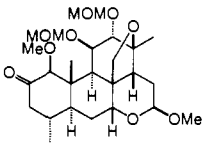
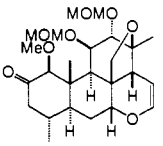
the resulting C(12) hydroxyl was reprotected as a methoxymethyl ether, giving rise to **10**, mp 159–160 °C, in 85% overall yield. Selective formation of the Δ^1 methyl enol ether and reduction of the C(11) keto function followed by protection of the resultant alcohol as a methoxymethyl ether provided **11**.

With the stereochemical features of ring C in place, attention was focused on introduction of a keto function at C(2) and a hydroxyl group at C(15). Hydroboration of the methyl enol ether in **11** and subsequent oxidation [PCC (3.0 equiv), NaOAc (2.5 equiv), CH_2Cl_2, Celite, 0 °C → room temperature] provided crystalline **12**, mp 205.5–207.0 °C, in 91% overall yield. Selective

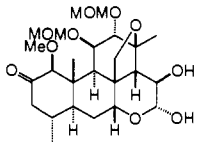


12

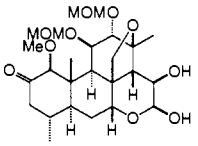


13

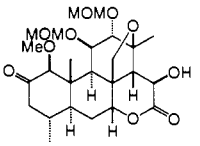
hydrolysis (5% HCl/THF, 1:1, 0 °C → room temperature) of the protected lactol followed by treatment with methanesulfonyl chloride (1.5 equiv) in methylene chloride containing triethylamine generated the sensitive dihydropyran **13**, which was treated directly with osmium tetraoxide to give rise (82%) to **14** and **15** in a 3:2 ratio. Upon treatment of the mixture of **14** and **15** with excess



14



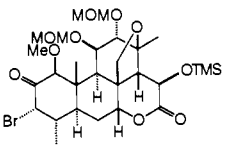
15



16

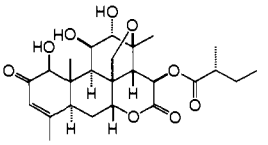
manganese dioxide in chloroform there was obtained a 54% yield of crystalline hydroxy lactone **16**, mp 224–225 °C, along with recovered (39%) lactol **15**.[10a] Exposure of **15** to 5% hydrochloric acid/tetrahydrofuran (1:2) gave rise (96%) to a 3:2 equilibrium mixture of **14** and **15**, which could be resubmitted to the manganese dioxide oxidation.[10b]

The synthesis of pre-simalikalactone D (**3**) was realized via a two-step sequence. Treatment of **16** with excess lithium hexamethyldisilazane in tetrahydrofuran at −78 °C followed by sequential addition of chlorotrimethylsilane (−78 → 0 °C) and *N*-bromosuccinimide (0 °C) provided crystalline bromo ketone **17**, mp 216–217 °C, in 93% yield. Much to our surprise, exposure of **17** to 1.5 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0 °C → room temperature) provided a 92% yield of pre-simalikalactone D (**3**), mp 209.5–211.0 °C.

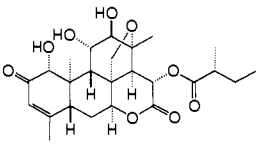


17

Completion of the synthesis of simalikalactone D necessitated determination of the absolute configuration of the α-methylbutyrate ester group attached at C(15). Toward this end, (±)-**3** was treated with (*R*)-2-methylbutyric anhydride[11] [Et_3N (4.0 equiv), DMAP (1.5 equiv), CH_2Cl_2, 5 h] to give rise to a 92% yield of two diastereomers, which were deprotected [1. $AlCl_3$ (15 equiv), NaI (15 equiv), CH_3CN/CH_2Cl_2 (2:1), 0 °C, 25 min; 2. BBr_3 (15 equiv), CH_2Cl_2, −45 °C, 45 min] in ca. 70% overall yield,



18

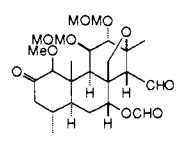


19

providing two diastereomers **18** and **19** which were readily separated by HPLC.[12,13] Synthetic (+)-**18** was found to be identical (mp, mmp, $[\alpha]_D$, IR, HPLC, ^1H NMR, ^{13}C NMR) with a sample of natural (+)-simalikalactone D kindly provided by Dr. J. Polonsky.

Acknowledgment. Generous support from this work from the National Cancer Institute, National Institutes of Health (Grant CA28865), is gratefully acknowledged. We thank Dr. Judith Polonsky (Gif-Sur-Yvette) for a sample of natural simalikalactone D. We are especially grateful to Dr. Kevin Babiak, Cara Weyker, and Larry Miller (Searle) for carrying out the analytical and preparative HPLC work on the four synthetic diastereomers of **1**.

(10) (a) Stereoelectronic factors have been observed previously in the manganese dioxide oxidation of carbohydrate derivatives [Fraser-Reid, B.; Carthy, B. J.; Holder, N. L.; Yunker, M. *Can. J. Chem.* **1971**, *49*, 3038; also see Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 41–47]. (b) Use of Fetizon's reagent (Ag_2CO_3/Celite/benzene) in the oxidation of **14** and **15** led to substantial quantities of the C(15),C(16) cleavage product i, in addition to the desired hydroxy lactone **16**.



i

(11) (*R*)-2-Methylbutanoic acid, prepared according to the Evans protocol [Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737; Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141], was converted (DCC, CH_2Cl_2, 0 °C) into (*R*)-2-methylbutyric anhydride, bp 55 °C (0.1 mm), $[\alpha]^{25}_D$ −33.8° (*c* 0.014, CH_2Cl_2), in 91% yield.

(12) The HPLC separation was carried out on a Beckmann instrument (Model 101) using a preparative Chiracel OD column (10 mm i.d. × 50 cm) (mobile phase, absolute EtOH/hexane, 30:70 (v/v), flow rate, 4.2 mL/min, UV detection at 230 nm). The retention times of **18** ($[\alpha]^{25}_D$ +45.8° (*c* 0.006, dioxane)) [simalikalactone D ($[\alpha]^{25}_D$ +43.2°(*c* 0.006, dioxane))] and diastereomer **19** ($[\alpha]^{25}_D$ −63.7° (*c* 0.006, dioxane)) were 12.3 and 8.1 min, respectively.

(13) Initially, (±)-**3** was treated with commercially available (*S*)-2-methylbutyric anhydride (Et_3N, DMAP, CH_2Cl_2, 5 h), and the resulting mixture of C(15)-acylated compounds were deprotected [a. $AlCl_3$, NaI, CH_3CN/CH_2Cl_2 (2:1), 0 °C; b. BBr_3, CH_2Cl_2, −45 °C], giving rise to two diastereomers which were readily separated by HPLC (retention times 8.0 and 13.2 min), and shown not to be identical to simalikalactone D by coinjection with an authentic sample of **1**.

Silicon-Directed Aldol Condensation. Evidence for a Pseudorotational Mechanism

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Received December 3, 1991

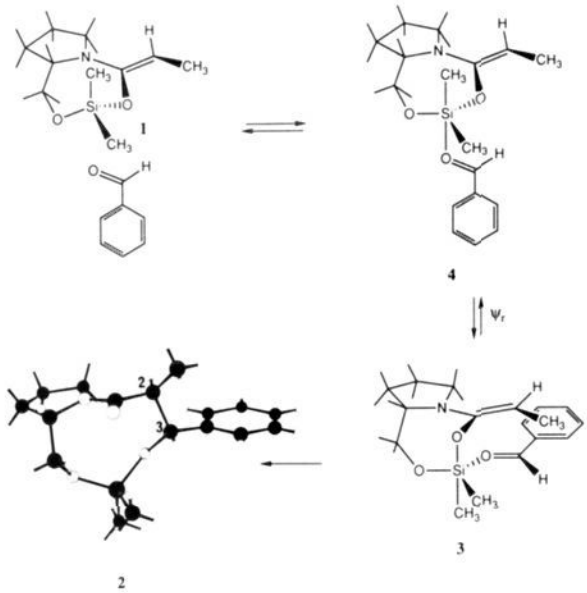
Mechanistic studies of the reaction of the (*S*)-prolinol-derived *O*-silyl ketene *N,O*-acetal **1** with aromatic aldehydes are reported. Experiments with three *O*-silyl ketene *N,O*-acetals derived from different 1,2-amino alcohols are also described and lead to a coherent mechanistic picture involving pseudorotation of trigonal bipyramidal organosilicon intermediates.

Benzaldehyde and **1** react to form the (2*S*,3*R*)-anti aldol product **2** (77%) and traces of the (2*S*,3*S*)-syn product (2%).[1] The reaction proceeds readily at ambient temperature in solvents which are poor σ-donors (CH_2Cl_2, hexane, benzene, CH_3CN) but not at all in tetrahydrofuran or *N,N*-dimethylformamide, an observation suggestive of coordination of the aldehyde carbonyl

(1) Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672.

0002-7863/92/1514-2765$03.00/0

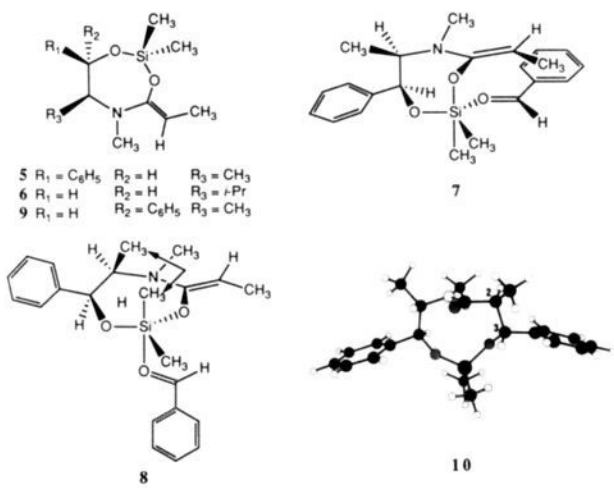
Scheme I



oxygen to the silicon atom. The rate of reaction in hexane (ϵ = 2) is within 20% of that in acetonitrile (ϵ = 37), a fact which disfavors mechanisms involving highly polar transition states. Kinetic analysis in benzene over a 60-deg range (20–80 °C) shows the reaction to be rigorously second-order, first-order in each reactant, and provides the following activation parameters: $\Delta H^{\ddagger}$ = 12.0 ± 0.5 kcal/mol and $\Delta S^{\ddagger}$ = −41 ± 2 eu. The reaction order and large, negative entropy of activation are consistent with an associative mechanism involving pentacoordinate silicon.[2] Further evidence supporting this proposal and the relative energetics of species along the pathway are derived in part from the following experiments. Reaction of **1** with a mixture of C_6H_5CHO and C_6H_5CDO (1:1, 0.5 equiv) affords **2** disproportionately enriched in deuterium. The derived secondary deuterium isotope effect[3] (k_H/k_D = 0.76 ± 0.05) suggests a later transition state, involving C–C bond formation rather than, for example, Lewis acid–base complexation. Kinetic analysis of the reaction of **1** with a series of para-substituted benzaldehydes shows that electron-withdrawing substituents accelerate the reaction (Hammett ρ = 3.5 ± 0.2), again consistent with rate-determining C–C bond formation and not Lewis acid–base complexation.[4] At high σ values, the Hammett plot is found to be nonlinear, signaling a change in mechanism. This may be interpreted as a transition toward rate-determining complexation. Attempts to observe intermediates in the reaction have not been successful. Monitoring of the reaction by ^1H and ^{13}C NMR spectroscopy within the temperature range −80 to 23 °C shows only **1**, benzaldehyde, and **2**. If a Lewis acid–base complex of **1** and benzaldehyde exists as an energy minimum, then the equilibrium for its formation lies to the left.

The following arguments provide a logical basis for the detailed mechanism of Scheme I. X-ray crystallographic data suggests the trigonal bipyramid (tbp) **3** as a reasonable precursor to **2**.[1,5] The transition state is viewed to lie somewhere between structures **3** and **2** and to involve C–C bond formation, in line with evidence presented above. An appealing feature of this hypothesis is the nature of Si–enol(O) bonding in the transition state (essentially utilizing a p orbital on oxygen), allowing for continuous overlap during C–C bond formation and Si–O bond cleavage.[1] Furthermore, this proposal involves apical departure of the enol oxygen. Though **3** is derived from X-ray data, it arises as well upon analysis of all tbp isomers; the two carbon atoms involved in bonding are found to be proximal in structure **3** alone. The equatorial positioning of the aldehyde in structure **3** is noteworthy. Direct formation of **3** from benzaldehyde and **1** requires attack of benzaldehyde along an edge of the silicon-centered tetrahedron.[6] Alternatively, and more in keeping with the consensus of mechanistic studies in the area, **3** may be envisioned to arise by face-centered attack of benzaldehyde on **1** followed by pseudorotation of the resulting tbp containing apically-bound aldehyde.[6,7] Derivation of such a pathway is simpler when the reaction is analyzed in reverse. In theory, a series of pseudorotation steps (maximum of three) can interconvert **3** with any of its nine isomeric tbp's, four of which contain apically-bound aldehyde.[8,9] In consideration of the three tbp isomers accessible from **3** by a single pseudorotation, structure **4**, in which the aldehyde is apically bound, uniquely accommodates the experimental data from studies of a series of related *O*-silyl ketene *N*,*O*-acetals, described below.[10]

(1*R*,2*S*)-Ephedrine- and (*S*)-valinol-derived *O*-silyl ketene *N*,*O*-acetals **5** and **6** are prepared in analogy to **1**.[1] Neither substrate is observed to undergo aldol addition with benzaldehyde below 110 °C; above this temperature the ketene acetal decomposes. These results are difficult to rationalize in light of structure **3** alone; corresponding structures can be constructed from **5** and **6** and appear not to be unduly strained (e.g., see **7**[11]). By contrast,



(2) (a) Tandura, S. N.; Voronkov, M. G.; Alekseev, N. V. In *Structural Chemistry of Boron and Silicon*; Boschke, F. L., Ed.; Springer-Verlag: New York, 1986; Vol. 131, p 99. (b) Corriu, R. J. P. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Part 2, Chapter 20.

(3) Review: Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.

(4) A study of the racemization of tetracoordinate silane by a series of para-substituted benzaldehydes led to a Hammett ρ value of −1.52 ± 0.06 (ref 8d,f).

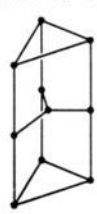
(5) Schaefer, W. P.; Widdowson, K. L.; Myers, A. G. *Acta Crystallogr.* **1991**, *C47*, 2575.

(6) (a) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.

(7) (a) Corriu, R. J. P.; Guerin, C.; Moreau, J. E. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Part 1, Chapter 4. (b) Holmes, R. R. *Chem. Rev.* **1990**, *90*, 17.

(8) Pseudorotation of trigonal bipyramidal silicon compounds: (a) Klanberg, F.; Muetterties, E. L. *Inorg. Chem.* **1968**, *7*, 155. (b) Gibson, J. A.; Ibbott, D. G.; Janzen, A. F. *Can. J. Chem.* **1973**, *51*, 3203. (c) Farnham, W. B.; Harlow, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4608. (d) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 309. (e) Stevenson, W. H., III; Wilson, S.; Martin, J. C.; Farnham W. B. *J. Am. Chem. Soc.* **1985**, *107*, 6340. (f) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 6352.

(9) The presence of two identical ligands reduces the number of stereoisomers from 20 to 10. The graphical representation of these isomers and their pseudorotation pathways (see ref 7b) is simplified accordingly and may be represented by the trigonal prism shown. The center point is uniquely defined



as that isomer with the identical ligands apical. The identical ligands are equatorial in the remaining (three) isomers in this plane, which also serves as a mirror plane in relating the remaining six isomers (provided the ligands are achiral).

the proposed initially-formed tbp's analogous to **4** (e.g., **8**[11]) suffer from a severe steric interaction between an alkyl group on the ligand and an apical substituent within the tbp. In other words, though the corresponding transition structures for aldol reaction of **5** and **6** with benzaldehyde seem reasonable, there appears to be no low-energy pathway for their formation. Further consideration of structure **8**[11] suggests that a viable intermediate might be produced by epimerization of the methyl-bearing carbon, a proposal supported by experiment. (1*S*,2*S*)-Pseudoephedrine-derived ketene *N*,*O*-acetal **9** undergoes smooth aldol condensation with benzaldehyde at 60 °C to form the (2*S*,3*R*)-anti aldol product **10** (mp 156–158 °C) in 70% yield. X-ray analysis of **10** shows the structure to be analogous to **2**, supporting, though certainly not proving, a common reaction mechanism.

In summary, it is proposed that attack of benzaldehyde on **1** produces **4**, which then undergoes pseudorotation and (rate-determining) C–C bond formation to afford **2**. The formation of other tbp isomers by attack on a different tetrahedral face of **1** with subsequent pseudorotational isomerizations to **4** (at least two are required) is not ruled out; however, the proposed mechanism is simpler. This mechanism follows rationally from consideration of the experimental data and appears to correlate results obtained with several different substrates. Finally, in addition to providing mechanistic insight, the pseudoephedrine-derived *O*-silyl ketene *N*,*O*-acetal **9** is anticipated to be of value in the synthesis of enantiomerically pure anti aldol products.

Acknowledgment. Generous financial assistance from the National Science Foundation and the David and Lucile Packard Foundation is gratefully acknowledged. We are indebted to Professor Kurt Mislow for helpful discussions.

Supplementary Material Available: A Hammett plot of the reaction of **1** with a series of substituted benzaldehydes (1 page). Ordering information is given on any current masthead page.

(10) Structures **3** and **4** may represent energy minima or simply points along the surface leading to **2**; the data available at this time do not allow resolution of this issue.

(11) The enantiomer is depicted for visual comparison of homochiral structures.

Asymmetric Synthesis of (−)-Quinocarcin

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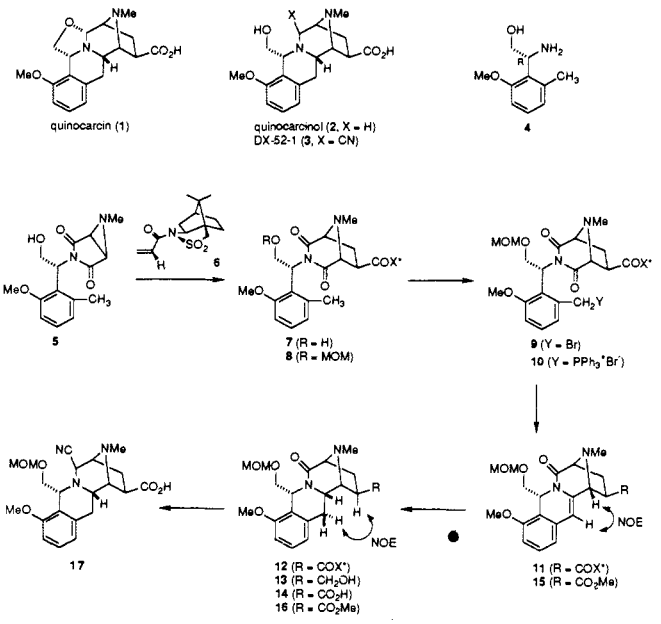
Received December 23, 1991

Quinocarcin (**1**)[1] is an antitumor antibiotic isolated from *Streptomyces melanovinaceus* whose structure was deduced from the X-ray analysis of quinocarcinol (**2**), an inactive homologue which lacks the hemiaminal function. Quinocarcin itself is rather labile but can be converted to a more stable amino nitrile derivative DX-52-1 (**3**) by treatment with CN^-, and **1** can be regenerated with $AgNO_3$ or strong acid.[2] The antitumor activity of **1** appears to be tied to the inhibition of DNA and/or RNA synthesis.[3] Quinocarcin's absolute configuration was not determined, but a computational study suggests that the enantiomer shown may be preferred for binding to DNA.[4] Although total syntheses of racemic **1** and **2** have been reported,[5] recent work has focused on developing enantiospecific approaches to these molecules.[6] We now report the first asymmetric synthesis of (−)-**1**.

The synthesis begins with (*R*)-phenylglycinol derivative **4**,[7] which is converted to the aziridine imide **5**[8] in 31% overall yield via a five-step sequence analogous to one used in our model studies.[9] Building on our previously elaborated strategy,[10] an auxiliary-controlled 1,3-dipolar cycloaddition reaction would be used to assemble the 3,8-diazabicyclo[3.2.1]octane moiety of **1**.[11] In the event, portionwise addition of (+)-acryloyl sultam **6**[12] to an irradiated (2537 Å, quartz) solution of **5** in 1,4-dioxane resulted in a very clean reaction to give **7** (X* = (+)-sultam), the cycloadduct resulting from addition of the intermediate azomethine ylide to the *exo-si* face of the dipolarophile **6**, in 61% isolated yield. At this juncture, the free hydroxyl function was masked (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 86%) to give the MOM ether **8**.



Benzylic bromination of **8** (0.01 M, NBS, $CHCl_3$, *hν*) afforded the monobromide **9**, which was directly converted to the phosphonium salt **10** (Ph_3P, $CHCl_3$, 56% over two steps). Treatment of **10** with *t*-BuOK resulted in the formation of a phosphonium ylide, which, upon heating (DMF, 120 °C), cyclized to give the required dihydroisoquinoline **11** in 79% yield.[13] The regioselectivity of this intramolecular imide olefination can be ascribed

(1) (a) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468. (b) Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1705.

(2) (a) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. (b) Saito, H.; Kobayashi, S.; Uosaki, Y.; Sato, A.; Fujimoto, K.; Miyoshi, K.; Morimoto, A.; Hirata, T. *Chem. Pharm. Bull.* **1990**, *38*, 1278.

(3) (a) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268. (b) Fujimoto, K.; Oka, T.; Morimoto, M. *Cancer Res.* **1987**, *47*, 1516. (c) Kanamaru, R.; Konishi, Y.; Ishioka, C.; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakui, A. *Cancer Chemother. Pharmacol.* **1988**, *22*, 197.

(4) Hill, G. C.; Wunz, T. P.; Remers, W. A. *J. Comput.-Aided Mol. Des.* **1988**, *2*, 6029.

(5) (a) (±)-**2**: Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neil, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421. (b) (±)-**1**: Fukuyama, T.; Nunes, J. J. *Ibid.* **1988**, *110*, 5196.

(6) (a) Saito, S.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1988**, *29*, 6301. (b) Saito, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Terashima, S. *Ibid.* **1989**, *30*, 7423. (c) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Ibid.* **1990**, *31*, 2105.

(7) This compound was prepared in >99% ee by asymmetric azidation (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011) of the (1*S*,2*R*)-norephedrine derived oxazolidine imide of 2-methoxy-6-methylbenzeneacetic acid followed by reduction. Details will be provided in the full account of this work.

(8) All of the compounds depicted in this paper exhibited satisfactory spectral and/or analytical data.

(9) **4** → **5**: (1) maleic anhydride, Et_2O; (2) Ac_2O, NaOAc, 120 °C; (3) 5 N HCl, THF; (4) MeN_3, toluene; (5) *hν* (Hg, Pyrex), 1,4-dioxane. (See ref 10 for details.)

(10) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

(11) For a related approach to quinocarcin, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Ibid.* **1990**, *31*, 1012.

(12) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035.

(13) Flitsch, W.; Langer, W. *Liebigs Ann. Chem.* **1988**, 391. This application of Flitsch's imide olefination protocol to the synthesis of dihydroisoquinoline systems is, to our knowledge, unprecedented.

0002-7863/92/1514-2767$03.00/0