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A Practical Asymmetric Synthesis of the Antiviral Agent Lobucavir, BMS-180194

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Abstract:

A practical synthesis of the antiviral agent lobucavir, [1*R*-(1α,2*β*,3α)]-2-amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-6*H*-purin-6-one (BMS-180194), is described. The key chiral intermediate, [1*S*-(1α,2*β*,3α)]-3-hydroxy-1,2-cyclobutanedimethanol, dibenzoate ester, was made by an asymmetric [2 + 2] cycloaddition of dimenthyl fumarate with ketene dimethyl acetal followed by sequential diester reduction, benzoylation, deketalization, and stereoselective ketone reduction. Regioselective N9-alkylation of the tetra-*n*-butylammonium salt of 2-amino-6-iodopurine with the derived cyclobutyltriflate furnished the purinecyclobutyl dibenzoate. Methanolysis followed by acid hydrolysis produced lobucavir in a 35% overall yield with an ee > 99%.

Introduction

Lobucavir, BMS-180194 (Figure 1),[1−7] has potent activity against a variety of herpes family viruses (herpes simplex virus, human cyctomegalovirus, varicella-zoster virus), as well as hepatitis B virus and human immunodeficiency virus. Lobucavir presently is undergoing clinical trials, and we have developed a practical synthesis to produce multikilogram quantities of this potential medicinal agent as a single enantiomer.

Literature methods for the synthesis of substituted cyclobutanes are not suitable for the multikilogram scale preparation of lobucavir.[1−13] The synthetic sequences are often lengthy or use environmentally unfriendly reagents, e.g., dithioketene acetal or dinitrogen tetraoxide. In some cases, the reactions are difficult to scale-up (e.g., ozonolysis, photolysis). In Ichikawa's group's[4] synthesis of lobucavir, the key step is an asymmetric [2 + 2] cycloaddition of thioketene dimethyl acetal with the fumarate ester **1a** using a chiral titanium catalyst (11% yield in 12 steps, Scheme 1). The asymmetric synthesis of lobucavir reported by Pariza et al.[5] employed dimenthyl fumarate **1b** and thioketene dimethyl acetal to produce cyclobutanone **3a** in 27% overall yield. Intermediate **3a** was then converted to a cyclobutylamine for the stepwise construction of the guanine moiety. Cotterill and Roberts[9] prepared mesylate **6** via a photochemical rearrangement of bicyclic epoxycyclobutanone **4** in 3% overall yield over 11 steps (Scheme 2). Hsiao and Hannick[10] obtained chiral cyclobutanone **3b** from *R*,*R*-(+)-diethyl tartrate via the key oxirane intermediate **7** in 32% overall yield over 10 steps. The corresponding bis-(t-BuPh$_2$Si) ether

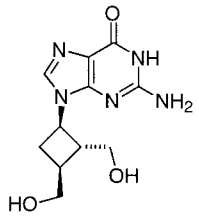
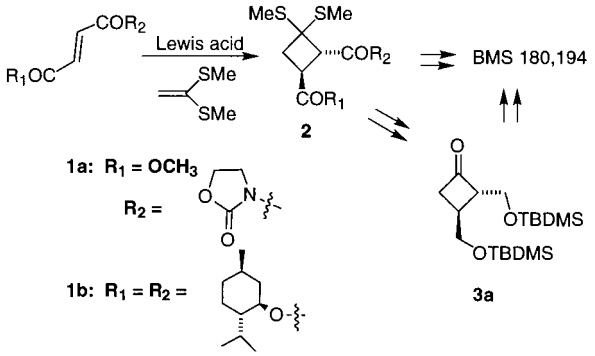


Figure 1. **BMS 180194 (lobucavir).**

Scheme 1



† Chemical Process Research
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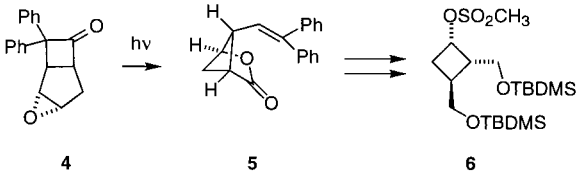
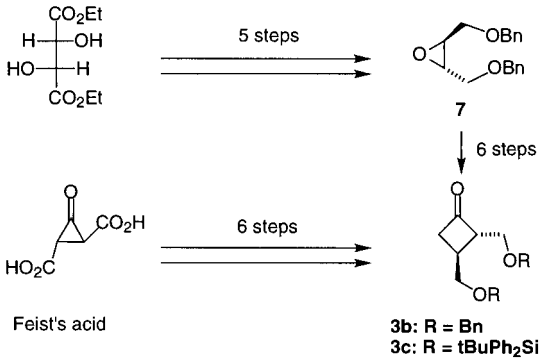
Scheme 2



4 5 6

Scheme 3



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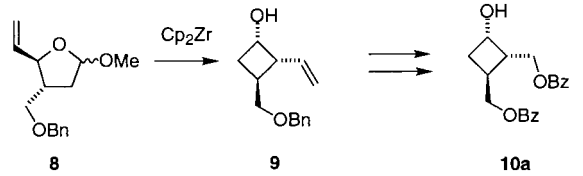

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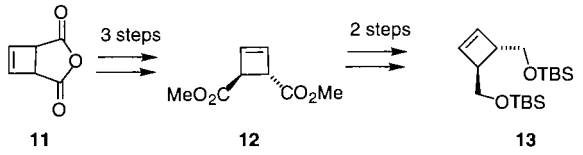

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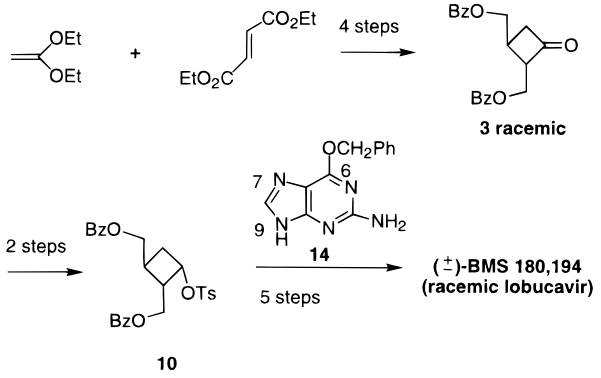
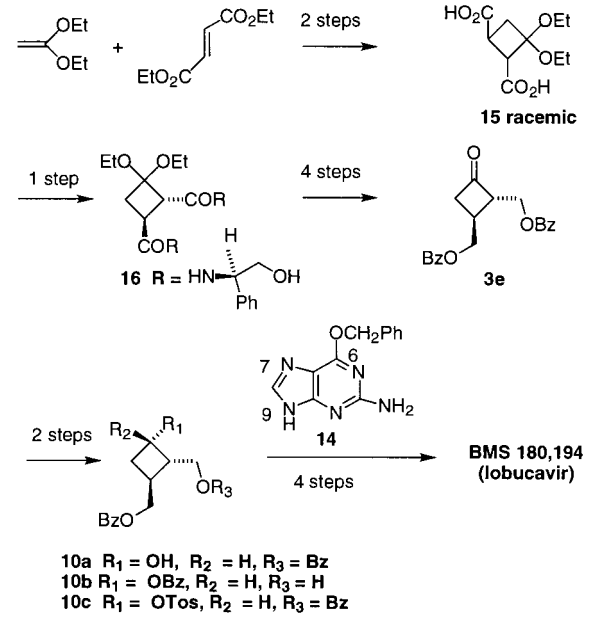


Scheme 7

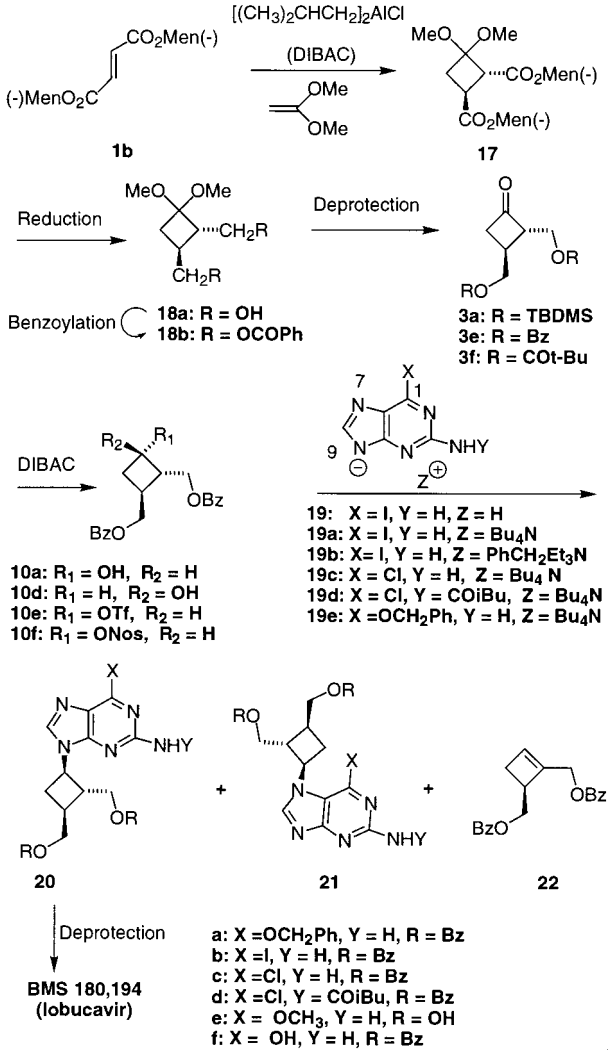


3c was also made by them via Feist's acid route employing a cumbersome chemical resolution (Scheme 3). Taguchi and co-workers[11] reported a nine-step synthesis of the cyclobutanol **10a** (20% overall yield) from a sugar derivative involving a rearrangement of the vinylfuranoside **8** to the cyclobutanol intermediate **9** (Scheme 4). Schneller and co-workers[12] made intermediate **10a** and its antipode by the enzymatic hydrolysis of the corresponding racemic acetate. Jung et al.[13] reported a chiral synthesis of cyclobutene **13** (Scheme 5) from the photocycloadduct **11** employing an enzymatic resolution followed by epimerization of a half acid ester intermediate. Adenine was introduced by the opening of an epoxide, and the extra hydroxyl group on the cyclobutane ring was removed by the free radical decomposition of a thiocarbonate derivative.

At present, the two most promising routes for the construction of the cyclobutane ring of lobucavir are ring expansion of resolved Feist's acid and asymmetric [2 + 2] cycloaddition of a ketene acetal with a fumaric acid derivative. Slusarchyk et al.[1a] reported an initial Bristol-Myers Squibb synthesis (Scheme 6) of racemic lobucavir (5.4% overall yield in 11 steps). Racemic cyclobutanone **3**, prepared via an achiral [2 + 2] cycloaddition, was converted to the tosylate **10** and then coupled with 2-amino-6-benzyloxypurine **14**. Bissachi et al.[2] subsequently described the synthesis of optically pure lobucavir (Scheme 7) (1.5% overall yield in 13 steps) that utilized a chemical resolution. This synthesis was later modified considerably to address several problems. The synthesis of 1*S*,2*S*-cyclobutanone **3e** via the chemical resolution of cyclobutanedicarboxylic acid diamide **16** required a prohibitively expensive reagent, (*R*)-2-phenylglycinol, and used the highly toxic chemicals dinitrogen tetraoxide and carbon tetrachloride. The highly stereoselective reduction of the cyclobutanone **3e** to the 1*S*,2*S*,3*S*-cyclobutanol **10a** was done with the expensive reagent LS-Selectride, and this reaction also produced the rearranged side product **10b**. Coupling of the purine derivative **14** with the cyclobutyltosylate **10c** was the most problematic step in this synthesis due to formation of a cyclobutene elimination product and the corresponding N7-alkylation product. Intermediate **10a** and the final product lobucavir required column chromatography for their purification.

Ahmad[6] subsequently disclosed in a preliminary communication that the asymmetric [2 + 2] cycloaddition of ketene dimethyl acetal with dimenthyl fumarate **1b** in the presence of a Lewis acid produced the cycloadduct **17** with high diastereoselectivity (Scheme 8). Cycloadduct **17** was

Scheme 8



converted to the key cyclobutanone intermediate **3e** via the reduction of ester groups, dibenzoylation, and deacetalization.

The methods generally used for the transformation of cyclobutanones to the purine derivatives proceed via either cyclobutylamine or a cyclobutanol intermediate.[8] Since the synthesis via cyclobutylamine requires a stepwise construction of the guanine moiety, the more convergent approach involving N9-alkylation of a purine derivative with cyclobutanol or an activated derivative is often preferred. 2,3-Disubstituted cyclobutanones are generally reduced to the desired 1,2-*cis* cyclobutanols either by enzymes[14] or with sterically hindered reducing agents, e.g., LS-Selectride.[1] The coupling of cyclobutanols with purine derivatives by the Mitsunobu method is generally inefficient and fraught with purification difficulties.[15] The regioselective N9-alkylation of the 6-substituted purines with the O-activated cyclobutanols is also inefficient due to the competing N7-alkylation. Although several approaches have been adopted to tackle this historical problem, there is no general method applicable to different systems.[8,16−18] We reported in a preliminary communication the reaction of the tetra-*n*-butylammonium salt of 2-amino-6-iodopurine (**19a**) with the cyclobutyl triflate **10e** to form the dibenzoate **20b** in high yield with 93% N9-regioselectivity and its subsequent conversion to the final product.[3] In this paper we provide the full description of this synthesis of lobucavir, obtained in 35−40% overall yield in 10 steps.

Results and Discussion

A practical synthesis of lobucavir (BMS 180194) was achieved via a convergent approach (Scheme 8) in four phases. The optically pure 2*S*,3*S*-cyclobutanone **3e** was prepared via the diastereoselective [2 + 2] cycloaddition of ketene dimethyl acetal with dimenthyl fumarate **1b** followed by reduction, benzoylation, and hydrolysis of the ketal. The second stage involved stereoselective reduction of cyclobutanone **3e** to the 1*S*,2*S*,3*S*-cyclobutanol **10a**. In the next phase, purine cyclobutyldibenzoate **20b** was prepared by the regioselective N9-alkylation of the n-tetrabutylammonium salt of 2-amino-6-iodopurine (**19a**) with the cyclobutyltriflate **10e**. Finally, we developed a single-step conversion of the intermediate **20b** to lobucavir.

Synthesis of Cyclobutanone 3e via Diastereoselective [2 + 2] Cycloaddition. Diastereoselective [2 + 2] cycloaddition of l-dimenthyl fumarate **1b** with ketene dimethyl acetal catalyzed by diisobutylaluminum chloride (DIBAC) (toluene, −70 °C) produced the cycloadduct **17** in 98% yield and 90% diastereomeric excess.[6] Recrystallization from MeOH furnished pure **17** in 83% yield (de > 99%). Thus, we have replaced the less desirable dithioketene acetal by a diketene acetal in the diastereoselective [2 + 2] cycloaddition reaction. Two mole equivalents of the Lewis acid was essential for this reaction. The catalyst was precomplexed with dimenthyl fumarate, and then ketene dimethyl acetal was introduced at below −70 °C to minimize polymerization of the latter. The catalyst considerably enhanced the rate of the reaction. In the absence of the catalyst, no cycloaddition occurred at ambient temperature, and a complex mixture of products was obtained at 80 °C. The reaction is inefficient at temperatures above −60 °C due to the polymerization of the ketene dimethyl acetal, although facial selectivity in this reaction is maintained even at −40 °C. The synergistic stereodifferentiating influence of the two chiral auxiliaries in diester **1b** resulted in this remarkable facial selectivity, which is reminiscent of some [4 + 2] Diels−Alder cycloaddition reactions.[19−21]

Several other Lewis acids were examined for the cycloaddition reaction. Et_2AlCl was the only other catalyst that formed the cycloadduct **17** in yield and diastereoselectivity

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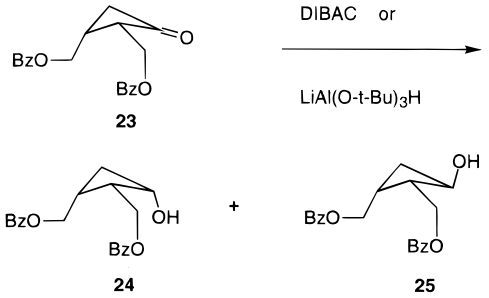
comparable to that of DIBAC. The homogeneous complexes of Et_2AlCl and DIBAC with dimenthyl fumarate produced the best results. Similar observations were made by Walborsky et al.[20] and Yamamoto et al.[21] for Lewis acid-catalyzed Diels−Alder reactions. Catalysts that did not form homogeneous complexes with dimenthyl fumarate, e.g., BF_3, $TiCl_4$, $SnCl_4$, or $AlCl_3$, led to extensive decomposition of the ketene dimethyl acetal.

Reduction of the cycloadduct **17** with LAH formed the diol **18a** in quantitative yield. The chiral auxiliary l-menthol was easily recovered by partitioning the quenched reaction mixture between heptane and water. Benzoylation of the diol **18a** to **18b** followed by acid hydrolysis of the ketal furnished crystalline cyclobutanone **3e** in 90% overall yield. The alternate protecting groups, t-BuMe_2Si or benzyl, produced the corresponding cyclobutanone diethers **3a** and **3b** as oils, and these were considered unsuitable for purification on a large scale.

Stereoselective Reduction of Cyclobutanone 3e to the Cyclobutanol 10a. Slusarchyk et al.[1a] and Bisacchi et al.[2] reported the reduction of 2,3-*trans* disubstituted cyclobutanone **3e** to 1*S*,2*S*,3*S*-cyclobutanol **10a** with LS-Selectride in excellent diastereoselectivity. However, LS-Selectride is available only as a solution in THF and is very expensive. The process typically produced 5−10% of the undesired rearrangement product **10b** (Scheme 7), and the workup of the reaction was cumbersome for large scale synthesis. Reduction of **3e** with L-Selectride was unsatisfactory, as it produced **10a** with only 77% diastereoselectivity.[1a] We identified DIBAC as an alternative reagent for a more practical diastereoselective synthesis of cyclobutanol **10a**.

DIBAC has been used only rarely for the reduction of cyclic ketones. Ashby and Noding[22] studied the addition and reduction reactions of alkylaluminum halides, including Et_2AlCl, with 4-*tert*-butyl cyclohexanone. Giacomelli and co-workers[23] described the reduction of acyclic and a few cyclic ketones with DIBAC and chiral alkylaluminum reagents. We have discovered that the reduction of *trans*-dibenzoyl cyclobutanone **3e** with DIBAC in CH_2Cl_2 at −35 °C followed by a quench with MeOH and aqueous NH_4Cl at low temperature furnished carbinol **10a** with 92% diastereoselection. It is noteworthy that quenching of the reaction at low temperature completely suppressed rearrangement of the benzoyl group from its primary position in **10a** to a secondary site in **10b**. Simple workup followed by recrystallization gave product **10a** with high purity (ee > 99%) and in 70−80% yield. Furthermore, the wrong isomer **10d** can be recycled by Swern oxidation back to cyclobutanone **3e**. This reduction method was used to prepare several kilograms of **10a**. The reduction of **3e** with DIBAC in toluene produced **10a** with 90% diastereoselectivity. The reduction was not efficient in THF. Toluene is always preferred over CH_2Cl_2 as a solvent for enviromental safety considerations. However, CH_2Cl_2 is the solvent of choice for this reduction as the reactions could be easily scaled-up to produce **10a** with reproducibly high stereoselectivity. Reduction of the *tert*-butyldimethylsilyl-protected cyclobutanone **3a** and the dipivaloyl ester **3f** with DIBAC formed the corresponding 1,2-*cis* cyclobutanols with 91 and 95% diastereoselectivity, respectively. Reduction of **3e** with isobutylaluminum dichloride formed **10a** with high stereoselectivity, but, presumably because of enolization, 10% of the unreacted cyclobutanone **3e** was obtained. Cyclobutanone **3e** also was reduced with $IrCl_4$ [H_3PO_3, HCl, EtOH, reflux][24] with high stereoselectivity (98% **10a**), but the yield was very low. As expected, in analogy with the substituted cyclohexanones, the reduction of **3e** with sterically less demanding reducing agents, e.g., LAH or $NaBH_4$, produced predominantly the more stable 1,2-*trans* epimer **10d**.

Scheme 9



Cis-2,3-disubstituted cyclobutanone **23** was prepared for a comparison of the stereochemistry of reduction with DIBAC (Scheme 9).[25] The differing stereoselectivities were striking. Reduction of **23** with DIBAC was almost stereospecific, producing the less stable *all-cis* epimer **24** (99% diastereoselectivity).[26] *All-cis* stereoreoselectivity also was obtained during the reduction of **23** with $LiAl(OtBu)_3H$ to **24** (83% diastereoselectivity).[27a] Reduction of *trans*-2,3-disubstituted cyclobutanone **3e** with $LiAl(OtBu)_3H$ formed the more stable epimer **10d** with 93% diastereoselectivity.

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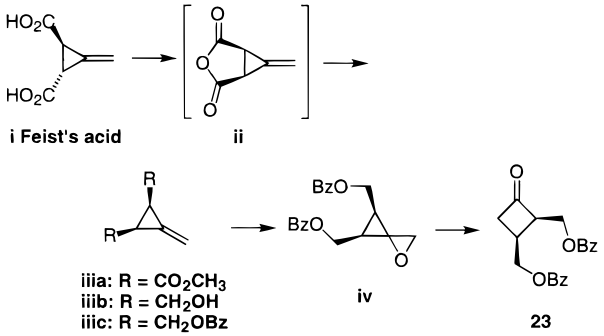
(25) (a) Racemic 2,3-*cis* cyclobutanone dibenzoate **23** was prepared from the Feist's acid (**i**) via *cis*-anhydride (**ii**)[25b] by modified procedures. Esterification of the *cis*-anhydride (**ii**) [in situ, $(MeO)_3CH$, MeOH, H_2SO_4, yield 64%] followed by reduction ($LiAlH_4$, THF) to diol **iiib**[25c] and benzoylation [$(PhCO)_2O$, Et_3N, DMAP, EtOAc] produced **iiic** in 78% yield. Olefin **iiic** was epoxidized (MCPBA, CH_2Cl_2, yield 99%) and then rearranged (LiI, EtOAc, yield 99%) to cyclobutanone **23**.[8] (b) Ettlinger, M. G.; Kennedy, F. *Chem. Ind.*, **1957**, 891. (c) Gajewski, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 4450.



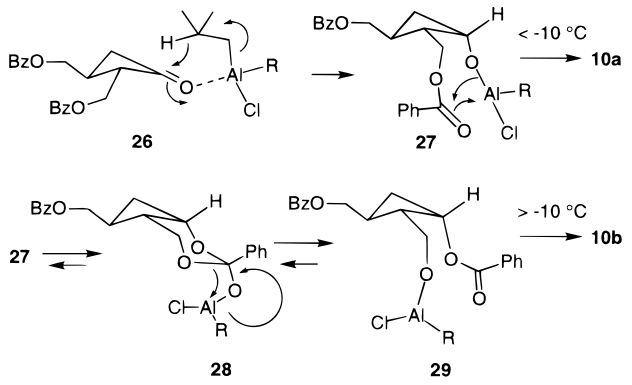
(26) (a) Haubenstock, H.; Eliel, E. L. *J. Am. Chem. Soc*., **1962**, *84*, 2363. (b) Haubenstock, H. *J. Org. Chem.* **1973**, *38*, 1765.
(27) (a) Dehmlow, E. V.; Buker, S. *Chem. Ber.* **1993**, *126*, 2759. (b) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263 and cited references.

In *cis*-isomer **23**, the α-face of the carbonyl is severely blocked by a bulky pseudoaxial group at the C3 position; therefore, attack from the β-face is kinetically preferred. Besides this overwhelming steric effect, a conformational change of the carbonyl plane in cyclobutanone **23** also may be favorable for hydride attack from the β-face. The observed stereoselectivity is consistent with the classical steric approach control model of Dauben.[27,28]

We also explored catalytic hydrogenation of cyclobutanone **3e** under a variety of conditions as a more viable alternative to DIBAC.[29] Reduction of **3e** with H_2 and commercial ruthenium black in alcohol solvents formed the α-epimer **10a** with ~85% selectivity.[30] Selectivity for **10a** was also high (82%) with tris(triphenylphosphine)rhodium(I) chloride in the presence of diphenylsilane.[31] Moderate selectivity (~75% **10a**) was obtained with freshly made Ru black or with Ru/alumina. However, in general, catalytic hydrogenations of **3e** were often problematic due to incomplete reduction or overreduction of the phenyl rings.

A plausible mechanism for the rearrangement of **10a** to **10b** is shown in Scheme 10. During reduction of **3e**, the hydride transfer in the aluminum complex **26** occurs from the less hindered β-face via a six-center transition state[37] to produce the alanate **27**, which is stable at low temperature. On quenching with acid at low-temperature intermediate **27** furnished the desired product **10a**. At higher temperature (> −10 °C), intermediate **27** is in equilibrium with isomeric alanate **29**, with the bulkier group (alanate) at the primary position. Presumably, rearrangement occurs via the bicyclic intermediate **28**. It was interesting to find that isolated carbinol **10a** on treatment with 1 mol equiv of DIBAC in THF−CH_2Cl_2 (1:1) at room temperature gave a mixture of **10a** and **10b** in a 1:4 ratio. When this mixture was treated with DBU in THF at room temperature for 70 h, the ratio of **10a**:**10b** changed to 3:2. Thus, the equilibrium is favorable for **10a** as the free alcohol. However, in the presence of the strongly oxophilic aluminum counterion, the bulkier alkoxyaluminum moiety prefers to reside at the sterically less encumbered primary position.

Scheme 10



Regioselective N9-Alkylation of 2-Amino-6-iodopurine 19. Alkylation of 2-amino-6-benzyloxypurine **14** with cyclobutyltosylate **10c** (or the corresponding mesylate) in the presence of K_2CO_3 and 18-crown-6 in DMF at 110 °C produced the N9-alkylation product **20a** in 50% chromatographed yield.[2] The ratio of N9 to N7 isomers (**20a** and **21a**) was 76:24 (Table 1, entry 1). Cyclobutene **22** also was formed (7%) in this reaction. Problematically, this reaction was irreproducible even on a 1−10 g scale. The change of alkali metal counterions to Na or Li (made from **14** and NaH or LiH) resulted in no improvement in the yield or regioselectivity in this reaction.

Table 1. **N9-Regioselective alkylation of the substituted 2-aminopurines**

entry	purine	electrophile	ratio N9:N7	N9-isomer (yield, %)
1	**14**	**10c**	76:24	**20a** (50)[a,b]
2	**19e**	**10c**	75:25	**20a** (44)[c,d]
3	**19a**	**10f**	89:11	**20b** (64)[e]
4	**19a**	**10e**	93:7	**20b** (76)[f]
5	**19b**	**10e**	93:7	**20b** (70)[f]
6	**19c**	**10e**	80:20	**20c** (74)[f]
7	**20d**	**10e**	80:20	**20d** (54)[f]

[a] K_2CO_3, 18-crown-6, DMF, 110 °C, 20 h. [b] 7% **22**. [c] K_2CO_3, DMF, 110 °C, 10−20 h. [d] 15% **22**. [e] CH_3CN, 60−90 °C, 5−10 h. [f] CH_2Cl_2, 25 °C, 3−5 h.

Jones and Roberts[18a] observed increased N9-regioselectivity in reactions with 6-chloropurines compared to 6-alkoxypurines. Geen et al.[18b] have reported a further enhancement in N9-regioselectivity during alkylations with 6-iodopurines. We prepared 2-amino-6-iodopurine **19** from 2-amino-6-chloropurine and aqueous HI in 90% yield by improvement of a literature method (yield 35%).[3,33] Unfortunately, the reaction of 2-amino-6-iodopurine **19** with tosylate **10c** (K_2CO_3, DMF, 110 °C) resulted in extensive degradation under these harsh reaction conditions. Evidently, the limited solubility of purine alkali metal salts and the low reactivity of the cyclobutyl tosylate (or mesylate) caused problems in this reaction.

There are a few reports on the use of the more soluble tetraalkylammonium salts of purines, mostly used in situ, in the alkylation reactions.[34] We prepared the tetra-*n*-butylammonium salts **19a,c**−**e** as isolated, pure solids by reacting tetra-*n*-butylammonium hydroxide in stoichiometric amounts with the corresponding purines. Unlike the corresponding alkali metal salts, these salts are very soluble in DMF. Salt

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(36) It was interesting to find that the reaction of purine salt **19b** with the triflate of the isomeric cyclobutanol **10d** produced exclusively the corresponding diastereomeric N9-alkylation product. This observation was made by Dr. Y. Pendri. Evidently, the steric hindrance of the α-side chain next to the leaving group further blocked the attack at the N7 site.
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19a, although sparingly soluble in CH_2Cl_2 at ambient temperature, readily dissolved during reactions with the electrophiles. In the absence of a reactive electrophile, **19a** was alkylated by CH_2Cl_2 to produce a mixture of the corresponding bis-methylene products. As expected, at high temperature these salts undergo "self-alkylations" to form several byproducts.

Alkylation of the tetra-*n*-butylammonium salt **19e** with tosylate **10c** (DMF, 110 °C) gave **20a** in 44% chromatographed yield (Table 1, entry 2). The N9-regioselectivity was the same (75%) as with the alkali metal salts. The elimination side product **22** was formed in 15% yield. The tetra-*n*-butylammonium salts of 6-chloro and 6-iodopurines **19c** and **19b**, respectively, decomposed extensively during reaction with the tosylate **10c** due to the lability of the halogeno purines and the high reaction temperature. Reaction of the tetra-*n*-butylammonium salt of 2-amino-6-iodopurine (**19a**) with the more reactive cyclobutylnosylate **10f** could be performed at 60−90 °C in acetonitrile. Although high (89%) N9-regioselectivity was achieved, the yield was improved only moderately (to 64%), and product isolation required chromatography (Table 1, entry 3). Consequently, we next explored the possible use of trifluoromethanesulfonate (triflate) as a leaving group.

Triflates are known not only for their high reactivity but also for their instability. There are only a few reports of their use in the alkylation of purines.[18a,35] We prepared cyclobutyltriflate **10e** from cyclobutylcarbinol **10a** and triflic anhydride in quantitative yield. While triflate **10e** is a white solid, it was not isolated because of stability concerns. After workup, the solution of triflate in CH_2Cl_2 was concentrated to an optimal volume for further reaction with the purine salts. We were encouraged to find that reaction of **10e** with the tetra-*n*-butylammonium salt of 2-amino-6-iodopurine (**19a**) at ambient temperature furnished **20b** with 93% N9-regioselectivity in 76% crystallized yield (Table 1, entry 4).[36] The minor N7-isomer **21b** was easily separated by fractional crystallization from hot EtOH. In addition, the reaction conditions were sufficiently mild to entirely prevent elimination to the cyclobutene **22**. The tetra-*n*-butylammonium triflate byproduct from the alkylation reaction could not be completely removed during workup. Some of it remained in the organic phase even after extensive aqueous washes. An efficient crystallization protocol subsequently was developed to remove the low levels of tetra-*n*-butylammonium triflate in the product. At the same time, after screening of several phase-transfer counterions, we found that benzyltriethylammoniun triflate has greater solubility in water and is completely washed away from the organic phase during workup. Reaction of benzyltriethylammoniun salt **19b** with triflate **10e** gave **20b** with 93% regioselection in 70% crystallized yield (Table 1, entry 5). Thus, either of these phase-transfer counterions can be used for the large scale synthesis of **20b**. The phase-transfer agent cations may be recovered from the large scale reactions and recycled.

For comparison, alkylation of the tetra-*n*-butylammonium salt of 2-amino-6-chloropurine (**19c**) with triflate **10e** gave **20c** in 74% chromatographed yield with 80% N9-regioselectivity (Table 1, entry 6). We further found that N2-acylation of the purine did not significantly influence the N9-regioselectivity. Reaction of the tetra-*n*-butylammonium salt of N2-isobutyryl-6-chloropurine (**20d**) with the triflate **10e** in CH_2Cl_2 formed **20d** with 80% N9-regioselectivity in 54% yield upon chromatography (Table 1, entry 7).

In situations involving reversible reactions, e.g., with sugar derivatives, α-haloalkyl ethers, and, in a few instances, Michael acceptors, extremely high N9-regioselectivity has been obtained during reactions with purines or persilylated purines.[8,16,17,37] The reaction of tris-trimethylsilyl guanine with triflate **10e** in the presence of TMSOTf produced exclusively the corresponding N7-regioisomer. In the presence of fluoride ion, a mixture of N9 and N7 products was obtained. Therefore, this simpler approach did not work to our advantage.

Conversion of 6-Iododibenzoate 20b to Lobucavir (BMS-180194). In the final phase of the synthesis, an efficient single-step process was developed for the conversion of the 6-iododibenzoate **20b** to optically pure lobucavir. The direct hydrolysis[8,17,38] of **20b** with aqueous HCl or aqueous NaOH gave lower quality product in moderate yields. Methanolysis of **20b** with NaOMe formed the 6-methoxy diol **20e**, which on refluxing with aqueous HCl furnished lobucavir in 93% overall crystallized yield and ee > 99%. The transesterification procedure is superior due to easy extractive removal of the neutral byproduct methylbenzoate from the aqueous solution of the HCl salt of the intermediate 6-methoxypurinediol **20e** and, therefore, is the method of choice. Alternatively, treatment of 6-iododibenzoate **20b** with a weaker acid (aqueous AcOH, heat) formed the guanine cylobutyldibenzoate **20f** in 77% yield. Further deprotection of **20f** to lobucavir was achieved either by transesterification with catalytic NaOMe (79% yield) or by saponification with aqueous NaOH (91% yield).

In summary, we have developed a practical asymmetric synthesis of lobucavir as a potentially viable commercial synthesis. The asymmetric cycloaddition reaction of dimenthyl fumarate with ketene dimethyl acetal furnished cyclobutane diester **17**. Thus, chemical resolution or the use of dithioketene acetal was circumvented. Reduction of diester **17** followed by benzoylation and deprotection gave optically pure cyclobutanone **3e** in high yield. Stereoselective reduction of cyclobutanone with DIBAC, instead of the expensive reagent LS-Selectride, formed cyclobutanol **10a**. The synthesis of final intermediate **20b** by an efficient regioselective alkylation of the tetra-*n*-butylammonium salt of 2-amino-6-iodopurine (**19a**) with cyclobutyltriflate **10e** made this convergent approach practical**.** Finally, dibenzoate **20b** was deprotected to give lobucavir in 35−40% overall yield (ee > 99%) in 10 steps. The synthesis has been implemented to produce over 100 kg of lobucavir for clinical studies.

Experimental Section

Experimental details for the preparation of cyclobutanone **3e** were previously described in a preliminary communica-

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tion.[6] Details for the alkylation of the cyclobutanol **10a**, via its triflate **10e**, with tetra-*n*-butylammonium salt **19a** to give dibenzoate **20b** and subsequent conversion to lobucavir were previously reported in a note.[3] These reactions have been scaled-up further by our colleagues in the Kilo lab and Pilot plant.

Preparation of [1S-(1α,2*β*,3*β*)]-3-Hydroxy-1,2-cyclobutanedimethanol, Dibenzoate Ester (10a). A 3-L, three-necked flask equipped with a mechanical stirrer, internal digital thermometer, addition funnel, and nitrogen inlet was charged with 2385 mL of anhydrous dichloromethane. After cooling to −40 °C, diisobutylaluminum chloride (156.6 g, 886 mmol, 1.27 mol equiv) was added. To this cold solution was added, dropwise via addition funnel over 63 min, a solution of cyclobutanone **3e** (235 g, 699 mmol) in dichloromethane (600 mL). The reaction was maintained at −40 °C for an additional 70 min. TLC analysis (silica gel, toluene:ether, 1:1, R_f of **3e** = 0.64, **10a** = 0.36, and *β*-isomer **10b** = 0.27, visualized by UV and *p*-anisaldehyde reagent) indicated that the reduction was essentially complete. The reaction was quenched by the slow addition of methanol (502 mL). During the quench, the temperature rose from ∼−40 to −32 °C over 1 h. The cooling was removed, and a saturated aqueous solution of ammonium chloride (502 mL) was added. After being stirred for 18 h, the mixture was filtered through anhydrous magnesium sulfate (502 g), and the filter cake was washed well with dichloromethane. The filtrate was concentrated at reduced pressure, and the residue was dried under pump vacuum at 35 °C to give 287.3 g of crude product. The slightly wet solid was crystallized from 2 L of MeOH and 400 mL of H_2O to give 160.6 g (yield 68%) of **10a**; HPLC HI (215 nm, Zorbax-cyano column, H_2O−CH_3CN gradient) 99.95%. This substance was identical to the literature compound.[2,6] Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.38; H, 5.94; H_2O, 0.27. Found: C, 69.92; H, 5.87; H_2O, 0.27 (KF).

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