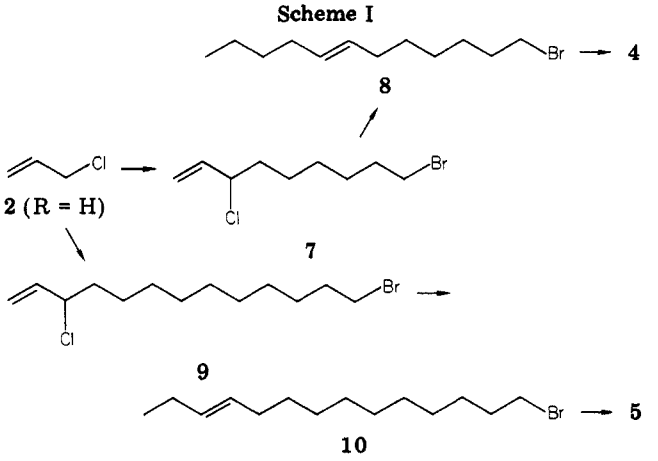
Communications

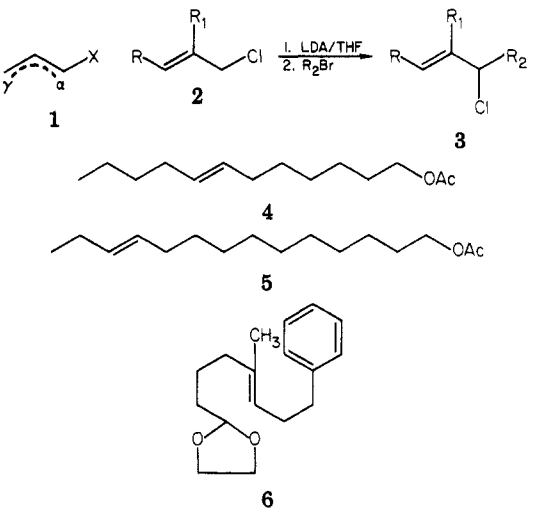
α-Haloallyllithium Species. Coupling with Alkyl Bromides

Summary: The regiospecific α-alkylation of in situ generated α-chloroallyllithium species with primary alkyl bromides and the synthetic utility of the derived secondary allylic chloride intermediates are described.

Sir: Heteroatom-substituted allyl carbanions **1** have received considerable attention directed at evaluating their synthetic potential and at understanding their modes of reactivity with electrophiles.[1] The expanding list of heteroatoms examined in these capacities includes boron, nitrogen, oxygen, silicon, phosphorus, sulfur, and selenium in a variety of oxidation and bound states.[1,2] Perhaps the first examples of heterosubstituted allyl carbanions to be examined and employed were the halogen-substituted species by Kharasch in 1939.[3] Since that time, these species have received only limited synthetic attention and have not in general proven to be viable synthetic agents owing to their rapid "self-consumption".[4,5] We report here that allyl chloride anions generated in situ via lithium diisopropylamide deprotonation of the corresponding allyl chloride undergo exclusive α-alkylation with primary alkyl bromides (e.g., **2** → **3**).[6] The derived secondary allyl chloride intermediates **3** are useful synthetic "building blocks" which we illustrate by direct, facile syntheses of the disubstituted olefinic insect sex pheromones from *A. leucotreta* (**4**) and *S. littoralis* (**5**) and of a trisubstituted olefin **6**, which serves as a model precursor for a polyene cyclization route to polycyclic diterpenoids and steroids.

Scheme I





We have observed that alkylation of the in situ generated carbanion **1** (X = Cl) occurs with high regioselectivity at the α-position (>97%) for a variety of primary alkyl bromide electrophiles and allyl chloride anions (Table I). It should be noted that some structural modification of the allyl chloride component is possible as demonstrated by the employment of allyl, methallyl, and crotyl chloride anion precursors. In addition, synthetically useful selection of the primary position in a primary–secondary dibromide alkylating agent occurs in the alkylation process. Secondary bromides do not produce synthetically acceptable yields of alkylation products (≤10%).

Our synthesis of the *A. leucotreta* sex pheromone **4** (Scheme I) proceeded by alkylation of allyl chloride anion with 1,6-dibromohexane to yield 9-bromo-3-chloro-1-nonene (**7**, 88%). Treatment of **7** with di-*n*-propylcuprate in THF effected exclusive (79%) S_N2' displacement at the allylic position,[8] without competing coupling at the brom-

(1) For reviews of heteroatom-substituted allyl carbanions see: (a) Ahlbrecht, H. *Chimia* **1977**, *31*, 391; (b) Seabach, D.; Geiss, K.-H. In "New Applications of Organometallic Reagents in Organic Synthesis"; Seyferth, D., Ed.; Elsevier: Amsterdam, 1976; p 1; (c) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701.

(2) For a thorough accompilation of various heterosubstituted allyl anions see: Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004.

(3) (a) Kharasch, M. S.; Sternfield, E. *J. Am. Chem. Soc.* **1939**, *61*, 2318. (b) Kharasch, M. S.; Nudenberg, W.; Sternfield, E. *Ibid.* **1940**, *62*, 2035. (c) Kharasch, M. S.; Nudenberg, W.; Fields, E. K. *Ibid.* **1944**, *66*, 1276.

(4) Cf.: (a) Wenkert, E.; Kakvzis, P., Dynak, J. N.; Swindell, C. S. *Synth. Commun.* **1979**, *9*, 11; (b) Olofson, R. A.; Doughert, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(5) α,α-Dihaloallyllithium has witnessed broad utility, however; for examples see: (a) Moss, R. A.; Munjal, R. C. *Synthesis* **1979**, 425; (b) Hiyama, T.; Shinoda, M.; Nozaki, H. *Tetrahedron Lett.* **1978**, 771; (c) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1588; (d) Seyferth, D.; Murphy, G. J.; Mauzé, B. *J. Am. Chem. Soc.* **1977**, *99*, 5317.

(6) In a typical reaction, a tetrahydrofuran (35 mL) solution of lithium diisopropylamide [10.0 mmol, generated via *n*-BuLi (10.0 mL of a 1.0 M solution in pentane) addition to diisopropylamine (1.212 g, 12.0 mmol)] was then added slowly via syringe to a tetrahydrofuran (20 mL) solution of methallyl chloride (0.900 g, 10.0 mmol) and 1,4-dibromobutane (3.240 g, 15.0 mmol) at −78 °C under an inert atmosphere. The solution was stirred at −78 °C for an additional 15 min and then quenched by dilution with pentane (50 mL) and addition to a saturated aqueous solution of ammonium chloride (50 mL). The aqueous solution was extracted with ether (50 mL), the combined organic layers were dried over potassium carbonate, and the solvents were removed in vacuo. The residue was chromatographed [silica gel (40 g); pentane eluant] to give 7-bromo-3-chloro-1-heptene[7] (1.495 g, 71%). If the alkyl bromide alkylating agent is the limiting reagent, then the following alternate reactant ratio should be employed under identical reaction conditions to maximize yields: lithium diisopropylamide (1.3 equiv), allyl chloride (1.6 equiv), alkyl bromide (1.0 equiv.).

(7) All new compounds synthesized possess infrared, proton and carbon-13 nuclear magnetic resonance, and mass spectra fully in accord with their assigned structures. Olefin geometric isomer ratios (*E*/*Z*) were determined by capilliary column vapor-phase chromatography and are reproducible within ±3%.

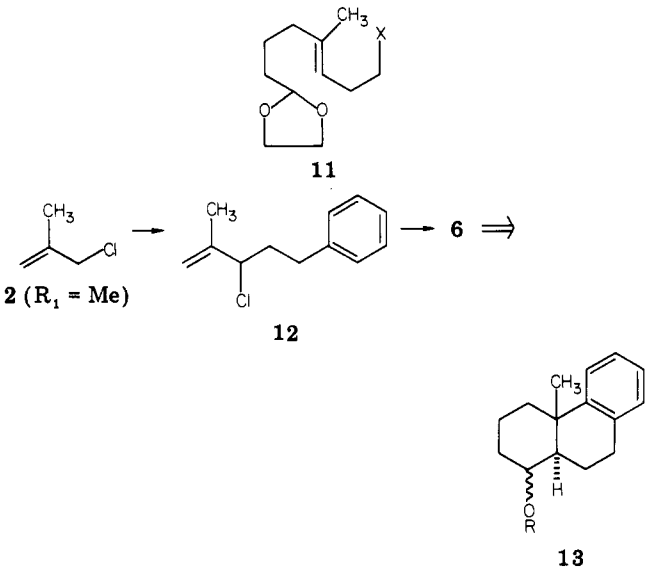
(8) For related examples see: (a) Posner, G. H. *Org. React.* **1974**, *22*, 253; (b) Anderson, R. J.; Henrick, C. A.; Siddall, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 735.

0022-3263/81/1946-1504$01.25/0

Table I. Examples of Allyl Chloride Alkylation[7]

allyl chloride	alkyl bromide	product	% yield
3-chloropropene	1-bromobutane	3-chloro-1-heptene	81
	1,3-dibromopropane	6-bromo-3-chloro-1-hexene	72
	1,4-dibromobutane	7-bromo-3-chloro-1-heptene	84
	1,6-dibromohexane	9-bromo-3-chloro-1-nonene	88
	1,10-dibromodecane	13-bromo-3-chloro-1-tridecene	85
	2-bromopentane	3-chloro-4-methyl-1-heptene	⩽10
	1,4-dibromopentane	7-bromo-3-chloro-1-octene	78
2-methyl-2-chloropropene	1-bromobutane	3-chloro-2-methyl-1-heptene	85
	2-phenyl-1-bromoethane	3-chloro-2-methyl-5-phenyl-1-pentene	53
	1,3-dibromopropane	6-bromo-3-chloro-2-methyl-1-hexene	66
	1,4-dibromobutane	7-bromo-3-chloro-2-methyl-1-heptene	71
(*E*)-1-chloro-2-butene	1-bromobutane	(*E*)-4-chloro-2-octene	55
	1,4-dibromobutane	(*E*)-8-bromo-4-chloro-2-octene	71

Scheme II



ide site, affording dodecenyl bromide **8** with predominant *E* olefin stereochemistry [*n*-PrMgBr (2.0 equiv), CuBr·SMe_2 (1.0 equiv), THF, −79 °C; *E*/*Z* = 85/15, 80%]. Conversion of bromide **8** into the corresponding acetate completed the synthesis of the natural product [NaOAc (5.0 equiv), AcOH, 80 °C; *E*/*Z* = 83/17, 76%]. In analogous fashion, allyl chloride anion was alkylated with 1,10-dibromodecane, affording **9** (85%) which was treated sequentially with lithium dimethylcuprate in THF [**10**, *E*/*Z* = 87/13, 71%] and sodium acetate in acetic acid to afford the *S. littoralis* sex pheromone **5** (*E*/*Z* = 85/15, 81%).

For an approach to steroids and polycyclic diterpenoids employing polyene cyclization,[9] we required suitably substituted and functionalized acetal derivatives possessing the general skeleton **11**. α-Chloromethallyl anion alkylation provides a direct, two-step entry into these substrates which we illustrate by the synthesis of a representative aryl acetal **6**, a polyene precursor to the polycyclic nucleus **13** of the diterpenoid podocarpane, abietane, primarane, and cassane families[10] (Scheme II). Thus, in situ methallyl chloride anion generation and alkylation with phenethyl bromide afforded exclusively the α-alkylation product **12** (53%). Subsequent treatment of **12** with the heterocuprate derived from 3-(ethylenedioxy)-1-propyl magnesium bromide[11] produced aryl acetal **6** with complete (>97%) S_N2' regiochemistry and high *E* olefin stereochemistry[8] [3-(ethylenedioxy)-1-propylmagnesium bromide (1.1 equiv), CuBr·SMe_2 (1.0 equiv), THF, −78 °C; *E*/*Z* = 78/22, 83%].

The facile syntheses of the acyclic, *E* olefinic frameworks of the natural products **4** and **5** and the model compound **6** establish the viability and synthetic utility of α-haloallyllithium agents. Certain functional groups with highly acidic protons would appear not be be compatible with this procedure for in situ anion generation–alkylation due to competing deprotonation and alkylation. However, allyl chloride (and bromide) appear to possess kinetic acidity enhanced over ketone and perhaps related carbonyl functions.[13] Within the constraints of the current methodology for their in situ formation, α-haloallyl anions should possess broad application in the construction of carbon skeletons. It should be noted that the ease with which allyl and benzyl halide[12] α-metalation occurs suggests that such deprotonation and subsequent "self-consumptive" alkylation processes could intervene in numerous synthetic operations. Indeed, we have observed the formation of allyl and benzyl halide[12] "dimers" as reaction products in the alkylation of several enolate anions and dianions and in the in situ generation of diverse carbanion species. We are currently examining the development of alternate (nonmetalation) modes for the generation of these species and thereby the extension of this chemistry to more complex α-halo allyl anion precursors and the implementation of this allyl chloride α-alkylation–cuprate displacement approach in the synthesis of more complex natural products.

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Registry No. **4** (isomer 1), 16695-41-3; **4** (isomer 2), 14959-86-5; **5** (isomer 1), 33189-72-9; **5** (isomer 2), 20711-10-8; **6** (isomer 1), 76599-50-3; **6** (isomer 2), 76599-51-4; **7**, 76599-52-5; **8** (isomer 1), 76599-53-6; **8** (isomer 2), 71655-20-4; **9**, 76599-54-7; **10** (isomer 1),

(9) For reviews of polyene cyclization see: (a) Johnson, W. S. *Bioorganic Chem.* **1976**, *5*, 92; (b) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9; (c) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1.

(10) For a related approach to the tetracyclic members of the α,β-unsaturated lactone class of diterpenes see: van Tameln, E. E.; Taylor, E. G.; Herden, T. M.; Kreft, A. F., III *J. Am. Chem. Soc.* **1979**, *101*, 7423.

(11) Cf.: Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217.

(12) (a) Hauser, C. R.; Brasen, W. R.; Skell, P. S.; Kantor, S. W.; Bradhag, A. E. *J. Am. Chem. Soc.* **1956**, *78*, 1653. (b) Hoeg, D. F.; Lusk, D. I. *Ibid.* **1964**, *86*, 928. (c) Hoeg, D. F.; Lusk, D. I. *J. Organomet. Chem.* **1966**, *5*, 1. (d) Caubere, P. *Tetrahedron* **1970**, *26*, 2637.

(13) When a mixture of allylbromide (1.0 equiv) and cyclohexanone (1.0 equiv) in tetrahydrofuran at −78 °C was treated with lithium diisopropylamide (0.5 equiv), 3-bromo-1,5-hexadiene (~85%) was the sole product isolated. These data suggest that allyl bromide is kinetically more acidic than cyclohexanone and that allyl bromide is a more effective electrophile than cyclohexanone for these allylic anions. Related results occur for allyl chloride.

76599-55-8; **10** (isomer 2), 76599-56-9; **12**, 76599-57-0; 3-chloropropene, 107-05-1; 2-methyl-3-chloropropene, 563-47-3; (*E*)-1-chloro-2-butene, 4894-61-5; 1-bromobutane, 109-65-9; 1,3-dibromopropane, 109-64-8; 1,4-dibromobutane, 110-52-1; 1,6-dibromohexane, 629-03-8; 1,10-dibromodecane, 4101-68-2; 2-bromopentane, 107-81-3; 1,4-dibromopentane, 626-87-9; 2-phenyl-1-bromoethane, 103-63-9; 3-chloro-1-heptene, 55682-98-9; 6-bromo-3-chloro-1-hexene, 76599-58-1; 7-bromo-3-chloro-1-heptene, 76599-59-2; 9-bromo-3-chloro-1-nonene, 76599-60-5; 13-bromo-3-chloro-1-tridecene, 76599-54-7; 3-chloro-4-methyl-1-heptene, 76599-61-6; 7-bromo-3-chloro-1-octene, 76599-62-7; 3-chloro-2-methyl-1-heptene, 71518-90-6; 3-chloro-2-methyl-5-phenyl-1-pentene, 76599-57-0; 6-bromo-3-chloro-2-methyl-1-hexene, 76599-63-8; 7-bromo-3-chloro-2-methyl-1-heptene, 76599-64-9; (*E*)-4-chloro-2-octene, 76599-65-0; (*E*)-8-bromo-4-chloro-2-octene, 76599-66-1; [3-(ethylenedioxy)-1-propyl]magnesium bromide, 76599-67-2.

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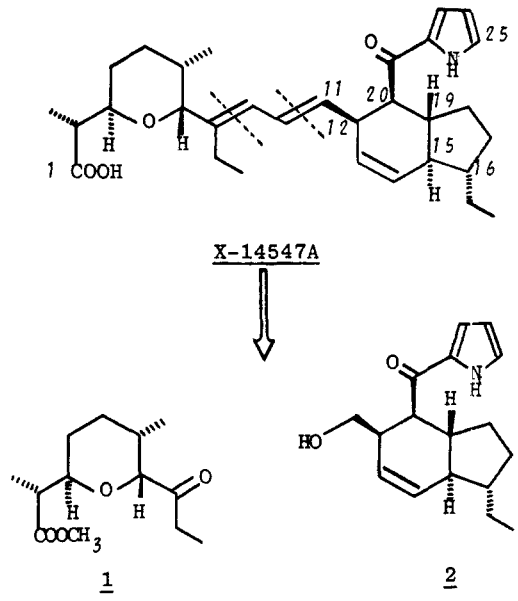
Ionophore Antibiotic X-14547A. Degradation Studies and Stereoselective Construction of the "Right Wing" (C_{11}-C_{25} Fragment) by an Intramolecular Diels-Alder Reaction[1]

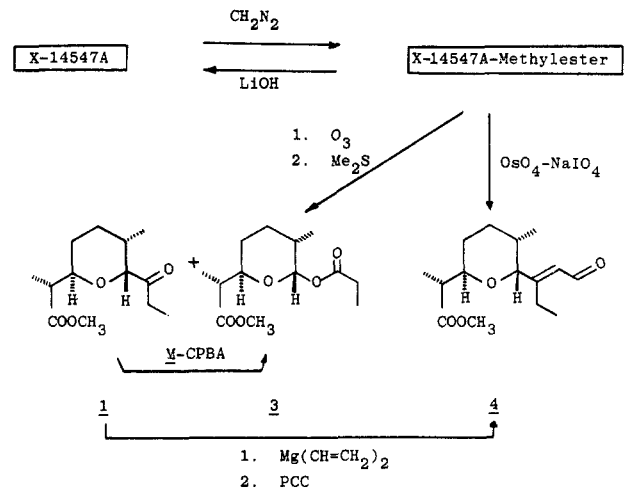
Summary: Studies directed toward the total synthesis of the ionophore antibiotic X-14547A are reported. Degradation methods led to a number of "left-wing" fragments, whereas synthetic operations led to a "right-wing" fragment, in a highly efficient and stereoselective manner via an intramolecular Diels-Alder reaction.

Sir: The ionophore antibiotics are becoming an increasingly interesting class of naturally occurring substances with regard to both biology[2] and synthesis.[3] X-14547A is a novel member of this family of compounds, recently isolated from *Streptomyces antibioticus* NRRL8167 by Westley et al.[4] and fully characterized by spectroscopic and X-ray techniques. Its biological properties include antibiotic activity against gram-positive bacteria, antihypertensive and antitumor activities, and improvement of ruminant feed utilization.[4,5] Structurally, X-14547A is a rather unique assembly of functionalities, including the rare frameworks of pyrrolylcarbonyl[6] and trans-fused tetrahydroindan systems.

Scheme I



Scheme II



A possible retrosynthetic analysis of X-14547A leads to a convergent scheme requiring the construction and coupling of fragments **1** and **2** (Scheme I). In this communication we report (I) the first degradation studies on X-14547A leading to the "left-wing" fragment **1** and (II) synthetic studies leading stereoselectively to the "right-wing" fragment **2**. The degradation studies provide useful information for an eventual total synthesis, whereas the synthetic work indicates solutions to the stereoselective construction of the novel tetrahydroindan and pyrrolylcarbonyl systems of X-14547A.

(I) Degradation Studies. A number of asymmetric centers of X-14547A are potentially vulnerable to epimerization, and it was of crucial interest to us to determine whether any damage to the stereochemistry was inflicted during hydrolysis of X-14547A methyl ester to the natural product. To answer this question we prepared the methyl ester of the antibiotic (CH_2N_2, ether, 0 °C, 100%) and subjected it to basic hydrolysis (10 equiv of LiOH, 1:1

(1) This work was first described at the 2nd Chemical Congress of the North American Continent, Las Vegas, Aug 1980, Abstract No. ORGN 156.

(2) Reviews: (a) Westley, J.W. *Adv. Appl. Microbiol.* **1977**, *22*, 177; (b) Pressman, B.C.; *Annu. Rev. Biochem.* **1976**, *45*, 501.

(3) Lasalocid A: (a) Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M,; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933; (b) Ireland, R. E.; Thaisrivongs, S.; Wilcox, C. S. *Ibid.* **1980**, *102*, 1155. Monensin: (c) Schmid, G.; Fukuyama, T.; Akasaka, K., Kishi, Y, *Ibid.* **1979**, *101*, 259; Fukuyama, T.; Wang, C-L.J.; Kishi, Y. *Ibid.* **1979**, *101*, 260; Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *Ibid.* **1979**, *101*, 262; (d) Collum, D. B.; McDonald, J. H., III; Still, W. C. **1980**, *102*, 2117; Collum, D. B.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2118; Collum, D. B.,; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2120. Calcimycin (A-23187): (e) Evans, D. A.; Sacks, C. F.; Kleschick, W. A.; Taber, T. R. **1979**, *101*, 6789; (f) Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.

(4) (a) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6786. (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. (d) Westley, J. W.; Liu, C.-M U.S. Patent 4 100 171, 1978.

(5) Westley, J. W., personal communication.

(6) The only other known polyether antibiotic containing the pyrrolylcarbonyl functionality is calcimycin (A-23187): Chaney, M. O; Demaro, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932.

0022-3263/81/1946-1506$01.25/0