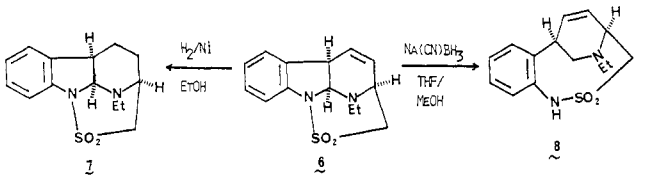
before coupling could occur. On the other hand, it is known[11] that para electron-withdrawing groups decrease the rate of the Claisen rearrangement. A decision concerning the mechanism will have to await further results.

Compound **3** (X = H) can be N-ethylated (Et_3O^+ BF_4^-) to the hydrofluoroborate salt (94%), mp 186 °C, which gives **6**, mp 158–159 °C, with alkali. The tertiary amine can be reduced to one of two products, depending on the reducing agent: H_2/Ni in ethanol gives the tetracyclic piperidine derivatives **7** (40%), mp 174 °C, while NaCN-(BH_4) in THF/MeOH gives **8** (75%), mp 107–108 °C.



The structure of the latter is assigned on the basis of its spectral properties[12] and by analogy with the cleavage of 5-substituted 3-(diethylamino)-1,2-benzothiazepine 1,1-dioxide with $LiAlH_4$.[13] Similar reduction of **3** (X = H) itself gave the corresponding **8** (NH instead of NEt), which exhibited only NH groups (no NH_2) in its IR spectrum, confirming the proposed direction of ring cleavage. Compounds **8** are novel bridged nine-membered sultam rings whose properties are being studied.

Acknowledgment. This work was supported by NSF Latin/American Cooperative Science Grant INT-8111977 (to R.A.A.) and by a grant from CNPq (Brazil) (to J.M.), for which we are grateful.

Registry No. **1** (X = H), 105019-32-7; **1** (X = Cl), 105019-34-9; **1** (X = NO_2), 105019-36-1; **2** (X = H), 105019-38-3; **2** (X = Cl), 105019-40-7; **2** (X = NO_2), 105019-42-9; **3** (X = H), 105019-43-0; **3** (X = Cl), 105019-44-1; **3** (X = NO_2), 105019-45-2; **5**, 105019-50-9; **6**, 105019-46-3; **6**·(H^+·BF_4^-), 105088-02-6; **7**, 105019-47-4; **8**, 105019-48-5; **8** (NH deriv.), 105019-49-6; $MeSO_2Cl$, 124-63-0.

Supplementary Material Available: Single-crystal X-ray analytical data (temperature factors, atomic coordinates, bond lengths and angles) for compound **3** (10 pages). Ordering information is given on any current masthead page.

(11) Gilchrist, T. L.; Storr, R. C. *Organic Reactions and Orbital Symmetry*, 2nd ed.; Cambridge University: Cambridge, 1979; p 273.
(12) IR ($CHCl_3$) 3380 (NH), 1320, 1130 cm^{-1} (SO_2); ^1H and ^{13}C NMR ($CDCl_3$) suggests the molecule exists in two conformations in solution.
(13) Abramovitch, R. A.; More, K. M.; Shinkai, I.; Srinivasan, P. C. *Heterocycles* **1976**, *5*, 95.

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Synthetic Elaboration of Diosphenols: Replacement of Hydroxyl by Halogen

Summary: Replacement of the enolic oxygen of diosphenols by chlorine or bromine may be achieved by treating the derived dimethylthiocarbamate with lithium chloride or bromide in hot acetonitrile/acetic acid.

Sir: In connection with applications of the diosphenol Claisen rearrangement[1] to natural products synthesis we sought to convert the products of this reaction, namely α-hydroxy-α,β-unsaturated ketones, to α-halo-α,β-unsaturated ketones.[2] Traditional reagents[3] (e.g., $SOCl_2$, $POCl_3$, PCl_5) for replacing hydroxyl by chloro or for preparing vinyl chlorides from monoketones utterly fail for diosphenols; after the fact this is not surprising since nucleophilic displacements at unactivated sp^2 carbon are very difficult, even with very good leaving groups.[4] We now report a new and very mild procedure for this transformation which we believe is based on the ability of the thiocarbamoyloxy group to function as both nucleofuge and nucleophile. The method is illustrated in (Scheme I) for the conversion of 1,2-cyclopentanedione into the known[5] 2-chloro-2-cyclopenten-1-one in 80% overall yield.

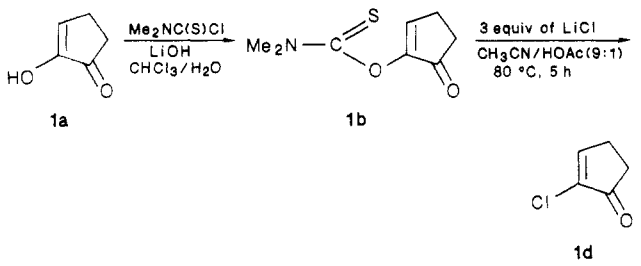
Thiocarbamoylation can be effected under several conditions (all under nitrogen): (a) sequential treatment at room temperature of a THF or DME solution of the diosphenol with 1.1 equiv of sodium hydride and 1.2 equiv of dimethylthiocarbamoyl chloride; (b) sequential treatment of a 1 M acetone solution of the diosphenol with 1 equiv of 10 M aqueous sodium hydroxide solution and 1 equiv of solid dimethylthiocarbamoyl chloride followed by heating at reflux for 30 min; (c) dropwise addition at room temperature of a concentrated chloroform solution of 1.2 equiv of dimethylthiocarbamoyl chloride to a solution of diosphenol in 1.2 equiv of 1 M aqueous lithium hydroxide solution. The last two procedures are more convenient than the first and give 70–85% yields of crystalline derivatives after a rapid filtration chromatography.

Replacement of oxygen by halogen is effected by treating 0.2 M solutions of dimethylthiocarbamates in acetonitrile/acetic acid 9:1 with 3 equiv of lithium bromide or chloride and heating at reflux (80 °C) for 5–24 h.[6] Workup consists of evaporation of most of the solvent, dilution with

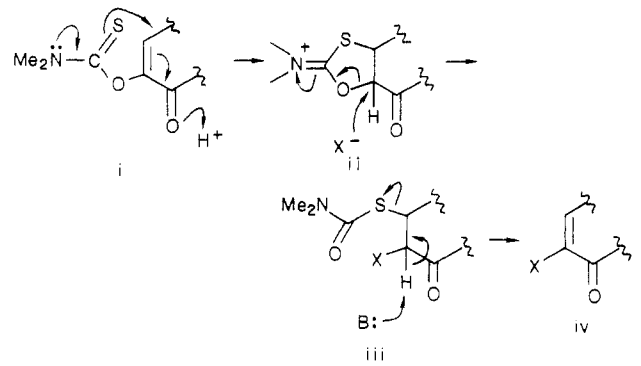
(1) (a) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803. (b) Dauben, W. G.; Ponaras, A. A.; Chollet, A. *J. Org. Chem.* **1980**, *45*, 4413. (c) Ponaras, A. A. *Tetrahedron Lett.* **1983**, *24*, 3. (d) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866.
(2) The synthetic utility of this array is well documented: (a) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088. (b) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855 and references therein. (c) Deprés, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036 and references therein. (d) Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205. (e) Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7607. (f) Kočor, M.; Kroszcyński, W. *Synthesis* **1976**, 813.
(3) (a) Brown, G. S. In *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Wiley-Interscience: New York, 1971; Part 1, p 593. (b) Stroh, R. In *Houben-Weyl Methoden der Organischen Chemie*; Müller, E., Ed.; Georg Thieme: Stuttgart, 1962; Vol. 5/3, p 830 ff.
(4) If the leaving group is activated by conjugation to an electron-withdrawing group (as in 1,3-dicarbonyl compounds and their derivatives) then substitution by addition–eleimination can occur. Diosphenols are somewhat analogous to phenols where, without activation, hydroxyl can be replaced by halogen only under drastic conditions: Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607 and references therein.
(5) Mitsuhashi, K.; Nomura, K. *Chem. Pharm. Bull.* **1965**, *13*, 951.
(6) The use of less solvent is recommended for large-scale reactions. Inferior yields of 2-halo enones are obtained if either zinc or tetraethylammonium halides are used or if the reaction is conducted in pure acetic acid at 80 °C. The chief side reaction under these circumstances is O–S interchange (thiono–thiolo rearrangement—cf. the Newman–Kwart reaction, ref 7).
(7) (a) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980. (b) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410.

0022-3263/86/1951-4741$01.50/0

Scheme I



Scheme II



ether and washing with saturated aqueous sodium bicarbonate solution. Table I summarizes the results from five diosphenols.

We have, as yet, been unable to replace hydroxyl by fluoro using this methodology. Thus treatment of **3b** with cesium fluoride (lithium fluoride is insoluble) in acetonitrile–acetic acid or with pyridinium poly(hydrogen fluoride)[8] in acetonitrile gave no detectable α-fluoro enone.[9] The reaction of diosphenol dialkylthiocarbamates with iodide ion results in replacement of hydroxyl by *hydrogen*;[1c] we will report the details of this reaction in a future publication.

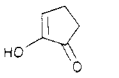
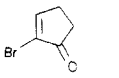
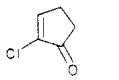
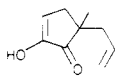
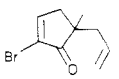
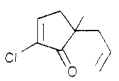
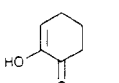
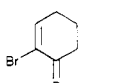
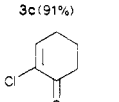
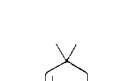
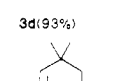
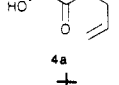
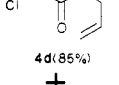
The rationale for investigating dialkylthiocarbamates as "activating groups" in this reaction was based on the high nucleophilicity of sulfur in thioamides. If intramolecular conjugate addition of sulfur to the α,β-unsaturated ketone system were to occur,[11] the resulting product ii could react with nucleophiles to generate iii. Elimination of dimethylthiocarbamic *S*-acid (or carbonyl sulfide and dimethylamine) would give iv (Scheme II).

In support of this hypothesis are three observations:

1. Leaving groups with poor prospect for cyclization in the manner i → ii are unreactive. Thus the brosylate, dimethylcarbamate, and even the phenylthionocarbonate derivatives of **2a** are inert to prolonged heating with lithium chloride in acetic acid at 120 °C.

2. The reaction is very sensitive to steric hindrance near the β-carbon, consistent with initial formation of ii. Thus, whereas **4b** undergoes substitution with LiCl in high yield (albeit slowly), **5b** does not. Diosphenol dialkylthiocarbamates bearing a substituent *on* the β-carbon are much less reactive than their unsubstituted counterparts and undergo several interesting reactions when treated with lithium halides in acetic acid.

Table I

1,2-diketone[a]	product (yield[b])	pertinent data[c]
 1a	 1c(90%)	NMR δ 2.3–2.9 (m, 4 H), 7.77 (t, J = 2.5 Hz, 1 H); IR 1718, 1590 cm^{-1}; mp 36–37 °C (lit.[d] mp 39–39.5 °C)
	 1d(96%)	NMR δ 2.3–2.9 (m, 4 H), 7.56 (t, J = 3 Hz, 1 H); IR 1723, 1600 cm^{-1}; *e*
 2a	 2c(90%)	NMR δ 1.16 (s, 3 H), 2.25 (d, J = 7 Hz, 2 H), 2.56 (dd, J = 3, 6 Hz, 2 H), 4.8–6.0 (m, 3 H), 7.77 (t, J = 3 Hz, 1 H); IR 1715, 1587 cm^{-1}
	 2d(96%)	NMR δ 1.16 (s, 3 H), 2.24 (d, J = 7 Hz, 2 H), 2.57 (dd, J = 3.5, 6 Hz, 2 H), 5.0–6.1 (m, 3 H), 7.52 (t, J = 3.5 Hz, 1 H); IR 1716, 1604 cm^{-1}
 3a	 3c(91%)	NMR δ 1.8–2.3 (m, 2 H), 2.3–2.8 (m, 4 H), 7.42 (t, J = 4.5 Hz, 1 H); IR 1682, 1598 cm^{-1}; mp 66–71 °C (lit.[f] mp 69–71 °C)
	 3d(93%)	NMR δ 1.8–2.3 (m, 2 H), 2.3–2.8 (m, 4 H), 7.12 (t, J = 4.5 Hz, 1 H); IR 1686, 1607 cm^{-1}; mp 67–68 °C (lit.[e] mp 67–72 °C)
 4a	 4d(85%)	NMR δ 1.18 (2 s, 6 H), 1.26 (s, 3 H), 1.8 (m, 2 H), 2.32 (d, J = 7 Hz, 2 H), 4.8–5.1 (dd, J = 3, 8 Hz, 1 H), 5.18 (s, 1 H), 5.3–6.1 (m, 1 H), 6.82 (s, 1 H); IR 1694, 1641, 1611 cm^{-1}
 5a	 5d(10%[g])	NMR δ 0.93 (s, 3 H), 1.01 (s, 9 H), 1.5–1.8 (m, 3 H), 2.23 (d, J = 7 Hz, 2 H), 4.8–5.1 (dd, J = 3, 8 Hz, 1 H), 5.19 (s, 1 H), 5.4–6.1 (m, 1 H), 7.07 (t, J = 2 Hz, 1 H); IR 1694, 1638, 1603 cm^{-1}

[a] Diketones **1a** and **3a** are well-known substances—see, for example: Hesse, G.; Krehbiel, G. *Ann.* **1955**, *593*, 35. Diketones **2a**, **4a**, and **5a** are products of diosphenol Claisen rearrangements (ref 1). [b] Yields for **2c**, **2d**, **4d**, and **5d** were determined by isolation; yields for **1c**, **1d**, **3c**, and **3d** were determined by gas chromatography with a calibrated internal standard. [c] NMR spectra were measured at 60 or 90 MHz in deuteriochloroform; IR spectra were taken as thin films or chloroform solutions. All new compounds were characterized by HRMS. [d] Reference 5. [e] Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1454. [f] Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544. [g] The major product from this reaction is O–S interchange (see footnote 6).

3. The reaction is acid-catalyzed. Thus treatment of **2b** with 3 equiv of LiCl in 1-butanol at 120 °C for 15 h produced no change; addition of 3 equiv of acetic acid gave, after an additional 19 h of heating, a 90% yield of **2d**.

The fact that substitution occurs readily with **4b** precludes general mechanisms requiring deconjugation of the enone system in some step.[12] Experiments designed to further define the mechanism and utility of these reactions are in progress.

Acknowledgment. We thank the National Science Foundation for their generous support. FT-IR and FT-

(8) Olah, G. A.; Welch, J. *J. Am. Chem. Soc.* **1975**, *97*, 208.

(9) Authentic 2-fluoro-2-cyclohexen-1-one (ref 10) is stable to the reaction conditions.

(10) Greenlee, M. L.; Fritzen, E. L., Jr.; Swenton, J. S. *J. Org. Chem.* **1978**, *43*, 4512.

(11) Second-row elements such as sulfur can cyclize by a 5-endo-trig pathway: Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(12) Initial deconjugation is probably involved in some (ref 12a,b) but not all (ref 12c) substitution reactions of α-halo-α,β-unsaturated ketones with nucleophiles: (a) Koga, T.; Tomoeda, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1848. (b) Koga, T.; Nogami, Y.; Toh, N.; Nishimura, K. *Synth. Commun.* **1983**, *13*, 1013. (c) Cromwell, N. H.; Eby, H. H.; Capps, D. B. *J. Am. Chem. Soc.* **1951**, *73*, 1230.

NMR spectra were run at the CUA Chemical Instrumentation Center.

Registry No. **1a**, 10493-98-8; **1c**, 10481-34-2; 1d, 3400-89-3; **2a**, 77426-28-9; **2a** (brosylate), 77426-30-3; **2a** (dimethylcarbamate), 104994-76-5; **2a** (phenylthionocarbonate), 104994-77-6; **2c**, 104994-72-1; **2d**, 104994-73-2; **3a**, 10316-66-2; **3b**, 104994-78-7; **3c**, 50870-61-6; **3d**, 3400-88-2; **4a**, 104994-71-0; **4d**, 104994-74-3; **5a**, 86137-11-3; **5d**, 104994-75-4; dimethylthiocarbamoyl chloride, 16420-13-6.

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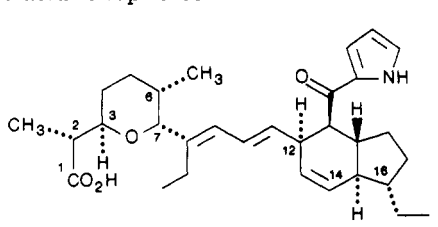
An Efficient Enantioselective Total Synthesis of (-)-X-14547A (Indanomycin)

Summary: A highly efficient and stereocontrolled enantioselective total synthesis of the antibiotic ionophore X-14547A (indanomycin) (1) is described. A particularly concise approach to the key pyranaldehyde intermediate **3** features the use of reductive lithiation to append the axial C(7) pyran side chain. A Wittig reaction was employed to couple the two major subunits **3** and **4** followed by intramolecular [4 + 2] cycloaddition to complete the framework.

Sir: The ionophoric antibiotics represent a stereochemically complex and synthetically challenging class of biologically important molecules.[1] In 1978, X-14547A (indanomycin), a novel member of this group of ionophores, was isolated at Hoffmann-LaRoche, and the structure and absolute configuration were established by Westley.[2] X-14547A exhibits activity against Gram-positive bacteria as well as antitumor and antihypertensive activity and functions as an effective growth promoter for ruminants.[5b] X-14547A also has the ability to complex and transport mono-, di-, and trivalent metal cations, an uncommon property among antibiotics except for a small number of carboxylic acid ionophores.

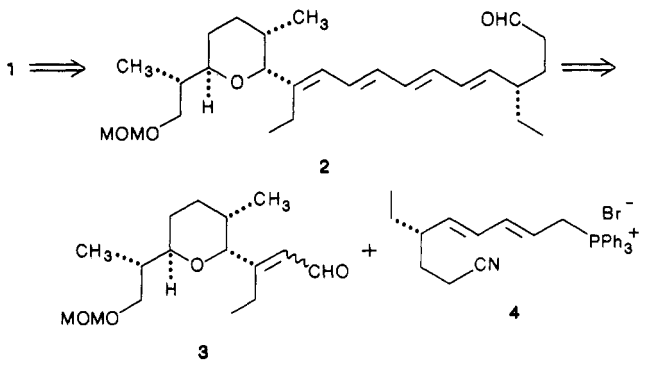


1

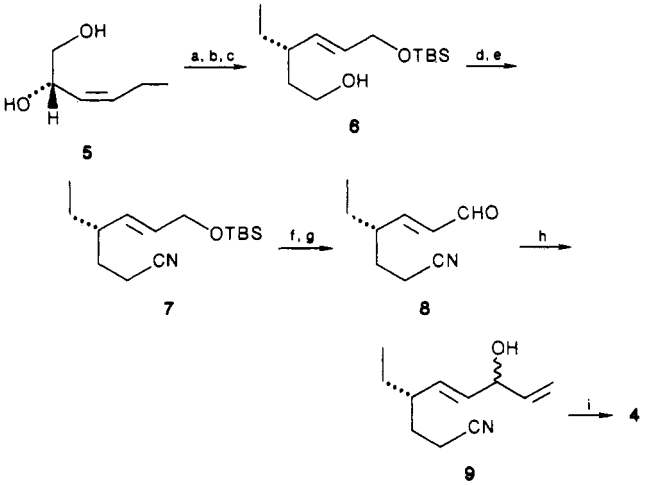
The unusual structural features of X-14547A, such as the 1(*E*),3(*E*)-butadienylhexahydroindene unit (one of two natural products to contain a trans-fused hexahydroindene ring system[3]) and the α-acylpyrrole (common to only a few other ionophores such as calcimycin (A-23187)[4]), have stimulated a number of recent synthetic studies, two of which have culminated in a total synthesis.[5i,l]

As our retrosynthetic analysis of **1** illustrates (Scheme I), we elected to utilize a tandem Wittig reaction-intramolecular Diels-Alder cycloaddition sequence to assemble the hexahydroindene framework late in the synthesis. A similar strategy was successfully employed by Roush and co-workers in their recent partial synthesis.[5g,j] It was thus envisioned that tetraene **2**, the required substrate for the Wittig-cycloaddition process, would become available via

Scheme I



Scheme II[a]



[a] Reagents: (a) TBDSCl (1.1 equiv), Et_3N (1.5 equiv), DMAP (catalytic), CH_2Cl_2, 23 °C, 10 h; (b) $CH_3C(OCH_3)_3$ (2.8 equiv), $CH_3CH_2CO_2H$ (catalytic), xylenes, Δ, 19 h; (c) *i*-Bu_2AlH (2.2 equiv), THF, -70 → 23 °C, 1.5 h; (d) *p*-TsCl (1.1 equiv), pyridine-CH_2Cl_2 (1:1), 23 °C, 10 h; (e) KCN (2.1 equiv), Me_2SO, 55 °C, 5 h; (f) *n*-Bu_4NF (1.04 equiv), THF, 0 °C, 20 min; (g) PDC (2 equiv), CH_2Cl_2, 23 °C, 12 h; (h) CH_2=$CHMgBr$ (3 equiv), THF, -78 → 23 °C, 30 min; (i) Ph_3P-HBr (1.1 equiv), CH_2Cl_2, 23 °C, 10 min.

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