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Enantioselective Methods for Chiral Cyclohexane Ring Synthesis¹

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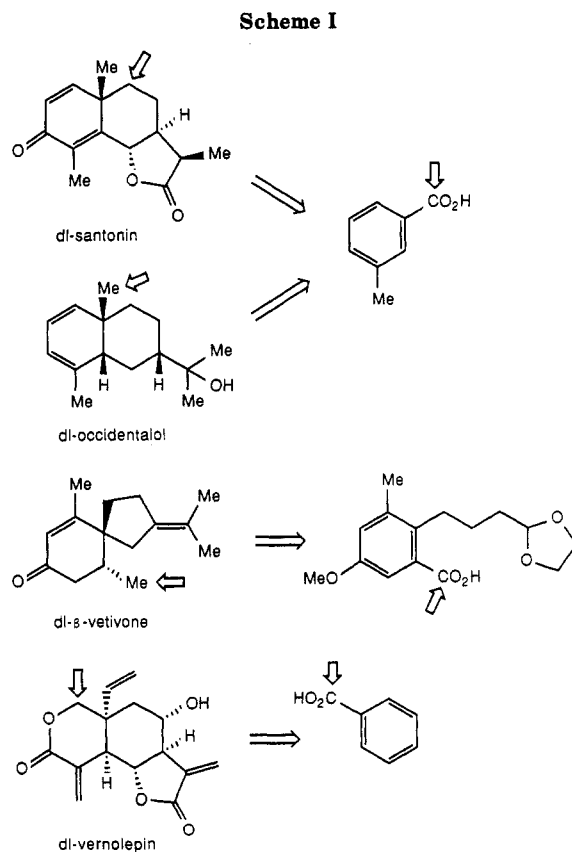
The cyclohexane ring occupies a pivotal position in organic chemistry. Stereochemical and mechanistic concepts have evolved from consideration of the chemical reactivity and spectroscopic properties of the cyclohexane ring system. Natural product chemists have discovered terpenoids, steroids, and alkaloids containing cyclohexane rings with a wondrous array of substituents, ring fusions, and degrees of unsaturation. Synthetic organic chemists of several generations have met the challenge of complex cyclohexane construction, but it has been only recently that enantioselective methods have been refined to provide exceptional stereocontrol. My research group has been involved in the development of such methods for the past five years. In this Account, I outline the highlights of our explorations.

Perspective

Asymmetric organic synthesis took a giant step forward in the period 1976–1978 as a result of reports of high diastereoselectivities for alkylation reactions of metalloenamines derived from chiral cyclohexanone imines and hydrazones.^{3,4} These and other studies directed at both cyclic and acyclic stereoselection established the importance of heteroatom substituents positioned in the chiral auxiliary to provide substrate rigidity by metal–heteroatom chelation. The more traditional concept of stereocontrol by incorporation of a stereogenic center (from the chiral auxiliary) within a rigid cyclic framework also has been used in the field of asymmetric synthesis.

It occurred to us that benzoic acid derivatives ought to be superb substrates for asymmetric syntheses of substituted cyclohexanes. A wide range of substituted benzoic acids are commercially available or may be

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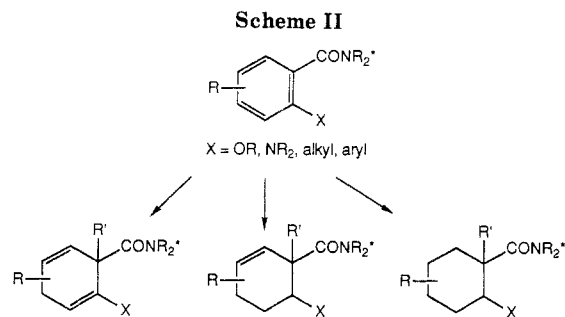


prepared by regioselective electrophilic aromatic substitution reactions or methodologies involving organo-

(1) Students of organic chemistry who desire a reprint of this article should direct their requests to the author.

(2) Schultz, A. G. *Acc. Chem. Res.* 1983, 16, 210.

(3) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 1–110.



metallic reagents. Furthermore, products of alkali metal in ammonia reduction (Birch reduction⁵) and reductive alkylation of achiral benzoic acids have been extensively utilized in syntheses of natural products that contain cyclohexane rings. Scheme I illustrates the flexibility of the reductive alkylation strategy for construction of several sesquiterpenes.

For syntheses of racemic santonin⁶ and occidentalol⁷ from reductive alkylation of *m*-toluic acid, Marshall and Wuts developed complementary methods to convert the carboxylic acid carbon atom to either a part of the annulated cyclohexane ring in santonin or the angular methyl group in occidentalol. Yamada's synthesis of racemic β -vetivone⁸ involved Birch reduction of a highly substituted benzoic acid and shows that the carboxyl-substituted carbon atom in the aromatic precursor need not reside at the quaternary center in the target structure. Vandewalle's synthesis of racemic vernolepin⁹ illustrates that reductive alkylation of benzoic acid provides sufficient latent functionality to fully develop the five contiguous asymmetric centers in the target structure.

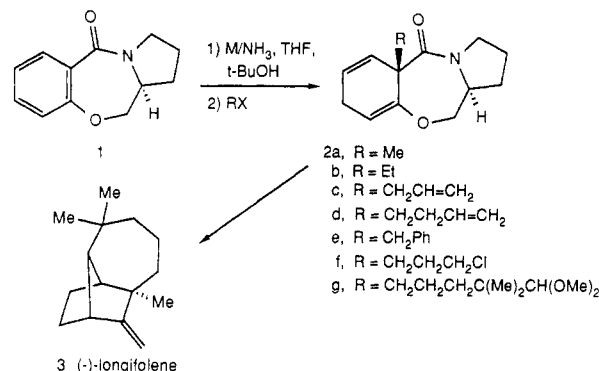
The essential aspects of our explorations over the last five years are summarized in Scheme II. It is now possible to prepare enantiomerically pure 1,4-dihydro-, tetrahydro-, and hexahydrobenzoic acid derivatives from 2-alkoxy-, 2-amino-, 2-alkyl-, and 2-arylbenzoic acids by employing alkali metal in ammonia reduction or reductive alkylation techniques either alone or in combination with heterogeneous or amide-directed homogeneous catalytic olefin hydrogenation. The inexpensive amino acid L-proline and the product of reduction with LiAlH₄, L-prolinol,¹⁰ serve as chiral auxiliaries to provide good to outstanding stereocontrol during amide enolate protonation or alkylation.

It is important to recognize that the very effective synthetic methodology to be described in this Account evolved from experimental observation. The reader will

be reminded that exciting chemistry can still be uncovered by the experimentalist who builds on observation rather than intricate preconceived hypotheses. Indeed, an accurately mapped approach was untenable because essential aspects of enolate structure and reactivity are not well understood.

The Method and General Mechanistic Considerations

Benzoxazepinone **1** is best prepared by the condensation-cyclization of 2-fluorobenzoyl chloride with L-prolinol.¹¹ Birch reduction of **1** at -78°C with alkali metals (Li, Na, or K) in NH₃-THF solution in the presence of 1 equiv of *tert*-butyl alcohol and alkylation of the resulting enolate with alkyl halides at -75°C gives predominately the diastereomeric series **2a-g**. Diastereoselectivity is only moderate with MeI (diastereomeric ratio 85:15), but with more sterically demanding alkyl halides such as ethyl iodide, allyl bromide, 4-bromo-1-butene, etc., diastereoselectivities are greater than 98:2. Assignment of configuration for the series **2a-g** was facilitated by conversion of **2g** to (-)-longifolene (**3**)¹² and an X-ray structure determination performed on a derivative of **2a**.¹¹



The acyclic amide **4** afforded an opportunity to examine alkylations of an enolate (e.g., **5**) which was expected to have configuration opposite to that of the cyclic enolate derived from **1**. This supposition was based on principles of chelation control;³ in fact, Birch reduction¹³ of **4** and alkylation of the resulting enolate with methyl iodide provided **6a** with a diastereoselectivity of 260:1.¹¹ Other common alkylation reagents gave **6b-e** with comparable high levels of stereocontrol. Thus, both *R* and *S* configurations at C(6) of the 1,4-cyclohexadiene ring system are accessible from a single chiral auxiliary. The chiral auxiliary can be removed from **2** and **6** by relatively simple hydrolytic methodology.^{12,14} With these practical considerations established, we set out to examine reaction variables that might contribute to the remarkable differences in the sense of stereoselection obtained from **1** and **4**.

Our first goal was to establish the relative importance of potential chelation sites in enolate **5**; e.g., the ring

(4) For recent syntheses of enantiomerically pure cyclohexane derivatives, see: Herradon, B.; Seebach, D. *Helv. Chim. Acta* 1989, 72, 690 and references cited therein.

(5) (a) For interesting insight to "the origin of the Birch reduction", see: Birch, A. J. *J. Chem. Educ.* 1975, 52, 458. Wooster, C. B. (to E. I. du Pont de Nemours and Co.) U.S. Patent 2,182,242; *Chem. Abstr.* 1940, 34, 1993. (b) For reviews of alkali metal in ammonia reduction and reductive alkylation of aromatic compounds, see: Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* 1986, 3, 35 and references cited therein.

(6) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* 1978, 43, 1086.

(7) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* 1977, 42, 1794.

(8) Yamada, K.; Nagase, H.; Hayakawa, Y.; Aoki, K.; Hirata, Y. *Tetrahedron Lett.* 1973, 4963.

(9) (a) Zutterman, F.; de Wilde, H.; Mijngheer, R.; de Clercq, P.; Vandewalle, M. *Tetrahedron* 1979, 35, 2389. (b) For a related route that begins by the Birch reduction of *p*-methoxybenzyl alcohol, see: Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* 1978, 100, 1940.

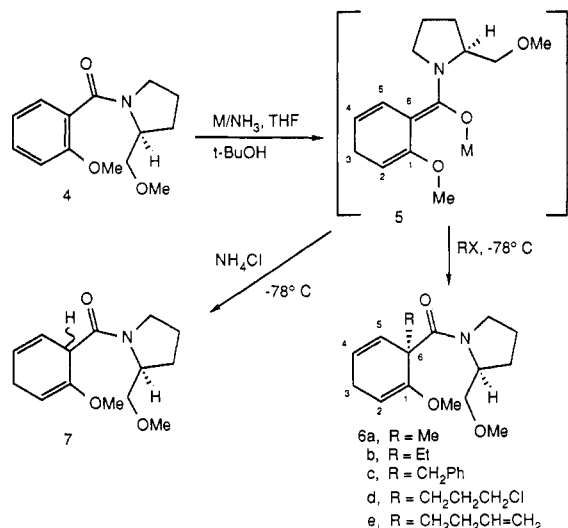
(10) For a discussion of the use of L-prolinol in asymmetric synthesis, see: Enders, D.; Kipphardt, H. *Nachr. Chem., Tech. Lab* 1985, 33, 882.

(11) Schultz, A. G.; Macielag, M.; Sundaraman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* 1988, 110, 7828.

(12) Schultz, A. G.; Puig, S. *J. Org. Chem.* 1985, 50, 915.

(13) Reduction of *N,N*-dialkylbenzamides with lithium can sometimes result in significant carbonyl group reduction. Functional-group reduction usually can be avoided by utilization of potassium metal; if the lithium enolate is required, then exchange with LiBr is recommended. For an investigation of the reaction parameters for Birch reduction and reductive alkylation of benzonitriles and benzamides, see: Schultz, A. G.; Macielag, M. *J. Org. Chem.* 1986, 51, 4983.

(14) McCloskey, P. J.; Schultz, A. G. *Heterocycles* 1987, 25, 437.

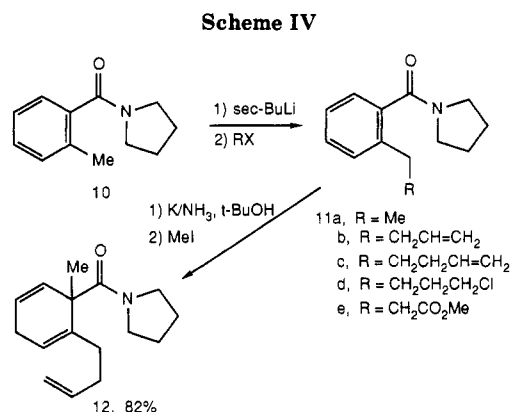
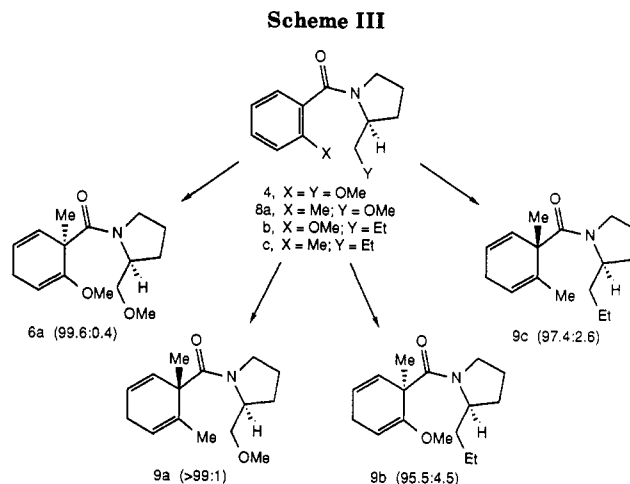


methoxy group vs the methoxy group on the chiral auxiliary. Scheme III shows the major stereoisomer and diastereoselectivities for reductive methylation (MeI) for 4 and substrates in which chelation sites on the aromatic ring and the chiral auxiliary have been modified. The complete reversal of the sense of stereoselection with the 2-methyl analogue (e.g., 8a → 9a) convincingly demonstrates the importance of the chelation site on the aromatic ring. The effect of the heteroatom on the side chain of the chiral auxiliary (8b → 9b and 8c → 9c) is small but significant. Although this secondary effect is interesting, the models that we have developed focus on the major perturbations resulting from the ring methoxy group; the side chain is considered to exert its effect primarily by steric interactions (vide infra).

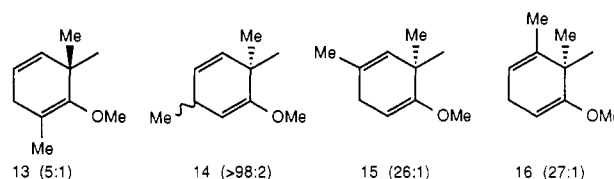
The C(6) configurational isomer of 9a can be obtained from 6a by simple carbonyl addition chemistry. Acid-catalyzed hydrolysis of the enol ether in 6a, followed by addition of MeMgBr and acid-catalyzed dehydration of the resulting carbinol, provided 9a (~70% yield) with inverted configuration at C(6). It is expected that carbonyl addition chemistry will complement the direct synthesis of the C(6) antipode from the relatively expensive D-prolinol-derived 2-alkylbenzamide.

The C(2) methyl group of the achiral benzamide 10 readily undergoes benzylic substitutions (Scheme IV).¹⁵ Reductive alkylation of 11b to give 12 occurs in 82% yield, demonstrating that, as expected, terminal olefins in the C(2) side chain are resistant to reduction by alkali metals in ammonia. Although currently in progress, chemistry related to that shown in Scheme IV is expected to provide enantiomerically pure substrates analogous to 12.

The effects of methyl group substitution at C(2), C(3), C(4), or C(5) on the stereoselectivity of methylation (MeI) of enolate 5 at C(6) have been examined.¹¹ The major stereoisomer resulting from each alkylation together with diastereoselectivities is illustrated in partial structures 13–16. These examples show that protonation at C(3) during Birch reduction is stereorandom (example 14) and that methyl group substitution at C(3), C(4), or C(5) does not substantially alter the stereoselectivity of enolate methylation. On the other



hand, methyl group substitution at C(2) results in an inversion of the sense of stereoselection to give 13 as the major diastereomer; reductive benzylation gives the C(6) benzyl analogue of 13 in 75% isolated yield with a remarkably high diastereoselectivity of 178:1.

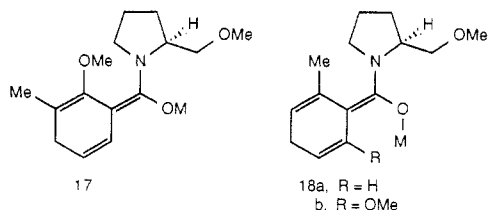


The effect of substitution at C(2) should be studied in greater detail, particularly with regard to variations in the group at C(2) and the alkylation reagent. However, it seems reasonable to conclude that the inverted sense of stereoselection displayed by 13 is a result of disruption of the internal chelation shown in enolate 5 by steric effects of the neighboring methyl substituent.¹¹

NMR studies have provided the basis for an assignment of configuration to the enolate generated from Birch reduction of 4; e.g., 5.¹¹ Enolate 17 is thought to be involved in the reductive alkylations of the corresponding 2-methoxy-3-methylbenzamide. Without the potential for internal chelation, the methoxy group might more favorably reside distant from the enolate oxygen atom. The effective size of the enolate oxygen atom in 17 could be very large as a result of enolate aggregation and coordination with solvent.

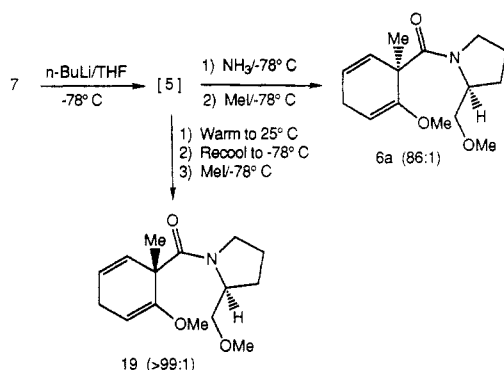
Analogous arguments have provided hypothetical structures for the enolates prepared by Birch reduction of 8a as well as 18b derived from the corresponding 2-methoxy-6-methylbenzamide. There is a satisfying

(15) (a) Green, N., unpublished results. (b) For a review of benzylic substitutions directed by a tertiary amide, see: Beak, P.; Snieckus, V. *Acc. Chem. Res.* 1982, 15, 306.



feature to the reactivity that must be proposed for enolates **5**, **17**, **18a**, and **18b**; the predominant direction of approach of the alkyl halide would be toward the α -face of C(6) for all of the enolates. It should be noted that this approach trajectory is anti to the side chain of the chiral auxiliary.

Reaction of enolate **5** with excess NH_4Cl at -75°C gave the 1,4-cyclohexadiene **7**. Deprotonation of **7** with bases such as *n*-butyllithium and lithium diisopropylamide provided opportunities to examine the behavior of enolate **5** under a variety of experimental conditions. While too involved to discuss in detail here, this study¹¹ uncovered extremely useful features of the reactivity of enolate **5**. Deprotonation of **7** with *n*-BuLi in THF at -78°C gave a modification of enolate **5** that exhibited no stereoselectivity on methylation at -78°C . However, the stereoselectivity of the reductive methylation of **4** could be approximated by addition of the appropriate amount of ammonia to **5** in THF ($\sim 10:1$ volume distribution of NH_3 to THF). When enolate **5** in THF was allowed to warm to 25°C prior to methylation at -78°C , the opposite C(6) configurational isomer **19** was obtained with diastereoselectivity $>99:1$. Diastereoisomer **19** also was the only product observed when ammonia was removed from Birch-reduced **4** prior to methylation at -78°C .¹⁶

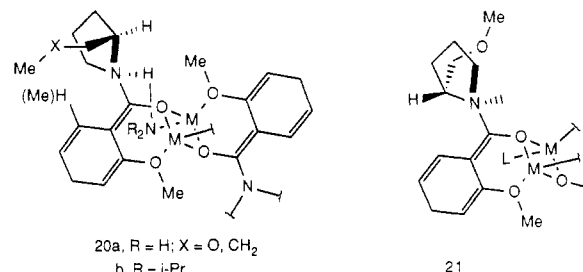


Thus, both *R* and *S* configurations at C(6) in a desired 1,4-cyclohexadiene should be available from a single chiral benzamide.¹⁷ Our unpublished work involving other alkylation reagents suggests that the solvent and reaction temperature effects observed for the production of **5a** and **19** will be quite general.

A consideration of NMR and enolate reactivity studies together with important structural studies appearing in the literature has allowed us to propose a model for the "kinetically generated" form of enolate **5** in ammonia solution.¹¹ This is shown as the partial structure **20a**, in which ammonia forms a bridge to both

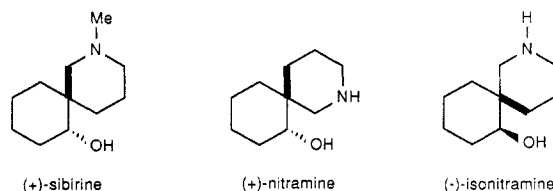
enolates in the dimeric aggregate. Computer-generated space-filling models of **20a** show that the β -face of C(6) is very effectively blocked by the side chain of the chiral auxiliary (CH_2OCH_3 in enolate **5** and $\text{CH}_2\text{CH}_2\text{CH}_3$ in the enolate generated from **8b**), while the α -face is quite exposed. It should be noted that the C(5) methyl substituent on enolate **18b** also is accommodated by model **20a**; there is relatively little steric interaction between the C(5) methyl group (shown in parentheses in structure **20a**) and the neighboring pyrrolidine ring. The model also explains why there is virtually no stereoselection when lithium diisopropylamide is used to deprotonate **7**. That is, the β -face of **20b** is blocked by the side chain of the chiral auxiliary, and the α -face is shielded by the bulky isopropyl groups on the amine bridge. Because of the hindrance at C(6), reactivity shifts to give 25% of the product of alkylation at C(2) of the enolate.

A model for the "thermodynamically generated" form of enolate **5** in THF solution is shown as the dimeric enolate aggregate **21**. This relaxed arrangement, obtained from **20a** by C-N bond rotation and nitrogen atom inversion, appears to have the side chain of the chiral auxiliary in the least congested environment away from the β -face of the enolate. A new ligand L, presumably a molecule of THF, would be at the coordination site occupied by ammonia in **20a**. The steric effects of the THF coordinated to the alkali metal and the removal of the β -facial obstruction would work in concert to direct alkylation to the β -face of the enolate.



It is important to emphasize that while models **20** and **21** are consistent with experimental data collected to date, they need a much firmer foundation. Undoubtedly, our understanding of the details of enolate structure will change with time and experience. At this stage, the models should serve only as guides to reactivity expectations and to further experimentation.

It is anticipated that alkali metal in ammonia reductive alkylations of benzoxazepinone **1**, the acyclic analogue **4**, and related chiral benzamides will find wide application in organic synthesis. Applications from our laboratory include syntheses of (-)-longifolene (**3**)¹² and the nitramine alkaloids (+)-sibirine, (+)-nitramine, and (-)-isonitramine.¹⁴

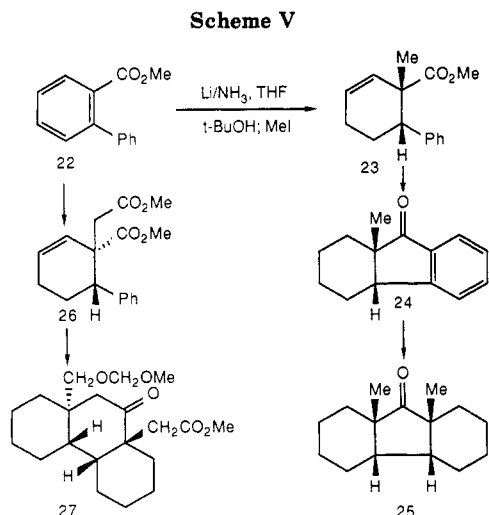


Biarylcarboxylic Acid Reductions

Reductive alkylations of biarylcarboxylic acid derivatives had not been reported in the literature¹⁸ prior to

(16) For an example of impressive solvent effects in the asymmetric alkylations of chiral metalloenamines prepared from β -keto esters, see: (a) Tomioka, K.; Ando, K.; Takemaso, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718. (b) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1345.

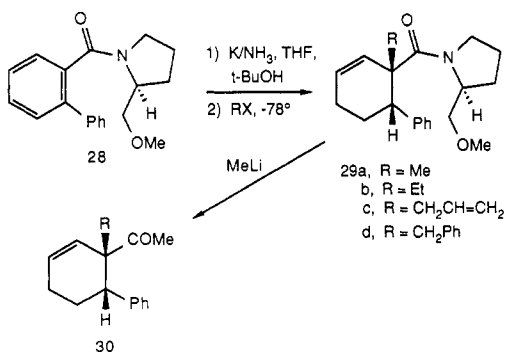
(17) The chiral benzamide **4** is now available from Aldrich Chemical Co., Inc.



our finding that it was possible to convert methyl 2-phenylbenzoate (**22**) (Scheme V) to the tetrahydrobenzoic ester **23** in 90% yield.¹⁹ In this case, sufficient lithium metal was added to insure reduction of two double bonds in the carbonyl-substituted aromatic ring, and 3 equiv of *tert*-butyl alcohol was required to serve as a source of protons for the reduced ring.

Scheme V also demonstrates the potential of biarylcarboxylic ester reductive alkylations for syntheses of ring systems common to several diterpenoid skeletons. Ester **23** was converted to the tricyclic ketone **24**, and a second stereodirected reductive alkylation and catalytic olefin hydrogenation afforded the *meso*-perhydrofluoren-9-one **25**. Analogous methodology following the reductive alkylation of **22** with methyl bromoacetate (77% yield of **26**) gave the perhydrophenanthren-9-one **27**.

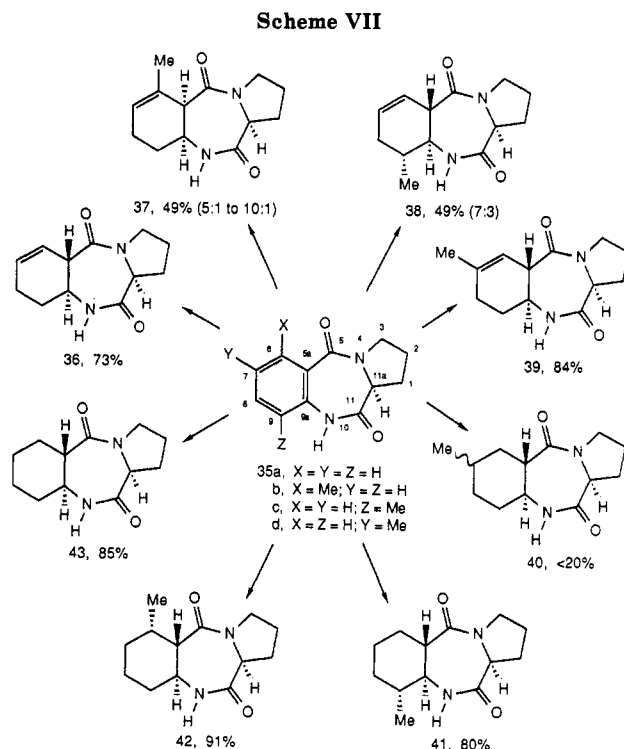
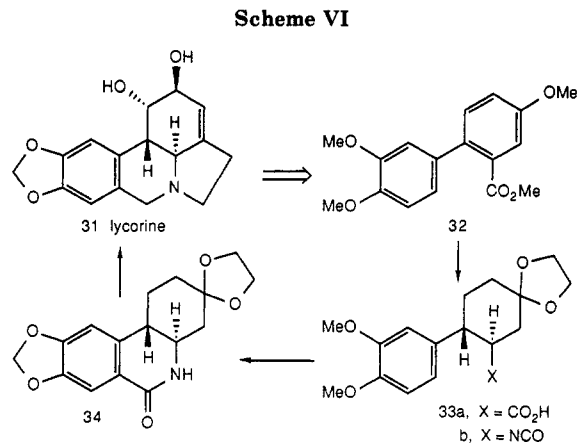
We were pleased to find that reductive alkylations of the chiral 2-phenylbenzamide **28** provided **29** as the major diastereoisomer (**29a**; 86% isolated yield). Stereoselectivity for protonation at C(4) is 10:1, and alkylation at C(3) occurs, as in the racemic series, anti to the phenyl substituent at C(4). Treatment of the tetrahydrobenzamide **29** with methyllithium gave methyl ketones **30**, thus demonstrating an alternative, synthetically attractive method for removal of the chiral auxiliary.



Birch reductions of biarylcarboxylic acid derivatives were expected to provide new strategies for the syn-

(18) Birch reductions of 2- and 4-biphenylcarboxylic acids have been reported to give dihydrobenzoic acids: (a) Franks, D.; Grossel, M. C.; Hayward, R. C.; Knutsen, L. J. S. *J. Chem. Soc., Chem. Commun.* **1978**, 941. (b) Rabideau, P. W.; Nyikos, S. J.; Huser, D. L.; Burkholder, E. G. *J. Chem. Soc., Chem. Commun.* **1980**, 210.

(19) Schultz, A. G.; Macielag, M.; Podhorez, D. E.; Suhadolnik, J. C.; Kullnig, R. K. *J. Org. Chem.* **1988**, *53*, 2456.



thesis of lycorine-type alkaloids.¹⁹ Initial studies in the racemic series focused on the conversion of **32** to lycorine **31** (Scheme VI).²⁰ This has been accomplished by Curtius rearrangement of **33a** to isocyanate **33b** and cyclization-functionalization of **33b** to give the tetracyclic lactam **34**; **34** has been converted to racemic lycorine **31** by Umezawa and co-workers.²¹ Birch reductions of oxygen-substituted chiral biarylcarboxamides have proven to be difficult to control; an enantioselective synthesis of **31** has not as yet been reduced to practice.

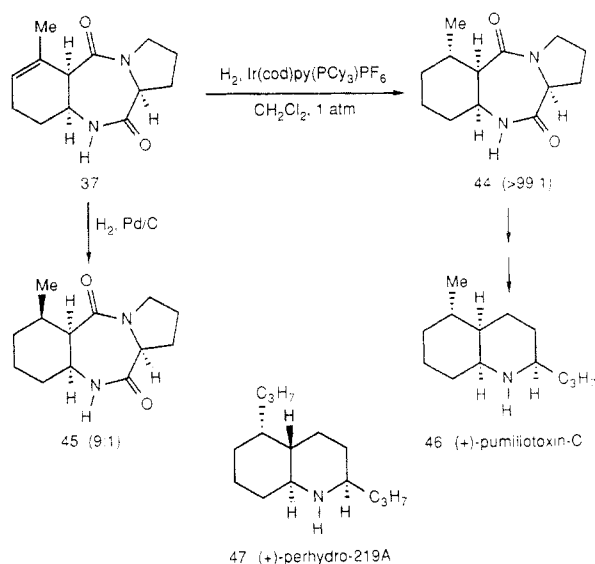
Anthranilic Acid Derivatives

Reduction of L-proline-derived diazepinedione **35a** with slightly greater than 4 equiv of potassium and 2 equiv of *tert*-butyl alcohol in ammonia and quenching of the C(5a) enolate with NH_4Cl gave **36** (Scheme VII).²²

(20) Podhorez, D. E., unpublished results. The 3,4-dimethoxy substitution pattern is utilized because the methylenedioxy bridge undergoes $\text{H}_2\text{C}-\text{O}$ bond cleavage at C(4) during Birch reduction. For a discussion of related hydrogenolysis reactions, see: Keefer, L. K.; Lunn, G. *Chem. Rev.* **1989**, *89*, 459.

(21) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475.

Scheme VIII



The C(6), C(9), and C(7) methyl substituted analogues were reduced under the same reaction conditions to provide 37, 38, and 39. The yields for isolated products are shown, and the ratios in parentheses refer to diastereoselectivities for protonation at C(5a). In every case shown in Scheme VII, protonation at C(9a) is completely stereoselective (kinetic control), but protonation at C(5a) is dependent on the precise method of quenching the C(5a) enolate.

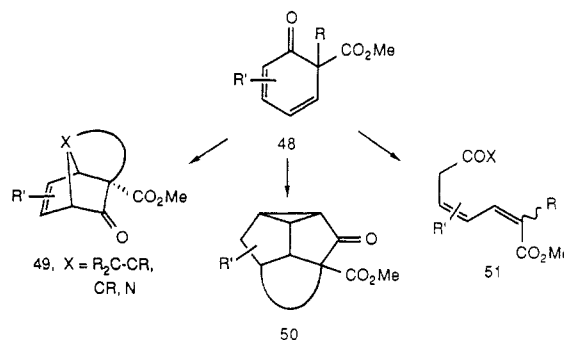
Reductions to the hexahydrobenzene oxidation state can be carried out by the use of 8 equiv of potassium and 5 equiv of *tert*-butyl alcohol. Product yields are excellent for formation of 41–43, but 40 is difficult to obtain by this procedure, because the trisubstituted double bond in 39 is reluctant to move into conjugation with the C(5) carbonyl group. It is noteworthy that the absolute configurations of up to three stereogenic centers on the cyclohexane ring are controlled by this experimentally simple methodology. The C(5a) enolates also undergo in situ alkylation,^{22,23} but we have concentrated on the utilization of substrates such as those shown in Scheme VII in the context of the decahydroquinoline alkaloid syntheses.

The total synthesis of (+)-pumiliotoxin C (46) required a stereoselective reduction of the C(6)–C(7) double bond in 37 from the β -face (Scheme VIII).²² Hydrogenation of 37 under heterogeneous conditions with 5% palladium on carbon gave an unfavorable 1:9 ratio of the desired 44 and its C(6) diastereoisomer 45. The proximity of the C(5) carbonyl group in 37 was used to advantage via coordination with the homogeneous catalyst/solvent system [Ir(cod)py(PCy₃)PF₆]/CH₂Cl₂²⁴ to give 44 in quantitative yield with better than 99:1 diastereoselectivity. This highly stereoselective process for amide carbonyl directed olefin hydrogenation is applicable to a wide range of substrates²⁵ and has proven to be an exceptionally useful adjunct to the enantioselective reductive alkylation of salicylic

acid derivatives.¹⁴ A modification of the methodology used to obtain 46 provided the first synthetic example of a new class of *trans*-decahydroquinoline alkaloids isolated from poison frogs of Colombia; e.g., (+)-perhydro-219A (47).^{26,27}

Applications to Cyclohexadienone Chemistry

A strong driving force for development of enantioselective syntheses of 1,4-cyclohexadienes emanated from an interest in the chemistry and photochemistry of 2,4- and 2,5-cyclohexadien-1-ones. We had demonstrated that racemic 2,4-cyclohexadien-1-ones 48²⁸ and 2,5-cyclohexadien-1-ones 52²⁹ are readily obtained from methyl 2-methoxybenzoates and that these substrates serve admirably in unique intramolecular cycloaddition and photorearrangement chemistry.³⁰ For example, Diels–Alder cycloadditions of 2,4-cyclohexadien-1-ones 48 give bridged bicyclo[2.2.2]octenones 49.³¹ Dipolar cycloaddition–rearrangement chemistry³² has provided access to bridged adducts of type 49 (X = CR^{12,33} or N³⁴). Bridged bicyclo[2.2.2]oct-5-en-2-ones 49 undergo triplet-state-sensitized oxadi- π -methane photorearrangement to fused carbocycles 50, which should be useful for polyquinane and related natural product synthesis.³¹ Ultraviolet irradiation of 2,4-cyclohexadien-1-ones³⁵ in the presence of nucleophilic solvents gives diene carboxylic acid derivatives (e.g., 51³⁴) generally in excellent yields.



Type A photorearrangements of 4-alkyl-4-carbomethoxy-2,5-cyclohexadien-1-ones 52 give bicyclo[3.1.0]hexenones 53,³⁸ while analogues with the

(26) McCloskey, P. J.; Schultz, A. G. *J. Org. Chem.* 1988, 53, 1380.

(27) Pyrrolobenzodiazepine-5,11-dione 35a is now available from Aldrich Chemical Co., Inc.

(28) (a) Schultz, A. G.; Dittami, J. P. *Tetrahedron Lett.* 1983, 24, 1369.

(b) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem.* 1984, 49, 4429.

(29) (a) Schultz, A. G.; Lavieri, F. P.; Macielag, M. *Tetrahedron Lett.* 1986, 27, 1481. (b) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* 1988, 29, 3907.

(30) For a review of the chemistry of cyclohexadienones, see: Waring, A. J. In *Advances in Alicyclic Chemistry*; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1966; Vol. 1, p 129.

(31) Schultz, A. G.; Lavieri, F. P.; Snead, T. E. *J. Org. Chem.* 1985, 50, 3086.

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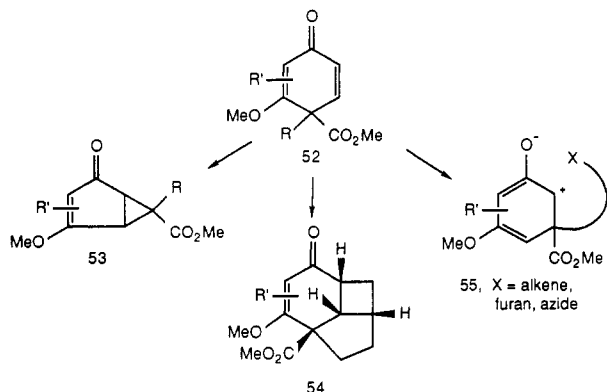
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4-(3'-alkenyl) or 4-(3'-pentynyl) groups undergo efficient 2 + 2 photocycloaddition to give fused cyclobutanes of type 54.³⁹ We have been particularly interested in the development of new intramolecular cycloaddition chemistry of oxyallyl zwitterions 55 that are generated by photorearrangement of bicyclohexenones 53.^{40,41}



Thus, a remarkable array of carbocyclic and heterocyclic ring systems are available by simple and generally efficient reactions of 2,4- and 2,5-cyclohexadien-1-ones. The stereoselective reductive alkylations of substrates such as 1 and 4 have played an important role in the

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elucidation of synthetic and mechanistic aspects of the indicated photorearrangements and cycloadditions.^{12,36-39}

Concluding Remarks

The basic stereochemical consequences of the method have been established, models to explain stereocontrol have been formulated, and synthetic applications that begin to define the potential of the strategy have been completed. Despite these advances, it seems that we have only scratched the surface. Other modes of enolate reactivity should be examined; enolate oxidations, aminations, and condensation reactions will offer unique synthetic opportunities. A better understanding of enolate reactivity and aggregation effects is expected to evolve from the next generation of chemical and spectroscopic studies.

Synthetic applications to date have been confined to issues of stereocontrol in targeted cyclohexane rings, but incorporation of ring contraction and expansion techniques will extend the scope of the methodology. Inasmuch as cyclohexenes and cyclohexanones undergo a multitude of ring-cleavage reactions, it is expected that enantiomerically pure polyhydroxylated acyclic materials and novel α -amino acids and α -hydroxy acids will be available by relatively straightforward modifications of the chemistry described in this Account.

It is a pleasure to acknowledge the very significant contributions of graduate and postdoctoral students; their names are recorded in the references. Support from the National Institutes of Health (Grants GM 26568 and GM 33061) is appreciated.

Quadrupole Ion Trap Mass Spectrometry

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In 1956 Paul described a device for containing gaseous ions in a small volume using only electric fields.¹ Three electrodes, two end-cap electrodes and a central ring electrode, each of hyperbolic cross section, form a chamber within which ions can be confined (Figure 1). Application of a radio-frequency (rf) voltage to the ring electrode establishes a quadrupole electric field in which the force on an ion is proportional to its distance from the center of the device; this allows ions of appropriate mass-to-charge ratios to have stable trajectories within

A cooperative effort was undertaken in 1984 between Purdue University and Finnigan Corporation to construct an ion-trap mass spectrometer capable of performing MS/MS experiments. It is not difficult to persuade students from the middle west to spend time in California, and graduate student John Louris spent a number of months at San José in 1985 assisting John Syka and George Stafford in building this instrument, which became the prototype of the commercial ion-trap mass spectrometer (ITMS). This Account picks up the story at this point, illustrating fundamental studies of ion chemistry and applications to chemical analysis of this newest breed of mass spectrometers.

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the chamber and to be trapped for many seconds. This apparatus, the "Paul trap" or the "quadrupole ion trap", quickly came to be used for mass spectrometry² and for spectroscopy of stored ions.³ For their pioneering work with ion traps, Wolfgang Paul of the University of Bonn and Hans Dehmelt of the University of Washington shared in the 1989 Nobel Prize for physics. As a mass spectrometer, the ion trap was and still is overshadowed by the quadrupole mass filter, also first described by Paul.⁴

In 1984 the first commercial quadrupole ion trap, based on a new method⁵ of selectively ejecting ions of

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