As our radical progenitors, we decided to employ 2-deoxy-2-halogeno glycosides, which are readily prepared from glycals by routine transformations, the iodine atom being introduced by the stereoselective process developed by Thiem and co-workers.[13] Thus, substrates **7** and **8** were prepared from the known glycals **5**[14] and **6**[15] in three steps as shown in Scheme II. In a similar fashion, the homologated analogues **10** and **11** were prepared from glycal **6** in seven steps in 31% combined overall yield.

Treatment of **7** with tri-*n*-butyltin hydride[16] led to the desired oxabicyclo[2.2.1]heptanes **12a** and **13a** (R^1 = Bz, R^2 = Et) as a 1.8:1 isomeric mixture in a surprising 91% isolated yield (Scheme III). The crystalline bicyclic products were easily separated by flash chromatography, and the stereochemical assignments derived from NMR experiments (COSY, HETCOR, NOE) indicated that in the major isomer the ester group lay on the less crowded side of the bicyclic structure. An expected increase in the stereoselectivity of the cyclization was achieved with the corresponding *tert*-butyl ester (*E*)-**8** which afforded a 4.5:1 mixture of bicyclic compounds **12b** and **13b** (R^1 = Bn, R^2 = *t*-Bu). No appreciable difference in the diastereomeric ratio was observed on changing to the cis isomer (*Z*)-**8**, which gave a 5.5:1 ratio of **12b** and **13b**.

Cleavage of the pyranose rings of **12** and **13** gave the cyclopentane derivatives **14** and **15**, respectively, in nearly quantitative yields under extremely mild conditions (MeOH, pyridinium *p*-toluenesulfonate [PPTs], or camphor sulfonic acid [CSA], room temperature), indicative of the strain inherent in these molecules. The latter products corroborated the configurational assignments of precursors **12** and **13**, which had been based on NMR data.

Next, we turned our attention to the preparation of six-membered ring carbocycles (Scheme IV). The homologated substrate **10** underwent cyclization[16] to afford the corresponding oxabicyclo[2.2.2]octanes **16** in 83% isolated yield as a 3:1 mixture of epimers, desilylation of which afforded the easily separable lactone **17** and hydroxy ester **18** in a 3:1 ratio. In the case of compound **11**, a similar reaction sequence led to **20a** and **21** (5:1).

Solvolytic cleavage of the oxabicyclo[2.2.2]octyl acetals proved to be much more difficult than with the oxabicyclo[2.2.1]heptyl counterparts. However, as typified with the benzoate **20b**, reaction with 1,3-propanedithiol and boron trifluoride–etherate led to the dithioacetal **22a** in good yields.

In conclusion, the results in Schenes III and IV show that a ready and highly efficient route to cycloalkanes is available which preserves all of the rich functionality of the carbohydrate precursor, the versatile anomeric center being masked to facilitate further manipulations. This valuable strategy, successfully applied here to the formation of cyclopentanes and cyclohexanes, appears to be well-suited for further development. Accordingly, employment of other radical traps and/or the selection of different starting sugars would lead to a variety of functionalized carbocycles and brings forth the interesting possibility of forming larger ring systems. These two factors together with the use of the bicyclic framework as a template to perform stereoselective transformations are currently under consideration.

Supplementary Material Available: Spectral data for bicyclic products **12** (**a** and **b**), **13** (**a** and **b**), **17**, **18**, **20a**, and **21** and for cycloalkanes **14** (**a** and **b**), **15**, and **22** (**a** and **b**) are provided (5 pages). Ordering information is given on any current masthead page.

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(13) (a) Thiem, J.; Karl, H. *Tetrahedron Lett.* **1978**, 4999. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (b) For two recent reports on radical cyclization where the Thiem protocol is used for the generation of the precursors, see: Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691. Mesmacker, A. D.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57.

(14) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.

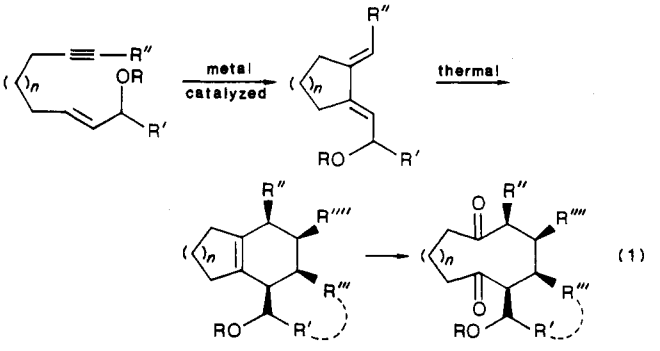
(15) Blackburne, I. D.; Burfitt, A. I. R.; Fredericks, P. F.; Guthrie, R. D. In *Synthetic Methods for Carbohydrates*; El Khadem, H. S., Ed.; American Chemical Society: Washington, DC, 1977.

(16) Typical cyclization procedure: A solution of the iodide (5.0 mM in dry toluene) was degassed with Argon and heated to reflux. *n*-Bu_3SnH (1.5 equiv) and catalytic AIBN in toluene were added via syringe pump over 2–4 h. Rotary evaporation of the solvent followed by flash chromatography (silica gel, EtOAc–petroleum ether) afforded the bicyclic products.

Hydroxy Group as a Regio- and Stereochemical Control Element for Sequential Metal-Catalyzed and Thermal Cyclizations

Summary: Stereocontrolled creation of fused ring systems from acyclic precursors invokes the powerful directive effect of the hydroxy group in which regioselectivity of a metal-catalyzed reaction totally changes and diastereofacial selectivity of the thermal step shows an unusual dependence on dienophile.

Sir: Rapid development of molecular complexity can simplify synthetic strategy.[1,2] Proceeding from acyclic substrates to polycyclic rings in two steps as outlined in eq 1 would constitute a useful approach toward such a goal.



(1)

In invoking this sequence, the allylic hydroxy or alkoxy group must serve (1) as a regiochemical control element in the metal-catalyzed cyclization to generate the conjugated 1,3-dienes rather than the nonconjugated 1,4-dienes

(1) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801; *Stud. Phys. Theor. Chem.* **1983**, *28*, 206; *Bull. Math. Biol.* **1983**, *45*, 849.

(2) For an excellent illustration, see: Wender, P. A.; vonGeldern, T. W. "Aromatic Compounds: Isomerization and Cyclization" In *Photochemistry in Organic Synthesis*; 1987; 226–55; Spec. Publ. R. Soc. Chem. 57.

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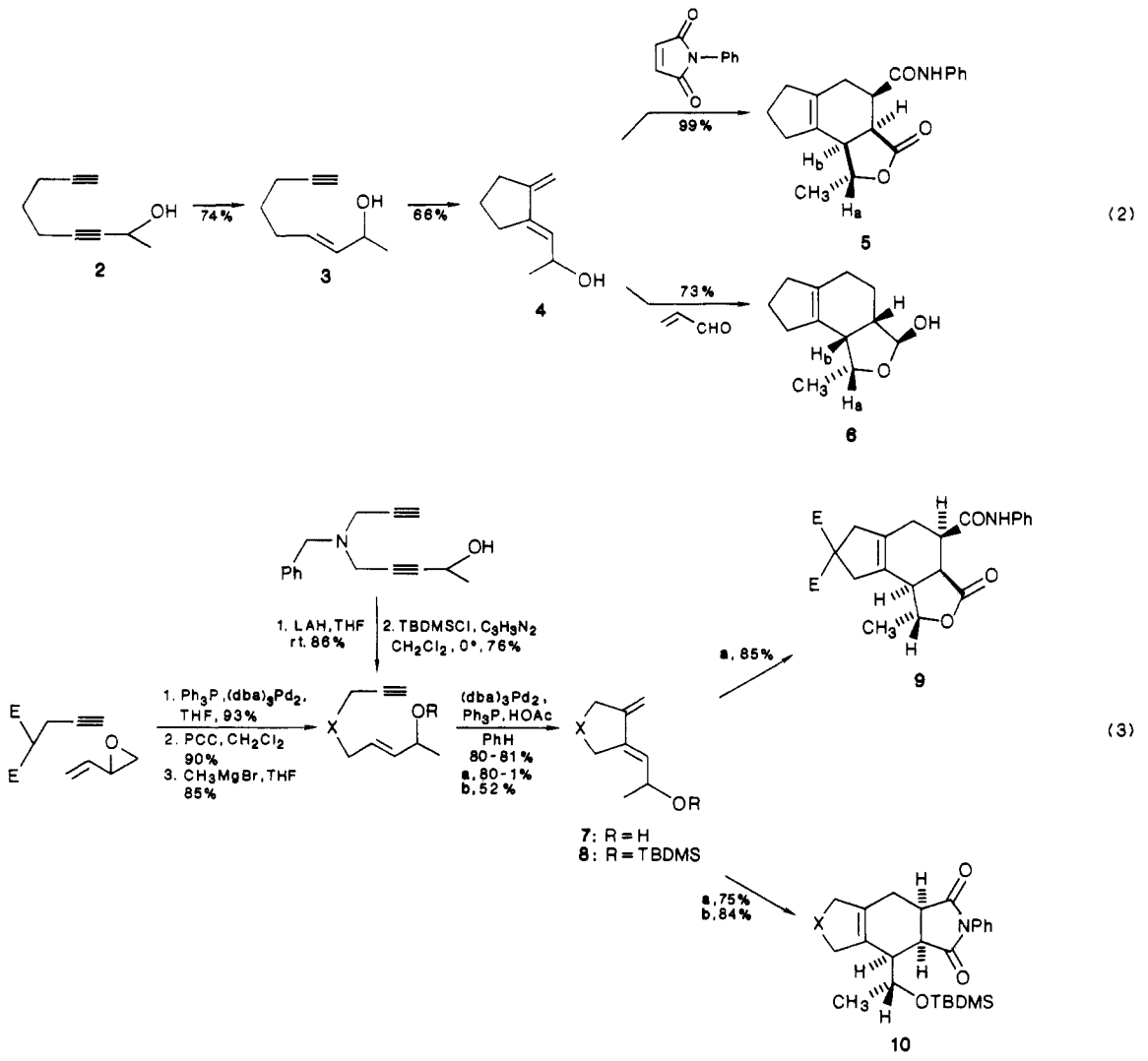


series a; X = CE_2; series b; X = NCH_2Ph

and (2) as a diastereochemical control element in directing the diastereofacial selectivity of the Diels–Alder reaction. The availability of enantiomerically pure allyl alcohol by the asymmetric reduction of alkynones[3] followed by acetylene reduction by LAH to the trans olefin[4] (or catalytic hydrogenation to the cis olefin) converts the sequence of eq 1 into an enantiocontrolled production of both the fused and medium or large ring systems.

The diynol **2** was reduced to the allyl alcohol **3** [LAH, THF, room temperature] to illustrate the sequence, and the latter was directly subjected to palladium-catalyzed cyclization[5] [2.5 mol % of $(dba)_3Pd_2 \cdot CHCl_3$, 5 mol % of Ph_3P, 5 mol % of HOAc, PhH, 60 °C]. Three features of this enyne cyclization are notable. First, the reaction succeeds without the aid of geminal substitution in the trimethylene chain to favor cyclization. Second, the hydroxy group does not need protection. Third, the hydroxy group directs the regioselectivity to exclusive formation of the 1,3-diene.[6,7] Cycloaddition of *N*-phenylmaleimide occurs at room temperature to give two adducts in the ratio of 10:1. The major adduct is assigned the structure **5** on the basis of the observation of $J_{ab} = 0$ Hz, which is consistent with the nearly 90° dihedral angle for these two protons being trans.[8] The determination of the regioselectivity of the cycloaddition of **4** with unsymmetrical dienophiles was examined utilizing acrolein. Thermal uncatalyzed cycloaddition proceeds readily at room temperature to give a single regioisomer. The observation of $J_{ab} = 8$ Hz in this adduct contrasted with the absence of coupling in **5** suggests the cis relationship as depicted in **6**.[7] *Thus, complementary diastereofacial selectivity occurs as a function of dienophile.*[9]

The direct observation of the lactone **5** led us to investigate whether acylation preceded cycloaddition and thereby influenced the diastereofacial selectivity. The related dienes **7**[7] and **8**[7] prepared as outlined in eq 3, series

(3) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. Brown, H. C.; Chandrasekharan, J.; Ramachandren, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.

(4) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595 and references therein.

(5) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.

(6) Cf. Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.

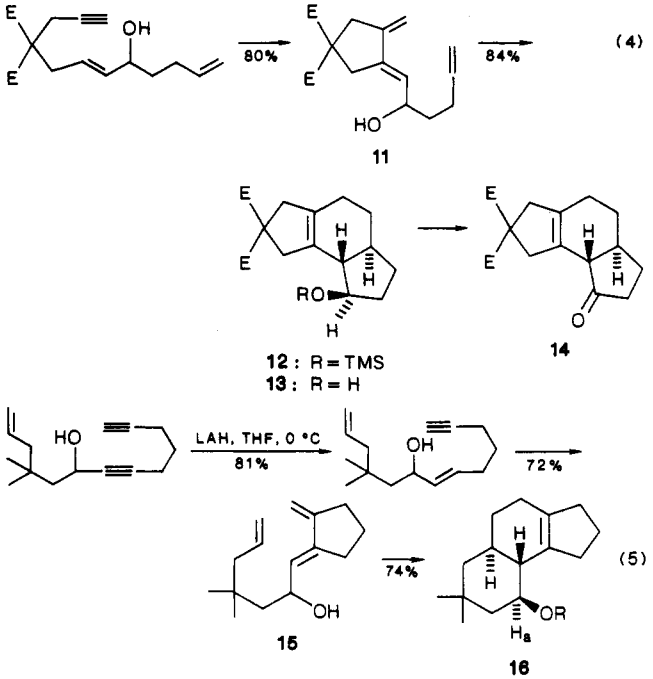
(7) All new compounds have been fully characterized spectrally and elemental composition has been established by high resolution mass spectroscopy and/or combustion analysis.

(8) (a) Although Franck et al. points out a danger in assigning stereochemistry in related systems by coupling constants, his data does support the trans coupling being smaller than the cis coupling as long as the isomeric pairs have the double bond in the same position (see entries 1–4 of Table III of this paper). (b) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.

(9) Cf. Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *Chem. Commun.* **1988**, 167. Kozikowski, A. P.; Nieduzak, T. R.; Konoike, T.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5167.

a, which illustrates the utility of Pd(0) chemistry in substrate synthesis,[10] were examined. As before, cycloaddition of the dienol **7** with *N*-phenylmaleimide at room temperature provides a 10:1 lactone mixture directly in which the major isomer is **9**.[7] Subjecting the silyl ether **8** to the same conditions gives an 8:1 mixture. Conversion of the major adduct to the same lactone **9** upon desilylation (HCl, HOAc, H_2O, THF, 93%) establishes structure **10**.[7] Thus, the diastereofacial selectivity with *N*-phenylmaleimide derives from the presence of the allylic oxygen substituent and not from prior acylation. Equation 3, series **b**, demonstrates the extension of the strategy to heterocycle construction. The compatibility of the amine in the enyne cyclization is noteworthy, but a full equivalent of acetic acid is required.

Equations 4 and 5 illustrate intramolecular versions of this sequence. The enyne cyclizations [$(dba)_3Pd_2{\cdot}CHCl_3$, Ph_3P, HOAc, PhH, room temperature to 60 °C] produces only the conjugated dienes **11** and **15**.[7] Cycloaddition

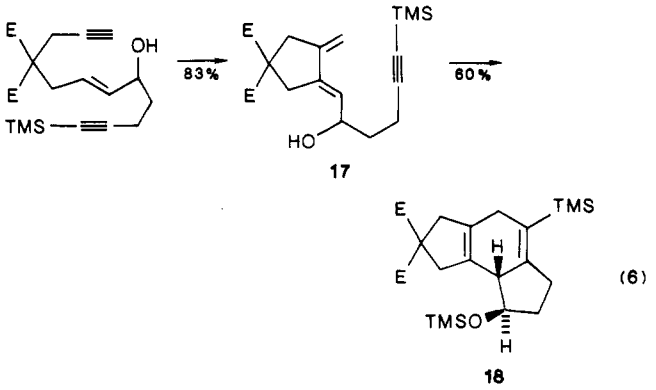


(4)

(5)

occurs under relatively mild conditions considering the absence of an activating group on the dienophile [BHT, BSA, $PhCH_3$, 172–180 °C] to give a 5.2:1 mixture of the alcohols **13**[7] from **11** and a single alcohol **16** from **15** after desilylation of the initial products [TBAF, THF, room temperature, 64%]. Moffatt–Swern oxidation [$(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2, −70 °C, 83%] of alcohol **13** produces a single ketone, which suggests that the adduct is epimeric at the alcohol. The stereochemistry suggested for the major cycloadducts depicted in **13** and **15** is based upon mechanistic considerations, spectroscopic data, and literature precedent.[11]

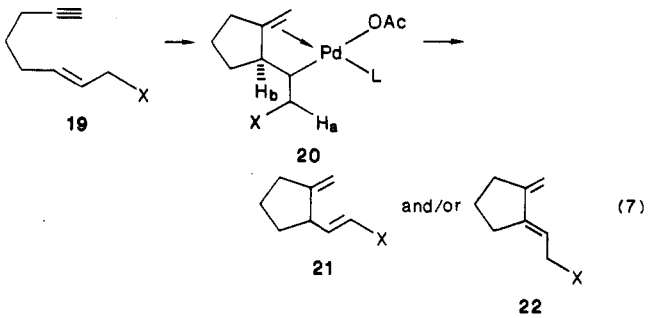
Employment of an acetylenic dienophile raises the intriguing question of the chemoselectivity achievable in the enyne cyclization (eq 6). The capping of one terminal acetylene with the trimethylsilyl group steers the reaction to give exclusively the diene **17**[7] [$(dba)_3Pd_2{\cdot}CHCl_3$, HOAc,



(6)

Ph_3P, PhH, room temperature]. Subsequent thermal cyclization at 140–180 °C ($PhCH_3$, BHT, BSA) produces a 6:1 epimeric mixture in which the major product is suggested as **18**,[7] the silyl ether deriving from concommitant silylation due to the use of BSA as an acid scavenger in the Diels–Alder reaction.

The strong regiochemical directing effect of the hydroxy or siloxy substituent on the enyne cyclization, while unexpected, appears to be very general (eq 7). Thus, we



(7)

can orient the cyclization of the generalized substrate **19** to form either the 1,4-diene **21** or the 1,3-diene **22** by varying the substituent X, whereby an electronegative substituent disfavors insertion into the C–H_a bond and, therefore, disfavors 1,4-diene formation.[12]

Having served the role of directing the regioselectivity of the enyne cyclization to produce the useful 1,3-dienes, the hydroxy or siloxy group serves a second role, that of directing the diastereofacial selectivity of the Diels–Alder reaction.[8b,9,11,13,14] The ability of an oxygen substituent adjacent to a diene to determine the diastereofacial selectivity in both inter- and intramolecular cycloadditions continues to be extensively discussed, sometimes with conflicting results. Our results show good to excellent diastereofacial selectivity with the dialkylidenecyclopentanes as the diene component in both the inter- and intramolecular versions.

(10) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.

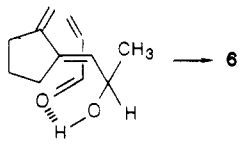
(11) Taber, D. F. *Intramolecular Diels–Alder Reactions and Alder Ene Reactions*; Springer Verlag: New York, 1984. Ciganek, E. *Org. React.* **1984**, *32*, 1. Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., et al.; Academic Press: New York, 1984; Chapter 7. Wurziger, H. *Kontakte (Darmstadt)* **1984**, 3. Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, 876.

(12) For the suggestion of $L_nPd(H)OAc$ as the catalytically active species, see: Trost, B. M.; Rise, R. *J. Am. Chem. Soc.* **1987**, *109*, 3161 and references therein.

(13) For some recent papers, see: Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625. Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710. Herczegh, P.; Zsely, M.; Szilagyi, L.; Bognar, R. *Tetrahedron Lett.* **1988**, *29*, 481. Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1988**, *110*, 4074. Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800. Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. Marshall, J. A.; Andra, J. E.; Grote, J. *J. Org. Chem.* **1986**, *51*, 1155. McDougal, P.; Rico, J. G.; Van Derveer, D. *J. Org. Chem.* **1986**, *51*, 4492. Jones, R. C. F.; Tunnicliffe, J. H. *Tetrahedron* **1985**, *50*, 3421. Sternbach, D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591. Schlessinger, R. H.; Wong, J. W.; Poss, M. A.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 3951.

(14) Houk, K. N.; Paddon-Row, M. N.; Rordan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Meta, J. T.; Li, Y.; Loucharich, R. J. *Science* **1985**, *231*, 1108. Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663.

The intermolecular cycloaddition shows a remarkable reversal of diastereofacial selectivity in going from *N*-phenylmaleimide to acrolein as the dienophile. The formation of adduct **5** (eq 2) corresponds to the facial selectivity suggested previously based upon experimental and theoretical studies.[14] The opposite facial selectivity observed in the formation of **6** may arise by the OH group serving as an "internal acid catalyst" in which event **23** corresponds to the most reasonable model for the transition state.



23

The ability to impose control upon the course of organic reactions represents an important strategy to achieve chemo-, regio-, and diastereoselectivity. The present results highlight the versatility of the hydroxy group in such a role for both transition-metal and thermal reactions to provide ready access to polycyclic structures from totally acyclic building blocks in a simple consecutive two-step sequence.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

Supplementary Material Available: Spectral data for compounds **4–6**, **7** (X = $C(CO_2CH_3)_2$), **8** (X = $C(CO_2CH_3)_2$), **8** (X = NCH_2Ph), **9**, **10** (X = $C(CO_2CH_3)_2$), **10** (X = NCH_2Ph), **11**, and **13–18** (4 pages). Ordering information is given on any current masthead page.

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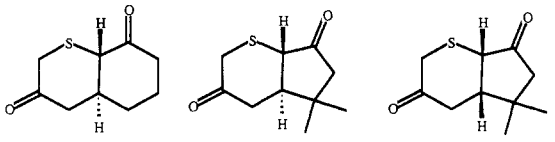
Synthesis of Optically Active Thiadecalins and Thiahydrindans by a Proline-Catalyzed Intramolecular Michael Reaction

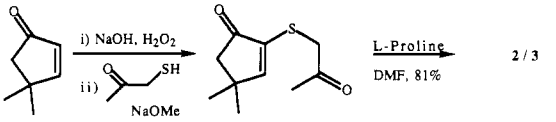
Summary: The *trans*-thiadecalindione **1** and the *trans*- and *cis*-thiahydrindandiones **2** and **3** were prepared from the corresponding α-thio enones **4** and **5** by a proline-catalyzed intramolecular Michael process. The optically pure enantiomers of **1** were obtained by fractional crystallization, allowing the assignment of an enantiomeric excess of 19–28% for the Michael reaction depending on reaction conditions. Additionally, thiadecalindione **1** was reduced by actively fermenting bakers' yeast to provide exclusively the product **7** resulting from reduction of the thiopyran ring carbonyl group.

Sir: During work directed toward the synthesis of compounds that contain medium-sized rings, we needed to synthesize the sulfur-containing diketones **1** and **2/3**. Because our strategy was to first bridge the sulfur ring with an optically active carbon chain and then to desulfurize to produce a medium-sized ring, it was desirable to acquire the heterocycles **1** and **2/3** in optically active form.



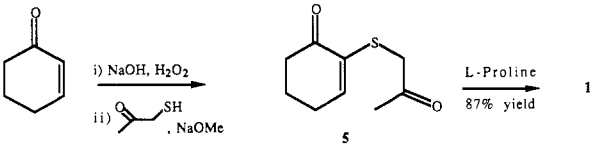
1 **2** **3**

Toward this end, 4,4-dimethylcyclopent-2-enone[1] was epoxidized in 60% yield with basic hydrogen peroxide[2] and the resulting epoxide opened regioselectively with mercaptoacetone.[3] Spontaneous dehydration then gave the crystalline enone **4**, in 75% yield.[4] The enone was stirred in dry dimethylformamide at 60 °C with 1 equiv of L-proline to give the diastereomeric sulfides **2** and **3** in approximately a 1:1 ratio (81%). The diastereomers were separated by silica gel chromatography and identified by the ^1H NMR coupling constants of the ring junction protons [**2**, J = 11.5 Hz, $[\alpha]_D$ −21.6° (c 3.60, $CHCl_3$); **3**, J = 8.0 Hz, $[\alpha]_D$ −19.9° (c 2.27, $CHCl_3$)]. Attempts to discern the enantiomeric excess of these compounds using various chiral shift reagents proved inconclusive.



4

Next, cyclohex-2-enone was epoxidized, as above, in 67% yield and treated with mercaptoacetone[3] to give the sulfur-functionalized enone **5** as a yellow oil in 54% yield. Enone **5** underwent cyclization in dry dimethylformamide at room temperature for 48 h with 1 equiv of L-proline to give exclusively the trans isomer **1** as a white solid [87%, $[\alpha]_D$ −58.7° (c 0.71, $CHCl_3$)].



5

On a somewhat larger scale 5 g of **5** was kept with L-proline at −15 °C for 7 days. The optical rotation of the product **1** was −85° (c, 0.90, $CHCl_3$), which was raised to −296° (c 1.23, $CHCl_3$) upon recrystallization from THF. Two further recrystallizations gave material of optical rotation −311° (c 1.01, $CHCl_3$), which did not change upon further recrystallization (overall yield ~45%).

The 300-MHz ^1H NMR spectra of the recrystallized and racemic compounds were then analyzed by using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III), [Eu(hfc)$_3$]. The racemic material showed marked splitting of nearly every signal, while no splitting or shoulders were observed for the triply recrystallized material. Since a prepared

(1) Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273.
(2) House, H. O.; Wasson, E. I. in *Organic Syntheses*; Wiley: New York, 1976; Collect. Vol. 4, p 552.
(3) Hromatka, V. O.; Engle, E. *Monatsh. Chem.* **1948**, *78*, 29.
(4) (a) Schultz, A. G.; Kashdan, D. S. *J. Org. Chem.* **1973**, *38*, 3814. (b) Tobias, M. A.; Strong, J. G.; Napier, R. P. *J. Org. Chem.* **1970**, *35*, 1709.

0022-3263/89/1954-2274$01.50/0