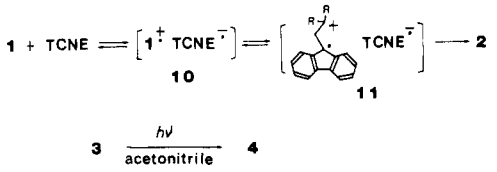
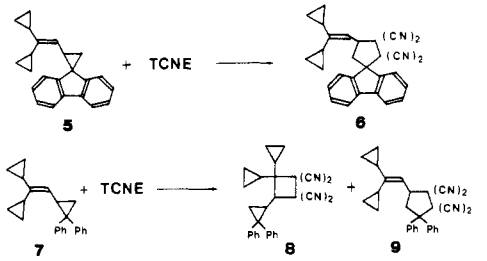
Scheme I



30 s in dichloromethane, ca. 24 min in ethyl acetate, 1.5 h in benzene). From the resultant colorless solution, a crystalline, 1:1 adduct, 3,3-dicyclopropyldibenzo[*f*,*h*]spiro[4.4]nonane-1,1,2,2-tetracarbonitrile (**2a**),[4] was obtained in 66% yield. The reaction of **1b** with TCNE proceeded slowly but analogously to give **2b** (overnight in dichloromethane at room temperature, 55%). In contrast, 1,1-dicylopropyl-2,2-diphenylcyclopropane (**3**) was practically

unreactive with TCNE under similar reaction conditions, although **3** differs from **1a** only in that **3** lacks a bond between the two phenyl groups to accomplish the fluorene skeleton. In acetonitrile at room temperature, the consumption of **3** was only 6% even after 20 h, although the formation of a trace amount of **4** was noted by the HPLC analysis of the crude reaction mixture.

The 2,2-dicyclopropylvinyl derivative **5** also reacted very readily with TCNE to give **6** (few seconds in dichloromethane, 83%). In contrast, **7** produced two cycloadducts,



8 (72%) and **9** (9%), in its slow reaction with TCNE (2 days in dichloromethane at room temperature). Since **5** and **7** are trisubstituted ethylenes, we expected that [$_\pi$2 + $_\pi$2] cycloadditions might take place.[2d,3,5] This was indeed the case in the reaction of **7**, but **5** produced exclusively **6**. Here, the effect of the fluorene unit was observed for the second time.

Now, the marked difference in the reactivity observed between **1a** and **3**, as well as between **5** and **7**, is evidently due to the presence or the absence of the fluorene unit in the substrates. According to Scott et al.,[6] an electron transfer is thermodynamically favored when the difference between the ionization potential (IP) of the donor and the electron affinity (EA) of the acceptor is less than 4–5 eV. Thus, on the basis of the fact that the IP of dibenzo[*d*,*f*]spiro[2.4]heptane (spiro[cyclopropane-1,9′-[9*H*]fluorene], IP^v = 7.84 eV)[7] is substantially lower than that of 1,1-diphenylcyclopropane (IP^v = 8.48 eV),[7] we propose that the electron transfer from the substrate to TCNE (EA = 2.8–2.9 eV) might readily occur to a considerable extent in the reactions of **1** and **5** but not in the reaction of **3**. As shown in Scheme I, the resultant **10** will open its cyclopropane ring when the three-membered ring carries good cation-stabilizing groups.[8] The second cation radical **11** will then react with a nearby TCNE anion radical to afford **2**.

It was further observed that thermally very low reactive **3** could react with TCNE in a reasonable rate under illumination with a halogen lamp (42% conversion at 12 °C in acetonitrile after 4 h) to give **4** (37%). The charge-transfer complex [λ_{max} 363 (sh) nm] might be excited by the illumination and the resultant excited state would collapse to an ion radical pair similar to **10**, which underwent subsequent transformations. Thus, the adequacy of Scheme I may be justified.

Registry No. **1a**, 37568-24-4; **1b**, 91266-61-4; **2a**, 91266-62-5; **2b**, 91266-63-6; **3**, 54159-42-1; **4**, 91549-28-9; **5**, 91549-29-0; **6**, 91266-66-9; **7**, 91266-64-7; **8**, 91266-65-8; **9**, 91266-67-0; **12**, 91266-68-1; **13**, 91266-69-2; TCNE, 670-54-2.

Supplementary Material Available: Spectral data of the products (8 pages). Ordering information is given on any current masthead page.

(4) Spectral data of the products are available in the supplementary material section.

(5) Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* **1973**, *38*, 1878.

(6) Scott, L. T.; Erden, W. R.; Brunsvold, W. R.; Schultz, T. H.; Houk, K. N.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1982**, *104*, 3659.

(7) Jason, M. E.; Gleiter, R., unpublished results. We are very grateful to them for sending us the IP^v values prior to the publication.

(8) We propose that **10** will open its cyclopropane ring prior to the attack by TCNE anion radical. The alternative possibility that the TCNE anion radical attacks **10**, yielding a biradical intermediate, which in the next step gives **2** (suggested by the referee), appears to be unlikely. This is because (i) **2** was 3,3-disubstituted spirononane-1,1,2,2-tetracarbonitrile but was not 4,4-disubstituted spirononane-1,1,2,2-tetracarbonitrile (the structural proof of **2** is given in the supplementary material), (ii) the reaction of **1a** proceeded significantly more rapidly than that of **1b**, and (iii) the zwitterionic intermediate derived from **11** was successfully trapped by methanol in the reaction of **1b** with TCNE (unpublished observations).

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Received March 28, 1984

Synthesis of Antibiotic X-14547A[1]

Summary: A highly stereoselective 16-step synthesis of antibiotic X-14547A is described.

Sir: Antibiotic X-14547A (**1**), a structurally unique member of the ionophore class,[4] has attracted considerable attention since its structure was reported in 1978.[5,6]

(1) Taken in part from the Ph.D. Thesis of S. M. Peseckis, Massachusetts Institute of Technology, Cambridge, MA, 1983.

(2) Holder of the Firmenich Career Development Chair in Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–84.

(3) National Cancer Institute Predoctoral Trainee (Training Grant No. T32-CA-09112).

(4) (a) Westley, J. W., Ed. "Polyether Antibiotics: Naturally Occurring Acid Ionophores"; Marcel Dekker: New York, 1983; Vol. I and II. (b) Dobler, M. "Ionophores and Their Structures"; Wiley: New York, 1981. (c) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. (d) Pressman, B. C. *Annu. Rev. Biochem.* **1976**, *45*, 501.

(5) (a) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6784. (b) Liu, C.-M.; Hermann, T. E.; Liu, M.; Bull, D. N.; Palleroni, N. J.; Prosser, B. L. T.; Westley, J. W.; Miller, P. A. *J. Antibiot.* **1979**, *32*, 95. (c) Westley, J. W.; Evans, R. H., Jr.; Sello, L. H.; Troupe, N.; Liu, C.-M.; Blount, J. F. *Ibid.* **1979**, *32*, 100.

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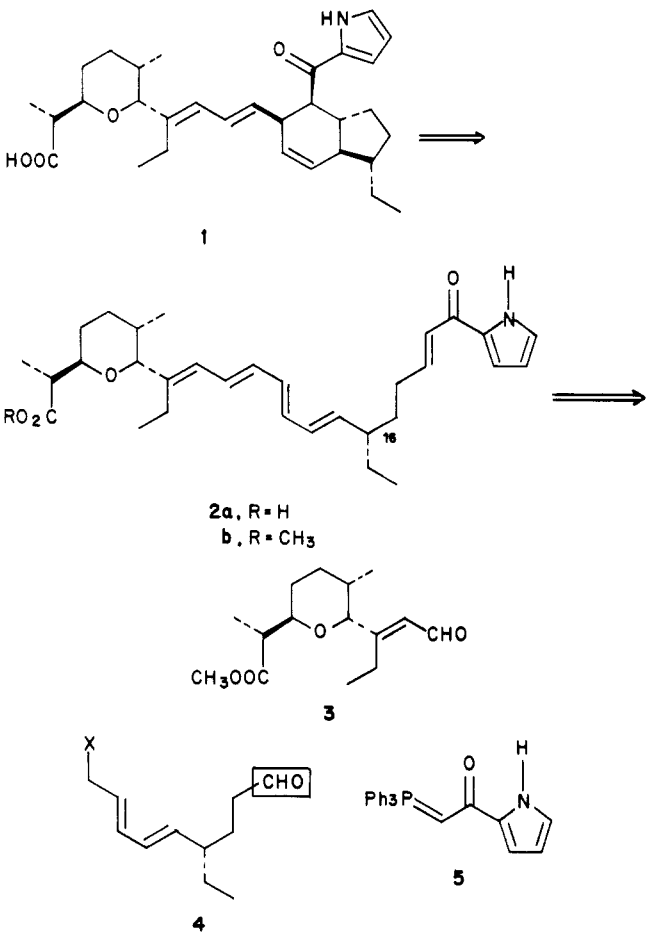
Scheme I



X-14547A is useful as a growth promotant for ruminants and also possesses antibacterial and antitumor activity. Remarkably, X-14547A is able to transport mono-, di-, and trivalent cations across solvent barriers even though it has only a single tetrahydropyranyl residue.[5a,b,7] While X-14547A crystallizes as a 2:1 complex with (*p*-bromophenethyl)ammonium ion,[5a] kinetic data suggests that it functions as a 1:1 complex with Pr^{3+} during cation transport.[7]

In light of the significant biological data, unique structure, and interesting physical properties we became interested in developing a synthesis of X-14547A.[6] Our hypothesis that the biosynthesis of **1** might involve an intramolecular Diels–Alder reaction (cf. **2a** → **1**)[6c,d] led to the general strategy outlined in Scheme I. Of special significance is the recognition that pentaene **2**, and hence **1**, could be assembled by a very brief sequence of operations from precursors **3**, **4**, and **5**. The successful synthesis outlined in Scheme II establishes the operational simplicity of this plan and also features a new method for the enantiospecific synthesis of α-chiral aldehydes (cf. **9** + **10** → **11** → **12**). In the present context we use this protocol to establish the critical C(16) stereocenter of **2**.

Sequential treatment of the readily available acetylenic ester **6**[8,9] with 1.3 equiv of *n*-BuLi (THF, −78 °C) followed by 1.6 equiv of I_2 (−78 → −30 °C, 2 h) afforded the corresponding iodoalkyne[9] in 95% yield. This intermediate was then reduced to (*Z*)-alkenyl iodide **7**[9] in 65–70% yield by a hydroboration–protonolysis sequence (1.2 equiv of 9-BBN, THF, 23 → 70 °C, 4 h; then 20 equiv of HOAc, 25 °C, 30 min).[10] Lithiation of **7** (2.2 equiv of *t*-BuLi, Et_2O, −78 °C, 1 h)[11] followed by addition of the resulting vinyllithium species to pinacol (chloromethyl)boronate (**8**;[12] 1.0 equiv, 5–7 h at −78 °C before being warmed to 23 °C)[13,14] afforded crude **9**[9a] which, without purification, was exposed to a slight excess of D-glyceraldehyde acetonide (**10**) (1.2 equiv, CH_2Cl_2, 23 °C, 12–24 h). This procedure afforded adduct **11**[9] $[\alpha]^{20}_D$ +15.7° (*c* 0.67, $CHCl_3$)) in 55% yield from **7** (70–75% based on **10** as the limiting reagent) as a 10:1 mixture of stereoisomers. The stereochemistry of **11** is the consequence (a) of a cyclic transition state[15] which transmits the olefinic stereochemistry of **9** to the anti relationship between C(3) and C(4) in **11** and (b) the high erythro selectivity realized in the addition of (*Z*)-crotylboronates to α,β-dialkoxyaldehydes.[16]

Aldehyde **12**[9a] ($[\alpha]^{21}_D$ +1.6° (*c* 1.44, $CHCl_3$)) was prepared from **11** in 78% overall yield by sequential reduction of the vinyl group with diimide (H_2NNH_2, $NaIO_4$, CH_3OH, 23 °C),[17] hydrolysis of the acetonide (4:1:1 HOAc–CH_3OH–H_2O, 60 °C, 1 h), and cleavage of the resulting triol by exposure to $NaIO_4$ in aqueous THF.[18] Treatment of **12** with the lithium anion of triethyl 4-phosphonocrotonate in THF (−78 → 23 °C) afforded the corresponding diene ester[9] ($[\alpha]^{20}_D$ +8.7° (*c* 1.2, $CHCl_3$)) which was reduced with $LiAlH_4$ in Et_2O to give **13**[9] ($[\alpha]^{22}_D$ − 1.6° (*c* 2.1, $CHCl_3$)) in 82% yield. This intermediate was then brominated (Ph_3PBr_2, CH_3CN, 0 °C), treated with sodium diisopropyl phosphite in C_6H_6 (44%), and deprotected by

(6) Two total syntheses of X-14547A have been reported: (a) Nicolaou, K. D.; Claremon, D. A.; Papahatjis, D. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 6969. (b) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, *630*. For other relevant synthetic studies, see: (c) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879. (d) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (e) Nicolaou, K. C.; Magolda, R. L. *Ibid.* **1981**, *46*, 1506. (f) Ho, P.-T. *Can. J. Chem.* **1982**, *60*, 90.

(7) Grandjean, J.; Laszlo, P. *J. Am. Chem. Soc.* **1984**, *106*, 1472.

(8) Prepared in 95% yield by silylation (*tert*-butyldiphenylsilyl chloride, imidazole, DMF, 23 °C) of commercially available 4-pentynol.

(9) (a) All new compounds were fully characterized by NMR, IR, and mass spectroscopy. (b) This compound gave a satisfactory combustion analysis (±0.3% for C, H).

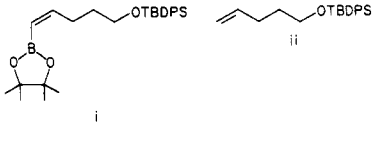
(10) Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086.

(11) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.

(12) Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137. See also: Matteson, D. S.; Majumdar, D. *Ibid.* **1979**, *170*, 259.

(13) The addition of organometallic reagents to (α-haloalkyl)boronate esters is a well-established method: (a) Brown, H. C.; DeLue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.; Sonoda, A. *J. Org. Chem.* **1977**, *42*, 4088. (b) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588. (c) Matteson, D. S.; Ray, R. *Ibid.* **1980**, *102*, 7590. (d) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529. (e) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398.

(14) If this reaction mixture is allowed to warm immediately from −78 °C to 23 °C, up to 23% of vinyl boronate i is produced. Crude **9** prepared as described in the text contains less than 5% of i but also contains up to 25% of vinyl ether ii. We have not yet been successful in numerous attempts to suppress the formation of ii.



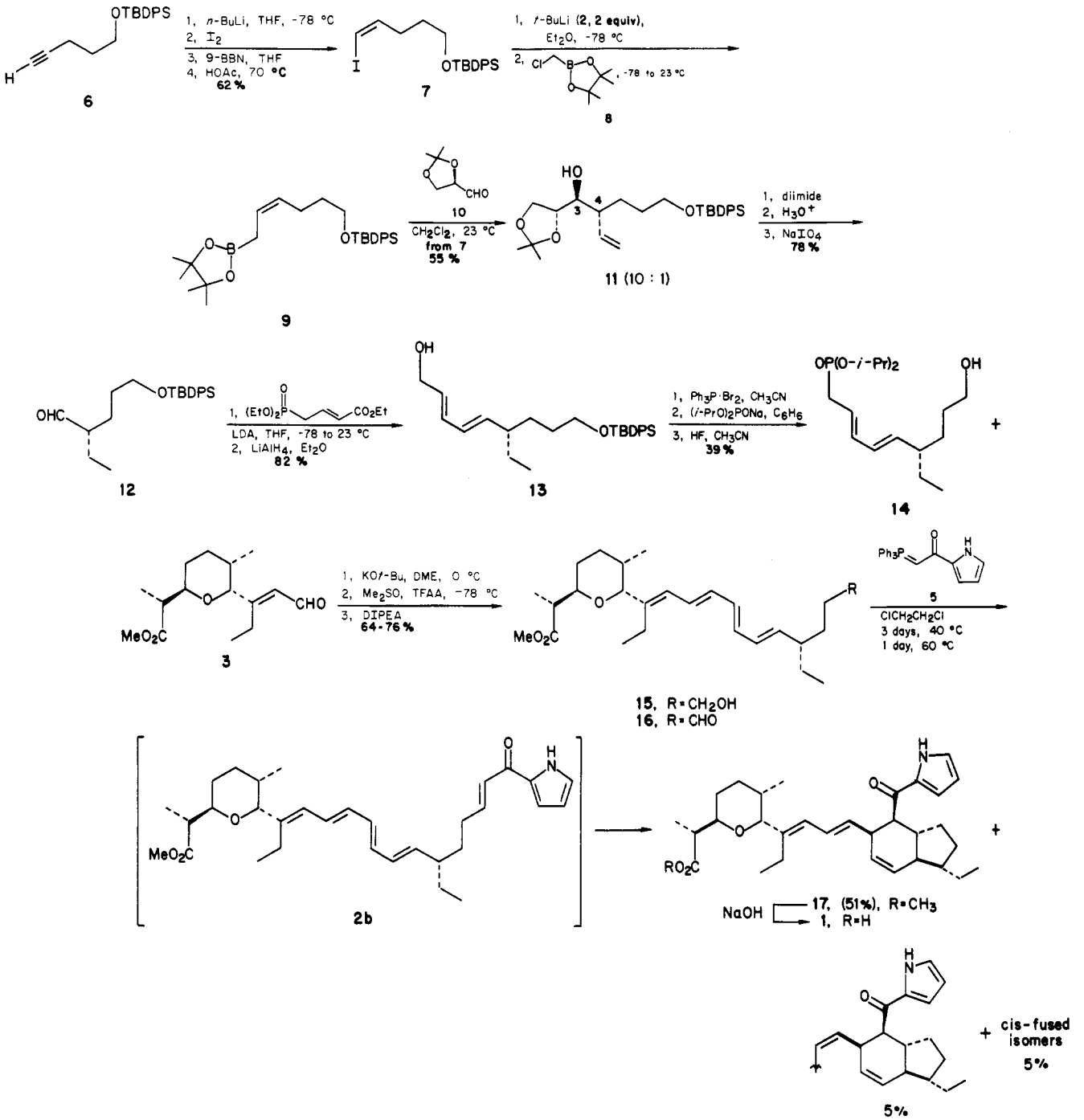
(15) Review: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(16) (a) The stereochemistry of the reactions of (*Z*)- and (*E*)-crotylboronates with α,β-dialkoxy aldehydes will be reported separately: Roush, W. R.; Adam, M. A.; Harris, D. J., manuscript in preparation. For other relevant stereochemical results, see: (b) Roush, W. R.; Harris, D. J.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2227. (b) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489. (c) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320.

(17) Hoffmann, J. M., Jr.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245.

(18) It should be noted that three alternative routes to **12** proved less successful in terms of yield and/or enantioselectivity than the boronate construction outlined in text. These alternative sequences are summarized in ref 1 and will be outlined in the full paper describing this work.

Scheme II



exposure to dilute HF in CH_3CN.[19] The overall yield of phosphonate **14**[9] ($[\alpha]^{22}_D$ −2.1° (*c* 1.40, $CHCl_3$)) from **13** was 39%.

The stage was now set for completion of the synthesis. Unsaturated aldehyde **3** was prepared from natural X-14547A according to the procedure described by Nicolaou.[20] A mixture of **3** and 1.2 equiv of phosphonate **14** in DME at 0 °C was treated with 1.2 equiv of KO-*t*-Bu in DME to give 83% of tetraene **15**[9a] ($[\alpha]^{23}_D$ −0.7° (*c* 1.2, $CHCl_3$)) as an 11:1 mixture of olefin isomers at the newly formed double bond.[21] This intermediate was oxidized to aldehyde **16**[9a] ($[\alpha]^{22}_D$ − 1.1° (*c* 0.96, $CHCl_3$)) in 80% yield by using the Swern Me_2SO–TFAA reagent.[22] Finally, when **16** was allowed to react with excess Wittig reagent **5**[6d] in 1,2-dichloroethane (homogeneous solution) at 40 °C for 3 days and at 60 °C for a fourth day, a mixture of cycloadducts was obtained from which isomerically pure X-14547A methyl ester **17** ($[\alpha]^{22}_D$ −303.2° (*c* 0.60, $CHCl_3$)) was isolated in 51% yield. Also obtained was 5% of the C(10,11) (*Z*)-olefin isomer of **17** and 5% of a mixture of cis-fused cycloadducts. Semisynthetic X-14547A methyl ester so prepared was identical in all respects with an authentic sample preparedby diazomethane esterification

(19) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *3981*.

(20) This method, as previously reported (ref 6e), affords a 4–5:1 mixture of (*E*)-**3** and the corresponding *Z* isomer, which we separated by semipreparative reverse-phase HPLC (Waters C-18 μ-Bondapak, 60:40 H_2O–CH_3CN).

(21) A 4:1 mixture of olefin isomers was obtained when the dimethyl phosphonate analogue of **14** was employed in the coupling sequence.

(22) (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297.

of the natural product.[23] Since Nicolaou[6a] and Ley[6b] have already described the hydrolysis of 17 to 1, our work completes the third synthesis of this natural product.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM 26782) and National Cancer Institute (Training Grant No. T32-CA 09112). We are grateful to the Ayerst Laboratories for a postdoctoral fellowship to S.M.P. and to Dr. J. W. Westley of Hoffmann-La Roche, Inc., for providing a generous sample of natural X-14547A.

Registry No. 1, 66513-28-8; 3, 76566-87-5; (*Z*)-3, 76566-88-6; 5, 76584-28-6; 6, 91266-03-4; 6 iodoalkyne deriv., 91266-04-5; 7, 91266-05-6; 8, 83622-42-8; 9, 91266-06-7; 10, 15186-48-8; 11, 91266-07-8; 11 dihydro deriv., 91266-08-9; 11 dihydrotriol deriv., 91266-09-0; 11 dihydro acetate deriv., 91266-17-0; 11 dihydrotriol triacetate deriv., 91266-16-9; 12, 91326-64-6; 12 crotonate deriv., 91266-10-3; 13, 91266-11-4; 13 phosphonate deriv., 91266-12-5; 14, 91266-13-6; 15, 91266-14-7; (*Z*)-15, 91326-65-7; 16, 91280-61-4; 17, 76567-01-6; (*Z*)-$C_{10,11}$-17, 91326-66-8; triethyl 4-phosphonocrotonate lithium anion, 91266-15-8.

Supplementary Material Available: Spectroscopic data and physical constants for all synthetic intermediates (9 pages). Ordering information is given on any current masthead page.

(23) A sample of 17 prepared from natural X-14547A had $[\alpha]^{20}_D$ −308.2° (*c* 1.24, $CHCl_3$). Nicolaou has reported $[\alpha]^{25}_D$ − 170.6° (*c* 1.4, $CHCl_3$) for 17 (see ref 6a).

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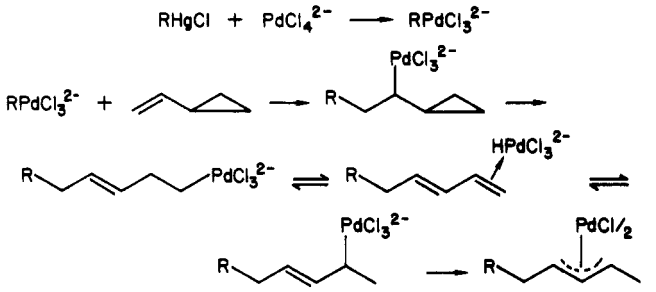
Mercury in Organic Chemistry. 30. Synthesis of (π-Allyl)palladium Compounds via Organopalladium Additions to Alkenyl- and Methylenecyclopropanes and Alkenyl- and Methylenecyclobutanes

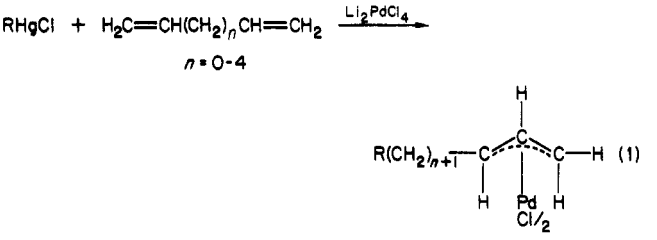
Summary: (π-Allyl)palladium compounds are readily available via organopalladium additions to alkenyl- and methylenecyclopropanes and alkenyl- and methylenecyclobutanes. This reaction apparently involves formation of a (cycloalkylcarbinyl)palladium intermediate which undergoes ring-opening and subsequent palladium migration to afford the (π-allyl)palladium product.

Sir: (π-Allyl)palladium compounds have recently become valuable intermediates in organic synthesis.[1,2] Two of the more useful methods of preparing these compounds involve the direct allylic hydrogen substitution of alkenes by palladium salts[3-8] and the insertion of palladium(0) reagents into the carbon–halogen or carbon–oxygen bond of allylic halides or acetates.[9-12] Recently, the reaction of

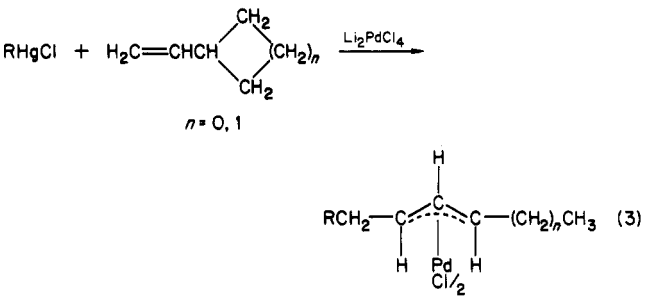
Scheme I



organomercurials, palladium salts, and either conjugated[13,14] or nonconjugated[15] dienes has provided a convenient new approach to (π-allyl)palladium compounds (eq 1).



Similarly, vinylmercurials may be reacted with palladium salts and simple olefins to afford (π-allyl)palladium compounds (eq 2).[16,17] We now report that the reaction of organomercurials, palladium salts, and alkenyl- or methylenecyclopropanes and alkenyl- or methylenecyclobutanes results in a novel ring-opening process and subsequent rearrangement, which affords a valuable, new, regioselective route to (π-allyl)palladium compounds (eq 3).



Our results to date are summarized in Table I. As can be seen in the table, aryl, methyl, vinyl and heterocyclic organomercurials can be employed in this reaction. With alkylmercurials bearing hydrogens beta to mercury, the (π-allyl)palladium product derived by palladium hydride addition to the olefin and subsequent rearrangement is isolated (entry 3).

A variety of olefins are observed to afford (π-allyl)palladium compounds by this procedure. Vinylcyclopropanes of various substitution patterns can be employed. Aryl substitution on the cyclopropane ring is observed to direct ring-opening toward the aryl group (entries 7 and 8).

(1) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.
(2) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer Verlag; New York, 1980.
(3) Tsuji, J.; Imamura, S.; Kiji, J. *J. Am. Chem. Soc.* **1964**, *86*, 4491.
(4) Trost, B. M.; Strege, P. E. *Tetrahedron Lett.* **1974**, 2603.
(5) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630.
(6) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1975**, *97*, 2534.
(7) Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611.
(8) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.
(9) Dent, W. T.; Long, R.; Wilkinson, A. J. *J. Chem. Soc.* **1964**, 1585.
(10) Sakakibara, M.; Takahashi, Y.; Sakai, S.; Ishii, Y. *J. Chem. Soc. D* **1969**, 396.
(11) Tsuji, J.; Iwamoto, N. *Chem. Commun.* **1966**, 828.
(12) Dent, W. T.; Long, R. British Patent 1 082 248, **1967**; *Chem. Abstr.* **1968**, *68*, 114748*j*.
(13) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542.
(14) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584.
(15) Larock, R. C.; Takagi, K. *Tetrahedron Lett.* **1983**, *24*, 3457.
(16) Larock, R. C.; Mitchell, M. A. *J. Am. Chem. Soc.* **1978**, *100*, 180.
(17) Larock, R. C.; Takagi, K.; Hershberger, S. S.; Mitchell, M. A. *Tetrahedron Lett.* **1981**, *22*, 5231.

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