yield. Recrystallization from $MeOH/CH_2Cl_2$ gave, in 81% yield, diastereomerically pure material, mp 178–180 °C[7,8] (see below). Catalytic dehydrogenation[14] of **16** (Pt, O_2, 1:1 diglyme/H_2O, 20 h, 55 °C) in the presence of a trace of sodium lauryl sulfate,[15] quite remarkably, gave the lactone **1** in quantitative yield after flash chromatography.[7] This product was identical (NMR, IR, MS, TLC, GC coinjection, HPLC) with authentic **1**,[2,16] and there was no evidence for even a trace of the C-25 epimer, easily detectable by GC coinjection (base-line separation) as shown with authentic 25-*epi*-**1**.[16]

Thus we have achieved the synthesis of pure **1** in 28% overall yield from the Inhoffen–Lythgoe diol **3**. It is particularly noteworthy that this approach is so highly stereoselective that no separation of diastereomers is required; indeed, the trace contaminants of unnatural epimers are simply eliminated by a single recrystallization of the tetrol **16**.

Acknowledgment. We are indebted to the National Institutes of Health, the National Science Foundation and Pfizer, Inc. for grants in support of this research, and to Dr. John D. Elliott for helpful discussions. We also thank Professor Henry Rapoport[15] and Dr. Peter W. Wovkulich[16] for their assistance.

(14) Heyns, K.; Paulsen, H. In "Newer Methods of Preparative Organic Chemistry"; Foerst, W., Ed.; Academic Press: New York, 1963; Vol. 2, pp 303–305.

(15) Professor H. Rapoport suggested these reaction conditions. In the absence of the surfactant the reaction proceeded sluggishly, due to the insolubility of **16**, affording **1** in ca. 50% yield after 40 h at 55 °C.

(16) Dr. Peter M. Wovkulich of Hoffmann-La Roche, Inc. kindly provided us with samples of 8α-hydroxy lactone (**1** with an α-OH in place of the C=O at C-8) and its C-25 epimer, which we oxidized to authentic **1** and 25-*epi*-**1** by their procedure.[2]

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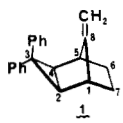
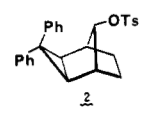
8-Methylene-*exo*-3,3-diphenyltricyclo[3.2.1.0^{2,4}]octane, a Probe for Addition Reaction Mechanism

Summary: The use of the title compound **1** as a mechanistic probe for addition reaction mechanism is suggested, based upon the pronounced proclivity of **1** to undergo quantitative and spectroscopically diagnostic rearrangement in ionic, but not nonpolar, additions.

Sir: Additions to the double bond in hydrocarbon **1** present interesting opportunities to explore the gererality of LRAMERO[1]-type rearrangements, which heretofore have been confined to solvolyses of secondary substrates such as **2**.[2]



1



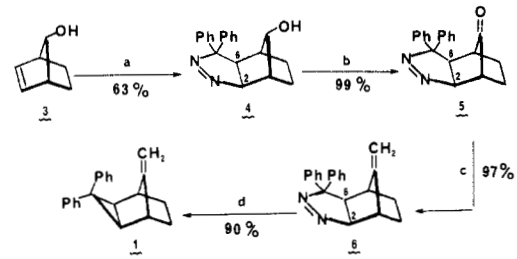
2

To investigate its potential for such rearrangement, **1** was synthesized as shown in Scheme I.

(1) Long-Range Aryl Migration coupled with Electrocyclic Ring Opening.

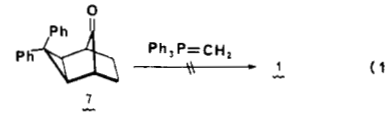
(2) For the latest paper in a series concerned with such electrocyclic effects in solvolysis, cf.: Wilt, J. W.; Curtis, V. A.; Congson, L. N.; Palmer, R. *J. Org. Chem.* **1984**, *49*, 2937.

Scheme I



[a] (a) Ph_2CN_2, 25 °C, 49 days; (b) PCC, CH_2Cl_2; (c) $Ph_3P{=}CH_2$, THF/hexane; (d) 165 °C.

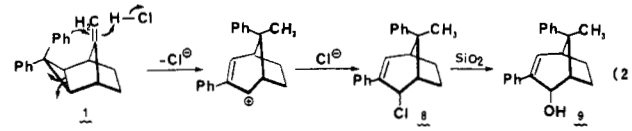
Addition of diphenyldiazomethane to *anti*-7-norbornenol (**3**) was best achieved by a "leave-it-alone" technique using the reactants with no solvent at room temperature.[3] Oxidation of the thus-formed exo[4] pyrazoline **4**, mp 158–158.5 °C dec ($C_{20}H_{20}ON_2$: calcd C, 78.90; H, 6.64. Found: C, 79.08; H, 6.70), with pyridinium chlorochromate easily afforded exo[4] ketone **5**, mp 154.5–155.5 °C, ν_{CO} 1770 cm^{-1} ($C_{20}H_{18}ON_2$: calcd C, 79.43; H, 6.01. Found: C, 79.22; H, 5.97), which underwent Wittig methylenation to produce exo[4] pyrazoline **6**, mp 163.5–164 °C, δ ($CDCl_3$) 4.1, 4.6; ν(KBr) 910 cm^{-1}, exocyclic $=CH_2$ ($C_{21}H_{20}N_2$: calcd C, 83.95; H, 6.72. Found: C, 83.65; H, 6.72). Finally, heating **6** led to waxy, crystalline hydrocarbon **1**, mp 72.5–73.5 °C, ^1H NMR δ ($CDCl_3$) 7.15, 3.70, 2.65, 1.65,[5] 1.50, all s, ratio 5:1:1:1:2, ν(KBr) 880 cm^{-1} ($=CH_2$), ^{13}C NMR δ ($CDCl_3$) 151.4, 147.1, 140.2, 130.7, 127.9, 127.4, 127.2, 125.6, 125.3, 99.7, 40.9, 36.7, 31.5, 28.7 ($C_{21}H_{20}$: calcd C, 92.58; H, 7.42. Found: C, 92.77; H, 7.36). Some points of interest attended the synthesis of **1**. All attempts to convert the known ketone **7**[6] to **1** by the Wittig reaction failed (eq 1).



(1)

Ketone **7** is clearly very hindered. Even methylmagnesium bromide failed to react with it, although methyllithium did so.[7]

The addition chemistry of **1** is under active investigation. But some early results testify to the utility of **1** as a probe substance. Ionic additions thus far investigated show that **1** indeed undergoes LRAMERO rearrangement readily. For example, addition of hydrogen chloride in CCl_4 led to **8** exclusively, as a 30:70 exo/endo mixture (eq 2). Chro-



(2)

matography converted the mixture to essentially pure *endo*-**8** and thence to alcohol **9** quantitatively, mp 116–117.5 °C ($C_{21}H_{22}O$: calcd C, 86.84; H, 7.65. Found: C, 86.68; H, 7.64). Definitive structural confirmation for *endo*-**8** and **9** rested upon the vinyl proton resonance, a

(3) Higher temperatures produced considerable benzophenone azine and the benzhydryl ether of **4** (mp 118.5–122 °C).

(4) This is the expected isomer, and the structure was confirmed by the clean doublet resonance ($J_{2,6}$ = 8 Hz) of H-2 at δ 4.9 (**4**), 5.1 (**5**), and 5.05 (**6**). Endo analogues exhibit a multiplet for H-2, caused by additional coupling to H-1.

(5) The singlet nature of this resonance for H-2,4 is characteristic of the exo tricycle, in contrast to the endo analogue. Cf. Wilt, J. W.; Sullivan, D. R. *J. Org. Chem.* **1975**, *40*, 1036.

(6) Wilt, J. W.; Malloy, T. P.; Mookerjee, P. K.; Sullivan, D. R. *J. Org. Chem.* **1974**, *39*, 1327.

(7) Mostly syn alcohol resulted (anti addition).

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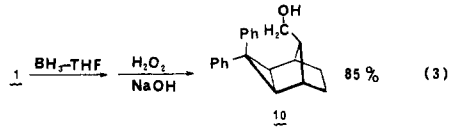
doublet (J = 8 Hz) at δ 6.30 and 6.50, respectively, together with the absence of the cyclopropyl proton singlet (H-2,4) in the δ 1.5–1.8 region characteristic of the unrearranged parent system.[8] Analogous LRAMERO rearrangement was observed in the additions of HBr, CF_3COOD, $HOAc/HClO_4$, and Br_2.

Contrariwise, hydroboration–oxidation of **1** (eq 3) led



to unrearranged syn alcohol **10**, mp 135–137 °C ($C_{21}H_{22}O$: calcd C, 86.84; H, 7.65. Found: C, 86.69; H, 7.61). This alcohol was characterized by the H-2,4 singlet resonance at δ 1.65. The syn epimeric configuration has been presently assigned to **10** because the δ CH_2O resonance is quite upfield (δ 2.2, d, J = 6 Hz), as would be expected from shielding caused by the proximate phenyl group.

Radical additions to **1** thus far have led to complex mixtures and work is continuing on this aspect, as well as others, of the chemistry of **1**. Even at this early stage, however, it is clear that **1** undergoes LRAMERO rearrangement extraordinarily rapidly whenever cationic character develops at C-8, whereas no skeletal change attends nonpolar addition. Moreover, rearrangement or its absence is easily detected by spectral (particularly ^1H NMR) analysis. The remarkably clean and efficient course of the additions recommends the use of **1** as a mechanistic probe.

Registry No. **1**, 96791-93-4; **3**, 694-70-2; **4**, 96791-94-5; **5**, 96791-95-6; **6**, 96791-96-7; **7**, 29302-44-1; **8** (isomer 1), 96791-97-8; **8** (isomer 2), 96791-98-9; **9**, 96791-99-0; **10**, 96792-00-6.

(8) Full spectral characterization of all products will be given later in a complete paper.

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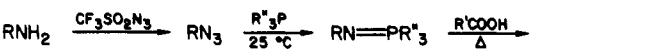
A New Synthesis of Peptides from Azides and Unactivated Carboxylic Acids

Summary: The title reaction, in which an azido compound is treated first with a tertiary phosphine, followed by warming in an inert solvent with a carboxylic acid, has been used to synthesize a number of small peptides and appears from mechanistic studies to proceed via a pentacoordinate phosphorus intermediate.

Sir: We describe a new method of amide bond formation involving treatment of an azido compound with a tertiary phosphine followed by heating in the presence of a carboxylic acid and application of this sequence to the synthesis of a series of small peptides. This reaction complements the recently reported synthesis[1] of optically pure azido carboxylic acids, esters, and peptides from their respective amino precursors; together they represent a novel method of peptide synthesis (eq 1) which is based on very different chemistry from that usually employed.

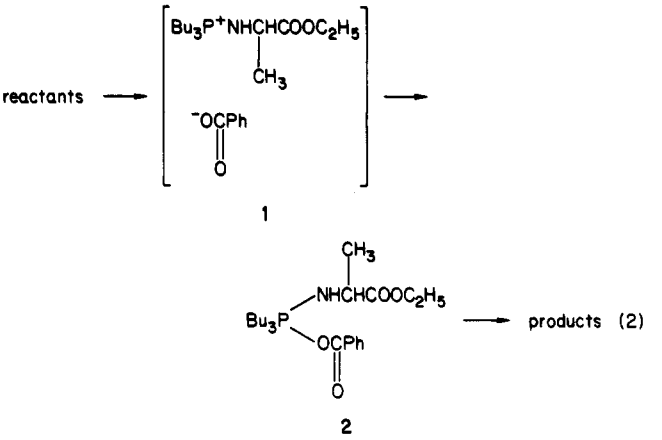
(1) Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173–5176.



R'CONHR + R"$_3$P=O (1)

It has been known for some time[2] that organic azides react under very mild conditions with trivalent phosphines to give iminophosphoranes. The latter compounds undergo Wittig-type reactions with aldehydes,[3] ketones,[4] ketenes,[5] and other compounds containing polarizable oxygen or sulfur.[6] By analogy with these reactions, a free carboxylic acid would be expected to react with an iminophosphorane to provide an amide as product. The reaction was first reported by Horner and Gross[7] in 1955; since the original version of this article was submitted, Garcia et al.[8] have reported the synthesis of a variety of simple amides using this reaction. The reported conditions employed high temperatures and long reaction times; we felt that it might be possible to devise a more practical version of this reaction suitable for the synthesis of peptides.

Initial studies in our laboratory verified that when a carboxylic acid is allowed to react with an iminophosphorane derived from an α-amino ester, an acylated amino acid (ester) is obtained. Benzoyl-DL-alanine ethyl ester was obtained in this way in 73% yield from ethyl DL-2-azidopropanoate and benzoic acid; the reaction employed tributylphosphine and the coupling step was carried out in refluxing toluene. Phosphorus NMR studies of this reaction reveal that an initial proton transfer to form salt **1** (eq 2) takes place upon mixing solutions of the reactants.



Upon heating, formation of products occurs concomitantly with loss of **1**, with no additional intermediates observed. The reaction appears to be much more sluggish in polar solvents such as dioxane or ethyl acetate; this is consistent with the formation of an uncharged intermediate (such as **2**) in the rate-determining step.

The intermediacy of **2** would be highly desirable for two reasons: first, this intermediate is not an especially "activated" carboxyl derivative; the driving force for amide bond formation would lie in the intramolecularity of the acyl transfer and the expulsion of the phosphine oxide rather than in the intrinsic reactivity of the acylating agent. The latter serves as the basis for most other peptide coupling methods but is often responsible for oxazolone-me-

(2) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 619–635.
(3) Schmidbaur, H.; Jonas, G. *Chem. Ber.* **1967**, *100*, 1120–1128.
(4) Wiberg, N.; Schwenk, G.; Schmid, K. H. *Chem. Ber.* **1972**, *105*, 1209–1215.
(5) Shaw, R. A.; Fitzsimmons, B. W.; Smith, B. D. *Chem. Rev.* **1962**, *62*, 247–281.
(6) Wabel, E.; Mucklejohn, S. A. *Phosphorus Sulfur* **1981**, *9*, 235–264.
(7) Horner, L.; Gross, A. *Liebigs Ann. Chem.* **1955**, *591*, 117–134.
(8) Garcia, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, *25*, 4841–4844.

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