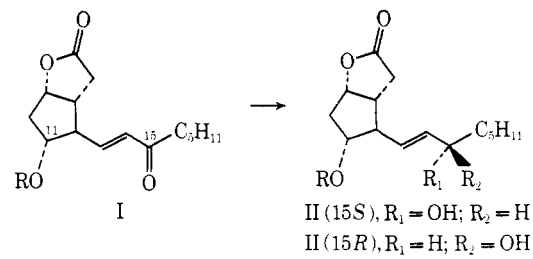
## Efficient Generation of the 15*S* Configuration in Prostaglandin Synthesis. Attractive Interactions in Stereochemical Control of Carbonyl Reduction

*Sir:*

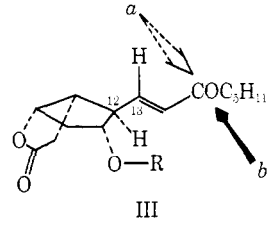
One of the most fascinating problems in the area of prostaglandin synthesis has been the development of synthetic approaches which control stereochemistry, particularly at C-15.[1] We have been interested for some time in devising a method to effect the conversion of I to II (15*S*)[2] with high stereoselectivity. This communication reports a rational attack on this problem.

(1) See, for example: (a) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971); (b) C. J. Sih, R. Price, R. Sood, R. G. Salomon, G. Peruzzotti, and M. Casey, *ibid.*, **94**, 3643 (1972); (c) E. J. Corey and T. Ravindranathan, *ibid.*, **94**, 4013 (1972); (d) E. J. Corey and P. L. Fuchs, *ibid.*, **94**, 4014 (1972); (e) J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *ibid.*, **94**, 4343 (1972); (f) R. Pappo and P. W. Collins, *Tetrahedron Lett.*, 2627 (1972).

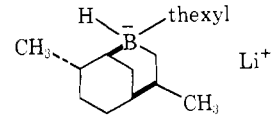
(2) Prostanoic acid numbering.




The reduction of I with R = $CH_3CO$, $CH_3(CH_2)_7CO$, or *i*-$Pr(CH_3)_2Si$ using borohydride type reagents, *e.g.*, $NaBH_4$–$C_2H_5OH$ at −30° or $Zn(BH_4)_2$–dimethoxyethane at 0° or various lithium trialkylborohydrides ($R_1R_2R_3BH^-Li^+$) at <−90°, affords II with a ratio 15*S*/15*R* of between 50/50 and 60/40. Similarly the 11-deoxy derivatives of I or $\Delta^{10(11)}$-dehydro-11-deoxy-I are reduced by these hydrides to equal mixtures of 15*S* and 15*R* alcohols. One reason for the difficulty in achieving selective reduction of I is the occurrence of both s-cis and s-trans conformations of the enone unit in I as can be seen from the infrared spectra of esters of structure I with varying R which manifest enone carbonyl absorption (in $CHCl_3$ at 25°) as a doublet of comparably intense bands at 5.90 (s-cis) and 5.97 $\mu$ (s-trans).[3] Even assuming that the ketone I adopts a trans coplanar arrangement of hydrogen at C-12 and C-13 as shown in III, stereospecificity of carbonyl reduction would demand not only a preferred direction of hydride attack (axis *a* or *b*) but also a single enone conformation. Therefore, it is not sufficient merely to choose a group R of sufficient steric bulk to block approach along axis *b*, but it is also necessary to control the enone conformation as s-cis in order to direct the formation of 15*S* alcohol.




III




IV

In an earlier phase of this work[1a] the derivatives I and II were prepared in which R = *p*-phenylbenzoyl, and it was found that this protecting group was advantageous since (1) the intermediates in the synthesis were nicely crystalline, (2) the 15*S* and 15*R* forms of II were readily separable by chromatography, and (3) the ultraviolet chromophore simplified analytical and chromatographic work. It was subsequently discovered[1a] that the reduction of I, *p*-phenylbenzoyl, favored formation of 15*S* alcohol to a larger degree than was observed with screening groups at C-11, *e.g.*, R = $CH_3(CH_2)_7CO$. Using the reagent IV[1a] in tetrahydrofuran–ether–pentane at −120 to −130°, it was possible to convert I, R = *p*-$C_6H_5C_6H_4CO$, to a mixture of 15*S* and 15*R* alcohols in a ratio of 82:18.[1a,4,5]

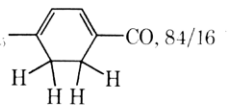
(3) See K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(4) The reagent IV is superior to all other trialkylborohydrides which have been tested so far for the selective formation of (15*S*)-II. The following reagents of the type $R_1R_2R_3BH^-Li^+$ have been found to give the 15*S*/15*R* ratios indicated: dicyclohexyl-*tert*-butyl (59/41); dicyclohexyltrityl (64/36); diisopinocamphenenylmethyl (68/32); triphenyl (67/33); tri-*exo*-2-norbornyl (59/41); diisobutyl-*tert*-butyl (74/26); di-*sec*-butylthexyl (80/20); tri-*sec*-butyl (78/22). In addition, IV yielded considerably higher ratios of 15*S*/15*R* II than did various cyclic boro-

A simple explanation for the effectiveness of the 11-*p*-phenylbenzoyl group in directing reduction of the 15-carbonyl function of I toward formation of (15*S*)-alcohol II is suggested by examination of scale molecular models (for example, Corey–Pauling–Koltun (CPK) type). As indicated in Figure 1, a molecular configuration for I, R = *p*-$C_6H_5C_6H_4CO$, can be derived in which the two side chains are at van der Waals contact along their full length if the enone unit is s-cis. Four adjacent atoms of the $C_6H_4$ group can be placed directly in $\pi$ contact with the cis enone unit. This configuration appears to be favorable in all respects except that the ester unit C–O–CO–C must be cisoid and must deviate moderately (*ca.* 30° dihedral) from the ideally coplanar arrangement. Although the two side chains of I, R = *p*-$C_6H_5C_6H_4CO$, can also be brought into proximity if the enone unit is s-trans, the $\pi$–$\pi$ contact of enone and $C_6H_4$ and the contact between $C_6H_5$ and $C_5H_{11}$ groups are less favorable. Thus, it seemed possible that the *p*-phenylbenzoate I would both favor the s-cis enone conformation and direct hydride addition to the side of C-15 opposite the ester chain.

On the basis of this hypothesis, we examined the reduction of three esters closely related to I, R = *p*-$C_6H_5C_6H_4CO$, using the reagent IV under the standard conditions at −120°. It was thought that good selectivity for formation of 15*S* alcohol should be observed in these cases. The substrates and the observed 15*S*/15*R* ratios are as follows[6]

Ia, R = *p*-*n*-$C_5H_{11}C_6H_4CO$, 82/18

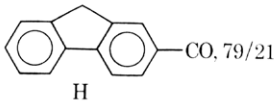
b, R = $C_6H_5$  CO, 84/16

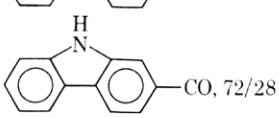
c, R = *p*-*n*-$C_4H_9OC_6H_4CO$, 80/20

These data clearly are consistent with the attractive interaction model, but they do not reveal any major possibility for improvement in stereoselectivity.

Although the linear arrangement of the aromatic rings in the *p*-phenylbenzoate I appeared optimum for maximum interaction of the side chains, an experimental test of various nonlinear modifications was made. No improvement in selectivity could be gained (reagent IV at −120°), in agreement with expectations based on the study of CPK models for the cases Id–f.[6] In the

Id, R = *m*-$C_6H_5C_6H_4CO$, 76/24

e, R =  CO, 79/21

f, R =  CO, 72/28

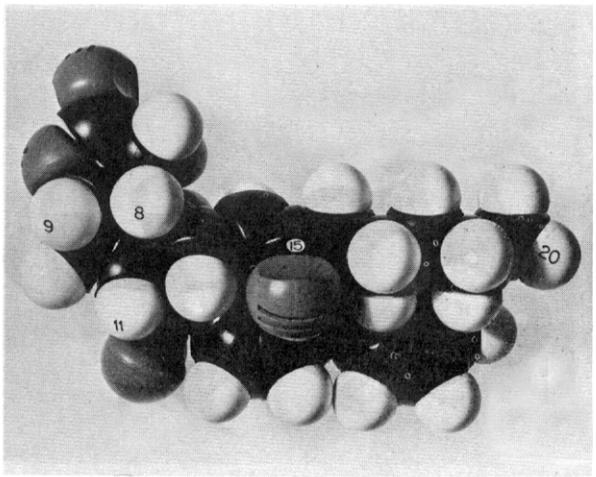



Figure 1. CPK model of I, R = *p*-$C_6H_5C_6H_4CO$, having s-cis arrangement for the $\Delta^{13(14)}$-en-15-one unit, coplanar H–C(12)–C(13)–H unit, extended *n*-amyl group, and maximum van der Waals contact between the enone side chain and *p*-phenylbenzoyl controller group. The s-cis enone unit occupies a position directly above four contiguous carbons of the $C_6H_4$ moiety. Numerals on the model refer to carbon position.

instances Ia–f as well as with the *p*-phenylbenzoate I, the molecular conformation with enone (either s-cis or s-trans) and ester side chains in maximum contact demands distortion of the ester unit C–O–CO–C from planarity. The five derivatives of the enone I specified in entries Ig–k were examined[6] to study structures in

Ig, R = *p*-$C_6H_5C_6H_4CH_2CO$, 70/30
h, R = *p*-*n*-$C_4H_9OC_6H_4CH_2CO$, 67/33
i, R = $C_6H_5NHCO$, 89/11
j, R = *p*-$C_6H_5C_6H_4NHCO$, 92/8
k, R = *p*-$C_6H_5C_6H_4OCO$, 86/14

which this adverse factor was essentially absent (reductions with IV at −120°). In the case of the substrates indicated in entries Ig and Ih for the conformers with the ester unit C–O–CO–C planar and cisoid, the contact between side chains is better for s-cis and s-trans arrangements of the enone side chain. However, there is a marked steric interference between the benzylic $CH_2$ group of the ester and the hydrogen attached to C-11 of the cyclopentane ring, which increases the separation between the enone unit and the adjacent *p*-$C_6H_4$ unit. The urethanes Ii,j can adopt a conformation with a planar C–N–CO–O unit and nonplanar C–O–CO–N unit which lack such steric repulsion and which make excellent contact with the s-cis enone side chain. As expected, Ii and Ij and the corresponding carbonate Ik are relatively more favorable for 15*S* alcohol formation. In particular, the *p*-phenylphenylurethane Ij represents an *outstanding case of stereochemical control achieved by the use of an exogenous directing group;* the conformer for maximum contact of side chains is shown in Figure 2.

The *p*-phenylphenylcarbamoyl group possesses all the advantages of the *p*-phenylbenzoyl group in prostaglandin synthesis. The preparation of I, R = *p*-$C_6H_5C_6H_4NHCO$, mp 116.5–117°,[7] $[\alpha]^{20}D$ −47.8° (*c*

hydrides derived from 1,5-cyclooctadiene (70/30 to 74/26) or 1,5,7-cyclododecatriene (67/33). Ratios of (15*S*)- and (15*R*)-II were determined in most cases by high-pressure liquid–liquid chromatography using a silica gel column and a Waters Associates instrument with a 254-nm absorption detector. The borohydrides were prepared[1a] either from trialkylboranes and *t*-BuLi or from RLi and dialkylboranes.

(5) Dialkylboranes are unsatisfactory reducing agents, since their use leads chiefly to 1,4 reduction to form from I a 13,14-dihydro 15-ketone.

(6) Determination of 15*S*/15*R* ratios by high-pressure liquid chromatography with detection by absorption measurement at 254 nm. It is recommended that the interested reader examine cases Ia–k using space-filling scale models to assess independently the acceptability of the hypothesis presented herein.

(7) New compounds were satisfactorily characterized by infrared, ultraviolet, proton magnetic resonance, and mass spectral measurements.

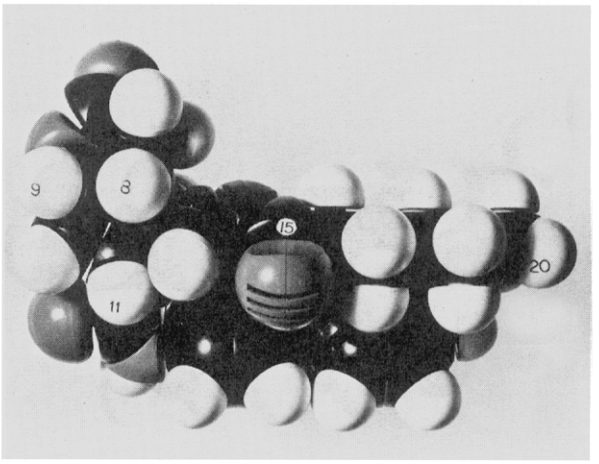



Figure 2. CPK model of I, R = $p$-$C_6H_5C_6H_4NHCO$, with s-cis arrangement of the $\Delta^{13(14)}$-en-15-one unit, antiplanar H–C(12)–C(13)–H unit, maximum contact between enone chain (extended $C_5H_{11}$) and $p$-phenylphenylcarbamoyl group. In this conformation the O–CO–N–C part of the urethane function is planar and the C–O–CO–N part is nonplanar, corresponding to amide delocalization in preference to ester delocalization. The s-cis enone unit contacts four adjacent carbons of the $NHC_6H_4$ unit. Numerals refer to carbon position.

1.0, $CHCl_3$), was carried out from the alcohol I, R = H, by reaction with the readily available $p$-phenylphenyl isocyanate, mp 58–58.5°[8] (1.2 equiv), in dry tetrahydrofuran (4 ml/g of isocyanate) and triethylamine (1.2 equiv) at 25° for 3 hr (yield, >90%). For reduction the $p$-phenylphenylurethane I in tetrahydrofuran–ether (1:4, 40 ml/g of I) at *ca.* −130°[9] was treated dropwise with a 0.23 *M* solution in tetrahydrofuran of the reagent IV[1a] (*ca.* 30 ml/g of I), reaction was continued for 4 hr at −130° and 2 hr at −115° (ethanol–liquid nitrogen bath), and the product was isolated by extraction after quenching of the reaction mixture with methanol and 1 *N*-hydrochloric acid. The total yield of II,[7] R = $p$-$C_6H_5C_6H_4NHCO$, was quantitative, and the ratio of 15*S* to 15*R* isomers in several runs was 92/8. For the synthesis of prostaglandins it was found to be expedient to utilize the product II directly and to remove the small amount of 15*R* by-product at the stage of prostaglandin $F_{2\alpha}$ or $E_2$ where the separation of 15*S* and 15*R* diastereomers is extremely simple. The conversion of II, R = $p$-$C_6H_5C_6H_4NHCO$, to the required diol II [R = H,[1a] oil, $[\alpha]^{23}D$ −7.1° (*c* 1.1, $CHCl_3$)] was accomplished in >90% yield by hydrolysis using 1 *M* aqueous lithium hydroxide at 120° for 72 hr, extraction of the basic reaction mixture at 0° with ether–ethyl acetate (1:1) to remove neutral and basic components, and relactonization by the addition of ethyl chloroformate (2 equiv) to the aqueous phase which had been neutralized with carbon dioxide.[10]

The highly selective reduction of I, R = $p$-$C_6H_5C_6H_4NHCO$, could also be carried out with thexyl di-*sec*-butylborohydride (88/12) and tri-*sec*-butylborohydride[11] (89/11).

(8) M. J. van Gelderen, *Recl. Trav. Chim. Pays-Bas*, **52**, 969 (1933).
(9) Cooling bath: *n*-pentane–liquid nitrogen; see R. E. Rondeau, *J. Chem. Eng. Data*, **11**, 124 (1966).
(10) This procedure for lactonization was developed in collaboration with Dr. A. Venkateswarlu in these laboratories.
(11) See H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, **94**, 7159 (1972).

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*Received September 8, 1972*

## Symmetry Selection Rules for Transition States

*Sir:*

The transition state for a chemical reaction is the lowest possible potential energy barrier (assuming one exists) between reactants and products. At the transition state there must exist directions along which the potential energy decreases as the atoms are displaced toward reactants or products. In other words, the curvature of the potential energy along such a direction must be negative. The unit vector leading from the transition state toward products along the direction of most negative curvature we define as the *transition vector*. It can be shown that this is the eigenvector of the force constant matrix **F** corresponding to the lowest eigenvalue, that this eigenvalue is negative, and that **F** can have no other negative eigenvalues.[1] Moreover, the transition vector, like all eigenvectors of **F**, must belong to one of the irreducible representations of the point group of the transition state.[2]

The purpose of this communication is to demonstrate the existence of selection rules governing the symmetry properties of the transition vector and, in fact, for a broad class of reactions, governing the structural symmetry of the transition state itself. These selection rules, presented in the form of three theorems, follow from group theoretical and geometric considerations alone. Consequently, they are valid for any potential surface which shows symmetry properly, whether it be numerically exact or approximate. The theorems are as follows.

1. The transition vector cannot belong to a degenerate representation of the point group of the transition state.

2. The transition vector must be symmetric with respect to a symmetry operation of the transition state which leaves reactants or products unchanged.

3. The transition vector must be antisymmetric with respect to a symmetry operation of the transition state which converts reactants into products.

The first theorem follows immediately from the requirement that at the transition state **F** must have one and only one negative eigenvalue.[3] The proofs of the

(1) J. N. Murrell and K. J. Laidler, *Trans. Faraday Soc.*, **64**, 371 (1968); see also J. N. Murrell and G. L. Pratt, *ibid.*, **66**, 1680 (1970). We have assumed that the potential surface is quadratic in the vicinity of the transition state, *i.e.*, that the transition vector does not correspond to a zero eigenvalue of the force constant matrix **F**. Aside from pure translations and rotations, it is unlikely that the first and second derivatives of the potential energy will simultaneously vanish along an eigenvector of **F**. This argument is essentially the same as that which underlies the noncrossing rule. K. R. Naqvi and W. B. Brown, *Int. J. Quantum Chem.*, **6**, 271 (1972).
(2) E. B. Wilson, Jr., J. C. Decius, and P. C. Cross, "Molecular Vibrations," McGraw-Hill, New York, N. Y., 1955, pp 106–107.