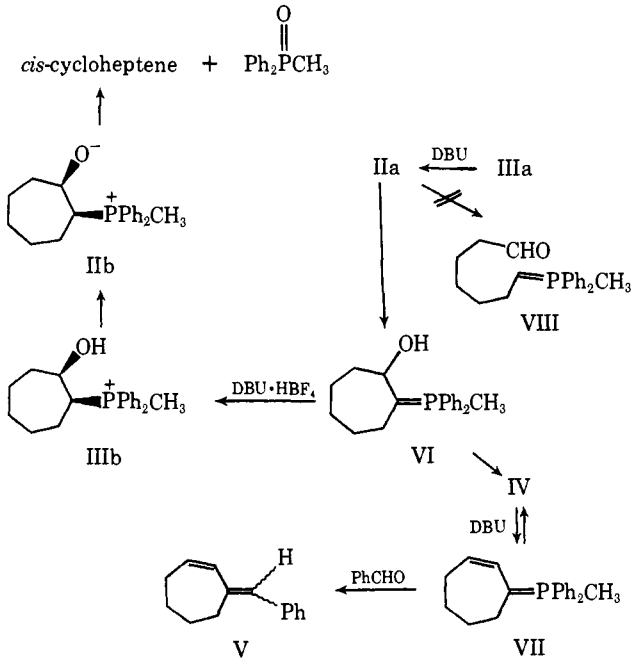
various experiments indicates equilibration of both IIa and IV with the corresponding methylides.

An alternate pathway for destruction of IIa, the retro-Wittig process leading to the ylide aldehyde VIII, is excluded by our results. Similar cleavage to ylides and carbonyl compounds has been claimed to explain loss of stereochemistry and the appearance of crossover products upon decomposition of phosphorus betaines prepared by other methods.[2a,3b,3d] The ultimate consequence of cleavage of IIa to VIII should be the appearance of *cis*-cycloheptene since VIII is expected to reclose to IIb. Alternately, intermolecular Wittig condensation of VIII would at least afford methyl-



diphenylphosphine oxide, but neither the oxide nor *cis*-cycloheptene are detected under aprotic conditions. Thus, elimination of hydroxide to form IV is faster than the retro-Wittig reaction. Retro-Wittig cleavage is also excluded for all of the other betaines which we have studied since inverted olefins are formed in good to excellent yield with high isomeric purity.[17]

The convenience of the betaine technique for olefin inversion suggests a variety of synthetic applications. Initial studies indicate that our method is general and can be extended to trisubstituted olefins provided that base-sensitive functional groups are suitably protected. These results will be presented in a full paper.

Acknowledgment. This work was supported, in part, by research grants from Eli Lilly & Co., the Graduate School of the University of Wisconsin, and the National Science Foundation.

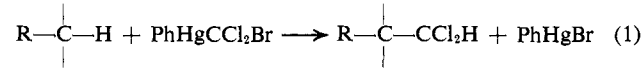
(18) Alfred P. Sloan Foundation Fellow, 1971–1973.

E. Vedejs,*,[18] P. L. Fuchs
Chemistry Department, University of Wisconsin
Madison, Wisconsin 53706
Received May 12, 1971

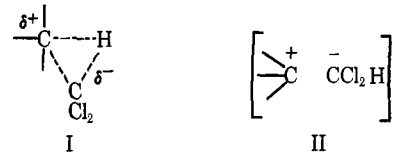
The Stereochemistry of the Insertion of Phenyl(bromodichloromethyl)mercury-Derived Dichlorocarbene into a Benzylic Carbon–Hydrogen Bond

Sir:

Our previous studies of the insertion of $PhHgCCl_2Br$-derived dichlorocarbene into the C–H bonds of alkanes and alkylbenzenes,[1] saturated ethers,[2] and tetraalkyl derivatives of silicon,[3] germanium,[4] and tin[3] showed that these reactions (eq 1) are promoted by substituents,



R, which would be expected to stabilize best a partial positive charge on carbon. A concerted process with transition state I or a hydride abstraction process involving a tight ion pair intermediate, II, were considered as being the most likely possibilities for the mechanism of the insertion reaction. The reaction of $PhHgCCl_2Br$ with $Me_3SiCH_2CDMe_2$ occurred with



almost complete deuterium retention.[3] The related insertion of dichlorocarbene into optically active bis-(*S*)-methylbutylmercury gave $MeEtCHCH_2HgCH_2CMeEtCCl_2H$ with overall retention of configuration (~23%).[5]

The report by Franzen and Edens[6] that insertion of CCl_2 (*via* $PhHgCCl_3$ or CCl_3CO_2Na) into optically active 2-phenylbutane gave practically inactive or completely inactive $PhCMeEtCCl_2H$, therefore, was rather surprising to us. Since this result was at variance with the picture of CCl_2 insertion into C–H bonds which had developed, we have reinvestigated the stereochemical course of dichlorocarbene insertion (*via* $PhHgCCl_2Br$) into optically active 2-phenylbutane.

The reaction of 79.4 mmol of phenyl(bromodichloromethyl)mercury[7] with 35 ml of (+)-2-phenylbutane[8] at

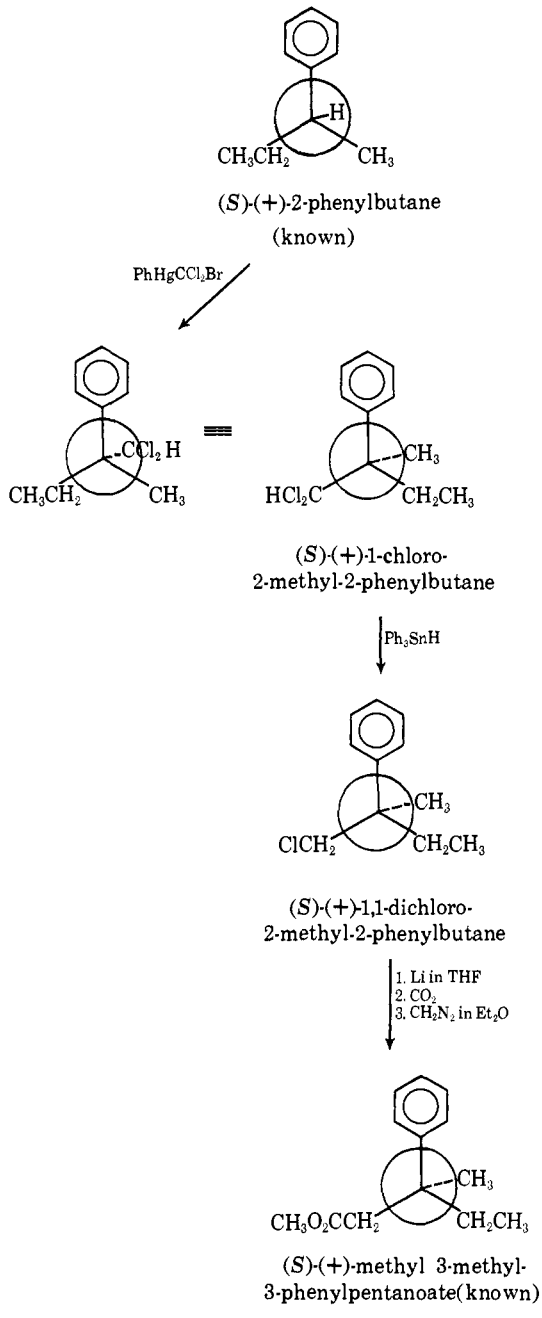
of benzaldehyde with VI to yield 2-benzylidenecycloheptanol[16] or 1-cycloheptenylphenylcarbinol,[16] followed by dehydration. However neither alcohol is present in the product mixture, and both alcohols are stable under the reaction conditions.

(16) E. A. Braude, W. F. Forbes, and E. A. Evans, *J. Chem. Soc.*, 2202 (1953).

(17) In response to a referee's comments, we do not imply that betaine reversal is necessarily ruled out in the experiments involving DBU and IIIa. It is conceivable that opening to VIII may be catalyzed in some way by the proton donor $DBU{\cdot}HBF_4$ to account for some of the cycloheptene, but there is no evidence or analogy to support such a process. The presence or absence of lithium cation is not a factor in cycloheptene formation; the yield of cycloheptene is unaffected when IIIa is treated with DBU and $LiBF_4$.

(1) D. Seyferth, J. M. Burlitch, K. Yamamoto, S. S. Washburne, and C. J. Attridge, *J. Org. Chem.*, **35**, 1989 (1970).
(2) D. Seyferth, V. A. Mai, and M. E. Gordon, *ibid.*, **35**, 1993 (1970).
(3) D. Seyferth, S. S. Washburne, C. J. Attridge, and K. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 4405 (1970).
(4) D. Seyferth, H. Shih, P. Mazerolles, M. Lesbre, and M. Joanny, *J. Organometal. Chem.*, **29**, 371 (1971).
(5) J. A. Landgrebe and D. E. Thurman, *J. Amer. Chem. Soc.*, **91**, 1759 (1969).
(6) V. Franzen and R. Edens, *Justus Liebigs Ann. Chem.*, **729**, 33 (1969).
(7) D. Seyferth and R. L. Lambert, Jr., *J. Organometal. Chem.*, **16**, 21 (1969).
(8) Prepared by the method of Bonner and Greenlee,[9] bp 95–97° (62 mm), $n^{25}D$ 1.4876, $[\alpha]^{25}D$ +24.032° (neat, l = 1 dm); lit.[9] $[\alpha]^{25}D$ +26.6°. The absolute configuration of 2-phenylbutane has been established.[10]

Scheme I



80° for 4 hr gave phenylmercuric bromide (92%) and 1,1-dichloro-2-methyl-2-phenylbutane (26%, bp 100–101° (2.0 mm), n^{25}D 1.5383). The latter was found to be optically active, having $[\alpha]^{25}$D +2.204° (neat, l = 1 dm).[11] Unconverted 2-phenylbutane was recovered from the reaction mixture and found to have unchanged optical rotation, $[\alpha]^{25}$D +23.932° (neat, l = 1 dm).

The optically active insertion product was converted to compounds whose absolute configuration had been established by other workers[12] *via* the reaction sequence shown in Scheme I. The steps in this sequence would not cause any changes in the configuration of the chiral center.

The optically active 1,1-dichloro-2-methyl-2-phenylbutane, $[\alpha]^{25}$D +2.204°, was reduced to 1-chloro-2-methyl-2-phenylbutane with triphenyltin hydride at 80° for 12 hr under nitrogen.[13] The monochloro compound, n^{25}D 1.5212, was the only product formed and had $[\alpha]^{25}$D +8.800° (neat, l = 1 dm). This chloride was converted to the lithium reagent by reaction with lithium dispersion in THF at −40° (initiation at −10° with iodomethane), and the $PhCMeEtCH_2Li$ solution thus formed then was poured into a slurry of Dry Ice in diethyl ether.[14] Acidification and subsequent work-up gave (+)-3-methyl-3- phenylpentanoic acid, mp 39–42°, in 62% yield; $[\alpha]^{25}$D +13.6° (*c* 3.47, $CHCl_3$); lit.[12] mp 43–44°, $[\alpha]^{25}$D +14.6° (*c* 3.8, $CHCl_3$). Methylation of the crude unrecrystallized acid with ethereal diazomethane produced (+)-methyl 3-methyl-3-phenylpentanoate, n^{25}D 1.5022, $[\alpha]^{25}$D +12.173° (neat, l = 1 dm); lit.[12] n^{25}D 1.5018, $[\alpha]^{25}$D +12.7° (neat, l = 1 dm).

Thus (+)-2-phenylbutane of greater than 90% optical purity was converted in this sequence of steps into (+)-methyl 3-methyl-3-phenylpentanoate of greater than 90% optical purity. One may conclude, therefore, that the insertion of phenyl(bromodichloromethyl)-mercury-derived CCl_2 into the benzylic C–H bond of (+)-2-phenylbutane occurred *stereospecifically, with retention of configuration.* This result is in striking contrast to that reported by Franzen and Edens,[6] but their claim that this CCl_2 insertion reaction gives racemic $PhCMeEtCCl_2H$ becomes understandable when the details of their experiment are considered. In the case of both reagents used, their starting (+)-2-phenylbutane was of low optical activity, $[\alpha]^{25}$D +3.400° in the experiment with CCl_3CO_2Na, +3.496° in the reaction with $PhHgCCl_3$, which corresponds to 12.8–13.2% optical purity. Rotations of +2.2–2.3° are observed for (+)-$PhCMeEtCCl_2H$ of >90% optical purity, and in the experiments of Franzen and Edens maximum rotations of *ca.* 0.29–0.30° thus would be expected. No doubt this provided the basis for their erroneous conclusion that racemization had occurred.

Our finding that CCl_2 insertion into the C–H bond of optically active 2-phenylbutane occurs with retention of configuration is in harmony with our present views of this insertion process, *i.e.*, that I or II, or a situation between these extremes, obtains. Speaking against a reaction course in which solvent-separated ion pairs are important is not only the observed stereochemical result, but also the finding that the optical activity of unconverted (+)-2-phenylbutane is completely retained.

Our studies of dichlorocarbene insertion reactions into benzylic (and other) C–H bonds are continuing. We will report on the full details of the present work and on a Hammett study of CCl_2 insertion into sub-

(9) W. A. Bonner and T. W. Greenlee, *J. Amer. Chem. Soc.*, **81**, 3336 (1959).

(10) D. J. Cram, *ibid.*, 74, 2149 (1952).

(11) In other experiments, a product with $[\alpha]^{25}$D values up to +2.288° was obtained. Control experiments established that the optically active product was stable to the reaction and work-up conditions during isolation and analysis by glc.

(12) D. J. Cram, A. Langemann, J. Allinger, and K. R. Kopecky, *J. Amer. Chem. Soc.*, **81**, 5740 (1959).

(13) L. Kaplan, *ibid.*, **88**, 4531 (1966), had shown that Ph_3CCH_2Cl is reduced, cleanly without appreciable rearrangement, by triphenyltin hydride, and thus such reduction of our insertion product should proceed without complications.

(14) This procedure had served in the conversion of neophyl chloride to $PhCMe_2CH_2Li$ in high yield with only a minimum of the rearrangement product, $PhCH_2CMe_2Li$: E. Grovenstein, Jr., and Y.-M. Cheng, *Chem. Commun.*, 101 (1970).

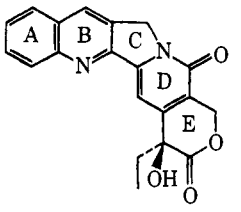
stituted cumenes currently in progress in the near future.

Dietmar Seyferth,* Ying Ming Cheng
Department of Chemistry, Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received June 18, 1971

The Total Synthesis of *dl*-Camptothecin

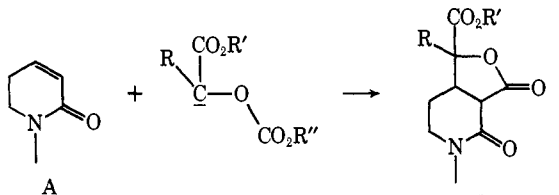
Sir:

Outstanding work by Wall and his associates[1] has led to the establishment of structure **1** for the antileukemic and antitumor alkaloid (+)-camptothecin, isolated from the tree *Camptotheca acuminata*, Nyssaceae, native to China.



1

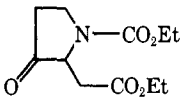
We now wish to report the first total synthesis of (±)-camptothecin. The keystone of the synthesis was the possibility that one might effect the fusion of a lactone ring by addition–cyclization of the carbonate of an α-hydroxy ester to an α,β-unsaturated lactam (*e.g.*, A → B). Such an annelation would introduce all of the necessary atoms of the camptothecin E ring,



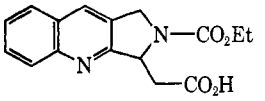
A B

leaving only necessary changes in oxidation states to be performed. The approach proved to be very successful and the transformation A → B represents a new annelation of α,β-unsaturated carbonyl compounds which will probably prove of general utility.

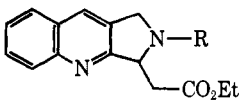
The known[2] tricyclic quinoline acid **2**, mp 180–182° (reported[2] mp 184–186°), was obtained in ~50% yield by the condensation of *o*-aminobenzaldehyde with the pyrrolidone **3**[3] in the presence of dilute sodium hydroxide. Hydrolysis of **2** by refluxing its solution in 50% hydriodic acid for 14 hr, followed by evaporation and subsequent esterification with ethanolic hydrogen chloride, afforded the amino ester **4** (isolated as an oil), ir 3.00 and 5.78 μ.[4] Reaction of **4** with the half-acid chloride of diethyl malonate[5] (benzene–aqueous sodium bicarbonate) gave the diesteramide **5**, ir 5.75 and 6.00 μ, which was cyclized on heating with 1.1 equiv of sodium ethoxide in 1:5 ethanol–toluene to the tetracyclic material **6**, mp 185–190°. Hydrolysis and decarboxylation of **6** occurred smoothly upon refluxing ~4 hr with 10% aqueous acetic acid to give the β-ketoamide **7** in 72% overall yield from **2**. Infrared absorptions at 5.78 and 6.02 μ and a parent ion at *m/e* 252 support the structural assignment of **7**.



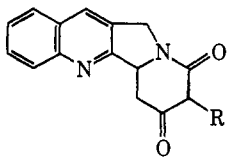
3



2

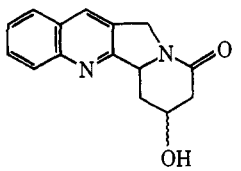


4, R = H
5, R = $COCH_2CO_2Et$

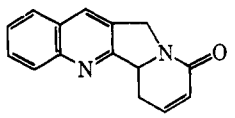


6, R = CO_2Et
7, R = H

Reduction of **7** with sodium borohydride in ethanol gave the β-hydroxy lactam **8**, mp 220–225° dec, in 95% yield. Treatment of **8** with refluxing acetic anhydride saturated with sodium acetate, under carefully deoxygenated conditions, gave in high yield the required unsaturated lactam **9**: mp 187–192°; *m/e* 236.0948; ir 6.00 and 6.04 μ.

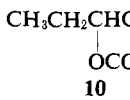


8

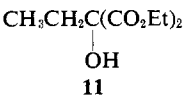


9

The other necessary component, the ester carbonate **10**, bp 110–111° (25 mm), was prepared in 95% yield from the reaction of ethyl α-hydroxybutyrate[6] with ethyl chloroformate in pyridine.



10



11

Formation of the anion of **10**, using 1 equiv of lithium diisopropylamide in tetrahydrofuran (THF) at room temperature, resulted in an expected facile rearrangement to the tartronic ester **11**. The anion of **10** proved, however, to be moderately stable at Dry Ice–acetone temperature; when a solution of the unsaturated lactam **9** in THF was added rapidly to a solution of 5 equiv of the lithium salt of **10**, generated in THF at −70°, yields as high as 85% of the pentacyclic lactone **12** (isolated as a glass) could be realized. Infrared absorption at 5.55, 5.72, and 6.00 μ and a parent ion at *m/e* 394 support the structural assignment of **12**. The overall yield from diethyl maleate (the precursor of **3**) to the lactam **12** approaches 20%. Dehydrogenation of **12** with either dichlorodicyanoquinone (DDQ) in refluxing *p*-dioxane, or lead tetraacetate in glacial acetic acid at room temperature, gave in high yield the pyridone **13**, mp 285–289° dec, *m/e* 390.1217, which has all the carbon, oxygen, and nitrogen atoms of the desired camptothecin.

(1) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. I. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).
(2) J. A. Kepler, M. C. Wani, J. M. McNaull, M. E. Wall, and S. J. Levine, *J. Org. Chem.*, **34**, 3853 (1969).
(3) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1961).
(4) All intermediates had ir and nmr spectra in agreement with the assigned structures. Key compounds were further characterized by exact masses and/or low-resolution mass spectra, as indicated in the text.
(5) L. Gol'dfarb, S. Z. Taits, and V. N. Bulgakova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 7, 1299 (1963).
(6) L. Schreiner, *Justus Liebigs Ann. Chem.*, **197**, 1 (1879).