alcohols 12 and 13, which were readily separable by flash chromatography.[9]

The requisite epoxide unit was introduced by the conversion of alcohol 12 to the primary tosylate, followed by oxidative deprotection of the *p*-methoxybenzyl ether and treatment of the resulting alcohol with sodium methoxide to yield epoxide 14 (Scheme II). Final installation of the *E,E* diene system was accomplished by reductive cleavage of the (benzyloxy)methyl ether and dehydration using the Burgess protocol,[10] affording the sensitive diene epoxide (2*S*,3*R*)-3.

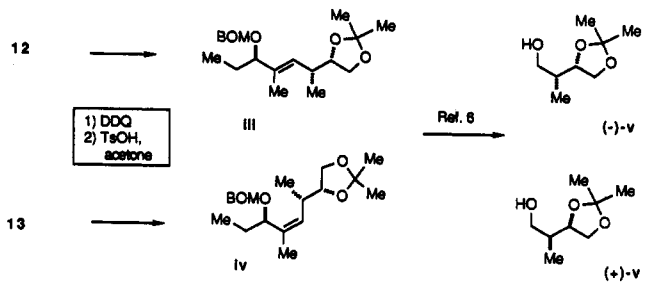
Treatment of epoxide (2*S*,3*R*)-3 with the Grignard reagents[11] derived from (*S*)- and (*R*)-1-bromo-2,4-dimethylpentanes afforded alcohols 15 and 16, respectively, each of which was accompanied by ca. 7% of an inseparable minor diastereomer.[12] Oxidation of 15 with catalytic tetrapropylammonium perruthenate[13] in the presence of *N*-methylmorpholine *N*-oxide gave a 98% yield of the ketone (6*R*,10*R*)-1 accompanied by the minor 6*S*,10*R* diastereomer. Similarly, oxidation of 16 afforded (6*R*,10*S*)-1 and the minor 6*S*,10*S* ketone product. The 500-MHz ^{1}H NMR, mass spectroscopic, and chromatographic properties of (6*R*,10*R*)-1 correspond to those of authentic matsuone; in contrast, the properties of the diastereomeric (6*R*,10*S*)-1 were clearly distinct from those of the natural pheromone.[14] Particularly diagnostic are the 500-MHz ^{1}H chemical shifts of signals assigned to the diastereotopic protons of the C_8 methylene group of matsuone diastereomers. Signals assigned to the C_8 protons of matsuone and (6*R*,10*R*)-1 appear at δ 2.19 (ddd, J = 16.8, 9.3, 5.5 Hz) and 2.29 (ddd, J = 16.8, 8.6, 6.4 Hz), while the corresponding protons of (6*R*,10*S*)-1 are observed at δ 2.13 (ddd, J = 16.8, 8.7, 6.1 Hz) and 2.32 (ddd, J = 16.8, 9.3, 5.5 Hz); the latter signals are notably absent from the spectrum of authentic 1.[15]

The relative configuration of matsuone is thus established as *priorty-reflective*. We note that the availability of both antipodes of matsuone[12] is expected to faciltate assignment of the absolute configuration to the natural pheromone by chiral-phase gas chromatographic analysis.[16] These studies, and the results of field tests utilizing individual stereoisomers of 1, will be the subject of future reports.

Acknowledgment. Support for this work was provided by a grant from the National Institutes of Health (GM-39990). We thank Arco Chemicals for a generous gift of (*S*)-(−)-glycidol. The support of Syracuse University in the form of a University Fellowship (C.L.C.) is gratefully acknowledged.

Supplementary Material Available: Experimental procedures and full characterization data for all new compounds and 500-MHz ^{1}H NMR spectra of matsuone and synthetic stereoisomers (23 pages). Ordering information is given on any current masthead page.

(9) Stereochemical assignments for 12 and 13 were confirmed by NOE studies and by conversion to the known triol derivatives v, as previously described.[6]



(10) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.

(11) Zimmerman, M. P.; Li, H.; Duax, W. L.; Weeks, C. M.; Djerassi, C. *J. Am. Chem. Soc.* **1984**, *106*, 5602.

(12) The minor diastereomeric products observed from Grignard couplings of (2*S*,3*R*)-3 reflect the stereochemical heterogeneity of this epoxide and are consistent with the optical purity of starting glycidol 4 (ee ca. 85%). We note that the presence of these minor diastereomers provides access to all four stereoisomers of ketone 1; thus, the ketone obtained from oxidation of 15 (and the accompanying minor diastereomer) contains 7% of the 6*S*,10*R* diastereomer, while oxidation of 16 affords (6*R*,10*S*)-1 accompanied by 7% of the 6*S*,10*S* diastereomer.

(13) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(14) The 500-MHz ^{1}H NMR spectrum of authentic matsuone,[1] obtained in benzene-d_6 with ca. 1–2 μg of material, exhibits signal envelopes in the δ 1.0–1.2 and 1.9–2.2 regions that are not present in either synthetic diastereomer. Our NMR sample of matsuone was purified to homogeneity prior to use, and we attribute these signals to the presence of minor solvent impurities.

(15) A similar chemical-shift pattern is observed for diastereomers of the *M. feytaudi* pheromone i (Cywin, C. L. Unpublished results).

(16) Schurig, V.; Nowothy, H. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 939. The limited availability of authentic 1 has to date precluded either a determination of optical rotation or NMR analysis using chiral shift reagents.

Lithiation and Isomerization of Allylic Amines as a General Route to Enamines and Their Carbonyl Derivatives[1]

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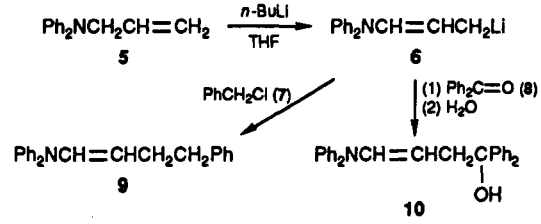
Summary: [3-(Diphenylamino)-2-propenyl]lithium, readily prepared by the lithiation of allyldiphenylamine with *n*-butyllithium in THF, undergoes alkylation either with organic halides or with carbonyl or azomethine derivatives to yield enamines, which can be converted by protons or other electrophiles into aldehydes or into five-membered heterocycles; lithiation of such allyldiarylamines with other reagents leads principally to isomerization to enamines (with lithium diisopropylamide) or to carbenoid intermediates (*tert*-butyllithium and potassium *tert*-butoxide).

Previous studies[2] have demonstrated that attempted metalation of tertiary allylamines (1) can lead both to

(1) Part 9 of the series of publications devoted to Functionalized Organolithium Reagents. Part 8: Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835. For general reference to the use of heteroatom-substituted allyllithium reagents as homoenolates, see: Barluenga, J. *Pure Appl. Chem.* **1990**, *62*, 595. This should lead the interested reader to the considerable literature on this topic.

0022-3263/91/1956-2955$02.50/0

Scheme I

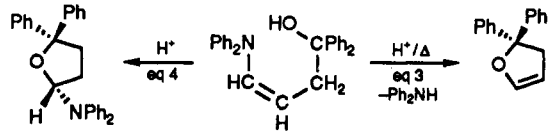


isomerization to the 1-propenylamine (**2**, eq 1) and to the two isomeric allylic metal derivatives (**3** and **4**). We now

$$R_2NCH{=}CHCH_3 \xleftarrow{R'M} \underset{\mathbf{2}}{R_2NCH_2CH{=}CH_2} \xrightarrow{R'M} \underset{\mathbf{3}}{R_2NCH(M)CH{=}CH_2} + \underset{\mathbf{4}}{R_2NCH{=}CHMCH_2} \quad (1)$$

$$\underset{\mathbf{9}}{PH_2NCH{=}CHCH_2CH_2Ph} \xrightarrow[-Ph_2NH]{H_3O^+} O{=}CHCH_2CH_2CH_2Ph \quad (2)$$

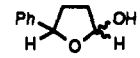
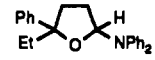
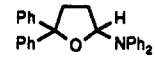
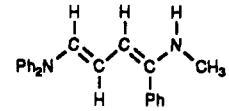
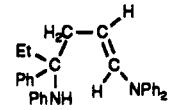
wish to report that primary allylic diarylamines, such as allyldiphenylamine (**5**), undergo quantitative lithiation with *n*-butyllithium in THF at 0 °C. The resulting lithium derivative reacts with electrophiles, such as benzyl chloride (**7**) and benzophenone (**8**) only at the allyl position distal to the amino group and thus reacts exclusively as if it existed as the [3-(diphenylamino)-2-propenyl]lithium (**6**) structure[3] (Scheme I). The resulting enamines **9** and **10** can be hydrolyzed to the corresponding aldehyde simply by passage through a column of silica gel (with good recovery of the Ph_2NH, eq 2) or can be cyclized to the corresponding heterocycle by electrophiles, either with (eq 3) or without (eq 4) the elimination of diphenylamine. The



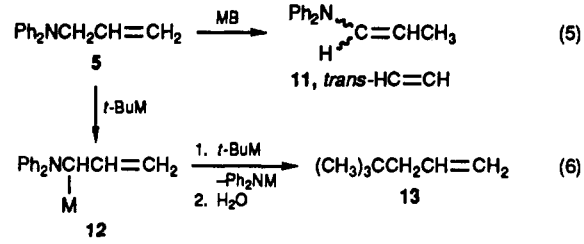
reaction products obtained from lithium reagent **6** and a variety of electrophiles, embracing alkyl, allylic, and benzylic halides and carbonyl, nitrile, and azomethine derivatives, are compiled in Table I. In all cases, even with aldehydes (entry 6) and enolizable ketones (entry 7), the preponderant product is that resulting from attack at the distal carbon of **6**.

The preparative advantages in metalating allyldiarylamines with *n*-butyllithium in THF become apparent when one considers how other metalating agents react with **5**: (1) LDA in THF catalyzes the isomerization of **5** quantitatively into a 45:55 mixture of *cis*- and *trans*-diphenyl-1-propenylamine (**11**, eq 5); (2) KH in THF isomerizes **5** exclusively to the *trans*-**11**; and (3) a mixture of *tert*-butyllithium and potassium *tert*-butoxide in hexane cleaves the C–N bond in **5** and produces **13**,[4] most likely via a carbenoid intermediate **12** (eq 6).[5]

Table I. Reactions of [3-(Diphenylamino)-2-propenyl]lithium with Electrophiles[a]

entry	electrophile	product[b]	yield[c] (%)
1	CH_3I	$CH_3CH_2CH_2C(H){=}O$	70
2	CH_3CH_2I	$CH_3CH_2CH_2CH_2C(H){=}O$	65
3	CH_3CH_2C-H_2CH_2I	$CH_3CH_2CH_2CH_2CH_2CH_2C(H){=}O$	60
4	$H_2C{=}CH$-CH_2Br	$H_2C{=}CHCH_2CH_2CH_2C(H){=}O$	80
5	$PhCH_2Cl$	$PhCH_2CH_2CH_2C(H){=}O$	85
6	$PhHC{=}O$		70[d]
7	$PhEtC{=}O$		80[d]
8	$Ph_2C{=}O$		65
9	$PhC{\equiv}N$		75[e]
10	$PhEtC{=}$ NPh		70

[a] Lithiation was achieved with *n*-BuLi in THF at 0 °C and reaction with the electrophile at 0–20 °C. [b] For all previously unreported products, satisfactory elemental, analytical, IR, NMR, and MS data were obtained. [c] The yields are for isolated, pure products and have not been optimized. [d] The yield given is that of the cyclic product indicated, together with that of the open-chain alcohol. [e] The initial adduct formed between **6** and $PhC{\equiv}N$ was treated with MeI before hydrolytic workup.



(5)

(6)

In summary, we have uncovered two efficient methods for converting allyldiphenylamine (**5**) and other primary allylic diarylamines into an enamine: (1) lithiation with *n*-butyllithium in THF and alkylation (Scheme I); and (2) isomerization with LDA (eq 5). All such enamines can be smoothly hydrolyzed to the corresponding carbonyl derivative in good to excellent yields. The methods open up possibly general routes to such enamines starting from primary allylic halides, $RCH{=}CHCH_2X$ (**14**), and to their corresponding or higher aldehydes, $R\text{-}CH_2CH_2CHO$ or $RR'CHCH_2CHO$. The requisite allylic diphenylamine, $RCH{=}CHCH_2NPh_2$, can be readily prepared from **14** and $LiNPh_2$ in THF.[6]

(2) Previous studies of isomerization include: (a) Hubert, A. J. *J. Chem. Soc. C* **1968**, 2048. (b) Riviere, M.; Lattes, A. *Bull. Soc. Chim. Fr.* **1967**, 2539. Previous metalation studies are the following: (a) Julia, M.; Schouteeten, A.; Baillarge, M. *Tetrahedron Lett.* **1974**, 672. (b) Albrecht, H.; Eichler, J. *Synthesis* **1974**, 672. The former group employed cumbersome allylic carbazole derivatives with *n*-BuLi and TMEDA complexes in ether; the latter group used allylic methylphenylamines with *n*-BuLi and KO-*t*-Bu mixtures. Both methods give variable amounts of alkylation at the allylic positions both proximal and distal to the nitrogen.

(3) At present, there is no structural information that would permit a decision between a covalent carbon–lithium at C_1 in **6** and an ion-pair structure with the higher electron density at C_1. It would be futile, indeed scientifically unsound, to attempt to conclude anything about the site or structure of the carbon–lithium bond in this allylic lithium reagent from its behavior in *chemical reactions*, such as these alkylations or even simple hydrolysis. Only *physical measurements* may supply such a structural answer. Here, we are invoking an operational definition of structure: from the exclusive alkylation at C_1, we deduce that C_1 might be the locus of the lithium (if no allylic rearrangement is involved).

(4) Compound **13** was identified by MS, ^1H NMR, and IR data (IR: 910 and 990 ($-CH{=}CH_2$) cm^{-1}).

(5) In a similar fashion, *N*-allylpiperidine is readily cleaved by a combination of *t*-BuLi and KO-*t*-Bu. There is little doubt that the first step in all such cleaves is allylic metalation. Eisch, J. J.; Shah, J. H. Unpublished studies.

Brief illustrative experimental procedures serve to demonstrate the utility of these methods. First, treatment of 35 mmol of **5** with 50 mmol of LDA in 50 mL of THF for 2 h at 0 °C and hydrolytic workup gave a 96% yield of a 45:55 mixture of the cis and trans isomers of diphenyl-1-propenylamine (**11**). Although stoichiometric amounts of LDA are employed in this case, such isomerizations can be effected by catalytic amounts of LDA as well. Second, treatment of 20 mmol of **5** with 22 mmol of *n*-BuLi in 100 mL of THF at 0 °C for 1 h gave a deep red solution; then, 20 mmol of $PhCH_2Cl$ were added and allowed to react for 6 h at 25 °C; hydrolytic workup and column chromatography of the dried and evaporated organic layer on silica gel (hexane:CH_2Cl_2 = 8:2 as eluent) gave, separately, 4-phenylbutanal (75%) and recovered diphenylamine (95%). Third, treatment of 20 mmol of **5** with 22 mmol of *n*-BuLi in 100 mL of THF at 0 °C for 3 h and the subsequent addition of 20 mmol of benzophenone gave upon the usual hydrolytic workup a crude product that was recrystallized from ethanol to yield 65% of 2-(diphenylamino)-5,5-diphenyltetrahydrofuran, mp 124-125 °C. Treating this with dilute, aqueous HCl eliminates diphenylamine and forms 2,2-diphenyl-2,3-dihydrofuran.

(6) A number of allylic diphenylamines, such as $CH_3CH{=}CHCH_2NPh_2$ and $PhCH{=}CHCH_2NPh_2$, have been prepared in this manner. Eisch, J. J.; Chiu, C. S.; Shah, J. H. Unpublished studies.

Acknowledgment. This research was supported by the National Science Foundation under Grant CHE-87-14911.

Site-Selective Hydroxylation of Steroids via Oxometalloporphinates Covalently Linked to Ring D: Introduction of Hydroxyl Groups into the C(9) and C(12) Position of 5α-Androstanes

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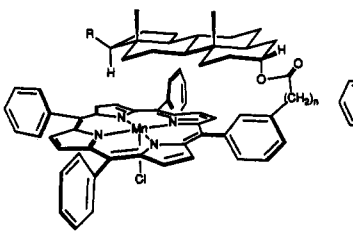
Summary: Oxidation of synthetic manganese(III) porphyrins attached to steroidal substrates at C(17) (cf. **2** and **3**) gives rise to hydrogen atom abstraction at C(9) and/or C(12), thereby leading to hydroxyl incorporation at these sites. The use of more robust metalloporphyrins (cf. **9**) results in substantial increases in the yields of hydroxylated 5α-androstanes.

A recent report[1] from this laboratory described the use of synthetic manganese(III) porphyrins in the remote hydroxylation of steroid substrates.[2] These covalently attached porphyrins, which were oxidized to the corresponding oxomanganese(V) species by iodosylbenzene, were capable of introducing functionality at specific, nonactivated sites on the steroid while maintaining the integrity of the carbon atom undergoing hydroxylation.[3] Herein we wish to report both expansions in the scope of this reaction and improvements in yields through the use of more robust "catalysts".

The site selectivity of these remote oxidation reactions is geometrically controlled, being governed by the steric constraints imposed by the steroid-porphyrin tether. The selectivity can, in principle, be altered by changing the point of attachment to either the porphyrin or steroid, or by adjusting the length and/or composition of the tether itself. Previous efforts in our laboratory focused on the use of "meta"-substituted tetraphenylporphyrins attached to 5α-androstan-3α-ol derivatives (cf. **1**).[1] The present study features the use of "ortho"-substituted porphyrins attached to the C(17) position of 5α-androstane (cf. substrates **2** and **3**) and leads to hydrogen atom abstraction at either C(9) and/or C(12) with hydroxyl incorporation at these sites. In addition, halogens have been incorporated into the 2,6-positions of the phenyl groups located at C(10), C(15), and C(20) on the porphyrin ring that serve to retard oxidative degradation of the porphyrin. We detail below the results of this investigation.



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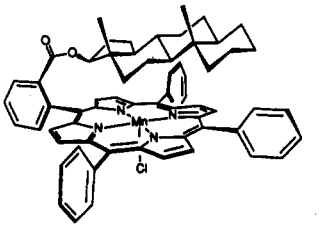

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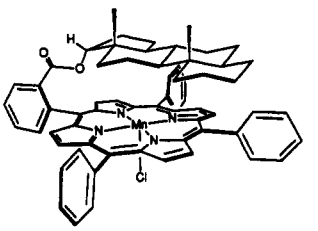

3

Our initial study centered around the manganese(III) (*o*-((androstanyloxy)carbonyl)phenyl)triphenylporphyrin **2**, which was prepared by a minor modification[4] of the Lindsey method[5] employing 5α-androstanyl formylbenzoate **4**[6] followed by metalation in the usual fashion.[8]

(1) Grieco, P. A.; Stuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799.

(2) For other approaches to remote functionalization of steroids, see: (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. (b) Mazur, Y., *Pure Appl. Chem.* **1975**, *51*, 145. (c) Barton, D. H. R.; Göktük, A. K.; Morzycki, J. W.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans 1* **1985**, 583. Also see: Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325.

(3) For model systems that mimic the hydroxylation of cytochrome P-450, see: (a) Chang, C. K.; Kuo, M.-S., *J. Am. Chem. Soc.* **1979**, *101*, 3413. (b) Hill, C. L.; Schardt, B. C., *Ibid.* **1980**, *102*, 6375. (c) Groves, J. T.; Nemo, T. E. *Ibid.* **1983**, *105*, 6243. (d) Dolphin, D.; James, B. R.; Leung, T. *Inorganica Chim. Acta.* **1983**, *79*, 25. (e) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462. (f) Cook, B. R.; Reinert, T. J.; Suslick, K. S. *Ibid.* **1986**, *108*, 7281.

(4) An 8:1 ratio of benzaldehyde to substituted *o*-formylbenzoate **4** was employed.

0022-3263/91/1956-2957$02.50/0