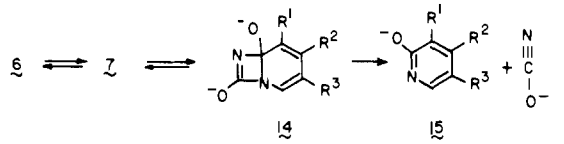
melting points,[15] the rearrangement product has been established as 5-methyl-2-pyridone (**12a**). This rearrangement appears quite general since the cycloadducts of uracil (**5a–d**), 5-fluorouracil (**5e,f**), and thymine (**5g**) undergo smooth conversion to pyridone. Only for the adducts **5e** and **5f** was a second rearrangement product noted. These compounds, formed in 17 and 9% yields, respectively, have been tentatively assigned as the novel pyrrole derivatives **13a** and **13b,** based on their ^{1}H NMR, ^{13}C NMR, UV, and combustion analyses. The structural assignments for the previously unknown pyridones are based on spectroscopy (^{13}C NMR, ^{1}H NMR, UV) and analytical data.

This unusual **5** → **12** conversion is another interesting rearrangement emanating from treatment of dihydropyrimidinediones with base.[11] Since 1 equiv of potassium *tert*-butoxide does not effect rearrangement, we surmise dianions of **5** are required for rearrangement. A reasonable mechanism involves ring opening of the dianion to **7** followed by an alternate mode of ring closure to **14** and fragmentation to the pyridone anion.[17,18] The facile **14** → **15** cycloreversion may be



related to the separation of charge resulting from the cleavage of **14** or reflect alkoxide acceleration of a reverse [2 + 2] cycloaddition. Prominent rate accelerations of [3,3][20] and [1,3][21] shifts by alkoxide moieties have already proven of mechanistic interest and synthetic value.[22] Anions and dianions of other carbo- and heterocyclic systems may also undergo facile rearrangements of the type noted here; additional studies in this area are currently in progress.[23]

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References and Notes

(1) For a critical review, see: Staley, S. In "Pericyclic Reactions", Lehr, R., Marchand, A., Eds; Academic Press: New York, 1977; Vol. I, pp 254–257.
(2) (a) Wharton, P. S.; Hiegel, G. A.; Ramaswami, R. *J. Org. Chem.* **1964,** *29,* 2441–2442. (b) Jones, M.; Temple, P.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1974,** 433–436. (c) Hines, J. N.; Peagram, M. J.; Whitham, G. H.; Wright, M. *J. Chem. Soc., Chem. Commun.* **1968,** 1593–1594. (d) Hines, J. N.; Peagram, M. J.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1973,** 2332–2337. (e) Klemer, A.; Rodemeyer, G. *Chem. Ber.* **1974,** *107,* 2612–2614.
(3) For leading references, see: Thiellier, H.; Koomen, G.; Pandit, U. *Tetrahedron* **1977,** *33,* 2603–2607, 2609–2612.
(4) Relatively little is known concerning the chemistry of aza-[5] and diazacyclooctatetraenes.[6] The parent azacyclooctatetraene is especially unstable, and the chemistry of these systems is largely undefined.[7,8]
(5) (a) McNeil, D. W.; Kent, M. E.; Hedaya, E.; D'Angelo, P. F.; Schissel, P. O. *J. Am. Chem. Soc.* **1971,** *83,* 3817–3818. (b) Snyder, J. P.; Lee, Ling; Farnum, D. G. *Ibid.* **1971,** *83,* 3816–3817.
(6) Trost, B. M.; Cory, R. M. *J. Am. Chem. Soc.* **1971,** *83,* 5573–5575. Trost, B. M.; Scudder, P. H.; Cory, R. M.; Torro, N. J.; Ramamurthy, V.; Katz, T. J. *J. Org. Chem.* **1979,** *44,* 1264–1269.
(7) For a review, see: Paquette, L. A. *Tetrahedron* **1975,** *31,* 2855–2883.
(8) (a) Paquette, L. A.; Kakihana, T.; Hansen, J. F.; Philips, J. C. *J. Am. Chem. Soc.* **1971,** *93,* 152–161. (b) Paquette, L. A., Kakihana, T. *Ibid,* **1968,** *90,* 3897–3898.
(9) For leading references on uracil photocycloaddition reactions, see: Wexler, A. J.; Hyatt, J. A.; Raynolds, P. W.; Cottrell, C.; Swenton, J. S. *J. Am. Chem. Soc.* **1978,** *100,* 512–520.
(10) The cycloadducts were isolated by silica gel chromatography and their purity was rigorously established by ^{13}C NMR. The alternate regioisomer was not observed.
(11) Wexler, A. J.; Swenton, J. S. *J. Am. Chem. Soc.* **1976,** *98,* 1602–1604.
(12) $\lambda_{max(H_2O)}$ 227 nm (log ε 4.01) and 302 (3.81) compared with that reported[13] for 5-methylpyridone, $\lambda_{max(H_2O)}$ 227 nm (log ε 3.81) and 302 (3.76).
(13) Spinner, E.; White, J. C. B. *J. Chem. Soc. B* **1966,** 991–995.
(14) Bell, C. L.; Egan, R. S.; Bauer, L. *J. Heterocycl. Chem.* **1965,** *2,* 420–429.
(15) The 5-methyl isomer has mp 181–183 °C, while the 4-methylpyridone has mp 124–125 °C.[16]
(16) "Pyridine and Its Derivatives, Supplement Part III", Abramovitch, R. A., Ed.; Wiley: New York, 1974, p 8661.
(17) All attempts to isolate an intermediate (i.e., **8**) by interrupting the reaction of **5a** and **5d** at various conversions to pyridone have been unsuccessful. An absorption at ~280 nm in the UV was observed in several cases, but the small yield of material prevented characterization. The use of additional trapping agents for intermediates in these reactions will be explored.
(18) The residue (primarily inorganic) from the reactions shows only five IR (KBr) absorptions at 2185 (vs), 1306 (m), 1212 (m), 652 (m), and 642 (m) cm^{-1}. Waddington[19] reports a mull IR (either Nujol or hexachlorobutadiene) of potassium cyanate showing five absorptions at 2170, 1300, 1205, 636, and 626 cm^{-1}.
(19) Waddington, T. C. *J. Chem. Soc.* **1959,** 2499–2502.
(20) (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975,** *97,* 4765–4766. (b) Seebach, D.; Geiss, K.; Pohmakotr, M. *Angew Chem., Int. Ed. Engl.* **1976,** *15,* 437. (c) Steel, W. C. *J. Am. Chem. Soc.* **1977,** *99,* 4186–4187. (d) Jung, M. E.; Hudspeth, J. P. *Ibid.* **1978,** *100,* 4309–4311. (e) Evans, D. A.; Baillargeon, D. J.; Nelsen, J. V. *Ibid.* **1978,** *100,* 2242–2243. (f) House, H. O.; Sayer, T. S. B.; Yau, C.-C. *J. Org. Chem.* **1978,** *43,* 2153–2157.
(21) (a) Franzus, B.; Scheinbaum, M. L.; Waters, D. L.; Bowlin, H. B. *J. Am. Chem. Soc.* **1976,** *98,* 1241–1247. (b) Theis, R. W.; Seitz, E. P. *J. Chem. Soc., Chem. Commun.* **1976,** 846–847. (c) Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977,** 2559–2562. (d) Thies, R. W.; Seitz, E. P. *J. Org. Chem.* **1978,** *43,* 1050–1057. (e) Wilson, S. R.; Mao, D. T. *J. Chem. Soc., Chem. Commun.* **1978,** 479–480. (f) Wilson, S. R.; Misra, R. N. *J. Org. Chem.* **1978,** *43,* 4903–4904.
(22) See also Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972,** *94,* 5897–5898.
(23) All new compounds gave satisfactory combustion analyses or exact mass measurement (**5e, 5g,** and **12c**).

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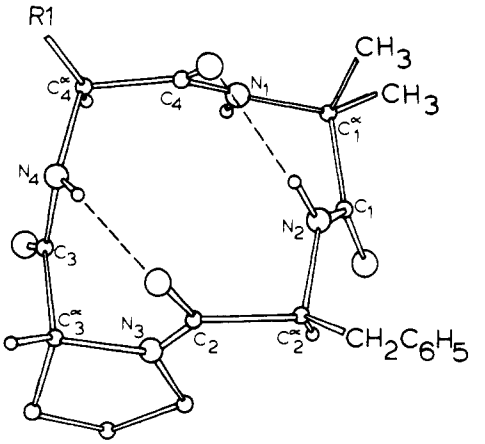
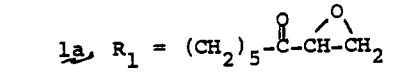
Stereoselective Hydrogenation of Dehydrophenylalanine in a Cyclic Tetrapeptide. Synthesis of [Ala^4]-Chlamydocin

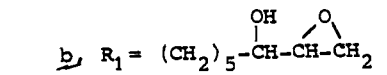
Sir:

Chlamydocin, cyclo[A^{i}bu-L-Phe-D-Pro-(L-2-amino-8-oxo-9,10-epoxidecanoic acid)] (**1a**), a cyclic tetrapeptide isolated from culture filtrates of *Diheterosporia chlamydosporia*





1a, $R_1 = (CH_2)_5-C(=O)-CH(O)-CH_2$



b, $R_1 = (CH_2)_5-CH(OH)-CH(O)-CH_2$

3, $R_1 = CH_3$

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Chart I

R_1-X-Phe[3-SBzl]-D-Pro-L-Ala-OCH_3
4, X = Gly; R_1 = Boc
5, X = A^{i}bu; R_1 = pMZ

R_1-X-Phe[(Z)Δ]-D-Pro-L-Ala-OR_2
6, X = Gly; R_1 = Boc **a**, R_2 = CH_3
7, X = A^{i}bu; R_1 = pMZ **b**, R_2 = Tcp

cyclo(X-Phe[(Z)Δ]-D-Pro-Y-Ala)
8, X = Gly **a**, Y = L
9, X = A^{i}bu **b**, Y = D

cyclo(X-L-Phe-D-Pro-L-Ala)
10, X = Gly
3, X = A^{i}bu

for its cytostatic activity,[1] has an unusual structure.[2] It is the first cyclic tetrapeptide in which, in crystalline analogue **1b**, all amide bonds are transoid (i.e., nonplanar trans amide bonds with ω twist angles of 14–24°)[3] and one of two peptides found to contain the epoxy ketone amino acid, 2-amino-8-oxo-9,10-epoxidecanoic acid.[4] The possible relationships between chlamydocin's novel structure, conformation, and biological activity led us to attempt its synthesis. We report here the synthesis of a model for the chlamydocin ring system, cyclo(A^{i}bu-L-Phe-D-Pro-L-Ala) (**3**).

Cyclic tetrapeptide rings this highly substituted (5α substituents) have not been synthesized previously and work with less substituted structures[5] suggested that direct cyclization of the precursor H-A^{i}bu-L-Phe-D-Pro-L-Ala-OTcp (**2**) might not proceed in acceptable yield. Indeed our first experiments toward synthesizing **3** via direct cyclization of **2** gave little (<1%) of the desired product under standard reaction conditions.[6] Consequently we have developed an alternate method for synthesizing **3** in which a dehydrophenylalanine residue (Phe[(Z)Δ])[7] is used to facilitate the cyclization reaction and then is reduced stereospecifically to L-Phe in the cyclic tetrapeptide. The rationale for this approach was based on the observations that dehydrophenylalanine units can increase the conformational space available to a peptide[8,9] and that a MePhe[(Z)Δ] unit in a cyclic tetrapeptide has been reduced stereospecifically.[10]

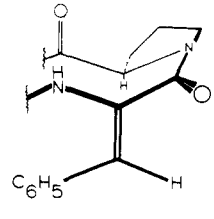
Model cyclic tetrapeptide **8a** was synthesized to study the stereospecificity of the reduction of the Phe[(Z)Δ] unit in a peptide related to chlamydocin (Chart I). Linear tetrapeptide **4** was prepared by stepwise addition of protected amino acids in solution to L-Ala-OMe. Conversion of **4** into the methylsulfonium salt followed by base elimination[11] gave the *Z* isomer **6a** (Calcd: C, 59.75; H, 6.82; N, 11.15. Found: C, 59.65; H, 7.0, N, 10.98. MS: *m/e* 502) which was converted into the trichlorophenyl ester **6b**.[6] Removal of the *tert*-butyloxycarbonyl group (4 N HCl in dioxane; 30 min, 25 °C) followed by cyclization (1.0 mM, 90 °C, pyridine, 8 h) gave cyclic tetrapeptides **8a** (15%; MS *m/e* 370.1640, calcd 370.1641; Gly (0.89), D-Pro (1.0), L-Ala (0.87)) and **8b** (14%; MS *m/e* 370.1640, calcd 370.1641; Gly (0.90), D-Pro (1.0), D-Ala (0.90)). The diastereomers were readily separated by chromatography over silica gel (**8a**, R_f 0.36; **8b**, R_f 0.43 (15% CH_3OH-$CHCl_3$)) and the optical configuration of alanine in each established by hydrolysis (6 N HCl, 20 h, 110 °C) followed by amino acid analysis[12] before and after reaction with L-amino acid oxidase[13] (**8a**, Ala (0.04); **8b**, Ala (0.90)). Hydrogenation of the L-Ala diastereomer **8a** (90%; 24 h, 1 atm, 10% Pd/C, methanol) gave **10** (MS *m/e* 372.1792, calcd 372.1798; Gly (1.02), L-Phe (0.97), D-Pro (1.0), L-Ala (1.03)). After treatment with L-amino acid oxidase, amino acid analysis gave Gly (1.0), Phe (0.03), D-Pro (1.0), Ala (0.05). As only the L-Phe containing product (>98%) was formed, the desired L-Phe is formed by a highly stereoselective reduction.

This sequence of reactions was repeated with peptides that contained the A^{i}bu residue[7] instead of the Gly residue. *p*-Methoxybenzyloxycarbonyl-A^{i}bu (pMZ-A^{i}bu)[14] was used instead of Boc-Gly (Chart I). Tetrapeptide **7a** (MS *m/e* 594. Calcd: C, 62.61; H, 6.44; N, 9.42. Found: C, 62.47; H, 6.55; N, 9.28) was converted to cyclic tetrapeptides **9a** (10% yield: MS *m/e* 398.1949, calcd 398.1953; A^{i}bu (1.15), D-Pro (1.0), L-Ala (1.08)) and **9b** (5%; MS *m/e* 398.1958, calcd 398.1953; A^{i}bu (1.22), D-Pro (1.0), D-Ala (1.08)) using the reaction conditions described for **8a** and **8b**. Hydrogenation of **9a** (identical conditions as **8a**) gave **3** (60%; MS *m/e* 400.2107, calcd 400.2111; A^{i}bu (1.13), L-Phe (1.0), D-Pro (1.0), L-Ala (1.04)). The configuration of L-Phe was established by reacting the hydrolyzed peptide **3** with L-amino acid oxidase. Amino acid analysis of the reaction mixture gave Phe (0.01), D-Pro (1.0), and L-Ala (0.12).

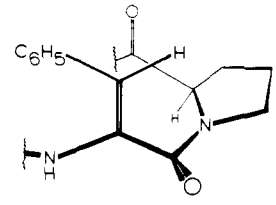
The use of a dehydrophenylalanyl residue in place of L-Phe appears to substantially increase the yield of cyclic tetrapeptide formed under identical reaction conditions. Cyclization of the relatively unhindered glycine peptide **6b** gave diastereomers **8a** and **8b** in a total yield comparable with yields obtained with other cyclic tetrapeptide systems.[5,6] Replacement of glycine with the more hindered α-aminoisobutyric acid residue does reduce the yield of cyclic tetrapeptide formed (15% overall), but the 10% yield of **9a** is sufficient to provide a usable pathway to this highly substituted cyclic tetrapeptide ring system and extension to the synthesis of chlamydocin itself appears feasible. The best yield that we have obtained for **3** beginning with **2** is only ~1%.

High chiral induction has been achieved upon hydrogenation of dehydroamino acid residues in diketopiperazines[15] and in tentoxin, a cyclic tetrapeptide,[10] and in the latter case the high stereoselectivity has been correlated with preferred solution conformation.[16] However reduction of dehydro residues in cyclic peptides does not always give high chiral induction. Shimohigashi et al.[17] reported that hydrogenation of dehydroalanine in the cyclic tetradepsipeptide AM-toxin I gave both D-Ala and L-Ala containing cyclic peptides in the ratio 62:38.

Reduction of the dehydrophenylalanine units in both **8a** and **9a** is highly stereoselective. Introduction of the more hindered A^{i}bu residue proximate to the double bond of Phe[(Z)Δ] does not affect stereoselectivity of the reduction, although the yield is reduced. In either case no D-Phe containing cyclic tetrapeptides were formed within the limits of our method for determining optical purity (±2%). L-Phenylalanine will be formed only when the catalyst approaches the unhindered side of the double bond when the Phe [(Z)Δ]-D-Pro unit is in partial conformation **11a** (^{13}C NMR data show that both **8a** and



11a



11b

9a have cis X-Pro bonds in polar and nonpolar solvents). Reduction of the other possible conformation **11b** does not occur since no D-Phe is formed. Molecular models suggest that the alternate conformation **11b** may be more strained than **11a** owing to conformational restrictions imposed by the proline ring. The conformations of **10** and **3** will be described in future communications.

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References and Notes

(1) H. Stahelin and A. Trippmacher, *Eur. J. Cancer*, **10**, 801–808 (1974).
(2) A. Closse and R. Huguenin, *Helv. Chim. Acta*, **57**, 533–545 (1974).
(3) J. Flippen and I. Karle, *Biopolymers*, **15**, 1081–1092 (1976).
(4) Other occurrence in Cyl-2: A. Hirotu, A. Suyuki, K. Aiyawa, and S. Tamura, *Agr. Biol. Chem.*, **37** (4), 953–954 (1973).
(5) K. Titlestad, *Acta Chem. Scand., Ser. B*, **31**, 641–661 (1977).
(6) D. H. Rich, P. Bhatnagar, P. Mathiaparanam, J. Grant, and J. Tam, *J. Org. Chem.*, **43**, 296–302 (1978).
(7) All amino acids except glycine are of the L configuration unless noted. Standard abbreviation for amino acids, protecting groups, and peptides recommended by the IUPAC-IUB Commission on the Biochemical Nomenclature (*J. Biol. Chem.*, **247**, 977 (1972)) are used. Additional abbreviations follow: BOC, *tert*-butoxycarbonyl; Phe[(Z)Δ], (*Z*)-dehydrophenylalanine; Phe[3SBzl], 3-benzylthiophenylalanine; Abu, α-aminoisobutyric acid; pMZ, *p*-methoxybenzyloxycarbonyl.
(8) D. H. Rich and P. Mathiaparanam, *Tetrahedron Lett.*, 4037 (1974).
(9) D. H. Rich and P. Bhatnagar, *J. Am. Chem. Soc.* **100**, 2218 (1978).
(10) W. Meyer, G. Templeton, C. Grable, R. Jones, L. Kuyper, R. Lewis, C. Sigel, and S. Woodhead, *J. Am. Chem. Soc.*, **97**, 3802–3809 (1975).
(11) D. H. Rich and J. P. Tam, *Tetrahedron Lett.*, 211–212 (1975).
(12) S. Moore, D. H. Spackman, and W. H. Stein, *Anal. Chem.*, **30**, 1185 (1958).
(13) P. Sieber, B. Riniker, M. Brugger, B. Kamber, and W. Rittel, *Helv. Chim. Acta*, **53**, 2135 (1970).
(14) F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1–16 (1962).
(15) N. Izumiya, S. Lee, T. Kanmera, and H. Aoyagi, *J. Am. Chem. Soc.*, **99**, 8346 (1977), and references therein.
(16) D. H. Rich and P. K. Bhatnagar, *J. Am. Chem. Soc.*, **100**, 2212 (1978).
(17) Y. Shimohigashi, S. Lee, T. Kato, and N. Izumiya, *Bull. Chem. Soc. Jpn.*, **51**, 584 (1978).

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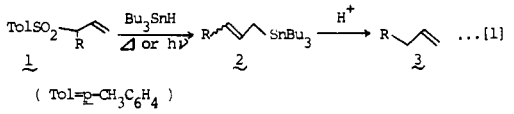
Regioselective Desulfonylation of Allylic Sulfones with Organotin Hydride Involving Double Migration of the Double Bond[1]

Sir:

Allylic sulfides, sulfoxides, or sulfones have been proven to be valuable synthetic intermediates for carbon-carbon bond formation via the sulfur-stabilized carbanions.[2,3]

In contrast to the various efforts to improve the regioselectivity in such allylic alkylation (α vs. γ),[3] little attention has been directed toward improving the regioselectivity in the reductive desulfurization process of the resulting allylic alkylated sulfur compounds.[4]

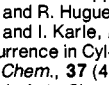
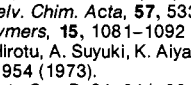
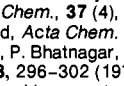
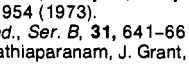
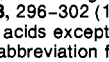
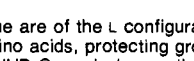
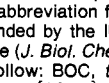
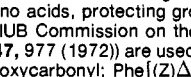
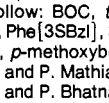
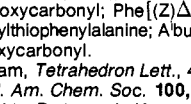
In connection with our recent finding on the desulfurizative stannylation of propargyl (or allyl) sulfides via an S_H' process,[5] we report here the completely regioselective desulfonylation of allylic sulfones to energetically less stable terminal olefins with tri-*n*-butyltin hydride involving double migration of double bond as outlined in eq 1.



Thus, α-alkylated allyl tolyl sulfone (**1**)[4a,6] reacted with twice the molar amount of tri-*n*-butyltin hydride[7] in the presence of the catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene for 2 h to afford allyltin derivatives (**2**) in good isolated yield.[8] The same stannylated products (**2**) were also obtained by a photochemical procedure at room temperature for ~10 h (see Table II).

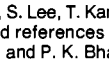
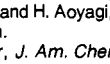
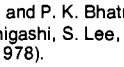
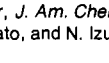
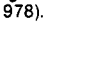
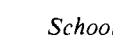
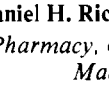
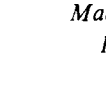
In both cases, the reaction was conveniently followed by the disappearance of the absorptions of tin hydride (1800 cm^{-1}) and sulfone (1315 ± 5, 1145 ± 5 cm^{-1}) and also the appearance of the new band at 960 and 980 cm^{-1} ($TolSO_2SnBu_3$)[8] in the IR spectrum. All allyltins obtained here were a mixture of trans and cis isomers.[9] The results of the thermal reaction are summarized in Table I.

Table I. Allyl Transfer from Sulfur to Tin

Sulfone	Product[10]	Yield (%)[a]
1a 	2a 	68
1b 	2b 	65
1c 	2c 	68
1d 	2d 	74
1e 	2e 	71

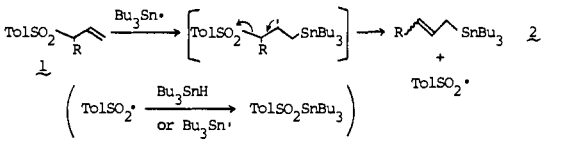
[a] Isolated yield.

Table II. Desulfonylation of Allylic Sulfones

Sulfone	Product	Yield (%)[a] method A[b]	method B[c]
1a 	3a 	80	57
1b 	3b 	80	66
1c 	3c 	87	62
1d 	3d 	84	73
1e	3e 	46[d]	26[d]

[a] Yields were determined by GC analysis. [b] Method A: thermal reaction in refluxing benzene for 2 h in the presence of AIBN. [c] Method B: photoreaction in degassed benzene solution for 10 h at room temperature using a Pyrex tube (100-W high-pressure mercury lamp). [d] Isolated yield.

The possible reaction scheme may be best explained in terms of the S_H' process similar to the allenyl transfer from propargyl sulfide.[5]



The present reaction provides a new general synthetic method for the preparation of allyltins. In view of the possible variation of the substituents (R),[4a] the method seems to have an advantage over the existing one, in which allylic Grignard reagents are generally employed.[11]

The present facile stannylation reaction, when combined with the ease protolysis of allyltins,[12] offers a unique methodology, in which the completely regioselective desulfonylation of allylic sulfones becomes available.

Thus we investigated the one-pot desulfonylation without isolation of allyltin species. Treatment of the above reaction mixture with concentrated hydrochloric acid or acetic acid produced terminal olefins (**3**) in good yield without contamination of internal ones (see eq 1). The results are summarized in Table II.

This is a first example of the completely regioselective desulfurization of allylic sulfones to energetically less stable terminal olefins in contrast to the method of Umani-Ronchi et al.[4a,13] Moreover, it is quite apparent that other electrophiles[14] besides the proton can be used in the destannylation step to generate other functional alkenes. α-Alkylation, followed by stannylation of allyl sulfones, and subsequent destannylation with various electrophiles provide an attractive entry to the preparation of functional alkenes in a completely regioselective manner.

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