(c 1.4, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 0.90 (s, 3 H, C-18H_3), 1.25–1.56 (m, 4 H), 1.70–2.04 (m, 5 H), 2.15 (dd, J = 9.3, 18.9 Hz, 1 H, C-14H), 2.44 (dd, J = 3.0, 16.8 Hz, 1 H, C-6βH_2), 2.77 (ddd, J = 0.6, 4.8, 11.1 Hz, 1 H, C-7αH_2), 2.84 (br d, J = 10.5 Hz, 1 H, C-9H), 3.00 (dt, J = 6.0, 12.9 Hz, 1 H, C-7βH_2), 3.37 (s, 3 H), 6.61 (d, J = 2.7 Hz, 1 H, C-4H), 6.74 (dd, J = 2.7, 8.7 Hz, 1 H, C-2H), 6.95 (d, J = 8.7 Hz, 1 H, C-1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.7 (CH_2), 27.2 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 34.7 (CH_2), 47.2 (CH_2), 48.2, 55.1 (CH), 64.5 (CH_3), 69.0 (CH), 111.9 (CH), 113.2 (CH), 125.9 (CH), 130.3, 135.9, 157.7, 219.0; IR (thin film) 3040, 2985, 2955, 2910, 2855, 2835, 2790, 2770, 2725, 1740, 1610, 1500, 1450, 1365, 1305, 1245, 1190, 1035 cm^{-1}; GCMS t_R = 15.9 (oven temp: 50 °C for 2 min, 15°/min to 280 °C for 5 min); EIMS m/z (rel int) 285 (M^+, 32), 284 (21), 257 (14), 256 (9), 162 (13), 161 (base), 146 (11). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.79; H, 8.07; N, 4.91. Found: C, 75.70; H, 8.14; N, 4.87.

The supernatants from above were combined and subjected to chromatography (eluted with 5% EtOAc/hexanes) to give 92 mg of **25** (>98% epimerically pure by ^1H NMR in C_6D_6) as fine white needles: mp 115–116 °C; $[\alpha]_D$ = −14.3° (c 0.42, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3 H, C-18H_3), 1.12–1.26 (m, 1 H, C-11αH_2), 1.43 (dt, J = 4.2, 13.5 Hz, 1 H, C-12βH_2), 1.98–2.51 (m, 7 H), 2.61 (br d, J = 15.0 Hz, 1 H, C-6βH_2), 2.66 (d, J = 3.9 Hz, 1 H, C-14H), 2.99 (dt, J = 4.7, 14.1 Hz, 1 H, C-7αH_2), 3.18 (br d, J = 10.8 Hz, 1 H, C-9H), 3.33 (ddd, J = 1.8, 5.4, 11.4 Hz, 1 H, C-7βH_2), 3.75 (s, 3 H), 6.58 (d, J = 2.4 Hz, 1 H, C-4H), 6.69 (dd, J = 2.4, 8.7 Hz, 1 H, C-2H), 7.07 (d, J = 8.7 Hz, 1 H, C-1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (CH_2), 23.7 (CH_3), 29.2 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 33.5 (CH_2), 48.7 (CH_2), 50.2, 55.2 (CH), 61.8 (CH_3), 69.4 (CH), 112.0 (CH), 113.0 (CH), 126.3 (CH), 131.1, 136.4, 157.8, 222.0; IR (thin film) 2965, 2920, 2835, 2800, 2735, 1735, 1610, 1500, 1460, 1370, 1260, 1240, 1130, 1035, 780 cm^{-1}; GCMS t_R = 15.7 min for **25** (oven temp: 50 °C for 2 min, 15°/min to 280 °C for 5 min); EIMS m/z (rel int) 285 (M^+, 32), 284 (21), 257 (14), 256 (9), 162 (13), 161 (base), 146 (11).

(−)-8-Azaestrone, 4. In a 10-mL round-bottom flask equipped with a reflux condensor, 152 mg (0.53 mmol, 1.0 equiv) of (−)-8-azaestrone methyl ether was treated with 2.0 mL of 48% aqueous HBr. The solution was heated to reflux for 10 h, cooled to rt, diluted with 20 mL of dichloromethane and 10 mL of water, and *slowly* neutralized with 2.1 g of $NaHCO_3$. After being stirred for 15 min, the layers were allowed to separate and the aqueous layer was extracted with $CHCl_3$ (5 × 20 mL). Following washing with brine and drying (Na_2SO_4), silica and Celite (100 mg each) were added to the combined organic extracts and the volatiles were removed. The resulting powder was loaded onto a column (15 g, silica) and eluted with 3% MeOH/CH_2Cl_2. **4** was obtained (114 mg, 80%) as fine white needles: mp 250–252 °C dec; R_f (5:95 MeOH/CH_2Cl_2) 0.44; $[\alpha]_D$ = −182.8° (c 0.28, EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.86 (s, 3 H), 1.30–1.41 (m, 2 H), 1.56–1.70 (m, 2 H), 1.98–2.23 (m, 5 H), 2.42–2.59 (m, 2 H), 2.81 (t, J = 5.7 Hz, 1 H), 2.89 (dd, J = 3.3, 10.2 Hz, 1 H), 3.04 (dd, J = 5.7, 10.5 Hz, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 6.49 (dd, J = 2.4, 8.4 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 1 H), 9.09 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.8 (CH_3), 22.3 (CH_2), 26.7 (CH_2), 29.3 (CH_2), 30.4 (CH_2), 34.4 (CH_2), 46.9 (CH_2), 47.5 (C), 64.2 (CH), 68.5 (CH_3), 113.0 (CH), 114.5 (CH), 125.8 (CH), 127.5 (C), 135.4 (C), 155.3 (C), 218.0 (C); IR (0.009M in $CHCl_3$) 3315, 3010, 2810, 2750, 1735 cm^{-1}; (KBr plate) 3350, 3020, 2950, 2915, 2860, 2805, 2745, 1725, 1610, 1505, 1455, 1365, 1290, 1190, 1160, 1055, 780 cm^{-1}; GCMS t_R = 11.8 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min); EIMS m/z (rel int) 272 (M^+ + 1, 5), 271 (M^+, 27), 270 (9), 243 (13), 242 (15), 214 (6), 148 (13), 147 (base), 146 (38), 91 (10). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.17. Found: C, 75.01; H, 7.86; N, 5.13.

Acknowledgment. The authors are grateful to the National Science Foundation for financial support of this work. We thank Professor R. W. Woody and Dr. N. Sreerama of the Department of Biochemistry for the CD spectral determinations and Professor J. M. Stryker and J. F. Daeuble, Indiana University, for a generous sample of triphenylphosphinocopper(I) hydride hexamer.

Supplementary Material Available: Proton and carbon magnetic resonance spectra for all compounds **3–5, 8, 11, 14, 15, 21, 22, 24,** and **25** and infrared spectra (Bohlmann–Wenkert bands) for **3, 4, 21, 24,** and **25** (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Chemoenzymatic Enantiocontrolled Synthesis of (−)-Specionin†

Tomas Hudlicky* and Michael Natchus

Chemistry Department, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received May 10, 1992

Specionin acetate **1a** has been synthesized from chlorobenzene in 15 steps and compared with an authentic sample. The chirality was incorporated into the synthesis by microbial dioxygenation of chlorobenzene using a mutant strain of *Pseudomonas putida*, 39D, to produce 1-chloro-2,3-dihydroxycyclohexa-4,6-diene, which was elaborated into enone **5**. Addition of the lithium dienolate derived from ethyl 4-(dimethyl-*tert*-butylsiloxy)-2-bromocrotonate to this enone provided vinylcyclopropanes **7**, which underwent a low-temperature vinylcyclopropane–cyclopentene rearrangement to tricyclic ketones **8** upon treatment with either trimethylsilyl iodide or tetrabutylammonium fluoride at −78 °C. Following the deoxygenation of the carbonyl and the convergent transformation of both C-4 isomers to a single allylic acetate **11** via either esterification or Mitsunobu inversion, the epoxidation and generation of the bisacetal was accomplished according to the known protocol. The overall yield of this synthesis was 9% for the sequence **5** to **11**. Spectral data and experimental details are provided for key compounds.

Introduction

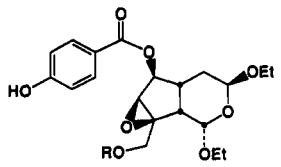
In addition to its biological activity as an antifeedant to the spruce budworm,[1] specionin **1**, an iridoid sesquiterpene,[2] has an interesting chemical history. Its structure was incorrectly represented as **2**[3] until an unambiguous

† Dedicated to Dr. E. L. Hampton, our martial arts teacher, on the occasion of his 40th birthday.

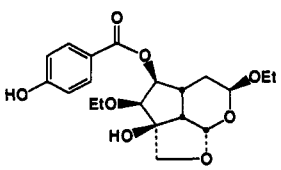
(1) Chang, C. C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605.

0022-3263/92/1957-4740$03.00/0

assignment was made through total synthesis in 1985.[4] Since that time several total syntheses have been reported.[5]



1 Specionin, R = H
1a Specionin Acetate R = Ac

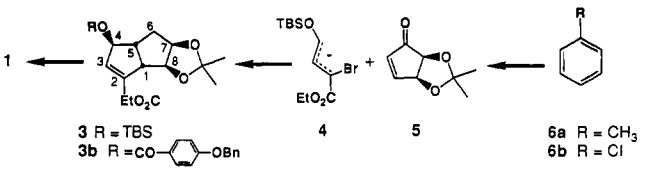


2

The development of mild conditions for the rearrangement of siloxyvinylcyclopropanes[6] prompted us to consider the [2 + 3] cyclopentene annulation as the protocol of choice for the construction of the diversely substituted cyclopentane ring of specionin. As illustrated in Figure 1, all of the carbons in specionin are assembled during the annulation sequence which starts from enone **5** obtained from either toluene **6a**[7] or chlorobenzene **6b**[8] in five steps via microbial oxidation.[9,10]

Results and Discussion

The dioxygenation of aromatic compounds, first described by Gibson nearly 20 years ago,[11] has only recently risen to prominence in the area of asymmetric synthesis. In the United Kingdom several research groups have been engaged in chiral syntheses emanating from the use of various arene cis-diols supplied by several chemical manufacturers.[12] Most notable are the efforts of Ley, Roberts, Carless, and Boyd who have used the microbial metabolites as key intermediates in the synthesis of oxygenated natural products.[9] In the U.S. most reports on the synthetic



3 R = TBS
3b R = CO–C6H4–OBn

Figure 1. Approach to specionin.

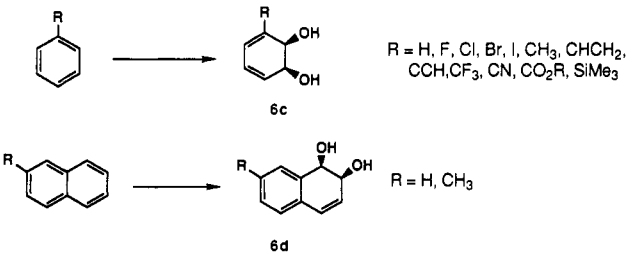


Figure 2. Some of the arene cis-diols available via biooxidation.

strategies that take advantage of the microbial dioxygenation of arenes originated in our group, although the use of benzene diol has been reported by Johnson.[13] The practical implication of the use of these metabolites as chiral synthons is obvious. We have devised a simple protocol based on symmetry considerations that allows for extremely brief enantiodivergent syntheses of carbohydrates from the optically pure haloarene diols. Recent publications from our laboratories highlight the use of symmetry in the design of oxygenated natural products.[9c,14] In contrast, the use of meso diols in asymmetric synthesis requires extra desymmetrizing operations, usually performed by either lipases or by reactions with optically pure reagents, and is therefore less efficient. The preparation of many arene cis-diols is now performed on an industrial scale: for example, 1-chloro-2,3-dihydroxycyclohexa-4,6-diene is routinely manufactured by Genencor International, Inc., in 2000-L fermentors.[15] Such operations yield, when appropriately optimized, 50 to 60 g/L/h of the appropriate diol. In our laboratory we routinely prepare 30–40 g in a 15-L fermentor, an amount sufficient to perform the desired synthetic studies. The conversion can be made quantitative with recycling of the substrate vapor.

The enzyme, toluene dioxygenase, appears to be remarkably specific with respect to the absolute stereochemistry of the resulting diols, yet seems to tolerate an enormous number of diversely functionalized arenes. Even though the precise structure of the enzyme has not been elucidated its production has been overexpressed on a *E. coli* JM109 mutant, containing the four structural genes of toluene dioxygenase. This clone is more efficient at the accumulation of diols than the 39D species.[16] The two organisms, *Pseudomonas putida* 39D and *E. coli* JM109, are specific for monocyclic aromatic compounds. The wild strain NCIB 11 and *Becherenchya* 8/36 are specific toward the oxidation of polycyclic fused aromatics and biphenyls, respectively. The absolute stereochemistry of arene cis-diols isolated from the fermentation broth can be determined by the recently published method of Boyd.[9e] A partial list of compounds available by this bioconversion is shown in Figure 2.

(2) For a current compilation of compounds in the Iridoid family see: (a) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173. (b) *Ibid.* **1990**, *53*, 1055. (c) El-Nagger, L. J.; Beal, J. L. J. *Nat. Prod.* **1980**, *43*, 649. (d) Devon, T. K.; Scott, A. I. *Handbook of Naturaly Occuring Compounds*; Academic Press: New York and London, 1972; Vol. 2.

(3) (a) See reference 1. (b) Van der Eycken, E.; Callant, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 367.

(4) Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719.

(5) (a) Hussain, N.; Leonard, J. *Tetrahedron Lett.* **1987**, *28*, 4871. (b) Kim, B. H.; Jacobs, P. B.; Elliot, R. L.; Curran, D. P. *Tetrahedron* **1988**, *44*, 3079. (c) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280. (d) Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.* **1988**, *110*, 3585.

(6) (a) Hudlicky, T.; Heard, N. E.; Fleming, A. *J. Org. Chem.* **1990**, *55*, 2270. (b) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691.

(7) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.

(8) Hudlicky, T.; Natchus, M.; Nugent, T. *Synth. Commun.* **1992**, *22*, 151.

(9) For recent examples of the applications of arene diols to synthesis see: (a) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741. (b) Carless, H. A. J.; Oak, O. Z. *J. Chem. Soc., Chem. Commun.* **1991**, 61. (c) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2907. (d) Roberts, S. M.; Downing, W.; Latouche, R.; Pitoll, C. A.; Pryce, R. J.; Ryback, G.; Williams, J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2613. (e) Boyd, D. R.; Dorrity, R. M. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 666.

(10) For comprehensive reviews of arene cis-diol chemistry see: (a) Brown, S. M. In *Organic Synthesis: Theory and Practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, in press. (b) Widdowson, D. A.; Ribbons, D. A.; Thomas, S. D. *Janssen Chimica Acta* **1990**, *8*, 3.

(11) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626.

(12) Over 20 diols derived from substituted aromatic compounds are commercially available from the following sources: Genencor International, Inc., Rochester, NY; ICI Fine Chemicals, Manchester, U.K.; Enzymatix, Cambridge, U.K.; Janssen Chimica, Geel, Belgium.

(13) Johnson, C. R.; Ple, P. A.; Su, L.; Heeg, M. J.; Adams, J. P. *Synlett* **1992**, 388.

(14) (a) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (b) Hudlicky, T.; Price, J. D.; Luna, H.; Andersen, C. M. *Isr. J. Chem.* **1991**, *31*, 229.

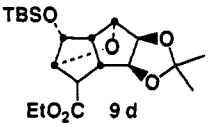
(15) The diols derived from chloro- and bromobenzene are now prepared crystalline and on a multikilogram scale by Genencor International, Inc.

(16) Gibson, D. T.; Zylstra, G. J. *J. Biol. Chem.* **1989**, *264*, 1490.

With the availability of the diols and the recently optimized synthesis of enone **5**[8] we were in position to apply the low-temperature annulation method to the synthesis of the key tricyclic intermediates **3a** and **3b**. The evolution of the [2 + 3] cyclopentene annulation took into account the increasing complexity of target natural products, as well as the requirement that any synthesis addressed today should be performed in the asymmetric mode only. Thus, the usual thermolysis of vinylcyclopropanes to cyclopentenes, used extensively in the synthesis of triquinane terpenes, gave way to conditions that would tolerate both increasing molecular weight and the presence of multiple functional groups. The synthesis of retigeranic acid defined the limit of molecular weight (and volatility) for the thermal rearrangements and marked also the beginning of a program aimed at the adjustments in the methodology toward asymmetric synthesis of target compounds.[6b]

As shown in Scheme I, the addition of enone **5** to the solution of lithium dienolate **4** derived from ethyl 4-(dimethyl-*tert*-butylsiloxy)-2-bromocrotonate at −110 °C led to vinylcyclopropanes **7** in 54% yield (mixture of exo and endo isomers with respect to the vinyl group, 85:15, 54%).[6a] This isomeric mixture rearranged to tricyclic ketones **8a** and **8b** (1:2, 82%) upon exposure to *n*-BuN^+F^- in THF.[6a] Treatment of **7** with TMSI/HMDS led to **8c** and **8d** (1:1, 89%) with recovery of *endo*-**7**, which did not rearrange at this temperature presumably because of an unfavorable orbital disposition of the vinylcyclopropane system.

Reduction of **8a** with $NaBH_4$ provided alcohol **9a** (90%) exclusively, whereas **8b** gave a mixture of **9b** and **9c** (3:4, 85%). Alcohol **9a** was deoxygenated using the Barton protocol ($NaH/CS_2/MeI$; $AIBN/Bu_3SnH$)[17] to **3a** (54%), which was subjected to DIBAL reduction (85%), acetylation (84%), and desilylation (81%) to give the allylic acetate **10c** which was esterified to **11** (70%) in an overall yield of 21% from **9a**. Alcohols **9b** and **9c** were transformed to **3c** using the same sequence in 44% and 59% yield, respectively. Oddly, NaH treatment of alcohol **9c** at room temperature led to a cagelike ether **9d**. This

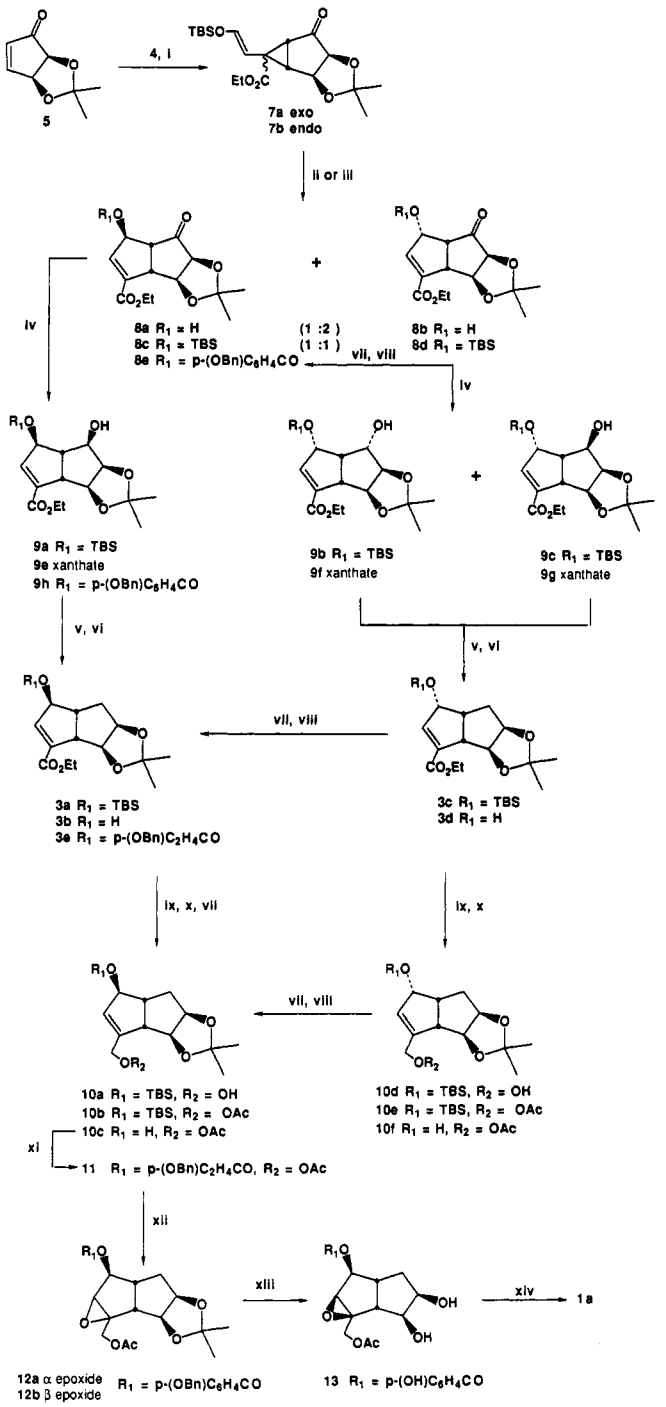


9 d

compound did not form when the reaction was performed at −10 °C. Following the initial separation and identification of all isomers and their ratios, the mixture of ketones **8** was reduced to a mixture of alcohols **9** (**9a**:**9b**:**9c** = 7:3:4, 85%), which were deoxygenated as a mixture to furnish **3a** and **3c**. These compounds were separated at this stage and transformed convergently to **11** in an identical series of reaction conditions except that the transformation of **3c** to **10c** was accomplished with inversion at C-4 by the Mitsunobu method[18] at the stage of acetate **10f** in 47% yield, Scheme I.

Several possibilities for the convergence of the diastereomeric tricyclic esters were investigated. The first and most frequently used was the aforementioned conversion of acetate **10f** to **10c** by Mitsunobu protocol.[18] The introduction of the protected benzoate ester was accomplished also at the stage of tricycle **3d**, which was converted to **3e** by Mitsunobu inversion. The attainment of this compound necessitated the study of a selective reduction of the two ester moieties. Selective reduction of acrylate

Scheme I[a]

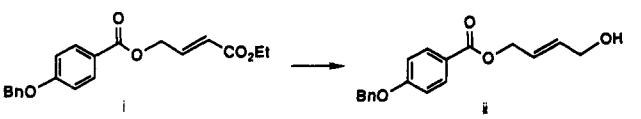


[a] Reagents: (i) LDA/HMPA/THF/−105 °C; (ii) TBAF/THF/−40 °C; (iii) TMSI/HMDS/THF/−78 °C; (iv) $NaBH_4$/EtOH; (v) $NaH/CS_2/MeI$; (vi) Bu_3SnH/AIBN/toluene; (vii) TBAF/THF; (viii) Ph_3P/DEAD/*p*-(OBn)$C_6H_4CO_2H$/THF; (ix) DIBAL/THF/−78 °C; (x) Ac_2O/pyridine; (xi) DCC/*p*-(OBn)$C_6H_4CO_2H/CH_2Cl_2$; (xii) *m*-CPBA/CH_2Cl_2; (xiii) Pd(C)/EtOH; (xiv) $NaIO_4$/EtOH/*p*-TsOH.

over the benzoate using DIBAL–H was accomplished on a model system[19] but provided a mixture of reduced

(17) For a review see: Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15.
(18) Mitsunobu, O. *Synthesis* **1981**, 1.

(19) Reduction of *i* with DIBAL at −78 °C gave ii as the major product (70–80%). Other minor products present were not identified.



products when applied to **3e**. In a third-generation approach, ester **3e** was prepared in a shorter and the most convergent manner from tricyclic ketones **8b** by Mitsunobu inversion.[18] The early convergence of **8c** and **8d** to the benzoate ester **8e** through selective deoxygenation of the ketone was therefore accomplished. However, due to the scarcity of material at this stage of the synthesis this approach was not further optimized because of the failure to adjust the conditions of the successful selective reduction of the acrylate from the model system scale to the small scale experiments using **8e**.

Epoxidation of benzoate ester **11** gave **12b** as the major product, in analogy with the epoxidation of a similar system.[20] The two epoxides (**12a**:**12b** = 3:7) were identified by their ^{1}H NMR signals at 3.69 and 3.66 ppm, respectively, and partially purified by filtration through silica gel.[21] Hydrogenation of **12b** in EtOH/H_2O over Pd/C led to the debenzylation of the *p*-(benzyloxy)-benzoate, and quite fortuitously, proceeded also with the concomitant deprotection of the acetonide under very mild conditions (HOAc/H_2O/THF at 55 °C is usually required).[22] It remained to cleave the diol in **13** according to a known procedure[5a] which provided **1a** whose spectral (^{1}H-NMR) and chromatographic (HPLC) properties matched those of an authentic sample kindly provided by Professor Leonard.

Conclusion

In summary, specionin acetate **1a** was attained in 10 steps from tricyclic ketone **8** (15 steps from chlorobenzene) in an overall yield of 9% (for the sequence **5** through **11**). We believe that this achievement illustrates quite well the irony of modern synthesis: All of the carbons and all but two stereocenters have been constructed in seven steps from chlorobenzene by the combination of biocatalysis (arene dioxygenase)[10,11] with modern annulation technology.[6] Yet eight more steps were required to manipulate the oxidation state and the functionalities of the oxygenated centers around the periphery of the skeleton. Although the length of our synthesis compares favorably with those in the literature, serious ameliorations are necessary before a process with a potential for commercialization would materialize. Clearly, improvements in functional group manipulations of this type should and will be pursued.

Experimental Section

All nonhydrolytic reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame dried under vacuum. Tetrahydrofuran, dimethoxyethane, and toluene were distilled from benzophenone ketyl. Dichloromethane, diisopropylamine, and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Thin-layer chromatography was performed on Kiselgel 60F-254 plates (analytical 0.25-mm thickness, preparative, 0.5 mm; EM Reagents). Flash chromatography was performed on Kieselgel 60 (EM Reagents, 230–400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution) or on a double-focusing VG 7070 E-HF instrument (exact mass). Infrared were recorded on a Perkin-Elmer 283B or 710B instruments. Proton and carbon NMR spectra were obtained on Bruker WP-270, Bruker WP-200, or Varian NR-400 instruments. Proton chemical shifts are reported in parts per million (ppm) relative to TMS as an internal reference (0.00). Carbon chemical shifts are reported in ppm relative to the center line of the $CHCl_3$ triplet (77.0 ppm), and the multiplicity is indicated by CH_3, CH_2, CH, C (DEPT experiments). Rotations were recorded on a Perkin-Elmer 241 digital polarimeter.

(7*S*,8*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-6-ol (9a, 9b, 9c) (preparative scale). A solution of ketones **8c** and **8d** (165 mg, 0.42 mmol, 1:1 mixture)[6a,b] in ethanol (4 mL) was cooled to 0 °C, and $NaBH_4$ (24 mg, 0.63 mmol) was added. After 30 min, TLC indicated complete consumption of starting material and the reaction was quenched with saturated NH_4Cl (2 mL) and warmed to room temperature. The aqueous layer was extracted three times with ethyl acetate; the extracts were combined, washed with brine, and dried over $MgSO_4$. Flash chromatography (10% deactivated silica gel, 4:1, 2:1 hexane/ether) gave 38.6 mg (23.4%) of 4-*endo*,6-*endo*-**9b**, 31.3 mg (18.9%) of 4-*endo*,6-*exo*-**9c**, and 70.4 mg (42.7%) of 4-*exo*,6-*exo*-**9a**. All diastereomers were clear oils except **9a** which was a waxy solid. In preparative-scale runs the mixture of stereoisomers was not separated but taken on through the next sequence.

4-*endo*,6-*endo*-9b: R_f = 0.45 (hexane–Et_2O (2:1)); $[\alpha]^{25}_D$ = −14.1; IR (neat) 3500 br, 2930, 2850, 1715, 1630, 1465, 1370, 1255, 1205, 1050, 855, 835, 775, 745, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.51 (dd, J = 2.2, 2.2 Hz, 1 H), 5.14 (ddd, J = 7.8, 2.2, 2.2 Hz, 1 H), 4.99 (dd, J = 5.0, 1.5 Hz, 1 H), 4.50 (d, J = 5.1 Hz, 1 H), 4.46 (d, J = 4.5 Hz, 1 H), 4.26 (m, 2 H), 3.49 (s, 1 H), 3.32 (ddd, J = 8.0, 8.0, 4.6 Hz, 1 H), 3.22 (m, 1 H), 1.48 (s, 3 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.33 (s, 3 H), 0.94 (s, 9 H), 0.19 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.19 (C), 144.17 (CH), 137.55 (C), 110.74 (C), 85.74 (CH), 84.44 (CH), 77.03 (CH), 76.77 (CH), 60.68 (CH_2), 56.74 (CH), 50.20 (CH), 27.30 (CH_3), 25.61 (CH_3, triple intensity), 25.07 (CH_3), 18.00 (C), 14.27 (CH_3), −4.97 (CH_3), −5.21 (CH_3); MS (70 eV, m/e (rel. int.)) 397 (15), 383 (9), 355 (17), 341 (30), 325 (65), 299 (30), 283 (100), 267 (100), 249 (100), 237 (70), 225 (85), 209 (95), 193 (45), 179 (35), 163 (50), 133 (100), 115 (35).

4-*endo*,6-*exo*-9c: R_f = 0.34 (hexane–Et_2O (2:1)); $[\alpha]^{25}_D$ = −39.7; IR (neat) 3460 br, 2920, 2850, 1720, 1630, 1465, 1370, 1255, 1055, 835, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dd, J = 2.1, 2.1 Hz, 1 H), 5.02 (ddd, J = 7.3, 2.1, 2.1 Hz, 1 H), 4.66 (dd, J = 5.2, 2.1 Hz, 1 H), 4.55 (dd, J = 4.9, 4.9 Hz, 1 H), 4.24 (m, 3 H), 3.19 (m, 1 H), 3.08 (ddd, J = 7.6, 7.6, 7.6 Hz, 1 H), 2.41 (d, J = 4.4 Hz, 1 H), 1.53 (s, 3 H), 1.34 (s, 3 H), 1.31 (t, J = 7.1 Hz, 3 H), 0.92 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.31 (C), 144.94 (CH), 136.25 (C), 111.41 (C), 81.75 (CH), 81.64 (CH), 76.45 (CH), 73.25 (CH), 60.76 (CH_2), 53.50 (CH), 51.81 (CH), 26.87 (CH_3), 25.83 (CH_3, triple intensity), 24.82 (CH_3), 18.13 (C), 14.27 (CH_3), −4.79 (CH_3), −4.99 (CH_3); MS (70 eV m/e (rel. int.)) 397 (1, $M^+ - 1$), 383 (2), 341 (10), 307 (4), 283 (7), 265 (35), 249 (20), 237 (15), 209 (20), 191 (15), 163 (30), 135 (25).

4-*exo*,6-*exo*-9a: mp 87.5–89.5 °C: R_f = 0.21 (hexane–Et_2O (2:1)); $[\alpha]^{25}_D$ = −52.7; IR (neat) 3500, 2940, 1715, 1617, 1260, 1055, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.54 (br s, 1 H), 4.75 (br s, 1 H), 4.67 (d, J = 5.3 Hz, 1 H), 4.44 (dd, J = 5.0, 5.0 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.57 (ddd, J = 9.0, 9.0, 4.7 Hz, 1 H), 3.52 (br d, J = 8.0 Hz, 1 H), 2.57 (dd, J = 7.6, 7.6 Hz, 1 H), 2.30 (d, J = 9.9 Hz, 1 H), 1.51 (s, 3 H), 1.31 (s, 3 H), 1.29 (t, J = 7.1 Hz, 1 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.47 (C), 142.99 (CH), 138.78 (C), 111.17 (C), 81.20 (CH, double intensity), 79.00 (CH), 75.85 (CH), 60.74 (CH_2), 57.47 (CH), 53.67 (CH), 26.71 (CH_3), 25.86 (CH_3, triple intensity), 24.82 (CH_3), 18.26 (C), 14.26 (CH_3), −4.61 (CH_3), −4.62 (CH_3); MS (70 eV m/e (rel. int.)) 398 (1, M^+), 383 (9), 354 (4), 341 (40), 313 (10), 255 (10), 237 (17), 224 (20), 209 (25), 86 (100), 75 (100); HRMS calcd for $C_{20}H_{34}O_6Si$ 398.2125, found 398.2101.

(7*S*,8*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-carbethoxy-6-[[(methylthio)thiocarbonyl]oxy]-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-ene (9e, 9f, 9g). A flame-dried 10-mL

(20) Leonard's epoxidation[5a] was stereoselective as was epoxidation of **10**. Whitesell's epoxidation[5d] was stereospecific whereas epoxidation of ester **11** gave a 3:7 ratio of α and β epoxides, **12a**:**12b**.

(21) All compounds have been fully characterized by IR, ^{1}H NMR, and mass spectra and either HRMS or combustion analysis. Because of scarcity of material (2 mg of acetate **11**) during the last stages of synthesis full purification and characterization of epoxides **12a** and **12b** was not possible due to the presence of excess perbenzoic acid. The allylic acetate **11** was taken through the entire sequence to **1a** and partially chromatographed for comparison with an authentic sample.

(22) The deprotection of acetonides of arene diols under the conditions of Pd/C-catalyzed hydrogenation was observed on several occasions in our laboratories. It is thought to occur by Pd-catalyzed ketal exchange with solvent (MeOH, EtOH). We are not aware of any conditions as mild as these available for ketal hydrolysis.

round-bottom flask was charged with a stirring bar and NaH (11 mg, 0.30 mmol, 60% dispersion in mineral oil) under an argon atmosphere. The NaH was rinsed once with dry THF (1 mL) and again covered with THF (0.5 mL) and cooled to 0 °C. The starting alcohol **9a** (65 mg, 0.048 mmol) was dried in a separate 10-mL round-bottom flask and added to the NaH suspension via cannula in dry THF (1.5 mL). The mixture was allowed to stir for 30 min at which time dry CS_2 (0.5 mL) was added. The mixture was allowed to warm to room temperature and stir for 30 min followed by addition of MeI (1.0 mL). TLC after 10 min indicated complete consumption of starting material so the reaction was quenched with saturated NH_4Cl (2 mL). The aqueous layer was extracted twice with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 22 mg of crude oil which was chromatographed over 10% deactivated silica with 4:1 hexane/ether to give pure xanthate **9e** (58 mg, 72%). Alcohol **9c** (6.2 mg, 0.013 mmol) was converted similarly to xanthate **9g** (5.2 mg, 70%). Alcohol **9b** (10.2 mg, 0.021 mmol) gave cyclic ether **9d** (9.0 mg, 88%) under these reaction conditions; however, xanthate **9f** (21 mg, 52%) was obtained cleanly when alcohol **9b** (33 mg, 0.083) was treated at −10 to −15 °C.

4-*endo*,6-*endo*-9f: R_f = 0.35 (hexane–Et_2O (4:1)); ^1H NMR ($CDCl_3$) δ 6.68 (dd, J = 2.16 Hz, 1 H), 6.08 (dd, J = 5.65, 2.01 Hz, 1 H), 4.95 (ddd, J = 7.25, 1.99, 1.99 Hz, 1 H), 4.85 (dd, J = 5.56, 1.47 Hz, 1 H), 4.63 (m, 1 H), 4.27 (q, J = 7.12 Hz, 2 H), 3.49 (ddd, J = 7.29, 7.29, 5.73 Hz, 1 H), 3.33 (br d, J = 7.48 Hz, 1 H), 2.45 (s, 3 H), 1.51 (s, 3 H), 1.32 (t, J = 7.01 Hz, 3 H), 1.30 (s, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H).

4-*exo*,6-*exo*-9e: R_f = 0.35 (hexane–Et_2O (4:1)); ^1H NMR ($CDCl_3$) δ 6.51 (dd, J = 2.0, 2.0 Hz, 1 H), 5.85 (dd, J = 7.2, 5.1 Hz, 1 H), 4.99 (ddd, J = 7.4, 1.9, 1.9 Hz, 1 H), 4.85 (dd, J = 5.1, 5.1 Hz, 1 H), 4.63 (dd, J_1 = 5.1, 1.4 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.45 (ddd, 1 H, J_1 = 7.6, 7.6, 7.6 Hz, 1 H), 3.33 (br d, J = 7.4 Hz, 1 H), 2.54 (s, 3 H), 1.49 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.27 (s, 3 H), 0.85 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H).

4-*exo*,6-*endo*-9g: R_f = 0.33 (hexane–Et_2O (4:1)); ^1H NMR ($CDCl_3$) δ 6.53 (t, J = 2.3 Hz, 1 H), 5.41 (dd, J = 9.0, 4.4 Hz, 1 H), 4.76 (dd, J = 4.7, 4.7 Hz, 1 H), 4.69 (m, 2 H), 4.24 (q, J = 7.2 Hz, 2 H), 3.61 (br d, J = 8.1 Hz, 1 H), 3.10 (dd, J = 8.3, 8.3 Hz, 1 H), 2.58 (s, 3 H), 1.52 (s, 3 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.28 (s, 3 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); MS (CI, m/e (rel. int.)) 469 (1), 443 (1), 429 (3), 413 (1), 399 (2), 391 (3), 383 (3), 371 (15), 357 (20), 325 (35), 323 (35), 251 (20), 233 (15), 207 (15), 193 (100), 133 (55), 85 (85).

9d: R_f = 0.27 (hexane–Et_2O (4:1)); IR (neat) 2930, 2890, 2850, 1730, 1450, 1375, 1260, 1245, 1225, 1205, 1175, 1155, 1130, 1050, 1030, 905, 865, 830, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.66 (d, J = 5.10 Hz, 1 H), 4.61 (d, J = 5.15 Hz, 1 H), 4.41 (dd, J = 1.10, 1.10 Hz, 1 H), 4.19–4.07 (m, 3 H), 2.76 (br d, J = 7.01 Hz, 1 H), 2.31 (dd, J = 2.74, 1.53 Hz, 1 H), 1.44 (s, 3 H), 1.30 (s, 3 H), 1.25 (t, J = 7.13 Hz, 1 H), 0.90 (s, 9 H), 0.10 (s, 6 H).

(7*S*,8*R*)-2-Carbethoxy-*exo*-6-hydroxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-*exo*-4-yl *p*-(Benzyloxy)benzoate (9h). Ketone **8e** (19 mg, 0.039) was dissolved in EtOH (1 mL) under argon and cooled to −30 °C. Sodium borohydride (6 mg) was added against a flow of argon, and TLC indicated that the reaction was complete after 1 h. The reaction was quenched with 1 mL of NH_4Cl (sat), diluted with 2 mL of water, and extracted 4× with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The crude mixture was chromatographed over 10% deactivated silica gel (hexane–EtOAc (2:1 → 1:1)) to give 18 mg (93%) of alcohol **9h** as a clear oil which still contains a slight amount of DCC derivative: R_f = 0.15 (hexane–EtOAc (4:1)); ^1H NMR ($CDCl_3$) δ 7.97 (ddd, J = 8.87, 2.04, 2.04 Hz, 2 H), 7.45–2.80 (m, 5 H), 6.99 (ddd, J = 9.02, 2.11, 2.11 Hz, 2 H), 6.77 (dd, J = 2.51, 2.51 Hz, 1 H), 5.81 (br s, 1 H), 5.12 (s, 2 H), 4.74 (d, J = 5.21 Hz, 1 H), 4.56 (dd, J = 4.95 Hz, 1 H), 4.27 (qd, J = 7.14, 1.12 Hz, 2 H), 3.85 (dd, J = 8.10, 4.51 Hz, 1 H), 3.62 (br d, J = 7.4 Hz, 1 H), 2.96 (d, J = 7.68 Hz, 1 H), 1.54 (s, 3 H), 1.35 (s, 3 H), 1.33 (t, J = 7.15 Hz, 3 H).

(7*S*,8*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-ene (3a, 3c). Xanthate **9c** (13 mg, .0267 mmol) was dissolved in 1.5 mL of dry toluene in a 10-mL round-bottom flask equipped with a condenser under argon. Tributyltin hydride (28.7 μL, 0.107 mmol) was added via syringe and the mixture brought to reflux. AIBN was added against a flow of argon, and the mixture was cooled to room temperature at which time TLC indicated complete consumption of starting material. The mixture was condensed under vacuum and chromatographed over 10% deactivated silica gel with hexane–EtOAc (4:1) as eluant to give 8.6 mg (84.5%) of pure **3c**. Xanthate **9e** (57.0 mg, 0.12 mmol) was similarly converted to exo isomer **3a** (33.9 mg, 76%). The two isomers were also prepared simultaneously from the mixture of **9e**, **9g**, and **9f** and then separated by chromatography.

4-*exo*-3a: R_f = 0.34, hexane–EtOAc (4:1); $[\alpha]^{25}_D$ = −82.6; IR (neat) 2920, 2845, 1715, 1625, 1465, 1370, 1260, 1050, 830, 775, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (t, J = 2.36 Hz, 1 H), 4.63 (d, J = 5.24 Hz, 1 H), 4.58 (dd, J = 4.82, 4.82 Hz, 1 H), 4.48 (br s, 1 H), 4.26 (q, J = 7.12 Hz, 2 H), 3.58 (br d, J = 6.56 Hz, 1 H), 2.86 (ddd, J = 9.82, 7.73, 7.73 Hz, 1 H), 2.20 (dd, J = 14.31, 8.07, 1 H), 1.49 (s, 3 H), 1.35 (ddd, J = 14.51, 10.16, 4.71 Hz, 1 H), 1.32 (t, J = 7.05 Hz, 3 H), 1.30 (s, 3 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.87 (C), 142.21 (CH), 138.86 (C), 109.98 (C), 82.97 (CH), 81.60 (CH), 80.66 (CH), 60.66 (CH_2), 56.75 (CH), 49.99 (CH), 35.08 (CH_2), 27.12 (CH_3), 25.87 (CH_3, triple intensity), 24.79 (CH_3), 18.32 (C), 14.30 (CH_3), −4.63 (CH_3), −4.69 (CH_3); MS (70 eV m/e (rel. int.)) 398 (1, M^+), 383 (9), 341 (40), 313 (10), 255 (10), 237 (17), 224 (20), 209 (25), 86 (100), 75 (100); HRMS calcd for $C_{20}H_{34}O_6Si$ 398.2125, found 398.2101.

4-*endo*-3c: R_f = 0.41, hexane–EtOAc (4:1); $[\alpha]^{25}_D$ = −8.87; IR (neat) 2945, 2842, 1715, 1625, 1457, 1365, 1350, 1190, 1115, 1045, 852, 835, 770, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.49 (dd, J = 1.85, 1.85 Hz, 1 H), 4.90 (ddd, J = 6.67, 2.91, 1.90 Hz, 1 H), 4.73 (d, J = 5.35 Hz, 1 H), 4.58 (ddd, J = 5.55, 2.77, 2.77 Hz, 1 H), 4.24 (qd, J = 7.22, 1.07 Hz, 2 H), 3.28–3.17 (m, 2 H), 1.92–1.89 (m, 2 H), 1.50 (s, 3 H), 1.31 (t, J = 7.11, 3 H), 1.29 (s, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.79 (C), 145.91 (CH), 134.70 (C), 109.78 (C), 84.58 (CH), 81.70 (CH), 76.23 (CH), 60.56 (CH_2), 56.12 (CH), 45.97 (CH), 31.67 (CH_2), 27.03 (CH_3), 25.74 (CH_3, triple intensity), 24.64 (CH_3), 18.14 (C), 14.29 (CH_3), −4.95 (CH_3), −4.98 (CH_3); MS (70 eV m/e (rel. int.)) 383 (4), 382 (4, M^+), 367 (13), 337 (5), 335 (22), 307 (10), 267 (40), 233 (10), 193 (70), 147 (30), 129 (25); HRMS calcd for $C_{20}H_{35}O_6Si_1$ 383.2254, found 383.2181.

(2*S*,3*R*)-8-(Hydroxymethyl)-6β-[(*tert*-butyldimethylsilyl)oxy]-2,3-(isopropylidenedioxy)bicyclo[3.3.0]oct-7-ene (10a, 10d). Ester **3a** (20.1 mg, 0.053 mmol) was dissolved in THF (3 mL) and cooled to −78 °C, and diisobutylaluminum hydride (789 μL, 1 M in THF, 0.79 mmol) was added dropwise via syringe. TLC indicated complete reaction after 20 min. The reaction was quenched at −78 °C with 1 mL of saturated NH_4Cl, diluted with 2 mL of H_2O, and extracted 3× with 5 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ at which time the solution thickened to a white, geletinous mass. This mixture was separated by centrifugation and the liquid filtered and evaporated to give 19.4 mg of crude oil which was purified over 10% deactivated silica gel with hexane–EtOAc (4:1 → 1:1) to give 15.2 mg (85%) of the allylic alcohol **10a** as a clear oil. The endo isomer of the ester **3c** (21 mg, 0.055 mmol) was reduced similarly to give 14.6 mg (78%) of clear alcohol **10d**.

***exo*-10a**: R_f = 0.21 (hexane–EtOAc (2:1)) ^1H NMR ($CDCl_3$) δ 5.56 (s, 1 H), 4.61 (dd, J = 5.01, 5.01 Hz, 1 H), 4.49 (d, J = 5.11, 1 H), 4.42 (s, 1 H), 4.31 (s, 2 H), 3.35 (d, J = 7.27 Hz, 1 H), 2.85 (ddd, J = 9.34, 7.88, 7.88 Hz, 1 H), 2.22 (dd, J = 14.37, 7.95 Hz, 1 H), 1.69 (s, 1 H), 1.48 (s, 3 H), 1.39 (m, 1 H), 1.30 (s, 3 H), 0.89 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H).

***endo*-10d**: R_f = 0.21 (hexane–EtOAc (2:1)) ^1H NMR ($CDCl_3$) δ 5.50 (dd, J = 1.8, 1.8 Hz, 1 H), 4.83 (ddd, J = 7.12, 1.77, 1.77 Hz, 1 H), 4.63 (ddd, J = 4.94, 4.94, 1.62 Hz, 1 H), 4.57 (dd, J = 5.37, 1.08 Hz, 1 H), 4.28 (m, 2 H), 3.18 (dddd, J = 8.80, 7.53, 7.53, 7.53 Hz, 1 H), 2.99 (br d, J = 7.23 Hz, 1 H), 2.02–1.83 (m, 2 H), 1.60 (dd, J = 5.77, 5.77 Hz, 1 H), 1.47 (s, 3 H), 1.29 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H).

(7*S*,8*R*)-2-(Acetoxymethyl)-4-[(*tert*-butyldimethylsilyl)oxy]-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-ene (10b, 10e). Alcohol **10a** (14 mg, 0.041 mmol) was dissolved in 0.3 mL of acetic anhydride and 0.3 mL of pyridine at rt and allowed to stand for 2 h. The mixture was then diluted with 5 mL of ether and washed 2× with 1 mL of $CuSO_4$ (sat.) solution to remove

pyridine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 14 mg of crude oil which was chromatographed over 10% deactivated flash silica gel (hexane–Et_2O (8:1 → 2:1)) to give 10.9 mg (69%) of pure acetate **10b**. The endo isomer (14 mg, 0.041 mmol) **10d** was converted similarly to acetate **10e** (13.4 mg, 84%).

***exo*-10b**: R_f = 0.44 (hexane–Et_2O (4:1)); $[\alpha]^{25}_D$ = −31.3; IR (neat) 2957, 2923, 2857, 1745, 1657, 1472, 1462, 1370, 1248, 1159, 1058, 835, 776, 668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.55 (br s, 1 H), 4.75 (d, J = 14.31 Hz, 1 H), 4.66 (d, J = 14.36 Hz, 1 H), 4.60 (dd, J = 5.04, 5.04 Hz, 1 H), 4.50 (d, J = 5.16 Hz, 1 H), 4.40 (br s, 1 H), 3.34 (br d, J = 6.87 Hz, 1 H), 2.84 (ddd, J = 8.20, 8.20, 8.20 Hz, 1 H), 2.20 (dd, J = 14.31, 8.07 Hz, 1 H), 2.10 (s, 3 H), 1.48 (s, 3 H), 1.38 (ddd, J = 14.54, 9.78, 4.86 Hz, 1 H), 1.30 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.63 (C), 142.19 (C), 129.31 (CH), 110.14 (C), 82.07 (CH), 81.92 (CH), 81.35 (CH), 61.65 (CH_2), 57.62 (CH), 50.93 (CH), 35.32 (CH_2), 27.18 (CH_3), 25.96 (CH_3, triple intensity), 24.86 (CH_3), 20.88 (CH_3), 18.37 (C), −4.55 (C), −4.56 (C); MS (CI, m/e (rel. int.)) 383 (4), 382 (1, M^+), 323 (65), 265 (40), 251 (50), 209 (15), 193 (100), 159 (20), 151 (75), 133 (40), 117 (50); NRMS calcd for $C_{20}H_{35}O_5Si$ 383.2254, found 383.2286.

***endo*-10e**: R_f = 0.46 (hexane–Et_2O (4:1)); $[\alpha]^{25}_D$ = −2.3; IR (neat) 2952, 2932, 2856, 1745, 1472, 1463, 1370, 1248, 1216, 1164, 1090, 1057, 869, 837, 776, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (dd, J = 1.57, 1.57 Hz, 1 H), 4.83 (ddd, J = 7.11, 1.62, 1.62 Hz, 1 H), 4.73 (dd, J = 13.88, 1.06 Hz, 1 H), 4.64 (dd, J = 13.83, 1.12 Hz, 1 H), 4.62 (m, 1 H), 4.56 (dd, J = 5.35, 0.99 Hz, 1 H), 3.18 (dddd, J = 8.77, 7.52, 7.52, 7.52 Hz, 1 H), 2.99 (br d, J = 7.14 Hz, 1 H), 2.09 (s, 3 H), 2.01–1.82 (m, 2 H), 1.47 (s, 3 H), 1.30 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.65 (C), 138.30 (C), 132.83 (CH), 109.95 (C), 83.11 (CH), 82.33 (CH), 76.30 (CH), 61.38 (CH_2), 57.10 (CH), 46.37 (CH), 31.83 (CH_2), 27.11 (CH_3), 25.81 (CH_3, triple intensity), 24.68 (CH_3), 20.90 (CH_3), 18.18 (C), −4.85 (CH_3), −4.91 (CH_3); MS (CI, m/e (rel. int.)) 383 (25), 382 (10), 381 (32), 367 (12), 341 (10), 331 (32), 323 (95), 283 (10), 267 (50), 209 (15), 193 (100), 151 (12), 133 (40), 117 (40); HRMS calcd for $C_{20}H_{35}O_5Si$ 383.2254, found 383.2256.

(7*S*,8*R*)-2-(Acetoxymethyl)-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-4-ol (10c, 10f). *exo*-TBDMS-protected alcohol **10b** (10.6 mg, 0.0312 mmol) was dissolved in 1 mL of dry THF under argon at room temperature, the mixture charged with TBAF·$3H_2O$ (19.7 mg, 0.062 mmol), and the mixture stirred for 1 h at which time TLC indicated complete consumption of starting material. The reaction was quenched with 0.5 mL of saturated NH_4Cl and diluted with 0.5 mL of water. The aqueous layer was extracted 4× with 4 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give 12.4 mg of crude oil which was chromatographed over 10% deactivated silica gel with hexane–EtOAc (4:1 → 1:2) to give 6.0 mg (81%) of pure alcohol **10c**. The *endo*-TBDMS-protected alcohol **10e** (13.2 mg, 0.035 mmol) was deprotected similarly to give 7.6 mg (82%) of alcohol **10f**.

***endo*-10f**: R_f = 0.32 (hexane–EtOAc (2:1)); ^1H NMR ($CDCl_3$) δ 5.61 (dd, J = 1.8, 1.8 Hz, 1 H), 4.90 (br d, J = 7.05 Hz, 1 H), 4.75 (ddd, J = 14.1, 1.2, 1.2 Hz, 1 H), 4.70–4.61 (m, 2 H), 4.59 (dd, J = 5.4, 1.3 Hz, 1 H), 3.25 (dddd, J = 9.26, 7.45, 7.45, 7.45 Hz, 1 H), 3.04 (br d, J = 7.2 Hz, 1 H), 2.10 (s, 3 H), 2.03–1.82 (m, 2 H), 1.67 (br s, 1 H), 1.47 (s, 3 H), 1.30 (s, 3 H).

***exo*-10c**: R_f = 0.28 (hexane–EtOAc (2:1)); ^1H NMR ($CDCl_3$) δ 5.69 (br s, 1 H), 4.78 (dd, J = 14.5, 0.8 Hz, 1 H), 4.68 (dd, J = 14.5, 0.9 Hz, 1 H), 4.62 (dd, J = 4.9, 4.9 Hz, 1 H), 4.52 (d, J = 5.2 Hz, 1 H), 4.41 (br s, 1 H), 3.34 (br d, J = 6.43 Hz, 1 H), 2.93 (ddd, J = 9.79, 7.42, 7.42 Hz, 1 H), 2.25 (dd, J = 7.95, 14.37 Hz, 1 H), 2.12 (s, 3 H), 1.62 (br s, 1 H), 1.47 (s, 3 H), 1.37 (ddd, J = 14.6, 10.0, 4.8 Hz), 1.30 (s, 3 H).

(7*S*,8*R*)-2-Carbethoxy-7,8-(isopropylidenedioxy)-6-oxobicyclo[3.3.0]oct-2-en-*exo*-4-yl *p*-(Benzyloxy)benzoate (8e). Method 1. Alcohol **8a**[6] (17 mg, 0.060 mmol) was dissolved in 2 mL of dry CH_2Cl_2 under argon, the flask charged with *p*-(benzyloxy)benzoic acid (34 mg, 0.15 mmol), 1,3-dicyclohexylcarbodiimide (31 mg, 0.0446 mmol), and DMAP (1 crystal), and the mixture stirred at room temperature for 6 h at which time TLC indicated incomplete reaction. The solvent was then removed under vacuum and the residue chromatographed over 10% deactivated silica gel with hexane–EtOAc (5:1 → 1:1) as eluent to obtain 21.7 mg (73%) of ester **8e** which is slightly contaminated with a DCC derivative. **Method 2.** Alcohol **8b**[6] (7.0 mg, 0.025 mmol) was dissolved in THF (0.5 mL) and the flask charged with *p*-(benzyloxy)benzoic acid (11.3 mg, 0.050 mmol), triphenylphosphene (13.0 mg, 0.050 mmol), and diethyl azodicarboxylate (7.8 μL, 0.050 mmol) at rt, and TLC indicated complete reaction after 1 h at rt. The mixture was evaporated under vacuum and chromatographed over 10% deactivated silica gel (hexane–EtOAc (8:1 → 2:1)) to obtain 9.4 mg (29%) of **8e** as a clear oil: R_f = 0.30 (hexane–Et_2O (4:1)); ^1H NMR ($CDCl_3$) δ 7.95 (ddd, J = 8.98, 2.33, 2.33 Hz, 2 H), 7.45–7.32 (m, 5 H), 6.98 (ddd, J = 8.97, 2.35, 2.35 Hz, 2 H), 6.90 (dd, J = 2.42, 2.42 Hz, 1 H), 5.89 (br s, 1 H), 5.12 (s, 2 H), 5.06 (d, J = 5.10 Hz, 1 H), 4.29 (qd, J = 7.17, 1.48 Hz, 2 H), 4.24 (d, J = 5.12 Hz, 1 H), 4.12–4.06 (m, 1 H), 3.46 (d, J = 7.1 Hz, 1 H), 1.45 (s, 3 H), 1.38 (s, 2 H), 1.34 (t, J = 7.14 Hz, 3 H).

(7*S*,8*R*)-2-Carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-4-ol (3b, 3d). Protected alcohol **3a** (11 mg, 0.029 mmol) was dissolved in THF, cooled to −40 °C, and treated with TBAF·$3H_2O$. The mixture was stirred for 10 min, slowly warmed to rt, and then stirred 1 h. The mixture was quenched with NH_4Cl(aq), diluted with 1 mL of water, and extracted 3× with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated to yield 10.5 mg of crude oil which was chromatographed over 10% deactivated silica gel with hexane/EtOAc (2:1) to give 6.5 mg (85.1%) of pure exo alcohol **3b**. The endo-protected alcohol **3c** (7.0 mg, 0.018 mmol) was deprotected similarly to endo alcohol **3d** (4.6 mg, 92%).

***exo*-3b**: R_f = 0.28 (hexane–EtOAc (2:1)); ^1H NMR ($CDCl_3$) δ 6.64 (dd, J = 2.44, 2.44 Hz, 1 H), 4.66 (d, J = 5.16 Hz, 1 H), 4.58 (dd, J = 4.88, 4.88 Hz, 1 H), 4.53 (br s, 1 H), 4.27 (qd, J = 7.1, 1.4 Hz, 2 H), 3.57 (br d, J = 6.92 Hz, 1 H), 2.96 (ddd, J = 10.20, 7.37, 7.37 Hz, 1 H), 2.25 (dd, J = 14.4, 7.95 Hz, 1 H), 1.48 (s, 3 H), 1.36 (ddd, J = 14.9, 10.2, 4.7 Hz, 1 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.30 (s, 3 H); MS (CI, m/e (rel. int.)) 269 (10, M^+ + 1), 253 (45), 251 (35), 233 (10), 211 (100), 193 (70), 177 (12), 165 (90), 147 (35), 137 (15), 121 (30), 119 (25), 108 (20), 91 (55), 79 (35).

***endo*-3d**: R_f = 0.35 (hexane–EtOAc (2:1)); ^1H NMR ($CDCl_3$) δ 6.57 (dd, J = 2.07 Hz, 1 H), 5.00 (br s, 1 H), 4.77 (d, J = 5.21 Hz, 1 H), 4.63 (dd, J = 4.84, 4.84 Hz, 1 H), 4.25 (q, J = 7.05 Hz, 2 H), 3.36–3.23 (m, 2 H), 1.99 (dd, J = 14.41, 6.82 Hz, 1 H), 1.87–1.76 (m, 2 H), 1.48 (s, 3 H), 1.31 (t, J = 7.12 Hz, 3 H), 1.30 (s, 3 H).

(7*S*,8*R*)-2-Carbethoxy-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-*exo*-4-yl *p*-(Benzyloxy)benzoate (3e). Method 1. Alcohol **3b** (6.0 mg, 0.022 mmol) was dissolved in 1 mL of dry CH_2Cl_2 under argon, the flask charged with *p*-(benzyloxy)benzoic acid (7.7 mg, 0.0336 mmol), 1,3-dicyclohexylcarbodiimide (9.1 mg, 0.0446 mmol), DMAP (1 crystal), and *p*-TsOH (1 crystal), and the mixture stirred at room temperature for 24 h at which time TLC indicated incomplete reaction. Extra DCC (4.5 mg) was added, and TLC indicated complete reaction after 24 h. The solvent was then removed under vacuum and the residue chromatographed on a preparative silica plate with hexane–EtOAc (5:1) as eluent to obtain 4.4 mg (41%) of pure ester **3e**. **Method 2.** Alcohol **3d** (4.6 mg, 0.017 mmol) was dissolved in THF (0.5 mL), the flask charged with *p*-(benzyloxy)benzoic acid (7.8 mg, 0.034 mmol), triphenylphosphene (9.0 mg, 0.034 mmol), and diethyl azodicarboxylate (6.0 mg, 0.034 mmol) at rt, and TLC indicated complete reaction after 1 h at rt. The mixture was evaporated under vacuum and chromatographed over 10% deactivated silica gel (hexane–ether (8:1 → 2:1)) to obtain 2.4 mg (29%) of clear oil. **Method 3.** Alcohol **9h** was converted to its xanthate as described above for **9a–c**, and this xanthate (12 mg, 0.021 mmol) was dissolved in toluene under argon and brought to reflux. A crystal of AIBN was added, and the reaction was shown to be complete after 10 min by TLC. The mixture was evaporated under vacuum and separated over 10% deactivated silica gel (hexane–ether (8:1 → 2:1)) to obtain 6.5 mg (65%) of **3e** as a clear oil: R_f = 0.37 (hexane–ether (4:1)); ^1H NMR ($CDCl_3$) δ 7.98 (ddd, J = 8.99, 2.09, 2.09 Hz, 2 H), 7.45–7.30 (m, 5 H), 6.98 (ddd, J = 8.89, 2.01, 2.01 Hz, 2 H), 6.72 (dd, J = 2.33, 2.33 Hz, 1 H), 5.58 (dd, J = 2.1, 2.1 Hz, 1 H), 5.12 (s, 2 H), 4.72 (d, J = 5.14 Hz, 1 H), 4.63 (dd, J = 4.86 Hz, 1 H), 4.28 (qd, J = 7.18, 1.22 Hz, 2 H), 3.62 (br d, J = 6.80 Hz, 1 H), 3.15 (ddd, J = 9.96, 7.50, 7.50 Hz, 1 H), 2.38 (dd, J = 14.51, 8.12 Hz, 1 H), 1.49 (s, 3 H),

1.33 (t, J = 7.23 Hz, 3 H), 1.31 (s, 3 H).

(7*S*,8*R*)-2-(Acetoxymethyl)-7,8-(isopropylidenedioxy)bicyclo[3.3.0]oct-2-en-*exo*-4-yl *p*-(Benzyloxy)benzoate (11). Method 1. Alcohol **10f** (7.6 mg, 0.028 mmol) was dissolved in dry THF under argon. To the mixture was added triphenylphosphene (14.9 mg, 0.058 mmol) and 4-(benzyloxy)benzoic acid (12.9 mg, 0.058 mmol) against a flow of argon followed by diethyl azodicarboxylate (8.97 μL, 0.058 mmol) via syringe. The deep yellow color from DEAD dissappeared after a few seconds, and TLC analysis indicated that the reaction was complete after 5 min. The mixture was evaporated to dryness under vacuum and the residue chromatographed over 10% deactivated flash silica with hexane–Et_2O (8:1 → 1:1) to obtain 6.4 mg (54.6%) of clear oil which was rechromatographed similarly to remove a slight contaminant from the DEAD reagent to give 6.4 mg (47.2%) of clear benzoate ester **11**: R_f = 0.15, hexane–EtOAc (4:1); $[\alpha]^{25}_D$ = −45.69; IR (neat) 3064, 3033, 2983, 2932, 1744, 1707, 1605, 1455, 1371, 1248, 1167, 1095, 1057, 951, 848, 771, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (ddd, J = 9.01, 2.64, 2.09 Hz, 2 H), 7.44–7.32 (m, 5 H), 6.98 (ddd, J = 9.01, 2.66, 2.14 Hz, 2 H), 5.78 (br s, 1 H), 5.47 (s, 1 H), 5.12 (s, 2 H), 4.82 (ddd, J = 14.8, 1.0, 1.0 Hz, 1 H), 4.71 (ddd, J = 14.9, 1.0, 1.0 Hz, 1 H), 4.66 (dd, J = 4.68, 4.68 Hz, 1 H), 4.55 (d, J = 5.09 Hz, 1 H), 3.38 (br d, J = 6.88 Hz, 1 H), 3.13 (ddd, J = 9.54, 7.74, 7.74 Hz, 1 H), 2.37 (dd, J = 14.78, 8.09 Hz, 1 H), 2.12 (s, 3 H), 1.55 (ddd, J = 14.85, 9.86, 4.84 Hz, 1 H), 1.47 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.52 (C), 166.13 (C), 162.49 (C), 146.30 (C), 136.20 (C), 131.66 (CH, double intensity), 128.66 (CH, double intensity), 128.19 (CH), 127.46 (CH, double intensity), 125.01 (CH), 129.91 (C), 114.42 (CH, double intensity), 110.28 (C), 82.81 (CH), 82.08 (CH), 81.70 (CH), 70.07 (CH_2), 61.39 (CH_2), 58.06 (CH), 47.51 (CH), 35.06 (CH_2), 27.13 (CH_3), 24.76 (CH_3), 20.83 (CH_3); MS (CI, m/e (rel. int.)) 479 (1, M^+), 463 (2), 419 (7), 361 (3), 251 (80), 229 (50), 211 (40), 193 (100), 151 (30), 133 (40), 121 (20), 105 (10), 91 (90); HRMS calcd for $C_{20}H_{34}O_6Si$ 479.2070, found 479.2063.

Specionin Acetate (1a). Acetate **11** (2 mg) was dissolved in methylene chloride and treated with excess *m*-CPBA at room temperature. NMR spectrum of an aliquot after 6 h indicated the presence of epoxy protons at 3.69 and 3.66 ppm corresponding to **12a** and **12b**, respectively. The reaction was quenched with aqueous bicarbonate and extracted with methylene chloride. The crude product was hydrogenated in EtOH over Pd(C) at 40 psi for 8 h to provide the debenzylated derivative **13** as evidenced by the absence of signals corresponding to the acetonide. To the filtrate from the hydrogenation was added sodium periodate and a crystal of *p*-TsOH and the mixture stirred at room temperature overnight, according to the published protocol.[5a] Purification of the crude product by filtration through silica and HPLC (C-18, $MeOH/H_2O$) gave **1a** identical with an authentic sample (vide NMR and HPLC).

Acknowledgment. The authors are grateful to the National Institutes of Health (GM-40648) for support of this work and to professor John Leonard (Salford University, UK) for ^1H NMR spectra and a sample of specionin acetate. Helpful discussions with professor James Tanko and Mr. Carlton Foster of Virginia Tech are appreciated. The authors also thank Dr. Alison Fleming and Dr. Nina Heard for their efforts in the development of the annulation methodology.

Supplementary Material Available: ^1H NMR spectra for compounds **9a–h**, **3a–e**, **8e**, **10a–f**, **11**, and **1a** (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Notes

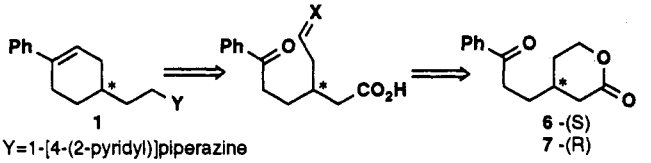
Synthesis of the Chiral 4-Substituted 1-Phenylcyclohexene PD137789 via Intramolecular Wittig Reaction

Stephen J. Johnson,* Suzanne R. Kesten, and Lawrence D. Wise

Department of Chemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105

Received March 9, 1992

The 4-substituted 1-phenylcyclohexene PD137789 (1) has dopamine agonist properties while its enantiomer appears to be an antagonist.[1] The two enantiomers are extremely difficult to resolve by standard methods and so far have only been separated by chiral HPLC. To provide a supply of PD137789 (1) for evaluation as a potential antipsychotic agent, we sought to develop a practical multigram chiral synthesis. We devised a strategy involving intramolecular cyclization with concomitant double-bond formation since this would generate and maintain the specific relationship between the double bond and the chiral center which is key to maintaining enantiotopic integrity. Such a strategy could exploit elements of existing approaches to chiral 3-substituted γ-butyrolactones as a means of generating the chiral center. Reactions which proceed through symmetric intermediates or isomerize the double bond had to be avoided since they would lead to racemization.



1 Y=1-[4-(2-pyridyl)]piperazine

6 -(S)
7 -(R)

Enzymatic differentiation of otherwise equivalent functional groups in symmetric prochiral compounds is an efficient source of enantiomerically enriched compounds since it is a catalytic process which optimally would convert all starting material to a single enantiomer.[2] In the case in point, the preferred substrate for this type of enantioselection would have the skeletal framework already in place for a subsequent cyclization. The ketal diester **4** fits this criterion.

A three-step synthesis of diester **4** was developed starting from commercially available methyl 3-benzoylpropionate.

(1) Caprathe, B. W.; Jaen, J. C.; Smith S. J.; Wise, L. D. U. S. Patent 4,975,445, Dec 4, 1990.

(2) Zhu, L.-M.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587. Ohno, M. *Enzymes in Organic Synthesis*; Ciba Symposium; 1985, *III*, 171. Toone, E. J.; Werth, M. J.; Jones, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 4946. Boland, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049.

0022-3263/92/1957-4746$03.00/0