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Tandem Claisen-Diels-Alder reactions in synthesis. A facile approach to anthracyclines

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Abstract
Acid 8b is available in seven steps from ketone 1. Quinone 5 represents a useful intermediate for the synthesis of anthracyclines.

Table I. Asymmetric Hydrovinylation of Cyclohexa-1,3-diene Catalyzed by the $Ni(COD)_2$–$AlEt_2Cl$–AMPP System[a] (AMPP Ligands $Ph_2PN(CH_3)CH^*RCH_2OPPh_2$)

		3-vinylcyclohex-1-ene			
starting amino acids	AMPP ligands,[b] R	$[\alpha]^{25}_D$, deg (c 1.00, toluene)	config[c]	T, °C	optical yields,[c] %ee
(2S,3R)-threonine	$CH_3CH^*(OPPh_2)$ (6)	+227.5	S	40	85
		+243.5		10	91
		+248.5		0	93
		+249		−20	93
		+250		−30	93[a]
(S)-phenylalanine	$PhCH_2$ (7)	−56.5	R	40	21
		−104.5		−5	39
		−139		−25	52
(S)-alanine	CH_3 (8)	−45	R	40	17
(S)-valine	i-Pr (9)	−26.5	R	40	10
		−30		−5	11
(R)-phenylglycine	Ph (10)	−12	R	−5	4
(S)-aspartic acid	$CH_2CH_2OPPh_2$ (11)	−75	R	40	28
(S)-glutamic acid	$(CH_2)_2CH_2OPPh_2$ (12)	−50	R	40	19

[a] An autoclave was successively charged with a pre-formed solution of AMPP ligands (0.4 mmol) and $Ni(COD)_2$ (0.4 mmol) in toluene (5 mL), a solution of Et_2AlCl (0.2 mL) in toluene (5 mL), and 1 (7 g, 87.5 mmol). Then, the autoclave was pressurized with a stoichiometric amount of ethylene. The reactions were monitored by ethylene consumption and were conducted to completion within 15 min at 40 °C. Under these conditions the selectivities in 2 approached 100%. 2 was purified by spinning column distillation. The reaction time at −30 °C is 225 min. [b] All compounds described here gave NMR (^{13}C, ^1H, and ^{31}P) spectra consistent with their structures. [c] See text. Results were reproducible to within 0.5%. Duplicate experiments were run for each entry.

Hydroboration[12] of **13** gave quantitatively a mixture of the four diastereoisomeric alcohols **14**–**17**. Optical yields were determined by GLC either on urethanes prepared from isopropyl isocyanate by using König's method[13] (glass capillary column, 50 m, coated with XE-60–*S*-valine–*S*-α-phenyl ethylamide, isotherm at 75 °C) or on urethanes from (+)-(*R*)-1-phenylethyl isocyanate (capillary column, 50 m, SE 52 isotherm at 160 °C). All optical yields evaluated by the two methods agreed within the experimental errors (±0.5%). Along hydrogenation and hydroboration reactions, the configuration of the asymmetric carbon in **2** was maintained, thus the *S* configuration of (+)-VCH has been deduced from the following reference compounds. (i) *trans*-(1*S*,2*S*)-2-Ethylcyclohexanol and *trans*-(1*S*,3*S*)-3-ethylcyclohexanol were prepared respectively from the corresponding racemic ketones by specific enzymatic reduction catalyzed by HLADH with recycling NADH.[14] (ii) *trans*-(1*R*,3*R*)-3-Ethylcyclohexanol and *cis*-(1*R*,2*S*)-2-ethylcyclohexanol were obtained from a stereospecific esterification with lauric acid carried out in organic phase and catalyzed by a lipase[15] (from the yeast *Candida cyclindracea*).

Optical yields for the different AMPP are reported in Table I. Relative to the optical yield of 85% obtained at 40 °C from threophos (**6**), the other ligands AMPP, particularly **9** and **10**, were much less enantioselective and, although AMPP ligands such as (*S*)-proliphos and D-ephos, obtained respectively from (*S*)-proline and D-ephedrine, have proved to be very effective toward asymmetric hydrogenation[6] and hydroformylation,[16] they were practically inefficient for reaction 1, as far as asymmetric induction is concerned. Potential tridentate ligand (2*R*,3*R*)-threophos (**6**) was one of the most effective ligands, giving quantitatively (+)-(*S*)-3-vinylcyclohex-1-ene. The extent of optical induction was readily upgraded to 93% ee by lowering the reaction temperature to 0 °C. Undoubtly, the antipode (2*S*,3*S*)-threophos would be able to produce (−)-(*R*)-3-vinylcyclohex-1-ene, with the same enantiomeric excess, so that this reaction could be a useful tool for production of chiral synthons; thus, we are preparing optically pure *trans*-perhydro-1-indanone from a Brown's annelation.[17]

Registry No. **1**, 592-57-4; (*S*)-**2**, 76152-63-1; (*R*)-**2**, 95421-88-8; **3**, 39994-75-7; **4**, 2313-74-8; **5**, 95421-89-9; **6**, 95421-90-2; **7**, 91662-87-2; **8**, 95421-91-3; **9**, 95421-92-4; **10**, 90032-62-5; **11**, 95421-93-5; **12**, 95421-94-6; **13**, 95421-95-7; **14**, 95529-72-9; **15**, 69854-63-3; **16**, 87759-26-0; **17**, 69854-64-4; $Ni(COD)_2$, 1295-35-8; Et_2AlCl, 96-10-6; $CH_2{=}CH_2$, 74-85-1; (2*S*,3*R*)-threonine, 72-19-5; (*S*)-phenylalanine, 63-91-2; (*S*)-alanine, 56-41-7; (*S*)-valine, 72-18-4; (*R*)-2-phenylglycine, 875-74-1; (*S*)-aspartic acid, 56-84-8; (*S*)-glutamic acid, 56-86-0; (±)-2-ethylcyclohexanone, 64870-41-3; (±)-3-ethylcyclohexanone, 64847-85-4.

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(17) Brown, H. C.; Negishi, E. *Chem. Commun.* **1968**, 594.

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Tandem Claisen–Diels–Alder Reactions in Synthesis. A Facile Approach to Anthracyclines

Summary: Acid **8b** is available in seven steps from ketone **1**. Quinone **5** represents a useful intermediate for the synthesis of anthracyclines.

Sir: The rearrangement of allyl phenyl ethers to *o*-allylphenols, termed the Claisen rearrangement,[1] has been less

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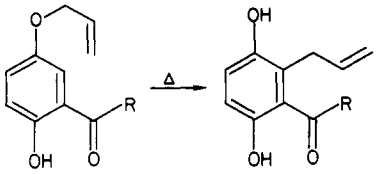
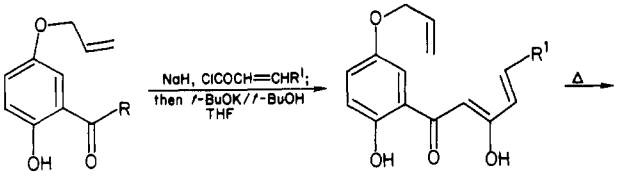
often used in organic synthesis than its aliphatic counterpart. A major drawback of this reaction is the formation of a mixture of regioisomers when unsymmetrical systems are employed. For example, both *m*-methylphenyl and *m*-methoxyphenyl allyl ether afford approximately equal amounts of isomeric products, yet certain *m*-acyl groups exert a pronounced directing effect.[2] In particular, with ketones such as **1** the exclusive product is hydroquinone **2**.[3] Extension to polycyclic systems by coupling the

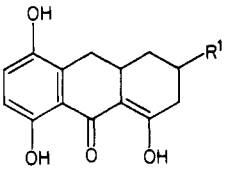


1 **2**

Claisen rearrangement with an intramolecular Diels–Alder reaction requires a diene unit in R. Ketone **3**, prepared by a modification[4] of the Baker–Venkataraman acyltransfer reaction,[5] contains a 1-acyl-2-ydroxybutadiene subunit. Interestingly, no intermolecular Diels–Alder



1, R=CH_3 **3a**, R^1=CH=$CHCH_3$; **b**, R^1=CH_3



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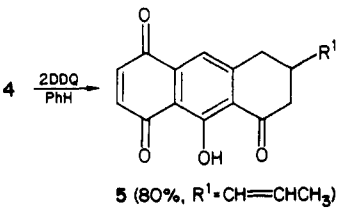
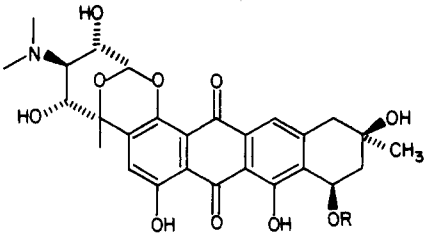
reactions of such dienes appear to be known and only one intramolecular example has been recorded.[6] A benzene solution of **3** was heated at 210 °C for 8 h. After filtration chromatography, **4a** was isolated in 60% yield. Similarly, **4b** was isolated in 84% yield. The absence of NMR absorptions for an allyl group in both **4a** and **4b** and in **4b** the emergence of a doublet at δ 1.10 support the assigned structures.[7a] Aromatization of the central ring was next attempted. Although a reaction sequence involving silylation of the non-hydrogen-bonded alcohol followed by selenenylation–deselenenylation was initially studied,[8] a very direct oxidation of **4** to naphthoquinone **5**[7b] was recently achieved using 2 equiv of DDQ[9] in benzene at ambient temperature. Quinone **5** contains functionality well suited for the synthesis of 11-deoxyanthracycline analogues. It already contains the requisite B and C ring functionality for both the nogarols **6**[10] and for 11-deoxy-



5 (80%, R^1=CH=$CHCH_3$)

daunomycinone **7**.[11] Appendage of the D ring by a



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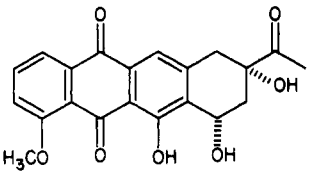

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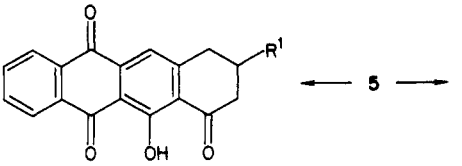
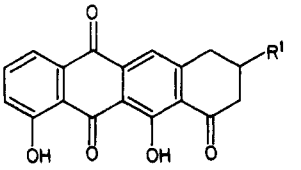
Diels–Alder reaction proved to be more difficult than expected. While there was ample literature precedent[12] for regiospecific cycloadditions to juglone and its derivatives, cycloadditions with acetoxybutadiene and (trimethylsilyloxy)butadiene proceeded poorly. The 4-deoxy compound (anthracycline numbering) **8a**[7a] could be prepared



8a, R^1=CH=$CHCH_3$ **8b**, R^1=CO_2H



9, R^1=CH=$CHCH_3$

in 30% overall yield by reaction with butadiene (4 days, 25 °C) followed by tautomerization to the hydroquinone (pTSA, THF, 25 °C) and oxidation with 2 equiv of DDQ. Permanganate oxidation afforded **8b**. Anthraquinone **9**[7b] was synthesized from **5** by a boron trifluoride etherate catalyzed Diels–Alder reaction with acetoxybutadiene followed by DDQ oxidation.[13] Some **8a** was also produced.

Variation of both diene substituent pattern and R^1 lends considerable flexibility to this approach. In view of the promising anticancer activity exhibited by the nogarols and other 11-deoxy compounds such as aclacinomycin,[14] new analogues will continue to be needed. Naphthoquininone

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5 available *in four steps* from commercially available materials represents a most direct synthetic intermediate for their synthesis.

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Registry No. 1 (R = CH_3), 40815-75-6; **3a**, 90554-78-2; **3b**, 90554-75-9; **4a**, 95999-44-3; **4b**, 95999-45-4; **5**, 95999-46-5; **8a**, 95999-47-6; **8b**, 95999-48-7; **9**, 95999-49-8; ClCOCH=CHCH=$CHCH_3$, 90554-82-8; $ClCOCH{=}CHCH_3$, 10487-71-5; acetoxybutadiene, 1515-76-0; butadiene, 106-99-0.

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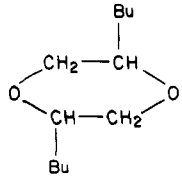
Ferric Chloride Induced Activation of Hydrogen Peroxide for the Epoxidation of Alkenes and Monoxygenation of Organic Substrates in Acetonitrile

Summary: In dry acetonitrile anhydrous $Fe^{III}Cl_3$ activates H_2O_2 for the efficient epoxidation of alkenes and the monoxygenation of alkanes, alcohols, ethers, aldehydes, thioethers, and sulfoxides.

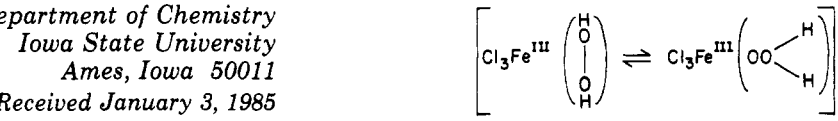
Sir: The recent observation[1] that iron(II) in ligand-free acetonitrile activates hydrogen peroxide to act as a monoxygenase and dehydrogenase (but *not* as an initiator of radical reactions via Fenton chemistry)[2] has prompted the consideration of other iron salts. Here we report that anhydrous ferric chloride ($Fe^{III}Cl_3$) in dry acetonitrile (MeCN) activates hydrogen peroxide to epoxidize alkenes and to monoxygenate or dehydrogenate other organic substrates.

Table IA summarizes the conversion efficiencies and product distributions for a series of alkene substrates subjected to the $Fe^{III}Cl_3$–H_2O_2/MeCN system. The extent of the $Fe^{III}Cl_3$-induced monoxygenations is enhanced by higher reaction temperatures and increased concentrations of the reactants (substrate, $Fe^{III}Cl_3$, and H_2O_2). For 1-hexene (representative of all of the alkenes) a substantial fraction of the product is the dimer of 1-hexene oxide, a disubstituted dioxane.[3]



With other organic substrates (RH) $Fe^{III}Cl_3$ activates H_2O_2 for their monoxygenation; the reaction efficiencies and product distributions are summarized in Table IB.[4] In the case of alcohols, ethers, and cyclohexane a substantial fraction of the product is the alkyl chloride, and with aldehydes [PhCH(O)] the acid chloride represents one-half of the product. In the absence of substrate the $Fe^{III}Cl_3$/MeCN system catalyzes the rapid disproportionation of H_2O_2 to O_2 and H_2O. Within the time constraints for the experiments (<20 min) there is no net reaction between H_2O_2 and the substrates or solvent in the absence of the $Fe^{III}Cl_3$ catalyst.

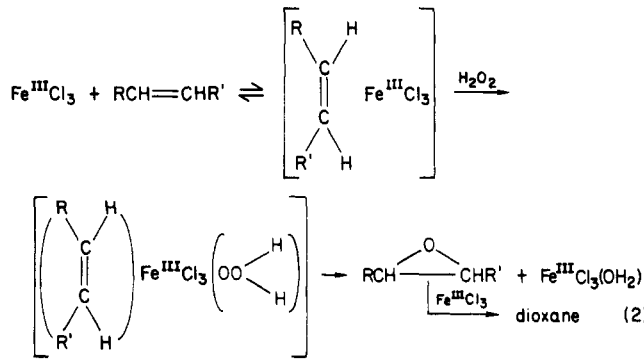
The activation of H_2O_2 by $Fe^{III}Cl_3$, which is an exceptionally strong Lewis acid and electrophilic center,[5] probably involves the initial formation of at least two reactive forms of an $Fe^{III}Cl_3$(HOOH) acid–base adduct that are in dynamic equilibrium (eq 1). We propose that this adduct



(1)

stimulates the disproportionation of H_2O_2 via concerted transfer of the two hydrogen atoms from a second H_2O_2. This dehydrogenation of H_2O_2 is a competitive process with the $Fe^{III}Cl_3$–substrate–H_2O_2 reactions. The controlled introduction of dilute H_2O_2 into the $Fe^{III}Cl_3$–substrate solution limits the concentration of H_2O_2 and ensures that the substrate–H_2O_2 reaction can be competitive with the second-order disproportionation process. The substrate reaction efficiencies in Table I appear to be proportional to the relative rates of reaction for the $Fe^{III}Cl_3$–H_2O_2 adduct with substrates and H_2O_2. The mode of activation of H_2O_2 by $Fe^{III}Cl_3$ is likely to be analogous to that by $Fe^{II}(MeCN)_4^{2+}$;[1] both are strong electrophiles in ligand-free dry MeCN and induce H_2O_2 to monoxygenate organic substrates.

The epoxidation of alkenes (Table IA) appears to involve an O-atom transfer from the end-on configuration of the $Fe^{III}Cl_3$(HOOH) adduct. The electrophilicity of $Fe^{III}Cl_3$ should promote the initial activation of the alkene bond prior to the binding of H_2O_2 (eq 2). The resulting epoxides



(2)

are rapidly dimerized to dioxanes. A control experiment has demonstrated that the complete conversion of an alkene to its epoxide is precluded; the more complete the conversion the higher the fraction of dioxane in the product mixture. With the cyclohexadienes and the stilbenes (PhCH=CHPh), the $Fe^{III}Cl_3$–H_2O_2/MeCN system promotes their dehydrogenation via a parallel catalytic process (Table IA), which may be equivalent to that for H_2O_2.

The present electrophilic activation of H_2O_2 by $Fe^{III}Cl_3$ for the epoxidation of olefins is much more facile and efficient than that by base in aqueous or methanolic sol-

(1) Sugimoto, H.; Sawyer, D. T. *J. Am. Chem. Soc.* **1984**, *106*, 4283.
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(3) Independent experiments confirm that $Fe^{III}Cl_3$ in dry MeCN catalyzes the rapid dimerization of epoxides to dioxanes.
(4) For all of the experiments summarized in Table I, the $Fe^{III}Cl_3$ catalyst remains completely in the Fe(III) state and there is no evidence for radical processes or for attack of the solvent. In dry MeCN the reduction potential for the $Fe^{III}Cl_3/Fe^{II}Cl_3^-$ couple is +0.46 V vs. NHE, and for the $Fe^{III}Cl_4^-/(Fe^{II}Cl_3^- + Cl^-)$ couple is +0.34 V.
(5) Donor solvents and ligands neutralize the acidity of $Fe^{III}Cl_3$. The addition of Cl^- to the $Fe^{III}Cl_3$–RH–H_2O_2/MeCN reaction system promotes formation of $Fe^{III}Cl_4^-$, which does not activate H_2O_2 for its disproportionation or for the monoxygenation of substrates and does not catalyze the dimerization of epoxides.

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