JOC Article

Stereochemistry of C-6 Nucleophilic Displacements on 1,1-Difluorocyclopropyldibenzosuberanyl Substrates. An Improved Synthesis of Multidrug Resistance Modulator LY335979 Trihydrochloride

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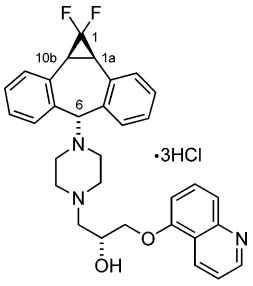
Studies of the displacement chemistry of 1,1-difluorocyclopropyldibenzosuberanyl alcohol **4** and its activated bromide derivative **6** have led to an improved approach to ***anti*-2**, a key precursor to LY335979 3HCl (**1**). Bromination of either ***syn*-4** or ***anti*-4** gave anti-oriented **6**, indicating thermodynamically controlled product stereochemistry via a stabilized 1,1-difluorohomotropylium ion intermediate. Reaction of **6** with piperazine proceeded irreversibly to provide an isomeric mixture of piperazine products, with the syn:anti product ratio increased by solvent effects. Reaction of **6** with pyridine and pyrazine, on the other hand, gave *anti*-pyridinium and pyrazinium salts, respectively, apparently via equilibration of initially formed syn products. Reduction of pyrazinium salt **11** with lithium borohydride/TFA provided ***anti*-2** unaccompanied by its syn isomer. A practical and expeditious approach to **1** was derived from these new results.

Introduction

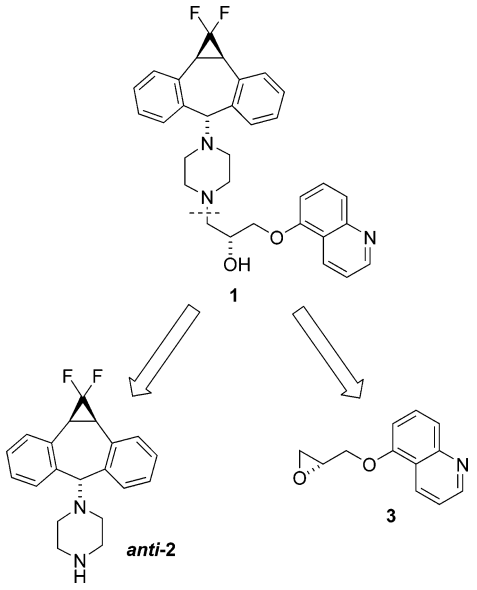
The development of multiple drug resistance is a serious limitation on the effectiveness of many oncolytic drugs. New findings on the biological basis of multiple drug resistance have permitted the rational search for modulators of specific resistance pathways.[1] Compound LY335979 3HCl (**1**) has been found to be a clinically useful modulator of *P*-glycoprotein-mediated multiple drug resistance in research beginning at the former Syntex Corporation and continuing[2] at Lilly Research Laboratories.[3] The expansion of clinical trials prompted us to embark on a program to create a practical and cost-effective synthetic approach to **1**.



1

LY335979·3HCl was first prepared at Syntex as part of an effort to improve upon the activity of MS-073,[4] a similar structure saturated in place of the difluorocyclopropyl group in **1**.

SCHEME 1



The Syntex strategy[5] for the synthesis of **1** is indicated retrosynthetically in Scheme 1.

One key disconnection was at the C−N bond joining the substituted piperazinyl moiety to the chiral 2-hydroxypropoxyquinoline linker via the substituted piperazine **2** possessing the required anti stereochemistry[6] and the known[7] (*R*)-epoxide **3**. Although other approaches could be envisioned, this one provided the greatest

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(1) Norman, B. H. *Drugs Future* **1998**, *23*, 1001−1013. Ford J M.; Hait, W. N. *Pharmacological Reviews* **1990** *42*, 155−99.

(2) LY335979·3HCl was licensed from Syntex Corporation in November, 1994. The Syntex serial number was RS-33295-198.

10.1021/jo049051v CCC: $27.50
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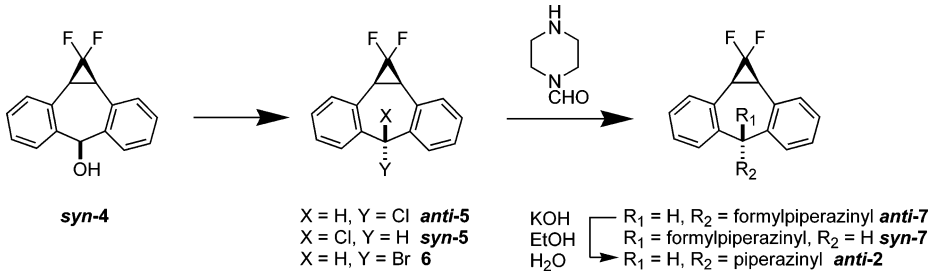
SCHEME 2



convergence and relied upon the opening of an epoxide by an amine, a well-known and stereochemically reliable reaction.

On the other hand, the synthesis of ***anti*-2** as described by the Syntex group was encumbered with relative stereochemical problems as indicated in Scheme 2.

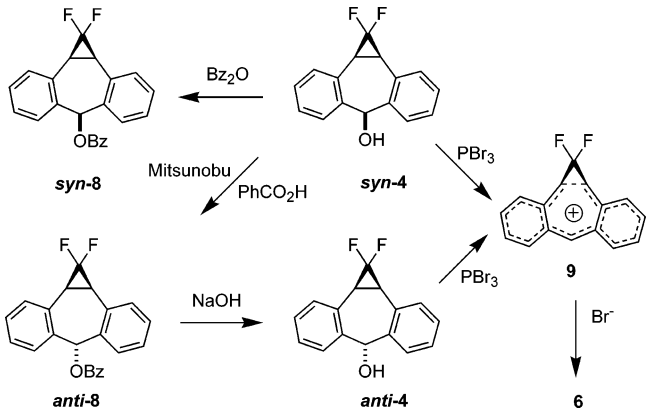
Chlorination of ***syn*-4** ($SOCl_2$) provided a mixture of chlorides **5** in an anti:syn ratio of about 90:10.[8] Reaction of the mixture with formylpiperazine, however, unfortunately gave rise to a nearly equal mixture of piperazinyl isomers ***anti*-7** and ***syn*-7** (anti:syn 55:45).[9] The mixture could be separated by chromatography, providing purified ***anti*-7**, which gave ***anti*-2** upon deprotection with strong base.

Although it was possible to utilize the original approach to ***anti*-2** for the preparation of relatively small quantities of LY335979, the unfavorable impact of ambiguous stereochemistry of the piperazine displacement step on efficiency of the synthesis quickly became apparent. We describe herein studies leading to successful resolution of the stereochemistry issue, leading to an expeditious approach to **1** suitable for commercial scale use.

Stereochemical Studies

Synthesis of Bromide 6 from *syn*-4. We found the bromination of dibenzosuberanol ***syn*-4** to be the method of choice for activating the molecule for amine displacement. Attempted preparation of sulfonate esters of ***syn*-4** failed to give useful products, apparently because of the instability of these intermediates. As mentioned previously, chlorination with $SOCl_2$ provided a mixture of stereoisomeric chlorides and was not otherwise advantageous. Reaction of **4** with either phosphorus tribromide in halogenated hydrocarbon solvents or, preferably, 48% aqueous HBr, however, gave crystalline dibenzosuberanyl bromide **6** (Scheme 2) as a single, anti stereoisomer in high yield.

SCHEME 3



The formation of **6** represented apparent inversion of the configuration of the hydroxyl-bearing center, but the cyclopropyldibenzosuberane-based structures of this series suggested the possibility of stabilized cationic intermediates instead of an S_N2 mechanism. The reaction sequence shown in Scheme 3 was carried out in order to clarify the mechanism of the formation of **6**. Reaction of ***syn*-4** with benzoic acid under Mitsunobu[10] conditions gave, after purification, ***anti*-8**. The assignment of anti stereochemistry to the product was supported by NMR data that showed no NOE at the cyclopropyl hydrogens upon irradiation of the C-6 proton. In contrast, the isomeric benzoate ***syn*-8**, prepared by esterification of ***syn*-4** with benzoic anhydride, clearly showed a NOE between the cyclopropyl and C-6 protons. Hydrolysis of ***anti*-8** with sodium hydroxide in methanol gave the previously unreported ***anti*-4**. Reaction of ***anti*-4** with phosphorus tribromide under the conditions described for conversion of ***syn*-4** to **6** gave *anti*-bromide **6** as the only product with *apparent retention* of configuration. These results clearly indicated that the stereochemical outcome of bromination of ***syn*-6** was not caused by Walden inversion and was best explained by an S_N1 mechanism involving the fluorinated dibenzohomotropylium ion[11] intermediate **9** (Scheme 3).

Thus formation of **6** occurred under thermodynamic control by (reversible) attack of bromide ion on **9**, and

(3) For an excellent review of the biological research on LY335979, see: Dantzig, A. H.; Law, K. L.; Cao, J.; Starling, J. J. *Curr. Med. Chem.* **2001** *8*, 39−50.

(4) (a) Sato, W.; Fukazawa, N.; Suzuki, T.; Yusa, K.; Tsuruo, T. *Cancer Res.* **1991**, *51*, 2420−4. (b) Suzuki, T.; Fukazawa, N.; San-nohe, K.; Sato, W.; Yano, O.; Tsuruo, T. *J. Med. Chem.* **1997**, *40*, 2047−2052.

(5) (a) Pfister, J. R.; Makra, F.; Muehldorf, A. V.; Wu, H.; Nelson, J. T.; Cheung, P.; Bruno, N. A.; Casey, S. M.; Zutshi, N.; Slate, D. L. *Bioorg. Med Chem Lett.* **1995**, *5*, 2473−2476. (b) Pfister, J. R.; Slate, D. L. U.S. Patent 5,643,909, 1997.

(6) For this article we define the relative stereochemistry in all structures related to **2** as anti on the basis of the relatively opposite positions of the cyclopropyl and C-6 substituent groups with respect to the dibenzocycloheptane ring. Syn refers to the orientation of these groups on the same side of the dibenzocycloheptane ring.

(7) Fukazawa, N.; Suzuki, T.; Kawauchi, N.; Komatsu, H.; Otsuka, K.; Nakajima Y. U.S. Patent 5,463,61, 1995.

(8) The anti:syn ratio of chlorides **5** was determined by repeating the reported experiment from ref 5b.

(9) The anti:syn ratio for the isomeric mixture of **7** was determined by HPLC of the crude product as a part of this work. A ratio of these isomers of anti:syn 52:48 after chromatographic separation was reported by Syntex (ref 5b).

(10) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.

(11) For a definitive paper on the chemistry of the dibenzohomotropylium ion, see: Childs, R. F.; Brown, M. A.; Anet, F. A. L.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2175−2183 and references therein.

any of the kinetically formed *syn*-bromide was apparently rapidly equilibrated to **6** via reversion to **9**. These results provided a framework for understanding the displacements of amine nucleophiles on **6**.

Displacements on 6 by Nitrogen Nucleophiles. A 3-fold excess of piperazine was successfully substituted for the much more expensive formylpiperazine in the preparation of ***anti*-2** without reduction in yield or formation of bis-substituted piperazine byproducts,[12] albeit with no effect on the ratio of piperazine products. These results shortened the synthesis of ***anti*-2** by obviating the protection and deprotection of the essential reagent, piperazine. The resulting isomeric mixture of piperazine products **2** were, however, not easily separated by preparative HPLC. We have previously reported an alternative, nonchromatographic separation scheme in which the gross amount of unwanted ***syn*-2** was removed by crystallization of the free base mixture from acetonitrile and the resulting enriched mixture was converted to the hydrochloride or hydrobromide salts and crystallized from dichloromethane.[13] Recrystallization from dichloromethane provided purified ***anti*-2** as its salt (anti:syn 99.5:0.5) in about 32% overall yield from bromide **6**.

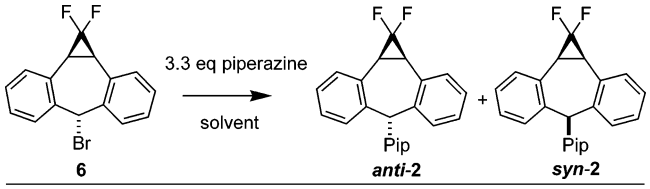
Formation of the isomeric piperazines was not reversible. Exposure of each of the isomers of **2** separately to the conditions of piperazine displacement in acetonitrile returned the compounds unchanged. We surmised that the reaction of **6** with piperazine resulted in almost indiscriminate, irreversible attack on the homotropylium ion **9** in view of the results of the foregoing study of the stereochemistry of formation of bromide **6**.

We hoped to influence the relative rates of the competing reactions by varying the reaction medium. The results of a study of solvent effects on the displacement of bromide **6** by piperazine are shown in Table 1.

A very slight concentration effect was noted in acetonitrile (entries 1−3), with the product ratio only slightly more favorable at lower concentrations. Acetonitrile, the standard solvent choice, proved to be the best for favoring ***anti*-2**. Other solvents examined gave less favorable anti:syn ratios, and tetrahydrofuran provided a good (relative) yield of the undesired syn isomer.

A search of the literature did not uncover any reports of reactions of other nitrogen heterocycles with dibenzocyclopropylsuberanyl halides. The following serendipitous experiment proved, however, to be very illuminating. Compound ***syn*-4** was reacted with piperazine in toluene in the presence of pyridinium tosylate in an effort to prepare piperazines **2** by direct displacement on **4**, thus precluding the activating step of bromination. The reaction failed to provide useful amounts of desired products, but a single pyridinium tosylate was isolated in 18% yield. The analogous pyridinium bromide (***anti*-10**, below) was obtained in quantitative yield, as a single stereoisomer, when bromide **6** was reacted with pyridine in chloroform at 57 °C.

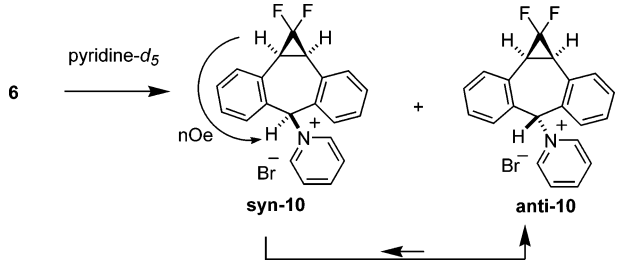
TABLE 1. Solvent Effects on the Stereochemical outcome of the Reaction of 6 with Piperazine



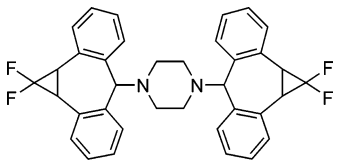
entry	solvent[a]	**2**, anti:syn
1	acetonitrile, $[\mathbf{6}]_{init}$ 0.125 M	55:45
2	acetonitrile, $[\mathbf{6}]_{init}$ 0.208 M	54:46
3	acetonitrile, $[\mathbf{6}]_{init}$ 0.62 M	42:58
4	acetone	41:59
5	isopropyl alcohol	40:60
6	ethyl acetate	39:61
7	methanol	36:64
8	ethanol	35:65
9	dimethyl formamide	34:66
10	chloroform	34:66
11	toluene	26:74
12	*tert*-butyl methyl ether	26:74
13	tetrahydrofuran	15:85

[a] Initial concentration of **6** was 0.156 M except as noted. For details see Experimental Section.

The following NMR experiment allowed assignment of anti stereochemistry to the product of the foregoing reaction. Bromide **6** was dissolved in pyridine-d_5 and the resulting process was followed, initially at 27 °C. The relative configuration of the initially predominant product (***syn*-10**) was assigned from observation of a NOE enhancement between the cyclopropyl fusion and C-6 protons. As the temperature was increased from 27 to 47 °C; however, the initial product was replaced by a new component that showed a similar proton NMR spectrum but lacked the NOE observed in the early product. Thus, structure ***anti*-10** was assigned to the final, more stable product.[14] These results are in accord with observations reported by Winstein et al.[15] of the solvolyses of the acetate esters of didesfluoro-**4** in which a syn-oriented product predominated (under kinetic control) regardless of the relative stereochemistry of the starting materials. *This is, to our knowledge, the first example of a reaction involving a dibenzohomotropylium species in which an initially formed syn displacement product is equilibrated to the (isolated) anti isomer.*



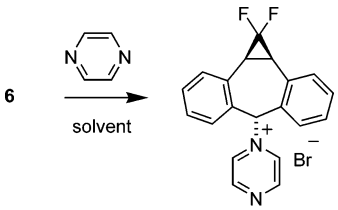
(12) A sample of the potential side product, *N*,*N*-dialkylated piperazine *i* (stereochemistry not determined), was prepared by reaction of **2** and **6** and determined not to be detectable in the purified product, **2**, by HPLC analysis.



(13) Astleford, B. A.; Barnett, C. J.; Kobierski, M. E.; Wilson, T. M. U.S. Patent 6,570,016, 2003. Astleford, B. A.; Barnett, C. J.; Kobierski, M. E.; Wilson, T. M. U.S. Patent 6,624,304, 2003.

(14) After 2 days at 57 °C, none of the initial product (***syn*-10**) could be observed by NMR.

TABLE 2. NMR Study of the Effect of Solvents on the Reaction of Bromide 6 with Pyrazine



11

entry	solvent	pyrazine molar excess	temp (°C)	reaction time (h)	yield (%)
1	none		110	0.5	91[a]
2	DMSO	3.0	37	4	93[a]
3	DMSO−CH_2Cl_2 (1:9)	3.0	30	25	88[a]
4	DMF	3.0	70	4.5	60
5	CH_3CN	6.0	75	24	25
6	CH_2Cl_2	3.0	25	4	18[a]
7	THF	6.0	55	23	0

[a] Isolated yield. Experiments 4, 5, and 7 were carried out in a NMR tube in the indicated deuterated solvent. Yields for 4, 5, and 7 are given as ratios of starting material to product at the indicated time.

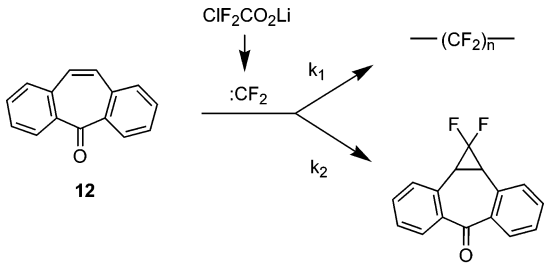
As expected, reaction of bromide **6** with neat pyrazine also provided the desired *anti*-difluorodibenzosuberanylpyrazinium bromide[16] (**11**), further confirming the stereochemical course of the reaction. In contrast to the pyridine experiment, however, the corresponding syn-oriented product was not observable by NMR, suggesting a relatively rapid equilibration of the isomeric products. Importantly, no bis-pyrazinium products could be detected in the isolated product. A number of solvents were screened for the reaction, and the results are summarized in Table 2. DMSO clearly provided best results for the pyrazine displacement, but addition of cosolvents to the DMSO reactions did not have a deleterious effect on the rate or yield.

Synthesis of LY335979·3HCl

As a result of the preceding studies we have developed a convenient, stereoselective, and scalable approach to **1** by incorporating pyrazine in place of piperazine for the incorporation of the piperazine ring as depicted in Scheme 4.

Optimization of Cyclopropanation. The implementation of this synthetic plan relied on an efficient and reliable method for the difluorocylopropanation of dibenzosuberanone (**12**). Alternative methods to the previously disclosed chlorodifluoroacetate pyrolysis[5] were examined. We found that lower-temperature methods, such as dehalogenation of dibromodifluoromethane with zinc or triphenylphosphine, and the reaction of methyltrifluoromethylstannane with sodium iodide[17] all failed to effect difluorocyclopropanation on the relatively electron-poor olefinic bond of **12** while reported examples were easily repeated. We concluded that difluorocyclopropanation of **12** required the high-temperature conditions of chlorodifluoroacetate pyrolysis.

We made several improvements to the Syntex difluorocyclopropanation protocol that made it more efficient and amenable to large-scale use. For example, large stoichiometric excesses (15−25 equiv) of alkali salts of chlorodifluoroacetic acid had been required in the original process to drive the reaction substantially to completion at the reported reaction temperature (160 °C). Although the yield as calculated on the consumption of **12** was acceptable at 60−70%, the very poor conversion of the (anhydrous) chlorodifluoroacetate salt caused the process to become unacceptably expensive. Additionally, the non-product-forming decomposition of excess carbene reagent generated copious amounts of gaseous and solid waste. We considered this problem to be one of competition between product-forming difluorocarbene insertion to the target olefin and many potential side reactions involving difluorocarbene: oligomerization to tetrafluoroethylene and its insertion products, higher polymers, and reactions with solvent.[18]



12 13

In preliminary experiments we observed that the amount of excess lithium[19] chlorodifluoroacetate required for complete consumption of **12** was inversely proportional to reaction temperature and directly proportional to the rate of addition of the solution of chlorodifluoroacetate salt. Thus, the rates of product formation (k_2) and other carbene processes (k_1) converged as temperature was increased, improving the competitiveness of difluorocyclopropanation. Slower addition rates increased the instantaneous ratio of difluorocarbene to available olefin substrate, thus favoring product formation (k_2). There were, of course, practical boundaries on both of these improvements. Accelerated rate calorimetry experiments indicated that **13** begins to undergo decomposition at 220 °C. Additionally, the concentration effect attributable to slow addition rates diminished as the concentration of **12** was reduced by the progress of the reaction. For pilot plant scale processing we obtained good results at tem-

(15) See ref 11.

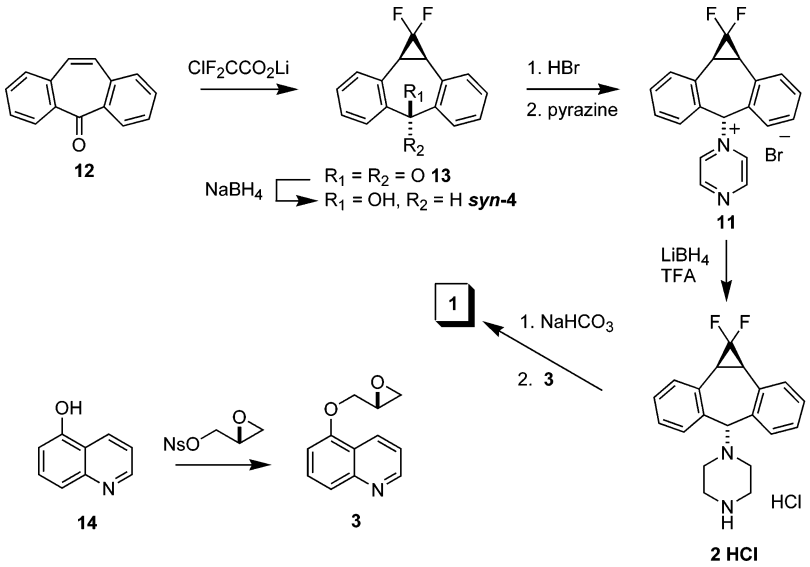
(16) Huff, B. E.;, LeTourneau, M. E.; Wilson, T. M.; Bush, J. K,; Reutzel-Edens, S. M. U.S. Patent 6,521,755, 2003.

(17) For a review of these and other difluorocyclopropanation methods, see: Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585.

(18) Detailed analysis of the byproducts was not carried out. The volatile fraction was presumed to consist of tetrafluoroethylene and, perhaps, hexafluorocyclopropane, and perfluorocyclobutane. A solid residue remained in the vessel with empirical formula CF_2, indicating that it was a polymer of tetrafluoroethylene. The various reactions of difluorocarbene that form these compounds have been documented. See: Birchall, J. M.; Fields, F.; Haszeldine, R. N.; McLean, R. J. *J. Fluorine Chem.* **1980**, *15*, 487.

(19) Sodium chlorodifluoroacetate was used in earlier examples of this reaction (ref 5; Beard, C.; Berkoz, B.; Dyson, N. H.; Harrison, I. T.; Hodge, P.; Kirkham, L. H.; Lewis, G. S.; Giannini, D.; Lewis, B.; Edwards, J. A.; Fried, J. H. *Tetrahedron* **1969**, *25*, 1219 and references therein). Our preference for the lithium salt was based on its increased solubility in the reaction medium. The resulting increased reaction concentration favored product formation and afforded better yields based on ClF_2CCO_2Li. (See Experimental Section.)

SCHEME 4



peratures of about 180 °C[20] and using a 5.6-fold molar excess of lithium chlorodifluoroacetate.

We were able to reduce the intermediate ketone **13** to ***syn*-4** without isolation, effecting a substantial improvement in cycle time. Thus, addition of 5.6 equiv of lithium chlorodifluoroacetate over 11.5 h at 180 °C provided the desired ketone **13**, which was converted to ***syn*-4** in situ with aqueous sodium borohydride in 70% overall yield from **4**.

Synthesis of *anti*-2. Reaction of ***syn*-4** with 48% HBr in dichloromethane with azeotropic removal of water conveniently provided a solution of bromide **6** in dichloromethane. Addition of pyrazine and DMSO and further reaction gave crystalline pyrazinium bromide **11**, precipitated from the reaction mixture after dilution with ethyl acetate in 88% overall yield from ***syn*-4**.

Reduction of the pyrazinium ring of **11** was required to assimilate this molecule into the synthesis of **1**. Catalytic hydrogenation conditions, even in the presence of added acid, were unsatisfactory as poor yields and difficult purification of the product were encountered.[21] Fortunately, lithium borohydride reduction of **11** in the presence of trifluoroacetic acid (TFA) gave much better results. The progress of the reduction and evolution of hydrogen could be conveniently controlled by the rate of introduction of borohydride into the reaction mixture. It was therefore possible to carry out the reaction at pilot plant scales with adequate control. The crystalline hydrochloride of ***anti*-2** was obtained by HCl treatment of the product in ethyl acetate in 70% yield from **11**.

Final Steps. Epoxide **3** was readily prepared by reaction of commercially available 5-hydroxyquinoline (**14**)[22] with glycidyl nosylate by a modified procedure utilizing potassium *tert*-butoxide in THF as base. As a practical matter, the choice of (*R*)-glycidyl nosylate as a reagent for the glycidylation might be questioned because of its relatively high price. The alkylation of glycidyl derivatives by arylalkoxide ions is, however, subject to racemization due to competing Payne-type epoxide opening (followed by reclosure of the epoxide) by intramolecular displacement of the leaving group. As the classic studies by McClure[23] and Sharpless[24] elegantly showed, the amount of racemization observed is inversely dependent upon leaving group reactivity in displacements of glycidol derivatives. Our own studies[25] of the reactions of chiral glycidol derivatives with 5-hydroxyquinoline indicated that glycidyl nosylate was the best reagent for this purpose, in agreement with the Syntex results.

The synthesis was easily completed from the key intermediates **2** and **3** by a modified version of the Syntex procedure. Piperazine **2** hydrochloride was converted to the free base with sodium carbonate in ethanol and reacted with epoxide **3** in acetonitrile without isolation. The reaction mixture was filtered through silica gel and then concentrated, and **1** was obtained as a crystalline salt by addition of ethanolic HCl in 74% yield.

Summary

We have established that nucleophilic displacement reactions on 1,1-difluorodibenzosuberanyl substrates relevant to the synthesis of LY335979 proceed via the corresponding homotropylium ion intermediate **9**. Halogenations give predominately or exclusively *anti*-halide derivatives under thermodynamic control. Displacements by cyclic amines provide different stereochemical outcomes, depending on oxidation state. Piperazine displacements lead to irreversibly formed mixtures of isomers,

(20) We were constrained to reaction temperatures of 180 °C or less at pilot plant scale because of reaction safety and vessel heating system limitations. For laboratory experiments a reaction temperature of 210 °C was preferred.

(21) There was some evidence (from analysis of side products) for self-condensation of partially reduced pyrazine intermediates, but none of these products were completely characterized.

(22) Purchased from Orgasynth (France).

(23) McClure, D. E.; Arison, B. H.; Baldwin J. J. *J. Am. Chem. Soc.* **1979**, *101*, 3666.

(24) (a) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 4(6), 1295−1304. (b) Sharpless, K. B.; Onami, T. H. PCT Int. App. WO 8800190 A1, 1988.

(25) Reaction of 5-hydroxyquinoline with (*R*)-glycidyl nosylate gave about 2% racemization in our hands as found by chiral HPLC analysis of the crude product. Optical purity was restored, however, by crystallization of the product (**3**) during isolation. Overall stereochemical outcomes for this reaction were in agreement with the Syntex results.[5]

whereas pyridine and pyrazine, on the other hand, afforded the anti heteroarenium salts with demonstrated equilibration of the initially predominant syn products. We have exploited the novel pyrazine displacement process (**6** → **11**) and several other innovative improvements to establish a highly efficient and practical route to LY335995 from dibenzosuberenone (**12**).

Experimental Section

(1aα,6α,10bα)-1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-ol (*syn*-4). A mixture of dibenzosuberenone (**12**,[5] 10.0 Kg, 48.5 mol) and 50 L of triglyme was heated to 180 °C. To this mixture was added a 50 wt % solution of 65 L (272 mol, 5.6 equiv) of lithium chlorodifluoroacetate in glyme at a rate of 0.5 equiv/h until less than 2.0% of the dibenzosuberenone was present by GC analysis (JW Scientific DB-1 methyl silicate 30 m × 0.25 mm column, 20 min run time, initial temp 150 °C, final temp 250 °C). The mixture was cooled to 35−45 °C over 2 h and was treated with 8.0 Kg of Hyflo[26] followed by 20 L of ethyl acetate. After stirring for 30 min, the suspended solids were removed by filtration through a prewetted (EtOAc) 7.0 Kg Hyflo plug and washed with 80 L of ethyl acetate. The combined filtrate and washes were distilled at 25−30 °C and 100 mmHg to a volume of approximately 60 L. To this solution of ketone **14** was added a 12 wt % solution of sodium borohydride in aqueous 14 M sodium hydroxide (5.3 Kg, 16.8 mol) over 1 h while maintaining the temperature below 40 °C. The reaction mixture was stirred at 20−25 °C for 3 h, at which time GC analysis (see above for conditions) showed less than 1% of **14**. A mixture of 50 L of water, 35 L of methanol, and 6.2 Kg of concentrated HCl was added over 40 min while maintaining the reactor temperature between 25 and 35 °C. The neutralized mixture was stirred for 45 min, and the precipitate was filtered, washed twice with 50 L of water followed by 30 L of methanol, and dried in a filter dryer at 45−50 °C. The crude product was reslurried in 65 L of methylene chloride for 35 min at 20−25 °C and 1 h at 0−5 °C on the filter dryer. The solid was filtered, washed with 25 L of cold methylene chloride followed by 2 × 20 L of cold heptane, and dried in a filter dryer at 45−50 °C to give 9.5 Kg (75%) of ***syn*-4**, mp 233 °C (lit.[5b] 230.1−230.6 °C): ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (d, J = 7.3 Hz, 2H), 7.24 (m, 4H), 7.20 (m, 2H), 6.72 (br s, 1H), 3.24 (d, J = 13.4 Hz, 2H), 2.07 (br s, 1H).

(1aα,6β,10bα)-*rel*-1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-yl Benzoate (*syn*-8). A solution of 4.19 g (16.2 mmol) of ***syn*-4** in 100 mL of tetrahydrofuran was treated with 2.0 g (50 mmol, 60% mineral oil dispersion) of sodium hydride followed by 4.5 g (20 mmol) of benzoic anhydride. The mixture was heated to 60 °C for 1 h. The reaction mixture was poured into 70 mL of ethyl acetate and quenched with 70 mL of 1 M hydrochloric acid. The organic phase was washed with saturated aqueous sodium carbonate, dried with magnesium sulfate, and concentrated to a solid. The crude solid was purified by silica gel chromatography using a 3:2 mixture of heptane−1,2-dichloroethane as eluent to provide 3.04 g (55%) of ***syn*-8** as a white solid, mp 230−231 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, J = 7.3 Hz, 2H), 7.88 (s, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.61 (t, J = 7.7 Hz, 2H), 7.53 (dd, J = 5.5, 4.7 Hz, 2H), 7.34 (dd, J = 6.5, 4.2 Hz, 2H), 7.25 (m, 4H), 3.40 (d, J = 13.2 Hz, 2H). Anal. Calcd for $C_{23}H_{16}F_2O_2$: C, 76.23; H, 4.45. Found: C, 75.93; H, 4.45.

(1aα,6α,10bα)-*rel*-1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-yl Benzoate (*anti*-8). A mixture containing 5.16 g (20 mmol) of ***syn*-4**, 3.17 g (26 mmol) of benzoic acid, and 6.55 g (25 mmol) of triphenylphosphine in 150 mL of tetrahydrofuran was cooled to −30 °C and treated with 5.05 g (25 mmol) of diisopropyl azodicarboxylate. The mixture was allowed to warm, stirred at ambient temperature for 1 h, and then heated to 60 °C for 4 h. The reaction was cooled to ambient temperature and concentrated. The resulting solid was chromatographed over silica gel (heptane−1,2-dichloroethane 3:2) to provide 5.00 g of a mixture of *anti*- and *syn*-benzoates (anti-syn 2:1, NMR). A 1.5-g portion of the mixture was combined with 5 mL of 5 N sodium hydroxide and 10 mL of tetrahydrofuran. The resulting mixture was heated to 65 °C for 7 h and then cooled to ambient temperature. The mixture was partitioned by addition of 10 mL of *tert*-butyl methyl ether, and the organic phase was dried with magnesium sulfate and concentrated, affording 1.14 g of white solid containing the desired *anti*-benzoate and a mixture of *anti*- and *syn*-alcohols. Chromatography of the mixture (silica gel, heptane−1,2-dichloroethane 3:2) afforded 302 mg of ***anti*-8** as a white solid, mp 162−164 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.44 (d, J = 6.8 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 6.72 (s, 1H), 3.49 (d, J = 12.5 Hz, 2H). Anal. Calcd for $C_{23}H_{16}F_2O_2$: C, 76.23; H, 4.45. Found: C, 75.92; H, 4.44.

(1aα,6β,10bα)-*rel*-1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-ol (*anti*-4). A mixture of 220 mg (0.66 mmol) of ***anti*-8**, 2.0 mL of 1 N sodium hydroxide, and 2.0 mL of methanol was heated to 65 °C for 28 h. The reaction was partitioned by the addition of 8 mL of *tert*-butyl methyl ether. The organic layer was dried with sodium sulfate and concentrated, affording 157 mg (92%) of ***anti*-4** as a white solid, mp 160 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.5 Hz, 2H), 7.28 (m, 2H), 7.22 (m, 4H), 5.51 (br s, 1H), 3.41 (d, J = 12.6 Hz, 2H), 2.60 (br s, 1H). Anal. Calcd for $C_{16}H_{12}F_2O$: C, 74.41; H, 4.68. Found: C, 74.12; H, 4.72.

(1aα,6β,10bα)-6-Bromo-1,1-difluoro-1,1a,6,10b-tetrahydro-dibenzo[*a*,*e*]cyclopropa[*c*]cycloheptene (6). PBr_3 method. To a mechanically stirred suspension of ***syn*-4** (18.4 g, 71.2 mmol) in 150 mL of dichloromethane that had been cooled to 10−17 °C was added phosphorus tribromide (9.6 g, 35.6 mmol) dropwise over 15 min. The cooling bath was removed, and the reaction mixture was stirred for 2 h at ambient temperature. Analysis by gas chromatography indicated complete consumption of **4**. Cold water (92 mL) and activated carbon (1.84 g) were added, and the resulting biphasic mixture was stirred for 30 min. The activated carbon was removed by filtration through Hyflo, and the layers were allowed to separate. The organic layer was washed twice with 184 mL of water and once with 184 mL of brine, dried over magnesium sulfate, and concentrated in vacuo to give 21.7 g (94.8%) of compound **6** as a light yellow foam. A 2.0-g portion was recrystallized from heptane, mp 120−122 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 1H), 3.40 (s, 1H), 5.77 (s, 1H), 7.16−7.38 (m, 8H). Anal. Calcd for $C_{16}H_{11}BrF_2$: C, 59.84; H, 3.45; Br, 24.88. Found: C, 59.96; H, 3.62; Br, 24.63.

General Procedure for Studies of the Reaction of 6 with Piperazine. A mixture of compound **6** (50.0 mg, 0.156 mmol), piperazine (44.0 mg, 0.511 mmol), and the appropriate solvent (1.0 mL) was heated to 50 °C (thermostated oil bath) for 18 h. The mixture was cooled to room temperature, sampled, and analyzed by HPLC (Zorbax SB-CN column, λ = 225 nm, 1.0 mL/min, 40 °C, 25 mM NaH_2PO_4, 0.1% TEA, pH 2.5) to determine isomer ratios**.** Results are shown in Table 1.

(1aα,6α,10bα)-1-(1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclo-hepten-6-yl)pyridinium Bromide (*anti*-10). A mixture of 200 mg (0.623 mmol) of **6** and 3 mL of pyridine was heated at 50 °C for 5 h. The reaction was allowed to cool, effecting a (partial) crystallization of the product. The reaction was diluted with 5 mL of *tert*-butyl methyl ether (MTBE), and the crystals were collected by filtration, washed with MTBE, and dried to yield 260 mg (100%) of ***anti*-10** (monohydrate) as a tan solid, mp 207−208 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 6.6 Hz, 2H), 8.54 (t, J = 7.6 Hz, 1H), 8.09 (t, J = 7.2 Hz, 2H), 8.00 (m, 3H), 7.45 (m, 2H), 7.40 (m, 4H), 2.65 (d, J = 12.6 Hz, 2H). Anal.

(26) A diatomaceous silica filter aid.

Calcd for $C_{21}H_{16}BrF_2N\cdot H_2O$: C, 60.30 H, 4.34, N, 3.35. Found C, 60.68; H, 4.35, N, 3.37.

(1aα,6α,10bα)-1-(1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-yl)pyrazinium Bromide (11). To a stirred slurry of 27.3 Kg (105.7 mol) of ***syn*-4** in 220 L of dichloromethane was added 24.1 Kg (143.0 mol) of 48% aqueous HBr. The resulting slurry was heated to reflux for 22 h with azeotropic removal of water via a Dean−Stark separator. After the mixture cooled to 20−25 °C, 14.0 Kg of anhydrous sodium sulfate and 7.0 Kg of activated carbon were added. The mixture was stirred at 20−25 °C for 1 h and filtered with Hyflo, and the filter cake was washed with 2 × 60 L of dichloromethane. The combined filtrate and washes were distilled (40−45 °C, atmospheric pressure) to provide a solution of **6** in 150 L of dichloromethane. To this solution was added 32.4 Kg (404.5 mol) of pyrazine followed by 16.5 L of dimethyl sulfoxide, and the resulting solution was heated to 30 °C for 25 h. The resulting yellow-orange suspension was diluted with 180 L of ethyl acetate, and the mixture was stirred at 20−25 °C for 2 h to complete crystallization of the product. The crystals were filtered, washed with 180 L of ethyl acetate, and dried in vacuo at 40 °C to provide 35.5 Kg (88%) of **11** as a light yellow crystalline solid, mp 165 °C: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (d, J = 2.7 Hz, 2H), 8.77 (t, J = 1.7 Hz, 2H), 7.74 (d, J = 7.5 Hz, 2H), 7.42−7.55 (m, 6H), 7.27 (s, 1H), 3.19 (d, J = 12.6 Hz, 2H); ^{13}C NMR (126 MHz DMSO-d_6) δ 152.5, 135.8, 135.4, 134.4, 133.2, 132.1, 129.9, 129.6, 112.9, 110.6, 108.3, 77.4, 28.7, 28.6; FD MS *m*/*e* 321 (M − Br). Anal. Calcd For $C_{20}H_{15}BrF_2N_2$: C, 59.87; H, 3.77; N, 6.98. Found: C, 59.84; H, 3.66; N, 6.83.

(1aα,6α,10bα)-1-(1,1-Difluoro-1,1a,6,10b-tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-yl)-piperazine Hydrochloride (*anti*-2 HCl). To stirred slurry of 35.4 Kg of **13** (88.2 mol) in 185 L of EtOAc was added trifluoroacetic acid (34.6 Kg, 303.5 mol). To this mixture was added a 2.0 M solution of lithium borohydride in THF (59.6 Kg, 66.5 L, 133.0 mol) over 1.5 h while maintaining the reactor temperature between 10 and 20 °C. The reaction mixture was stirred at 20−25 °C for 2 h. The reaction solution was added carefully to 351 Kg of 10% (w/w) aqueous potassium carbonate solution over 15 min while maintaining the vessel temperature below 25 °C. The mixture was stirred at 20 °C for 30 min, and the layers were separated. The organic phase was washed with 2 × 300 Kg of 10% (w/w) aqueous potassium carbonate solution and once with 185 Kg of 15% (w/w) aqueous sodium chloride solution and dried over 53.4 Kg of anhydrous sodium sulfate. After filtering the drying agent, 8.8 Kg (1.0 equiv) of 37% aqueous HCl was added (15−20 °C) over 35 min, and the resulting slurry was stirred at 20 °C for 9 h. The precipitate was filtered, washed with 100 L of ethyl acetate, and dried in vacuo (45 °C) to provide 24.7 Kg of *anti*-2 HCl (85.6%, or 21.1 Kg as *anti*-2 (HPLC assay), 66% yield), mp 274−278 °C (dec): ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (br s, 2H), 7.17−7.31 (m, 8H), 4.17 (s, 1H), 3.52 (d, J = 12.4 Hz, 2H), 3.11 (br s, 4H), 2.48−2.51 (m, 4H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.3, 133.4, 130.5, 129.6, 129.0, 128.4, 115.9, 113.6, 111.3, 76.2, 49.0, 43.6, 29.2, 29.1, 29.0; FD MS *m*/*e* 326 (M+). Anal. Calcd for $C_{20}H_{21}ClF_2N_2$: C, 66.20; H, 5.83; N, 7.72. Found: C, 66.08; H, 5.90; N, 7.72.

5-[(2*R*)-Oxiranylmethoxy]-quinoline (3). To a 0 °C suspension of 18.5 Kg (127.3 mol) of 5-hydroxyquinoline in 231 L of THF was added 15.1 Kg (127.3 mol) of potassium *tert*-butoxide (95% potency) in three portions, and the resulting thick slurry was stirred for 1 h at 20−25 °C. A solution of 33.0 Kg (127.3 mol) of (*R*)-glycidyl nosylate in 83 L of THF was then added over 1 h. The reaction mixture was stirred for 16 h at 23−26 °C, at which time HPLC analysis indicated that the reaction was complete. The reaction mixture was concentrated (50−100 mmHg) to about 200 L. A 440-L quantity of toluene was added, and the mixture was concentrated (50 mmHg) to a volume of about 200 L. Another 130 L of toluene were added, and the mixture was stirred for 30 min at 20−25 °C. The resulting inorganic precipitate was filtered and washed with 200 L of toluene. The combined toluene fractions were washed with a solution of 5.1 Kg (63.7 mol) of 50% aqueous NaOH in 330 L of water, and the aqueous layer was back-extracted with 130 L of toluene. The combined toluene layers were washed with 130 L of water, and approximately 160 L of toluene was distilled off to effect azeotropic drying of the solution. Basic alumina (16.5 Kg) was added to the dried yellow-orange toluene solution, and the mixture was stirred for 30 min at 20−25 °C. The alumina was filtered and washed with 200 L of toluene. The combined filtrate and wash were concentrated (50 mmHg) to about 100 L and heated to 45−55 °C. Heptane (500 L) was then added at such a rate to maintain the temperature at >45 °C. The solution was allowed to cool to 40 °C and was seeded. The crystallizing mixture was cooled to 0 °C over 2 h and then stirred at 0−5 °C for an additional 2 h. The crystals were filtered, washed with 100 L of heptane, and dried in vacuo (25 °C) to provide 19.1 Kg (74%) of **3** as a crystalline solid, mp 79−81 °C, 98.6% ee (chiral HPLC):[27] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (dd, J = 4.8, 2.7 Hz, 1H), 2.97 (m, 1H), 3.48 (m, 1H), 4.10 (dd, J = 11.0, 6.0 Hz, 1H), 4.43 (dd, J = 11.0, 2.7 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.38 (dd, J = 8.5 Hz, 4.1 Hz, 1H), 7.59 (m, 1H), 7.71 (d, J = 8.5 Hz, 1H), 8.61 (m, 1H), 8.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 153.9, 150.8, 149.1, 130.8, 129.2, 122.2, 120.8, 120.3, 105.3, 69.3, 50.0, 44.6.

[6(*R*)-(1aα,6α,10bα)]-4-(1,1-Difluoro-1,1a,6,10b)tetrahydrodibenzo[*a*,*e*]cyclopropa[*c*]cyclohepten-6-yl)-α-[(5-quinolinyloxy)methyl]-piperazineethanol, Trihydrochloride Salt (1). A suspension of 20.3 Kg of 2 hydrochloride (87% as 2, 48.9 mol) and 10.3 Kg (99.7 mol) of powdered sodium carbonate in 340 L of ethanol was stirred at 20−25 °C for 1.5 h. Addition of 9.83 Kg (48.9 mol) of **3** was completed in one portion, and the reaction mixture was heated to 60−70 °C for 36 h. The mixture was cooled to 20−25 °C, filtered through a 46-Kg plug of silica gel, and eluted with an additional 400 L of ethanol. The combined filtrate and washes were distilled at 45−55 °C (170−180 mmHg) to a volume of approximately 265 L and then heated to 60−70 °C with stirring. An 88-Kg solution of HCl (3.28 N in ethanol) was added over 35 min and transferred with 10 L of anhydrous ethanol. The solution was seeded, causing the trihydrochloride salt to precipitate. The mixture was cooled to 20−25 °C over 2 h and stirred at that temperature for 15 h. The precipitate was filtered onto a filter dryer, washed with 105 and 30 L of ethanol, and partially dried on the filter. Methanol (200 L) was heated to 50−60 °C and added to the wet cake to dissolve the crude product on the filter and transfer the solution to another vessel. An additional 170 L portion of methanol was used to complete the transfer. The solution was distilled at 35−45 °C and 200−300 mmHg to a volume of approximately 200 L. The mixture was again heated to 60−65 °C for 3 h to dissolve all solids and then was cooled to 20−25 °C over 30 min. The suspension was stirred for 3 h, and then 590 L of ethyl acetate were added to complete the crystallization. After stirring for 14 h at 20−25 °C, the precipitate was filtered, washed with 210 L of ethyl acetate, and dried in vacuo at 45 °C to provide 26.0 Kg (74.6%) of **1** as a light yellow crystalline methanol solvate. The solvate was converted to a crystalline hydrate (xH_2O) by equilibration in moist nitrogen. The hydrated crystals were correlated by physical and pharmacological data with material prepared at the Syntex laboratories.

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(27) A sample prepared under similar conditions showed an ee of 99.2% with an optical rotation of $[\alpha]^{25}_D$ −36.4 (*c* 2.10, EtOH), lit.[7] $[\alpha]^{23}_D$ −35.6.

Supporting Information Available: Table of ^{1}H NMR data for 1,1-difluoro-1,1a,6,10b-tetrahydrodibenzo-[*a*,*e*]cyclopropa[*c*]-cyclohepten-6-yl derivatives, ^{1}H NMR spectra for syn and anti compounds **4** and **8** and NOE spectra for syn and anti compounds **8** and **10**, and a table relating efficiency for the conversion lithium chlorodifluoroacetate to temperature in difluorocyclopropanation. This material is available free of charge via the Internet at http://pubs.acs.org.

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