or any derivatives thereof have been observed for these reactions. This cyclohexadienone annulation is regioselective such that the acetylene substituent becomes adjacent to the carbon monoxide derived carbonyl. The direction of the regioselectivity is the same as has been observed for the benzannulation reaction,[4] and it is confirmed by the magnitude (J = 3 Hz) of the coupling constants between the two vinyl hydrogens of **14** (R_S = H) and also confirmed by the independent synthesis described below. By way of comparison we have found that the 2,6-dimethylphenyl complex **5** reacts with (trimethylsilyl)acetylene to give the vinyl ketene **15** in 69% yield.[17] Vinyl ketenes have been observed before but only with silyl-substituted acetylenes and the reasons for this are unclear.[18]

The annulation of the carbene complex **16**,[20] which bears an asymmetric carbon, has been examined and occurs with substantial diasterioselectivity in the decalindienone products as indicated in Scheme IV.[16] The annulated products **17** can be obtained in good yields as the trans isomers with a minimum of 90% stereoselectivity in all cases. The trans configuration of **17** (and the regiochemistry as well) was confirmed for the reaction of **16** and propyne. A THF solution of the cycloadduct **17** (R = Me) was hydrolyzed with 10% aqueous HCl to give a 5.5:4.2:1 ratio of three of the four possible diastereomeric enediones **20**, which were separated and characterized. A trans configuration of the methyl groups for the two major diastereomers **20** was consistent with the spectral data and was confirmed by comparison with authentic samples which were prepared by a Lewis acid mediated Diels–Adler reaction of 2,6-dimethylbenzoquinone and *trans*-piperylene[23] followed by hydrogenation and epimerization.[22] The reaction of **16** with propyne also gave a 7% yield of the phenol **18**.[24] We have observed this type of product in other reactions of chromium carbene complexes and acetylenes and will report on their formation separately.

One possible explanation of the observed diastereoselectivity involves an electrocyclic ring closure of the 1-chromatriene functionality in intermediate **19**.[3] If there is an $A^{(1,2)}$ interaction[25] of the methoxyl and the pseudoaxial methyl group, then this would cause the chromium to approach from the face syn to the methyl. The origin of the differences in the reactivity of the complexes **5** and **11** (and **16**) are not clear at this time, nor is the fact that 3-hexyne gives reduced yields compared to terminal acetylenes. We are continuing to investigate these observations and have made similar ones for other reactions of Fischer carbene complexes and acetylenes.[26]

Cyclohexa-2,4-dienones are versatile intermediates that have been employed in number of syntheses.[27] That their synthetic potential has not been fully realized is largely due to the paucity of methods for their preparation.[28,29] The cyclohexadienone annulation of Fischer chromium carbene complexes provides for a direct, regio- and stereoselective approach to this ring system under neutral conditions at near ambient temperatures. It also offers quite attractive approaches to the synthesis of a number of natural products. We will report on further studies and applications of this reaction.

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Registry No. 5, 72532-29-7; **11**, 60920-65-2; **14** (R_L = Ph; R_S = H), 88563-56-8; **14** (R_L = Me_3Si; R_S = H), 88563-57-9; **14** (R_L = Bu; R_S = H), 88563-58-0; **14** (R_L = R_S = Et), 88563-59-1; **14** (R_L = Me; R_S = H), 88563-60-4; **14** (R_L = CH_2OAc; R_S = H), 88563-61-5; **15**, 88563-62-6; **16**, 88563-63-7; *trans*-**17** (R = Ph), 88563-64-8; *cis*-**17** (R = Ph), 88563-65-9; *trans*-**17** (R = Me_3Si), 88563-66-0; *cis*-**17** (R = Me_3Si), 88563-67-1; *trans*-**17** (R = Bu), 88563-68-2; *cis*-**17** (R = Bu), 88563-69-3; *trans*-**17** (R = Me), 88563-70-6; *cis*-**17** (R = Me), 88563-71-7; **18**, 88563-72-8; **20**, 88563-73-9; PhC≡CH, 536-74-3; Me_3SiC≡CH, 1066-54-2; $CH_3(CH_2)_3C$≡CH, 693-02-7; CH_3CH_2C≡CCH_2CH_3, 928-49-4; CH_3C≡CH, 74-99-7; $AcOCH_2C$≡CH, 627-09-8.

(15) Unless otherwise specified, satisfactory spectral data and elemental analysis or high-resolution mass spectra were obtained for all new compounds.

(16) The reactions were carried out under argon at 0.1 M in **11** with 1.5 equiv of acetylene. Workup involved opening to air, removal of reaction solvents, and purification of the cyclohexadienone by flash chromatography.[14] With acetonitrile as reaction solvent acetonitrile pentacarbonyl chromium[19] was also obtained in each case (50–70%). The reactions of **16** have not been examined in acetonitrile. We have not yet looked for any organometallic complexes in the THF reactions before subjecting to air oxidation.

(17) The *E* configuration of the vinylketene **15** was confirmed by a difference NOE experiment giving a 20% enhancement for the vinyl hydrogen upon irradiation at the methoxyl. The vinyl ketene **15** was unchanged after heating as a C_6D_6 solution in a sealed ampule at 200 °C for 24 h as monitored by ^1H NMR (500 MHz), IR, and TLC.

(18) Dötz, K. H.; Fuegen-Koester, B. *Chem. Ber.* **1980**, *113*, 1449.

(19) Ross, B. L.; Grasselli, J. G.; Ritchey, W. M.; Kaesz, H. D. *Inorg. Chem.* **1963**, *2*, 1023.

(20) Complex **16** can be prepared according to the general procedure in ref 11 by using a vinyllithium generated from the trisylhydrazone[21] of 2,6-dimethylcyclohexanone in 39% yield.[22]

(21) Chamberlin, A. R.; Stinke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(22) The full details on this synthesis will be reported in a full paper on this work.

(23) Stojanac, A. Dickinson, R. A.; Stojanac, N.; Woznow, R. J.; Valtentin, Z. *Can. J. Chem.* **1975**, *53*, 616.

(24) The reaction of **16** with 4 equiv of propyne gives a 28% of **17** and a 20% yield of **18**.

(25) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(26) Unpublished results from this laboratory.

(27) For examples, see: (a) Macas, T. S.; Yates, P. *Tetrahedron Lett.* **1983**, *147*. (b) Widmer, E.; Zell, R.; Grass, H.; Marbet, R. *Helv. Chim. Acta.* **1982**, *65*, 958. (c) Naf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. *Ibid.* **1981**, *64*, 1387. (d) Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. (e) Oppolzer, W.; Snowden, R. L. *Tetrahedron Lett.* **1978**, 3505. (f) Wenkert, E.; Berges, D. A.; Golob, N. F. *J. Am. Chem. Soc.* **1978**, 100, 1263. (g) Fukamiiya, N.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin trans. 1*, **1973**, 1843. (h) Danishefsky, S.; Dumas, D. *Chem. Commun.* **1968**, *1287*.

(28) For a review, see: Waring, A. J. In *Adv. Alicyclic Chem.* **1966**, *1*, 129.

(29) For examples, see ref. 27a,b,f and: (a) Schultz, A. G.; Dittami, J. P. *Tetrahedron Lett.* **1983**, 1369. (b) Berge, J. M.; Max, R.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 2230. (b) Berge, J. M.; Max, R.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, 2230. (c) *Org. Synth.* **1966**, *46*, 115. (d) Alder, K.; Flock, F. H.; Lessenich, H. *Chem. Ber.*, **1957**, *90*, 1709.

Stereocontrolled Total Synthesis of (+)-Actinobolin by an Intramolecular Diels–Alder Reaction of a Chiral *Z* Diene Derived from L-Threonine

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Bactobolin, recently isolated from the culture broth of a *Pseudomonas*, has been shown to be a structural analogue of actinobolin isolated from a *Streptomyces* in 1959.[1,2] The unique polyfunctional structure containing five asymmetric carbons located consecutively within such a simple bicyclic system and biological activity of actinobolin (**1**, free amine) and bactobolin (**2**, free amine) distinguish these molecules as unusually interesting targets for synthesis. We report here the first total synthesis of (+)-actinobolin. The key step of the present strategy is the stereocontrolled formation of the bicyclic γ-lactam **8** by the intramolecular Diels–Alder reaction of the *Z* diene **7**.[3] Among recent studies on the intramolecular Diels–Alder reactions, only Fuchs and his co-workers recently showed a remarkable success in the chiral and stereochemical control of a potential intermediate

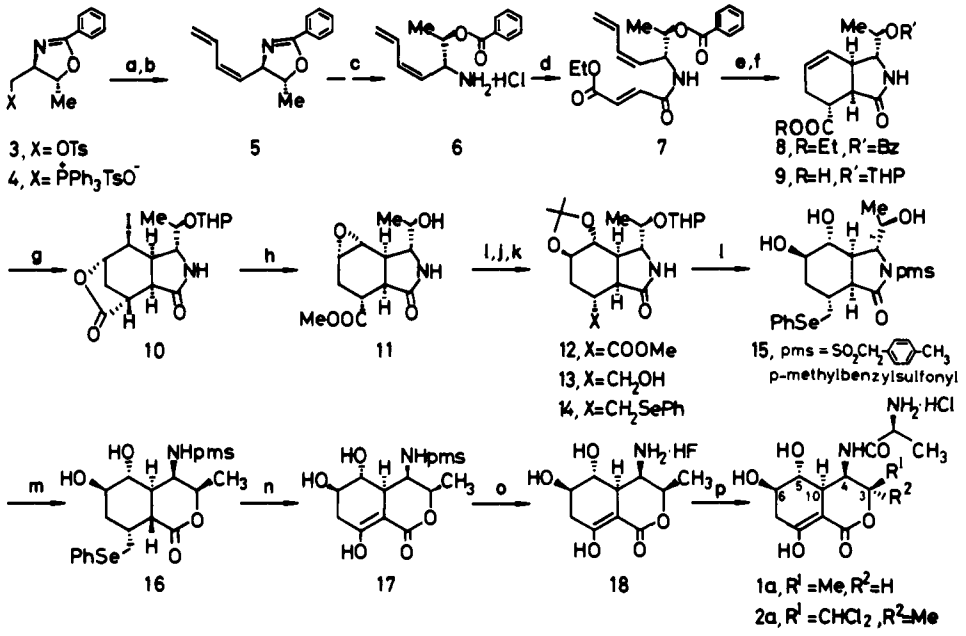
(1) Antotz, F. J.; Nelson, D. B.; Herald, D. L., Jr.; Munk, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 4933 and references cited therein.

(2) (a) Kondo, S.; Horiuchi, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1979**, *32*, 1069. (b) Ueda, I.; Munakata, T.; Sakai, J. *Acta Crystallogr., Sect. B* **1980**, *B36*, 3128.

(3) This work outlined here was presented at the 25th Symposium on the chemistry of Natural Products, Tokyo, Oct 19, 1982, Abstracts p 116.

0002-7863/84/1506-1133$01.50/0

Scheme I



for the synthesis of cytochalasin C by using a *Z* diene possessing a substituent at the pentadienylic position.[4] As shown in Scheme I, L-threonine was selected as the chiral synthon and converted into the tosylate **3** of (4*R*,5*R*)-4-(hydroxymethyl)-5-methyl-2-phenyl-Δ^2-oxazoline by four-step known procedures[5] (95% overall yield). The phosphonium tosylate **4** obtained by treatment of neat **3** with Ph_3P at 130 °C (85% yield) was directly subjected to Wittig reaction with acrolein, affording a diene **5** in 72% yield.[6] The ratio of *Z* and *E* isomers was determined to be 97 to 3 by gas chromatography, and the mixture was subjected to the following reactions without separation. Selective hydrolysis of **5** to **6** took place smoothly with 1 N HCl (95% yield). Reaction of **6** with ethyl (*E*)-3-(chloroformyl)acrylate[7] afforded crystalline *Z* diene **7** in 97% yield. The *Z* diene **7** was purified at this stage by recrystallization. Heating a solution of **7** in benzene at 180 °C in a sealed tube for 2 h produced **8** in 97% yield. Careful survey of the product by 400-MHz ^1H NMR showed that the desired Diels–Alder adduct was almost exclusively formed, and the very minor peaks were assumed to be due to the isomer. The ratio of **8** and the isomer was calculated to be at least 20 to 1. This finding demonstrates that cyclization has occurred stereoselectively through an expected preferred single diastereomeric transition state. The introduction of the vicinal hydroxyl groups with desired stereochemistry was completed in a stereospecific manner. The hydroxyl group of **8** was protected with THP to afford **9** quantitatively. Then, the THP derivative **9** was subjected to iodolactonization to afford γ-lactone **10** stereospecifically and quantitatively. Successive treatment of **10** with NaOH, CH_2N_2, and TsOH afforded epoxide **11**[8] quantitatively. Next, the epoxide **11** was subjected to acid-catalyzed cleavage to afford the desired glycol. The glycol was protected with an isopropylidene group and thence converted to the THP derivative to afford **12** (93% overall yield from **11**). The stereochemistry at C5 and C6 of **12** was fully supported by spectroscopic analysis.[12] The conversion described above clearly showed that the ethoxycarbonyl group was playing key roles in the present strategy. It not only activates the dienophile group but also controls the stereochemistry of the vicinal glycol of the six-membered ring. The ester group of **12** was reduced, and the resulting alcohol **13** was converted to the phenylseleno derivative **14** (96% overall yield from **12**). The crucial step of the present approach was found in the conversion of the γ-lactam **15** to δ-lactone **16**. The sulfonyl derivative **15** prepared from **14** and (*p*-methylphenyl)methanesulfonyl chloride ((pms)Cl)[9] (90% yield) underwent smooth cleavage with MeONa to afford the desired δ-lactone **16** in 86% yield.[10] The complete structure of **16** was unambiguously verified by X-ray analysis,[12] showing that the cis junction in **15** was isomerized to a trans junction in **16** under basic condition. Successive treatment of **16** with ozone and pyridine afforded the corresponding exomethylene derivative (92% yield). The oily material was further subjected to ozonolysis at −50 °C, affording **17** in 85% yield. Removal of the sulfonyl group of **17** proceeded smoothly with HF to afford the HF salt of **18**. The last step for the total synthesis of **1** was completed by condensation of **18** and ((benzyloxy)carbonyl)alanine followed by smooth hydrogenolysis (5 min) with H_2/Pd–C in MeOH–AcOH containing 2 N HCl, affording the hydrochloride **1a** (86% overall yield from **17**), identical with natural (+)-actinobolin hydrochloride:[11] $[\alpha]^{22}_D$ +55° (*c* 0.47, H_2O) for synthetic **1a**; $[\alpha]^{22}_D$ +59° (*c* 0.41, H_2O) for the natural sample. The total synthesis of (+)-actinobolin consists of 29 steps in good overall yield from L-threonine, and more significantly the present synthesis shows a notable example in which the intramolecular Diels–Alder reaction of a chiral *Z* diene with a substituent at the pentadienylic carbon is a very efficient methodology for the construction of polyfunctional bicyclic systems.

(4) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719 and references cited therein.
(5) Moss, R. A.; Lee, T. B. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2778.
(6) The Wittig reaction from the phosphonium iodide and acrolein afforded **5** only in 20% yield, and for such a Wittig reaction using phosphonium tosylate, see: Bestmann, H. J.; Kranz, E. *Chem. Ber.* **1969**, *102*, 1802.
(7) Anschütz, R. *Liebigs Ann. Chem.* **1928**, *461*, 189.
(8) Epoxidation of **8** with MCPBA afforded a mixture of α- and β-epoxides in 76% yield (about 1 to 1 ratio).
(9) Fukuda, T.; Kitada, C.; Fujino, M. *J. Chem. Soc., Chem. Commun.* **1978**, 220.
(10) The γ-lactam **14** was treated first with *n*-BuLi at −78 °C and then (*p*-methylphenyl)methanesulfonyl (pms) chloride was added at 0 °C.
(11) The small discrepancy in the optical rotation was considered to be due to mainly the hygroscopic property of **1a**.
(12) The X-ray and other physical data and methods of isolation and purification were all listed in the supplementary material.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Cancer Research (56-7) from the Ministry of Health and Welfare, Japan. We are also grateful to Prof. Y. Iitaka and Dr. H. Nakamura for X-ray analysis, and Drs. S. Kobayashi and T. Izawa for helpful discussion, and Dr. K. Fujita and T. Tsuri for experimental help at the early stage. We thank the Research Institute, Yoshitomi Pharmaceutical Industries, Ltd., for generous gifts of the natural product **1** and also Chemical Research Laboratories, Sankyo Co. Ltd., for the use of HF apparatus.

Registry No. **1**, 24397-89-5; **1a**, 88549-75-1; **3**, 88549-76-2; **4**, 88549-78-4; **5**, 88549-79-5; **6**, 88549-80-8; **7**, 88549-81-9; **8**, 88549-82-0; **9**, 88549-83-1; **10**, 88549-84-2; **11**, 88549-85-3; **12**, 88549-86-4; **12a**, 88549-94-4; **13**, 88549-87-5; **14**, 88549-88-6; **15**, 88549-89-7; **16**, 88549-90-0; **16** (*exo*-methylene derivative), 88549-91-1; **17**, 88549-92-2; **18**, 88549-93-3; **18a**, 88549-95-5; (*E*)-EtOCCH=CHCOCl, 26367-48-6; Z-Ala, 1142-20-7; L-threonine, 72-19-5; acrolein, 107-02-8.

Supplementary Material Available: Structural and physical data for Scheme I and X-ray data (9 pages). Ordering information is given on any current masthead page.

Complete Intramolecular Transfer of a Central Chiral Element to an Axial Chiral Element. Oxidation of (*S*)-4-Naphthyldihydroquinolines to (*S*)-4-Naphthylquinolines

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Asymmetric induction has become one of the cornerstones in modern synthetic methodology leading to a host of enantiomerically enriched compounds (EEC) and enantiomerically pure compounds (EPC).[1] The use of so-called chiral auxiliaries to induce biased stereochemical changes has allowed investigators to form C-H, C-C, C-O, and C-N bonds with high enantioselectivity (>90%) and enantiomerically pure compounds after removal of the auxiliary. Rare among these enantioselective processes is the *inter*molecular transfer of chirality[2] or the *intra*molecular transfer of chiral elements or stereogenic units[3] (that portion of the molecule where the symmetry is perturbed).[4]

In 1955 Berson[5] proposed an experiment to transform a chiral 4-aryl-1,4-dihydropyridine to a 4-arylpyridine with simultaneous destruction of the chiral element at C-4 in the former to an axial chiral element in the latter. Due to experimental difficulties the postulate that transfer of these chiral elements should occur could not be verified. Since that time, processes that involve conservation of chirality with simultaneous creation and destruction of chiral elements have come to be known as "self-immolative",[6] and examples are still rare. Although central to axial chiral element transfers (or vice versa) have been observed in allene systems[7] and a hetero-ene reaction,[8] we are unaware of any reports describing the type Berson sought to uncover, namely in the biaryl series.[9] We now report that this process indeed occurs, as Berson predicted, for the chiral dihydroquinoline *S*-**6a** to the quinoline *S*-**7** with >95% conservation of chirality. Our experiments were founded on an earlier observation in which pyridines and quinolines containing a chiral oxazoline in the 3-position led to high diastereoselective addition with organometallics to furnish 4-substituted-1,4-dihydropyridines or quinolines.[10,11] Thus, addition of naphthyllithium to the quinoline oxazoline **1** gave the dihydro derivative **2** (90%), which was analyzed for diastereomeric excess using HPLC. By converting an aliquot to the urethane **2a**, an 88:12 mixture of **2a**:**4a** was observed (reverse phase, 9:1 MeOH-H_2O, accuracy was ±1%). The remainder of **2** was then oxidized with dichlorodicyanoquinone (DDQ) in THF at −78 °C to give

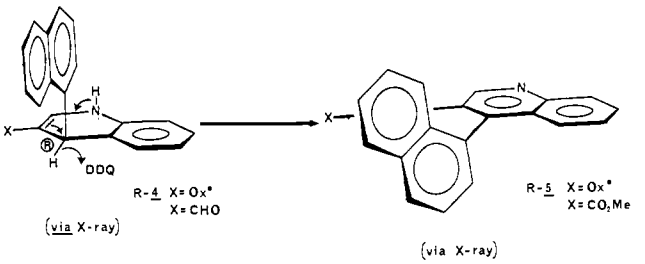
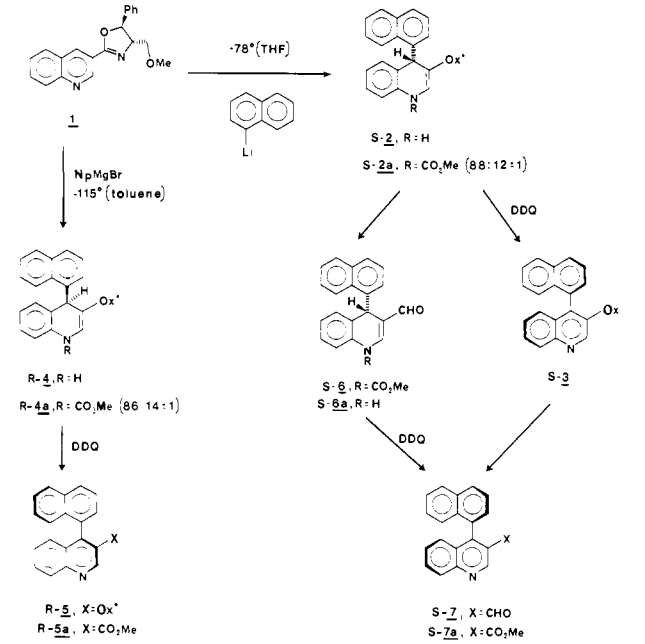


Figure 1.

Scheme I



(1) "Asymmetric Synthesis–A Multivolume Treatise", Morrison, J. D., Ed.; Academic Press: New York, 1984. "Modern Synthetic Methods"; Scheffold, R., Ed.; Verlag Sauerlander: Frankfurt, **1979**. Scott, J.; Valentine, D. *Synthesis* **1978**, 329. Apsimon, J. W.; Segun, R. P. *Tetrahedron* **1979**, *35*, 2797.

(2) The first example of a true chirality transfer in an intermolecular process was described for the reaction of (*S*)-2-octanol and (*S*)-pinacolyl alcohol with a bridged biphenyl ketone in the presence of aluminum *tert*-butoxide to give an optically active biphenyl: Newman, P.; Rutkin, P.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 465. For a related example, see: Morrison, J. D.; Ridgway, R. W. *J. Org. Chem.* **1974**, *39*, 3107.

(3) For a discussion on these and other terms and their usage to define stereochemical properties, see: Prelog, V.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 567. Mislow, K.; Siegel, J. *J. Am. Chem. Soc.*, submitted for publication.

(4) Warnhoff, E. W.; Lopez, S. V. *Tetrahedron Lett.* **1967**, 2723.

(5) Berson, J. A., Brown, E. *J. Am. Chem. Soc.* **1955**, *77*, 450.

(6) Mislow, K. "Introduction to Stereochemistry"; W. A. Benjamin: New York, 1966; p 12. Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971; pp 384–390.

(7) Hayashi, T.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 807. Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. "Stereochemistry"; Kagan, H., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 3, pp 10–11.

(8) Bertrand, M.; Roumestant, M. L.; Sylvestre-Panthet, P. *Tetrahedron Lett.* **1981**, *22*, 3589.

(9) The transformation of thebaine to phenyldihydrothebaine wherein four asymmetric centers are destroyed to give an optically active biphenyl was studied by: Berson, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 4170. However, this is a special case where the complexity of the molecule may play a significant role. Berson, realizing this problem, attempted to study an unencumbered system in simple 4-arylpyridines.[5]

(10) Meyers, A. I.; Natale, N. R.; Wettlaufer, D. G. *Tetrahedron Lett.* **1981**, *22*, 5123.

(11) For the synthesis of chiral binaphthyls using chiral or achiral oxazolines by direct substitution of alkoxy by organometallics, see: Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. Cram, D. J.; Wilson, J. *Ibid.* **1982**, *104*, 881.

0002-7863/84/1506-1135$01.50/0