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Review

A survey of the syntheses of active pharmaceutical ingredients for antiretroviral drug combinations critical to access in emerging nations

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ABSTRACT

It has been roughly 25 years since the threat posed by human immunodeficiency virus type 1 (HIV-1) became widely known. The cumulative death toll from HIV/AIDS is now greater than 25 million. There are approximately 33 million people living worldwide with this disease, of whom about 68% (22.5 million) live in sub-Saharan Africa (http://www.avert.org/worldstats.htm). A number of antiretroviral (ARV) drugs have been approved for treatment of HIV/AIDS. Inhibitors of HIV reverse transcriptase (RTIs) include the nucleoside/nucleotide drugs zidovudine, lamivudine, abacavir, didanosine, stavudine, emtricitabine and tenofovir disoproxil fumarate. Non-nucleoside RTIs include nevirapine, efavirenz and etravirine. Inhibitors of HIV protease (PIs) include saquinavir, ritonavir, lopinavir, nelfinavir, indinavir, fosamprenavir and atazanavir. Enfuvirtide inhibits the HIV fusion protein. The CCR5 chemokine antagonist maraviroc and the integrase inhibitor raltegravir were very recently approved by the US FDA. Fixed-dose combinations (FDCs) have been formulated to increase tolerability, convenience and compliance. First-line drug combinations are offered to treatment-naive patients, while second-line drugs are reserved for those who no longer respond adequately to first-line therapy. In developing countries a modest but increasing fraction of those infected have access to ARVs. The Clinton HIV/AIDS Initiative estimates that 2.4 million of the nearly 8 million individuals needing treatment in developing nations have access to some drugs. First-line FDCs used in resource-poor settings are largely combinations of two nucleoside RTIs and a non-nucleoside RTI or PI. The effectiveness of these combinations decreases over time, requiring a switch to combinations that retain potency in the presence of viral resistance. Increasing access to second-line FDCs and new developments in first-line ARV therapy are cost challenges. In high-income countries the cost of ARV therapy is largely irrelevant, except for "advanced salvage" drugs such as enfuvirtide. In resource-poor settings cost is a huge factor that limits drug access, resulting in high rates of new infection and subsequent mortality. IP coverage, where granted, can keep access prices for essential ARVs higher than would otherwise be the case. Large, innovator companies have made drugs available at prices very close to the cost of manufacturing for "lowest income" countries. Generic providers in India and elsewhere provide the largest supply of drugs for the developing world. The recent issuance of Voluntary and Compulsory Licenses (VLs, CLs) through the World Trade Organization's TRIP (Treaty Respecting Intellectual Property) provisions arguably contribute to bringing down access prices. The utilization of improved science, pooled purchasing and intelligent procurement practices all definitely contribute to access. This work surveys the production processes for several critical ARVs. These are discussed in terms of scale up, raw material/intermediates and active pharmaceutical ingredient (API) costs. In some cases new routes to APIs or critical intermediates are needed. Based on potential new chemistries, there are significant opportunities to reduce cost for a number of critical ARVs.

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Contents

1. Introduction

Although the death toll from HIV/AIDS over the last quarter century has reached many millions, AIDS has become a manageable chronic disease. An impressive range of compounds (exactly 25) have so far been approved for HIV/AIDS treatment (De Clercq, 2007). Combination therapy with three or more antiretrovirals (ARV) provides relief of symptomatic disease, with most patients achieving increased CD4 levels and undetectable viral load in circulating blood plasma. Significant progress has been made for increased access to ARVs, with over 2 million patients in developing countries receiving ARVs at this time (1Q2008). The fixed-dose combination (FDC) "triomune™" (AZT + 3TC + nevirapine) from Cipla presently sells for approximately $95–140 per patient year, and is the standard first-line FDC in many developing countries. The demonstrated clinical superiority of "Atripla®" (EFV + TDF + FTC) (De Clercq, 2006) and new WHO recommendations have created significant pressure to establish this as a new standard for first-line treatment. One of the major constraints for treatment access is cost. Approximately 65–90% of the cost of ARV therapy derives from the active pharmaceutical ingredient (API).

There is an urgent need to find cheaper alternatives for the production of critical ARVs. This paper discusses methods of producing the APIs efavirenz, emtricitabine, tenofovir disoproxil fumarate, abacavir, ritonavir, lopinavir and atazanavir. With increasing need for improved therapies, there is a strong economic interest in the production of these compounds. This paper describes the most useful commercial processes to produce these compounds. The present work is not exhaustive, but aims to analyze the present situation concerning production costs and favorable alternatives.

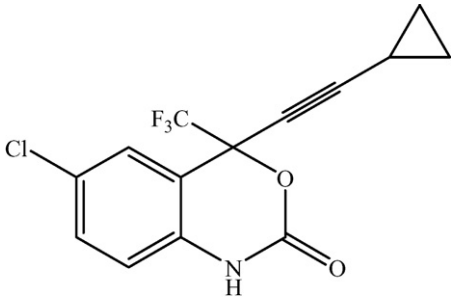
Previous reviews (for example, Izawa and Onishi, 2006; De Clercq, 2001, 2005; Painter et al., 2004; Rodriguez-Barrios and Gago, 2004; Stolk and Lüers, 2004; Peçanha et al., 2002; De Clercq, 1998; Flexner, 1998; Wlodawer and Vondrasek, 1998; Antunes, 1996) emphasized the synthesis of particular classes of compounds or disclosed the development of these APIs.

2. Background

API costs represent a substantial majority of the overall cost of a finished dosage form. The synthesis of an API usually requires several chemical processing steps in which new chemical bonds are formed and molecular complexity increases. API processes are normally carried out in solution, thereby limiting overall process efficiency. Formulation of APIs into a finished dosage form is usually a single process without a change in molecular complexity. Formulation processes typically utilize modest amounts of water, ethanol or no solvent, and additional ingredients (excipients) that are less expensive than the API. Much of the cost of formulation is associated with API losses during processing. Innovation to reduce API costs is therefore a natural focus for reducing price. Cost information in this paper was obtained directly from manufacturers of fine chemicals and generic ARVs. Price quotations from specific companies can only be judged within a framework that includes timing, volume, exchange rates and cost of raw materials. For this reason we will not attribute costs for APIs or intermediates to a specific company, unless this information is already available or has been agreed to by the supplier. The prices for APIs represent the cost of manufacturing plus a profit. In general, ARV APIs are sold at roughly 20% above the cost of production on a scale of several metric tons or more. A rough rule-of-thumb has been made for estimating the large-scale cost of key reagents and new molecules from prices available in the Sigma–Aldrich catalogue for laboratory supply (Laird, 2005). Although this is particularly useful for general purposes, we have not used this yardstick. All prices provided in this paper represent quotes provided by commercial vendors at "representative" production volumes that range from 1 metric ton upwards.

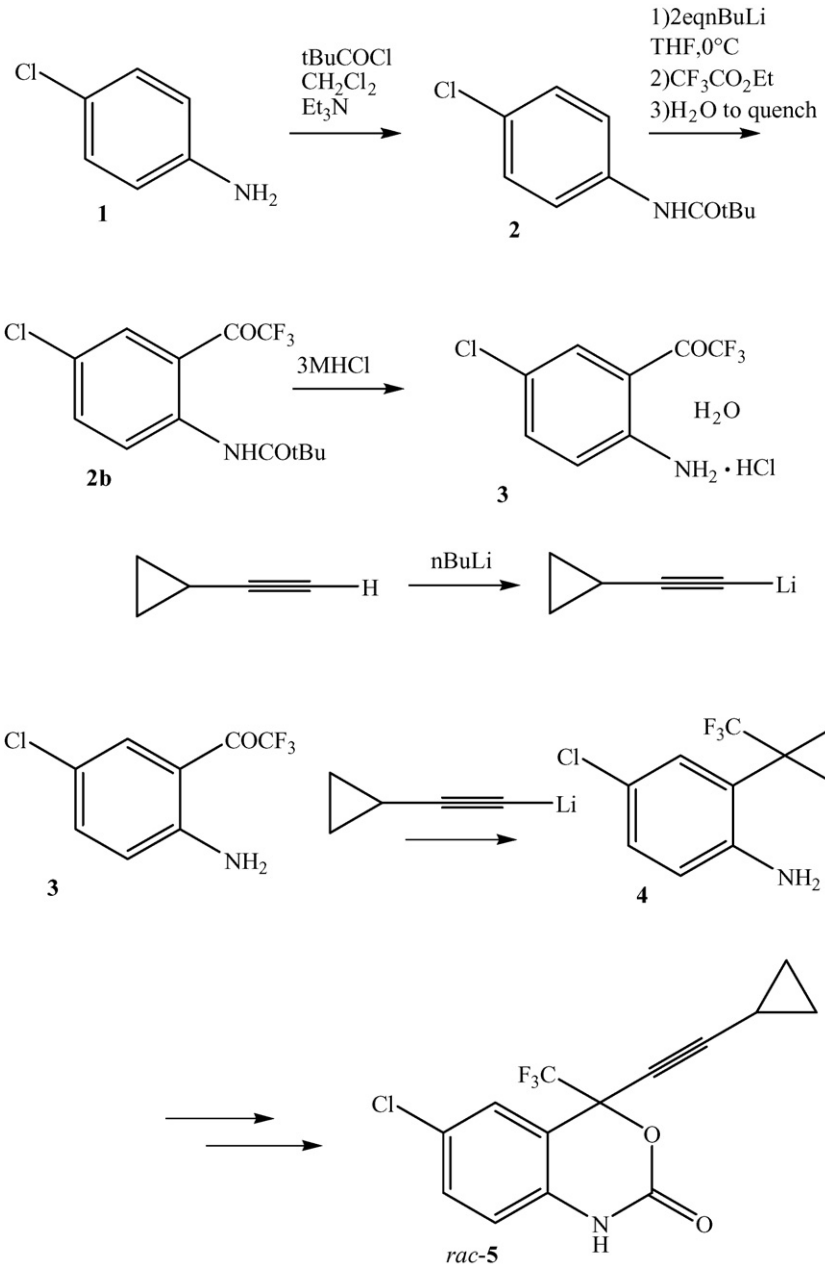
3. Efavirenz

Efavirenz (EFV) was discovered at the Merck Research Laboratories and licensed to Dupont Pharmaceuticals. Dupont carried EFV through development and commercialization. It is marketed as Sustiva® (Bristol-Myers Squibb) and Stocrin® (Merck). Young et al. (1996) obtained the original patent on the synthesis and HIV RT inhibition properties of efavirenz (**5**). Other researchers have improved this process (Radesca et al., 1997; Patel et al., 1999a,b, 2000). The initial synthesis of **5** as a racemate was followed by resolution through the *N*-camphanic imide to yield efavirenz with good (>98% e.e.) enantiomeric purity.



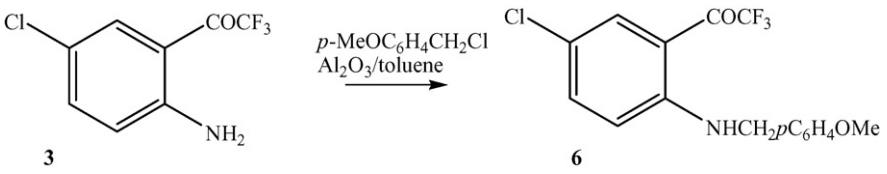
rac-Efavirenz

The conversion of **2**–**2b** by use of a directed *ortho*-metalation reaction (DOM; Snieckus, 1990) is a convenient means of introducing a trifluoromethyl ketone *ortho* to the amine function of **3**, isolated as the hydrochloride hydrate.

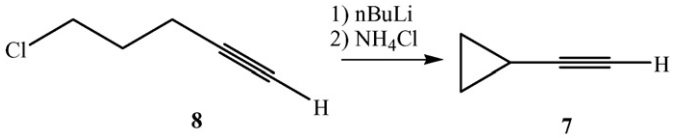


This sequence to *rac*-**5**, however, requires three reactions (see below) that make use of *n*-butyllithium. This chemistry requires anhydrous conditions, cryogenic processing and an inert atmosphere. The current cost of *n*-BuLi is approximately $40 USD/kg. It must, therefore, be appreciated that the use of *n*-BuLi in excess and/or in multiple processing stages will add significant cost to an API process. This is the case for the first asymmetric synthesis of EFV shown below.

Thompson et al. (1995) published an asymmetric addition of organolithium reagents in the presence of chiral aminoalcohol ligands for EFV. *N*-pivaloyl-*p*-chloroaniline **2** is converted to **3** as shown above and protected with a *p*-methoxybenzyl group to yield **6**.

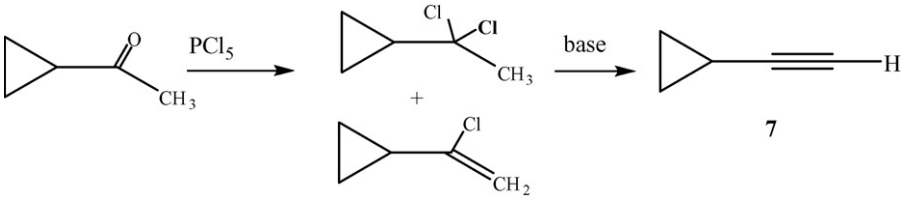


Cyclopropyl acetylene (**7**; CPA) was originally prepared by reacting 5-chloro-1-pentyne **8** with >2 equivalents of *n*-butyllithium. Starting **8** is prepared from 1-bromo-3-chloropropane and sodium acetylide. CPA is isolated by distillation through a column of good separation capacity (>30 theoretical plates) to give **7** of acceptable purity for use.

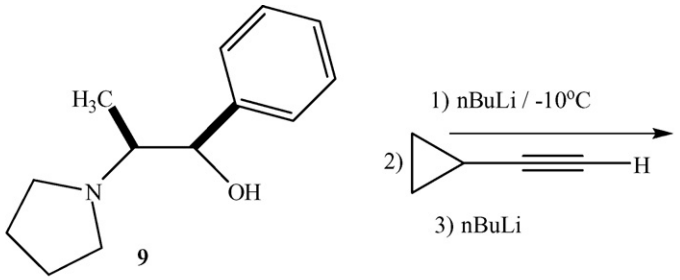


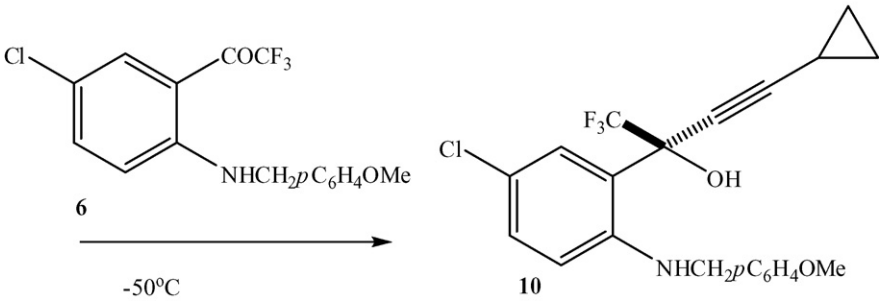
Commercial production of CPA uses inexpensive (<$10/kg) cyclopropylmethyl ketone. Reaction with phosphorous pentachloride yields a mixture of the geminal dichloride and vinyl chloride pictured below. Elimination with base is followed by recovery of CPA (b.p. ~55 °C) from the reaction by distillation. CPA is prepared in reasonable isolated yields (30–40% overall) although substantial losses occur during distillation. The quality of CPA is critical. A minimum purity of 98% is adequate for the route that utilizes a *p*-methoxybenzyl protecting group, while material of 99% purity is required for synthesis without protection.

Pierce et al. (1998) published the synthesis of ligand **9** from nor-ephedrine, and the commercial synthesis of EFV. Protected **10** is oxidized with *ortho*-chloranil or DDQ, yielding diasteoisomeric acetals **11**. Hydrolysis of **11** yields **4**. To drive the reaction equilibrium, $NaBH_4$ in methanol is used to reduce the *p*-methoxybenzaldehyde generated to *p*-methoxybenzyl alcohol. Phosgene is then used to convert **4** to (−)-efavirenz in a very clean, high-yielding reaction.

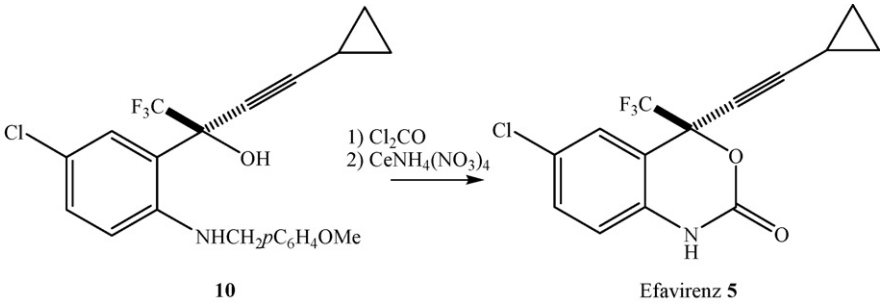


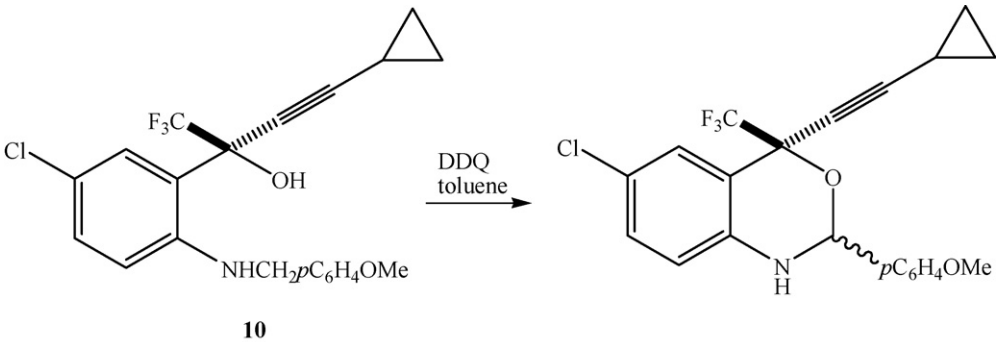
For the asymmetric addition, CPA and chiral aminoalcohol **9**; 1-(*R*)-2-(*S*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (also referred to as "PNE") are lithiated and aged together to form a solution aggregate. Enantiomeric excesses of 96–98% are routinely obtained during subsequent addition to **6**. The minor enantiomer is almost completely removed during the isolation of **10** by crystallization.



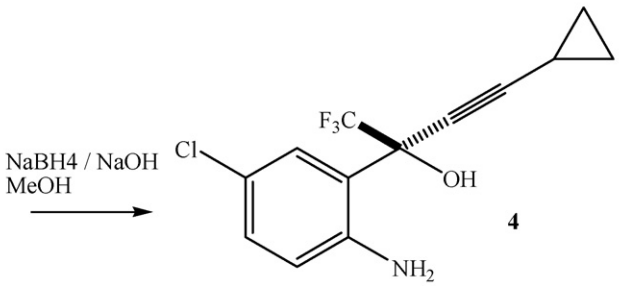


Conversion of **10** into (−)-**5** was achieved by cyclization with phosgene and deprotection with ceric ammonium nitrate (CAN). This particular sequence is not amenable to scale up, however, since EFV decomposes slowly in the presence of CAN.



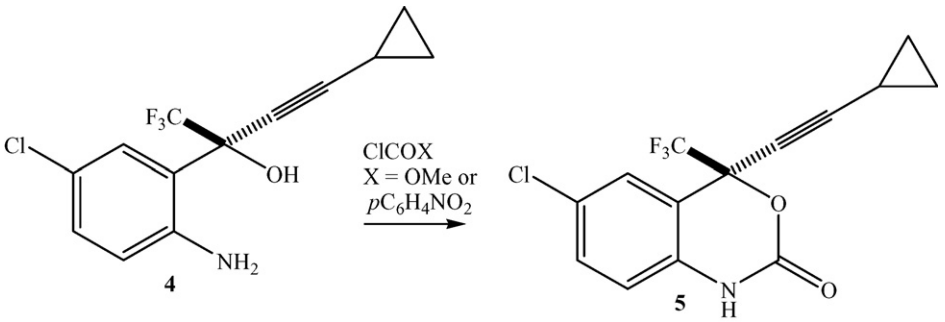


10 **11**



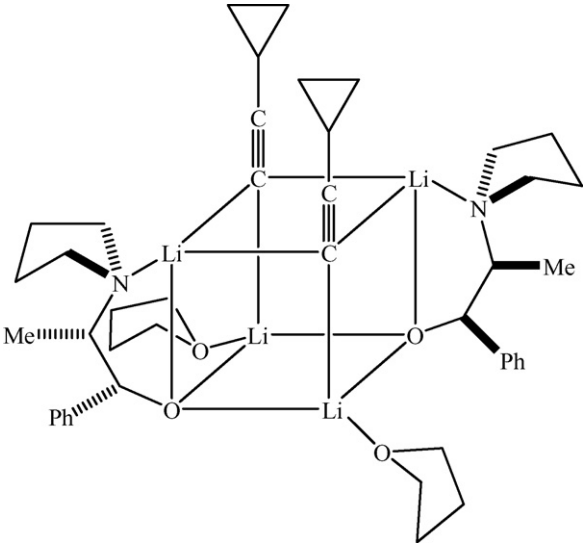
4

The use of chloroformates to produce **5** through an extra processing step and the intermediacy of carbamates was also described. This is a convenient alternative to phosgene (which is often not available for GMP production), though it is not "green" since chloroformates are themselves ultimately prepared from phosgene. Proceeding through carbamates also incurs higher losses during processing.



4 **5**

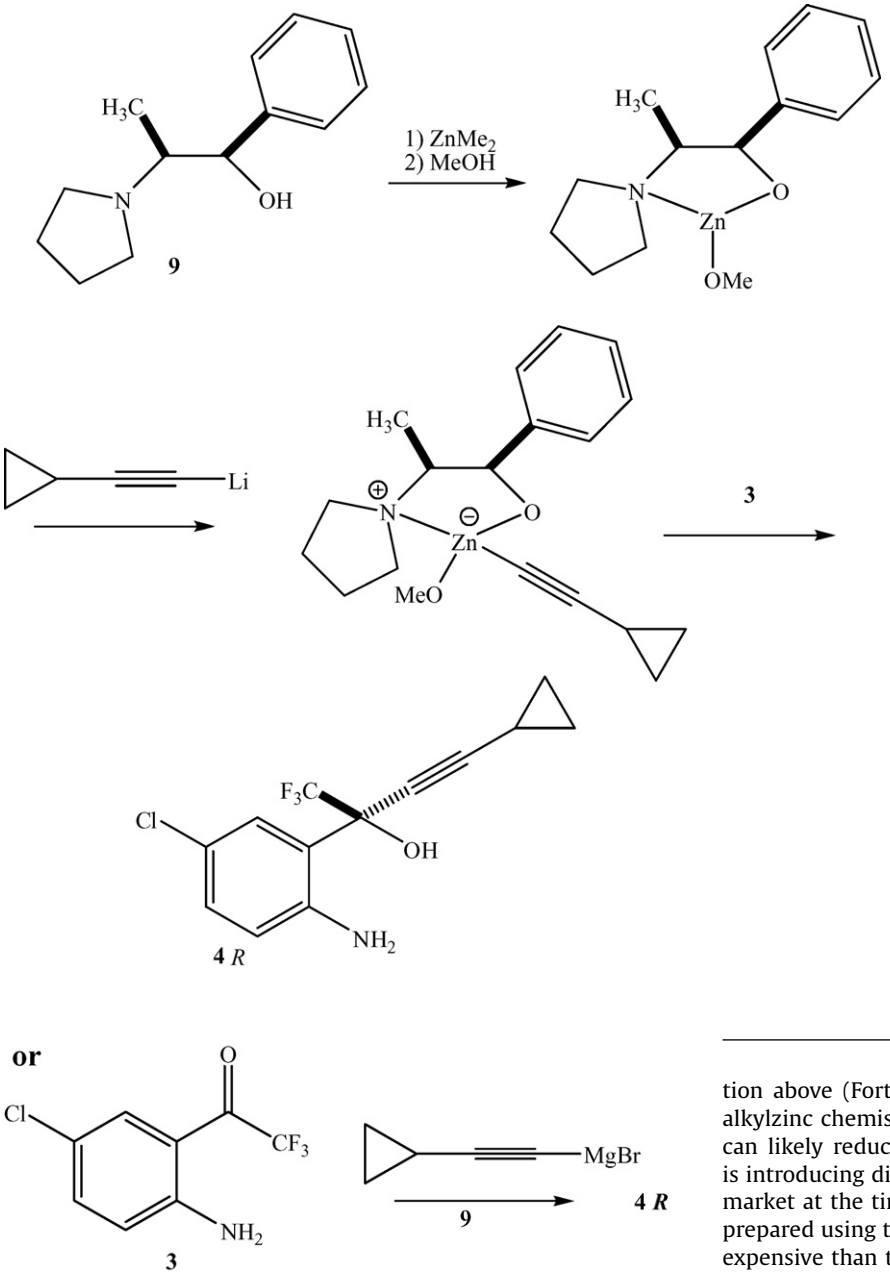
The nature of the lithium aggregates in this reaction and their influence on enantioselectivity was described by Thompson et al. (1998), while Choudhury et al. (2003) described recycling ligand **9** to improve process efficiency. Key features of the asymmetric addition step are (1) the N–H bond of **6** is not lithiated during the reaction, and (2) non-linear stoichometric effects on enantioselectivity are observed. A 2:2 cubic tetramer possessing C_2 symmetry is proposed to be responsible for induction of chirality. The product does not "disengage" from this aggregate during the reaction, so that 2 full mole equivalents of both CPA and **9** are needed to complete the reaction.



Although **10** can be considered a key intermediate towards **5**, *n*-BuLi is the largest single contributor to the final API price in the first asymmetric synthesis. CPA **8** costs in the range of $70–85/kg for material of 98% or 99% quality. Chiral ligand **9** is recycled through the citrate salt with minimal losses. A minimum of 7 mole equivalents of *n*-BuLi are used per mole of product produced. The price of *n*-BuLi is largely driven by the cost of lithium metal, and this price is not affected by the volumes of EFV produced.

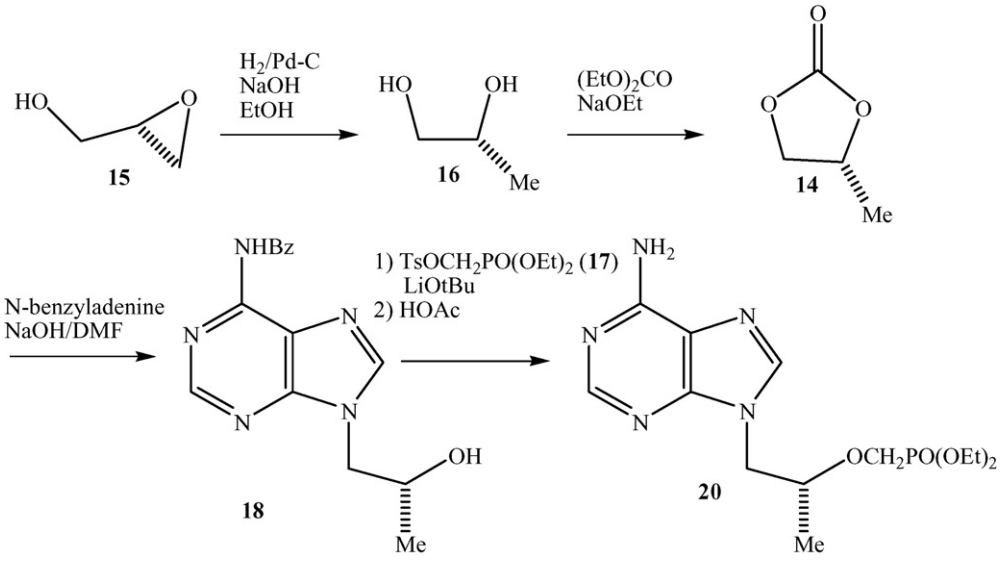
Although the original asymmetric addition is elegant, a shorter synthesis is available from organozinc chemistry (Tan et al., 1999). Dimethyl or diethylzinc generates zinc alkynes which add with enantioselectivity (Niwa and Soai, 1990) to aromatic aldehydes in the presence of chiral ligands. Reaction of dimethylzinc with chiral ligand **9** followed by trifluoroethanol and ClMgCPA (the choice of counterion is important) generates a zinc-ate complex that adds to unprotected **3** with up to 97.7% enantiomeric excess. This chemistry was originally introduced in Europe but is now practiced in India and China for production as well.

An interesting alternative is posed by the use of inorganic zinc(II) salts such as zinc(triflate) for asymmetric addition of alkynes (Frantz et al., 2000a,b; Sasaki et al., 2001; Li and Pu, 2004; Knöpfel et al., 2004). Diethylzinc is pyrophoric and difficult to transport. The use of "Carreira-type" chemistry replaces the use of diethyl- or dimethylzinc for this purpose. This can potentially reduce the manufacturing cost of EFV below current levels. In one example the use of a chiral ligand derived from chloramphenicol gives exceptional enantioselectivity. Efavirenz API produced from the "PMB" route can be purchased from suppliers approved by the US FDA and/or WHO Prequalification effort for about $650/kg in quantities of 5 metric tons or more. Efavirenz is produced under Voluntary License granted from Merck to the South African company Aspen Pharmacare and the joint venture with Matrix in India. Under certain circumstances the asymmetric addition of zinc alkynes to carbonyls or imines (see references above) can be catalytic in zinc and chiral ligand. This is the case for the asymmetric addition above (Fortunak and Pierce, unpublished data). The use of alkylzinc chemistry in India or China for production of efavirenz can likely reduce the cost of API very significantly. Akzo-Nobel is introducing diethylzinc in commercial quantities into the India market at the time of this writing. Finished dosage forms of EFV prepared using the dialkylzinc route to the API are about 25% less expensive than those using API prepared by the original route of manufacturing.

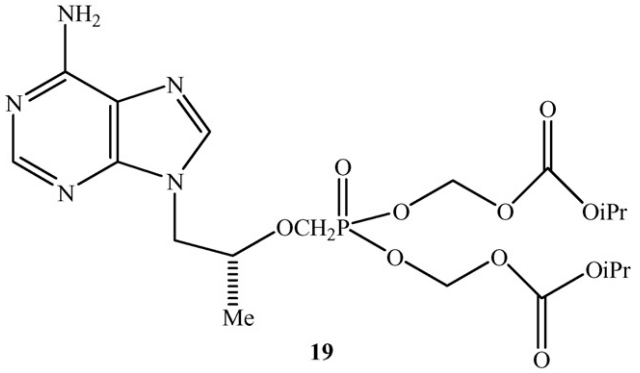


4. Tenofovir disoproxil fumarate (TDF)

Tenofovir disoproxil fumarate is an acyclic nucleotide inhibitor of HIV-1 reverse transcriptase (for review, see De Clercq and Holý, 2005). The first members of this series to be synthesized were PMPA, 9-[2-(phosphonomethoxypropyl) adenine] **12** (Arimilli et al., 1997; Tsai et al., 1995) and PMEA, 9-[2-(phosphonomethoxyethyl) adenine] **13** (Kim et al., 1990; Starrett et al., 1994). The efficacy of the (*R*)-enantiomer of PMPA against HIV-1 reverse transcriptase was published by Balzarini et al. (1993, 1996). The first synthetic approaches to these molecules (Holý and Rosenberg, 1982; Holý and Masojidkova, 1995; Holý et al., 1995) were unsuitable for scale up (Schultze et al., 1998). A significant improvement was the use of (*R*)-propylene carbonate (**14**; RPC) as a novel alkylating agent. An early synthesis of RPC was carried out from (*S*)-glycidol **15** by hydrogenation (5% Pd-C/EtOH/25 psi H_2/NaOH) to afford (*R*)-1,2-propanediol **16**. Subsequent condensation with diethyl carbonate yielded RPC **14**. Reaction of RPC with adenine in the presence of NaOH yielded **18**. Treatment of **18** in DMF with lithium or magnesium *t*-butoxide and diethyl tosyloxymethylphosphonate (DESMP, **17**) provided PMPA ethyl ester **20**.



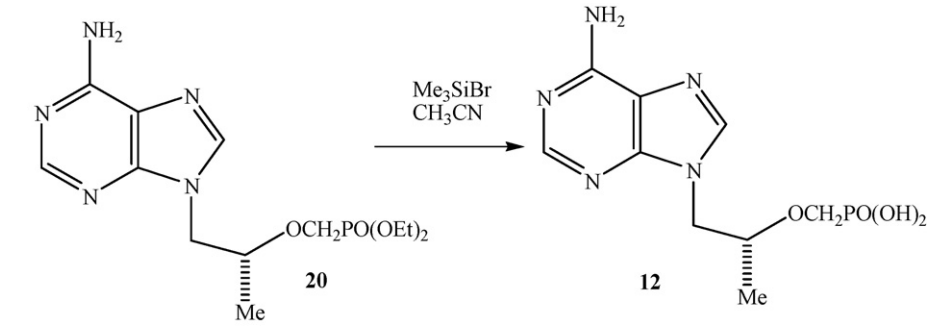
A 1998 patent from Gilead Sciences, Inc. describes the preparation of PMPA essentially as indicated. Robbins et al. (1998) and Naesens et al. (1998) identified bis(isopropyloxy-methylcarbonyl)-9-*R*-(2-phosphonomethoxy-propyl) adenine **19** as a prodrug of PMPA. The fumarate of this prodrug has been commercialized as Viread®.

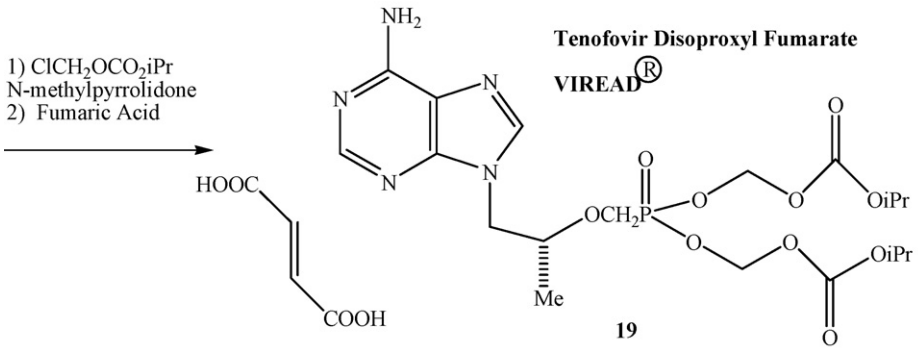


The production of **19** (tenofovir disoproxil) and analogous compounds, was described by Arimilli et al. (1997, 1999) and by Benzaria et al. (1996), the latter dealing with the PMEA **13** series. The production of **19** is carried out by reacting PMPA **12** with **21** in the presence of a hindered trialkylamine base and a minimum amount of a polar, aprotic solvent (NMP). The fumarate salt of tenofovir disoproxil is prepared and crystallized from 2-propanol after an aqueous workup and a solvent switch from ethyl acetate to 2-propanol.

Conversion into PMPA ethyl ester **20** is carried out essentially as described by Schultze et al. (1998). The conversion into PMPA **12** is carried out with bromotrimethylsilane in acetonitrile. The final step is condensation of **12** with chloromethylisopropyl carbonate (**21**, CMIC) using triethylamine in DMF or NMP at 55–65 °C. After dilution with isopropyl acetate and aqueous workup, the crude product is solvent-exchanged with isopropanol under reduced pressure. Fumaric acid is added and TDF is crystallized (Arimilli et al., 1999; Grim and Romanelli, 2003). Initial experiments described the crystallization as being induced from a super-saturated solution without stirring although patents describe a process of evaporative crystallization during removal of excess isopropanol by distillation. The alkylating agent **21** is prepared by reaction of isopropanol with chloromethyl chloroformate in pyridine/diethyl ether.

Yu et al. (1999) used sodium *t*-butoxide as the base for alkylation to prepare **20**. Magnesium *t*-butoxide has subsequently been found to be a superior base for this reaction. The quality of magnesium *t*-butoxide used in this reaction, however, is critical for reaction success. An alternative strategy to TDF was described by Jeffery et al. (2000) in which the adenine ring is formed late in the synthesis. The use of moving bed chromatography to separate the enantiomers of tenofovir has been described (Chapman et al., 2001). TDF does present a series of difficulties in minimizing production costs. Single-enantiomer **14** can now be obtained in multi-ton quantities for approximately $45/kg such that this is no longer a critical cost component. RPC cost may be reduced even substantially below this level as more efficient, enzymatic methods are scaled up for production. The phophonate ester, $TsOCH_2PO(OEt)_2$, (DESMP) to produce PMPA ester **20** can be purchased for about $26/kg. The hydrolysis of **20** to PMPA utilizes substantial excesses of bromotrimethylsilane. This reagent is expensive and causes deterioration of normal processing equipment. Alternatives to TMSBr for hydrolysis are known to include sodium iodide/TMSCl or hydrobromic acid.

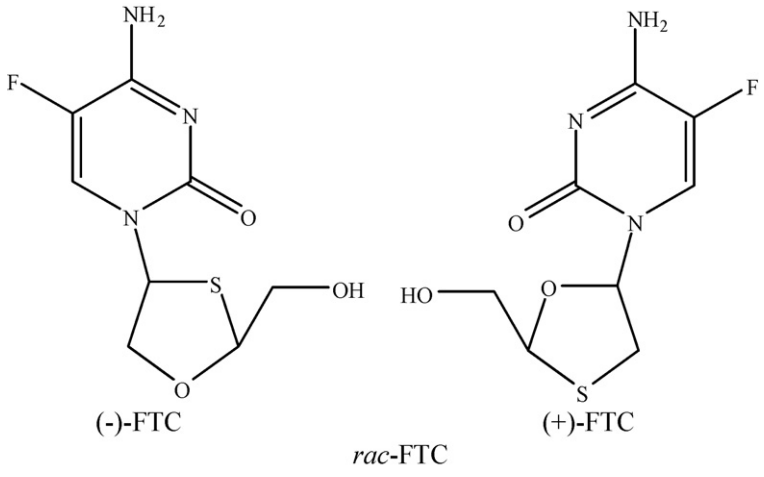




The biggest cost driver in the TDF process is the final stage alkylation, salt formation and crystallization. Tenofovir disoproxil can be abbreviated as bis(POC)PMPA where POC designates the isopropyloxycarbonyloxymethyl ester. Therefore, the conversion of PMPA to tenofovir disoproxil proceeds through mono(POC)PMPA and to bis(POC)PMPA (see below). PMPA hydrate is sparingly soluble in all common solvents except water, yet this is an unacceptable solvent or cosolvent for reaction. As the reaction proceeds, mono(POC)PMPA and then bis(POC)PMPA are increasingly soluble in organic solvents. Mono(POC)PMPA and bis(POC)PMPA are all unstable to water and base. From processing conditions disclosed in the Gilead patents, it can be surmised that these compounds have some degree of instability. This represents the difficulty of obtaining a high yield when making TDF. The crystallization of the TDF salt presents another problem. Fumaric acid forms a salt slowly in *iso*-propyl alcohol, and crystallizes in an uncontrolled fashion by self-nucleation during an evaporative crystallization. Very small crystals are obtained, such that substantial losses occur due to passage of fine particles through processing filters and decomposition of product in solution during extended processing times. The reasonable maximum yields of isolated TDF from this process are apparently about 50% from PMPA hydrate, although the chemical yield for the bond-forming step can be optimized to about 80% yield in situ. TDF is presently sold in multi-ton quantities for about $950/kg by generic providers in India, several of whom operate under Voluntary Licenses granted by Gilead Sciences.

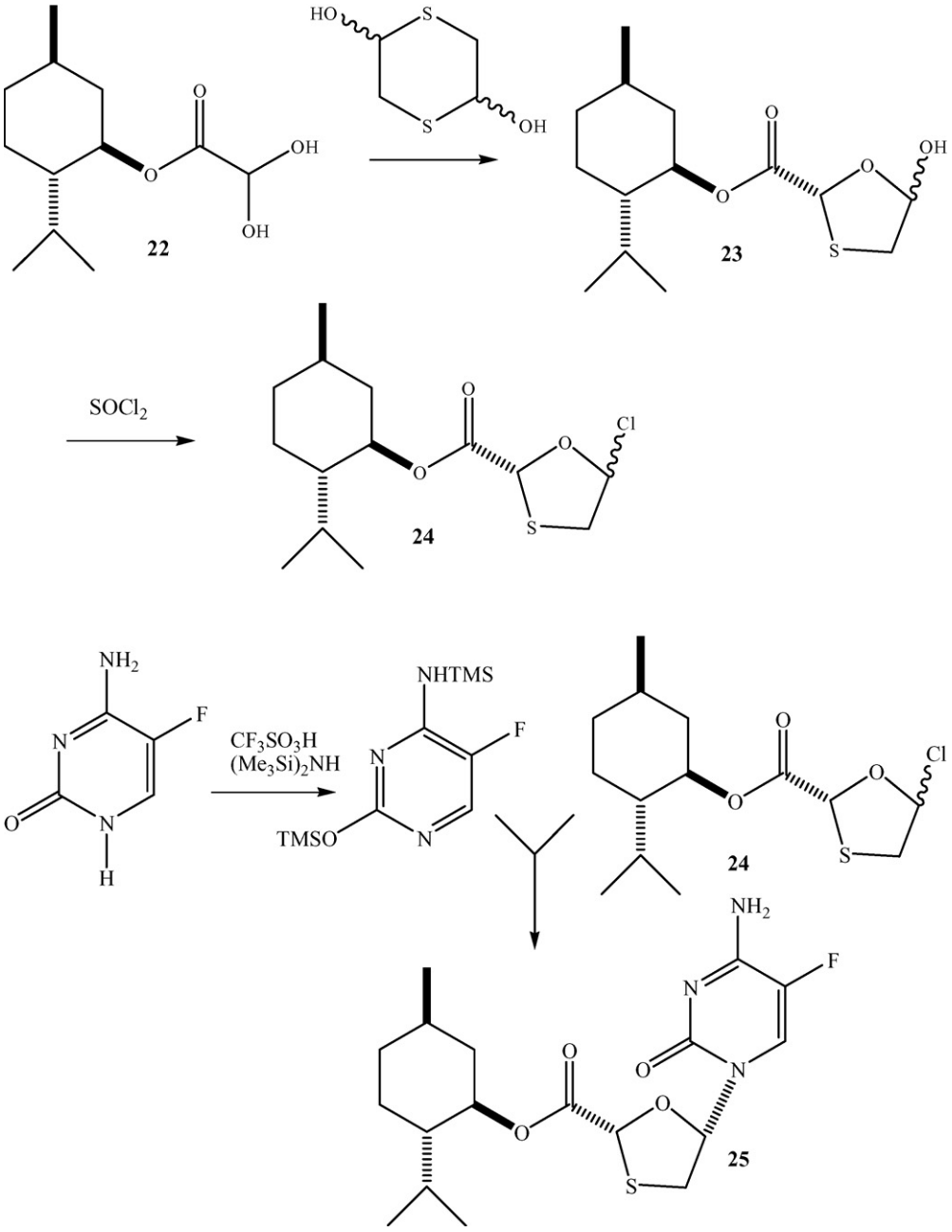
5. Emtricitabine

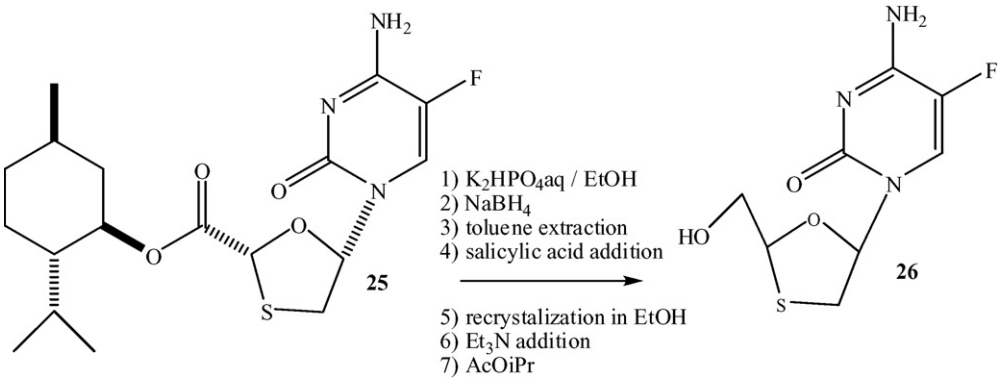
Emtricitabine, FTC (Emtriva®) is an inhibitor of HIV-1 reverse transcriptase for once-daily antiretroviral therapy (Cahn, 2004; Anon., 2004). Emtricitabine is a fluorinated L-nucleoside (Pankiewicz, 2000; Wang et al., 1998) closely related in structure and synthesis to lamivudine, 3TC (Coates et al., 2001). The use of emtricitabine has been restricted to co-dosing with TDF (Truvada™). Schinazi et al. (1992) described (−) and (±)-*cis*-5-fluoro-1-1[2-hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine, (−)-FTC and *rac*-FTC, while Frick et al. (1993) described the pharmacokinetics of FTC.



Several papers (Milton et al., 1995; Cousins et al., 1995) and patents have described the synthesis (and resolution) of 1,3-oxathiolanes and silylation of 5-fluorocytosine (Goodyear et al., 1995; Dionne, 1996). Caputo et al. (1999) described a chiral strategy for 1,3-oxathiolane-based nucleoside analogues. A substantial contribution in this field came from the Glaxo-Wellcome group (Goodyear et al., 2000) in the synthesis of the single-enantiomer lamivudine. Condensation of l-menthyl glyoxate hydrate **22** with 1,4-dithiane-2,5-diol yielded oxathiolane **23**. Chlorination of **23** with thionylchloride followed by treatment with silyl(5-fluoro)cytosine in TMSOTf yielded **25** through intermediate **24**.

Conversion into **26** was carried out by hydrolysis, reduction to an alcohol, and crystallization of the corresponding salicylate salt. Free base formation with triethylamine and recrystallization from isopropyl acetate gave the final API.



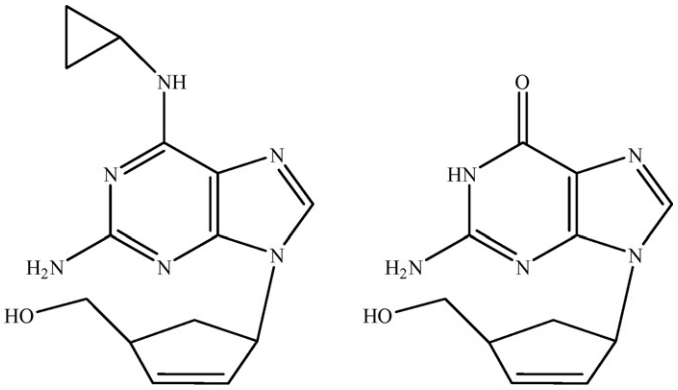


This sequence as indicated presents many industrial challenges, including hydrolysis of the menthyl ester, crystallization of the salicylate and conversion to the free base.

Other chiral precursors (Murth et al., 2002) and chromatographic processing (Xie et al., 2003) have been described. Subsequent developments removed the hydrolysis step and salicylate crystallization. 5-Fluorocytosine can be obtained via direct fluorination of cytosine using trifluoromethyl hypofluorite and fluorotrichloromethane as a solvent. 5-Fluorocytosine may alternatively be produced from fluoroacetic acid (Robins et al., 1976; Heidelberger and Duschinsky, 1957; Duschinsky and Heidelberger, 1960). The "sugar" moiety used for emtricitabine is also used for lamivudine (3TC) so that this manufacturing has been optimized. 5-Fluorocytosine pricing is the largest cost contributor to FTC. The volume demand for FTC is presently not large enough to capture full-scale economics. The great market opportunity for FTC is its use in Truvada® and Atripla®. There is a driving force to switch 3TC for FTC in this combination, though full proof of clinical equivalence is not yet available. Voluntary licenses have been granted for the use of both TDF and the two-drug combination with emtricitabine, Truvada®.

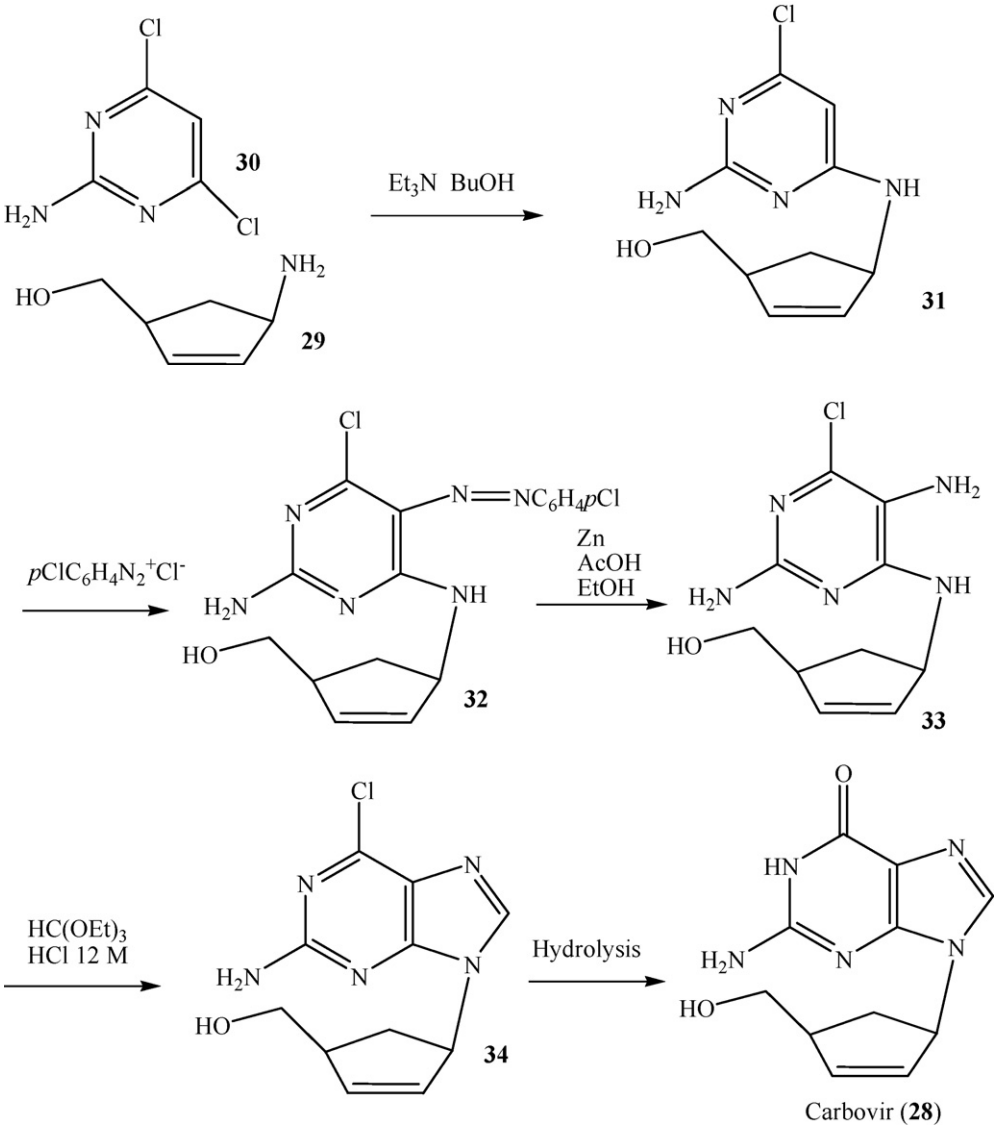
6. Abacavir

The Wellcome Research Group described the production of Abacavir in two patents (Daluge, 1991a,b). These processes were reviewed in Kleeman's Encyclopedia (Kleemann and Engel, 1999). Abacavir **27** is a cyclopropylamine derivative of carbovir **28**.



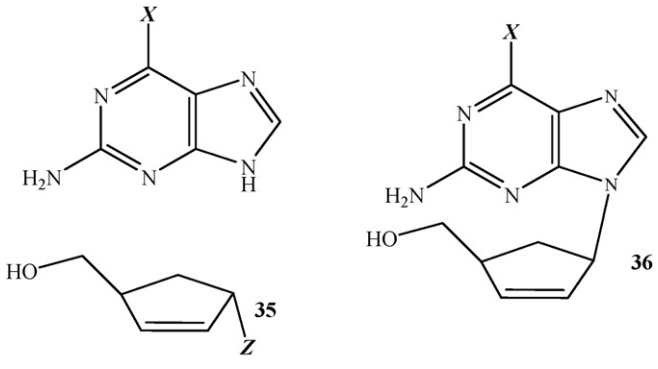
Abacavir (**27**) Carbovir (**28**)

Rac-cis-(+)-carbovir **28** (Vince and Hua, 1990) can be obtained from reacting *rac-cis*-4-(hydroxymethyl)cyclopentenylamine **29** and 2-amino-4,6-dichloropyrimidine **30** to give intermediate **31**. This is followed by coupling with the diazonium salt of *p*-chloroaniline, reduction, and imidazole ring closure with triethyl *ortho*-formate followed by hydrolysis.

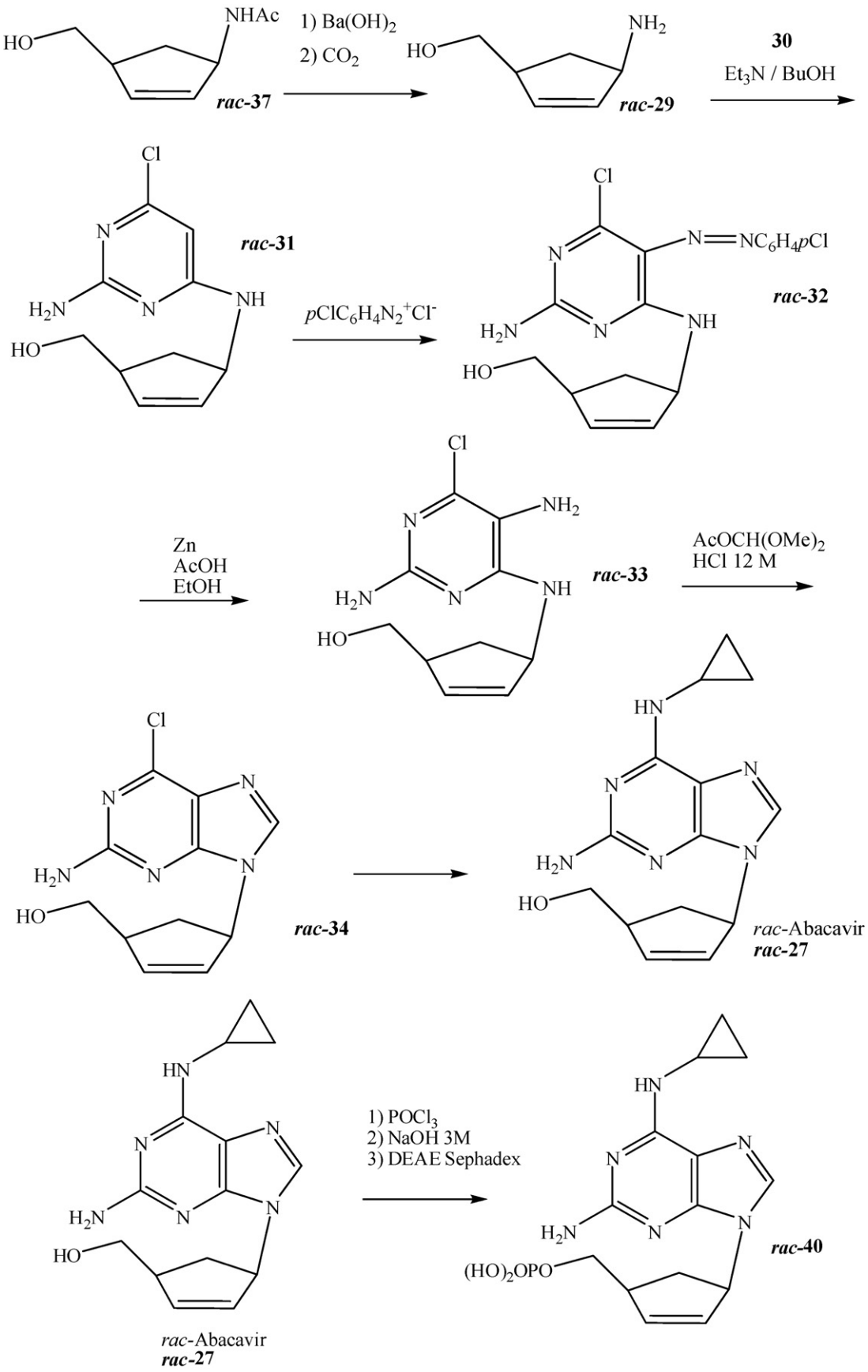


The main synthetic problem for producing single-enantiomeric abacavir is the production of **29** or equivalent. Berranger and Langlois (1995) used 3-hydroxyaminoborneol as a chiral template to produce (+)-carbovir **28**. Tanaka et al. (1996) described a beautiful, enzymatic asymmetrization process. Crimmins and King (1996) produced single-enantiomeric **28** via metathesis and Tsuji–Trost coupling (Amblard et al., 2005; Thorimbert et al., 2004; Agrofoglio et al., 2004; Torque et al., 2004; Chevrin et al., 2003; Branchadell et al., 2003; Trost, 2002; Genet and Savignac, 1999). It is important to emphasize the tremendous potential of the chiral Tsuji–Trost coupling in the production of abacavir **27**. Many other approaches have been published (Katagiri et al., 1997; Olivo and Yu, 1998; MacKeith et al., 1994; Brown and Hegedus, 2000; Södergren et al., 2000; Crimmins et al., 2000; Roulland et al., 2003; Nayek et al., 2004; Lloyd et al., 2004; Brabban et al., 1996; Hodgson et al., 1994; Asami et al., 1994; Evans et al., 1992; Trost et al., 1992). The reviews of Crimmins (1998) and Ferrero and Gotor (2000) cover methodologies through the late 1990s. The Wellcome patents describe processes for the production of the (±) intermediates for abacavir **27** and resolution (Daluge, 1991a,b). The key approach is based on conversion of an intermediate such as **35** to a suitably substituted purine or pyrimidine. Aminolysis of precursors such as **36** is also key.

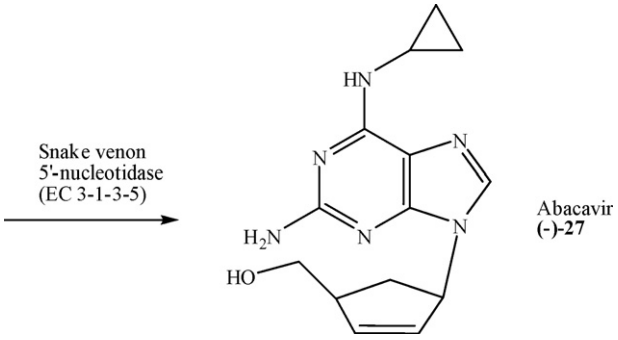
Wellcome's racemic process is very similar to that originating from the University of Minnesota (Vince and Hua, 1990; see also http://www.cptech.org/ip/health/umabc.html). Snake venom 5-nucleotidase (EC3.1.3.5) from *Crotalus atrox* can be used late in the sequence to produce enantiomerically pure (−)-**27**, although other means could be utilized.



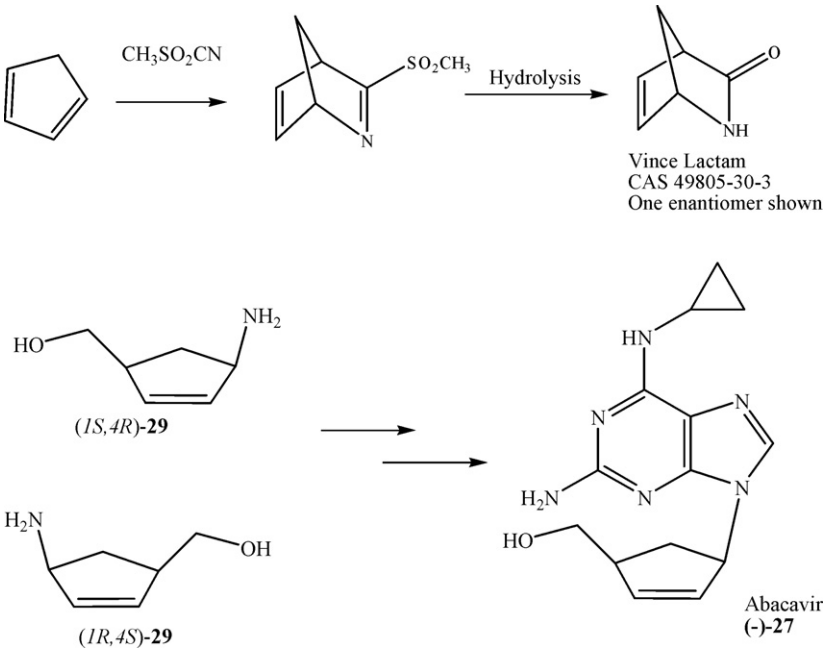
Chiral intermediates

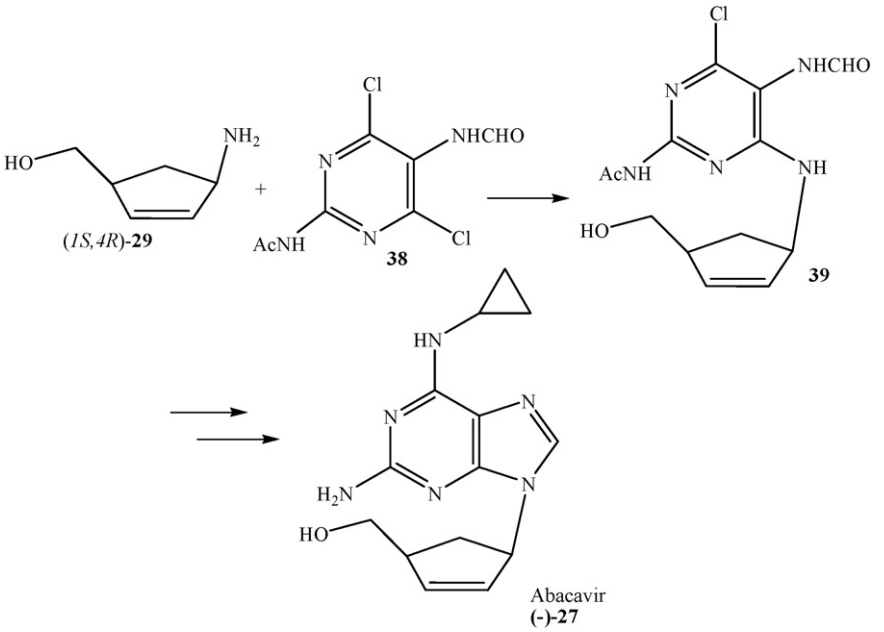

NHAc
HO
1) Ba(OH)2
2) CO2
rac-37
NH2
HO
rac-29
30
Et3N / BuOH
Cl
N
H2N
N
NH
HO
rac-31
pClC6H4N2+Cl-
N=NC6H4pCl
rac-32
Zn
AcOH
EtOH
NH2
rac-33
AcOCH(OMe)2
HCl 12 M
rac-34
HN
rac-Abacavir
rac-27
1) POCl3
2) NaOH 3M
3) DEAE Sephadex
(HO)2OPO
rac-40

The key "Vince" lactam intermediate for the synthesis of single-enantiomer carbovir is available from Lonza, a fine chemicals company that supplies advanced intermediates and starting materials headquartered in Basel, Switzerland. This material is priced at about $70/kg for several metric tons. "Vince" lactam is prepared through a Diels–Alder cycloaddition of cyclopentadiene and methanesulfonyl cyanide (MSC). MSC is generated in catalytic amounts and reacted with cyclopentadiene in a continuous fashion in situ. Hydrolysis of the intermediate in a two-phase methylene chloride:water solvent system liberates the lactam and enables methanesulfinic acid to undergo a new cycle of MSC formation (Rouhi, 2003; Griffiths and Previdoli, 1993). The resolution of (−)-**29** using dibenzoyl-D-tartaric acid has also been described in the above patents.

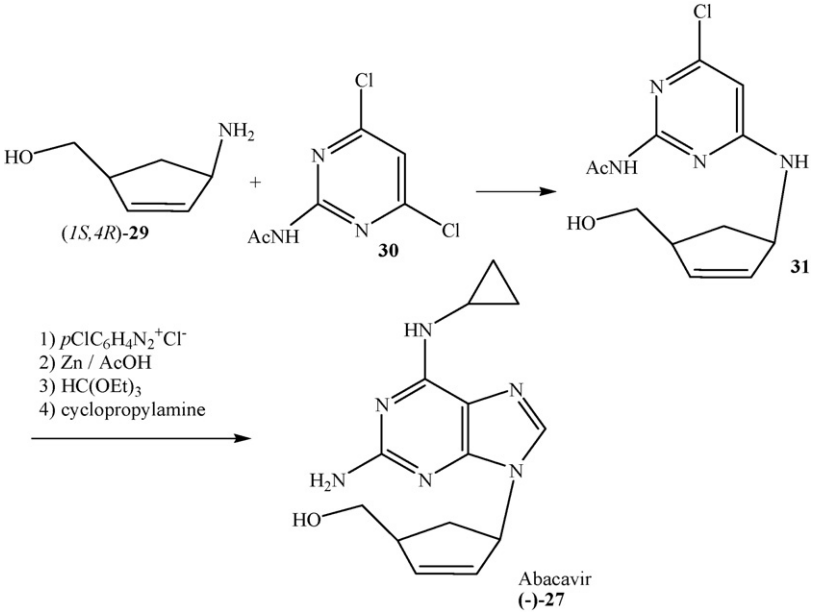


The coupling of (1*S*,4*R*)-**29** to *N*-(4,6-dichloro-5-(formylamino)-2-pyridindinyl) acetamide **38**, would produce **39**. This appears to be a suitable route to (−)-abacavir **27**.





Multiple processes have been described to prepare (1*S*,4*R*)-**29**. Prices of the beta-lactamase enzyme used to resolve (±)-**29** are not readily available. Chemical or lipase-mediated alternatives are very simple, however.



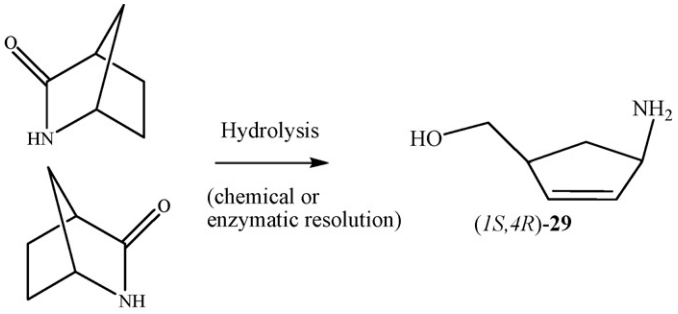
Four routes, therefore, could be used for the synthesis of abacavir:

- Resolution of (±)-**29** by chemical or enzymatic means.
- Production of (−)-**29** or a suitable analogue by enantioselective synthesis.
- The use of a chiral building block or template.
- The use of a chiral Pd-catalyst (not yet reported in the literature) using Tsuji–Trost chemistry.

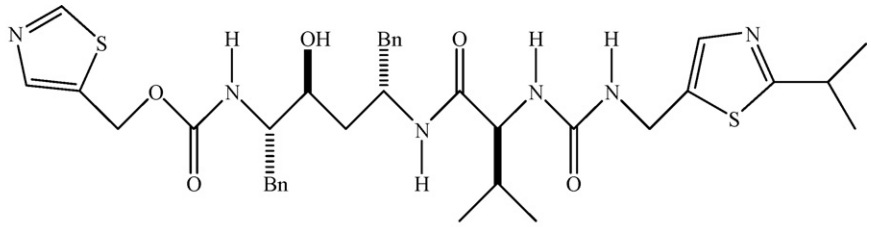
In terms of economy, the last alternative appears to be most preferred. The need for a cheaper production of (−)-**29** still exists at the time of this writing.

7. Ritonavir and lopinavir

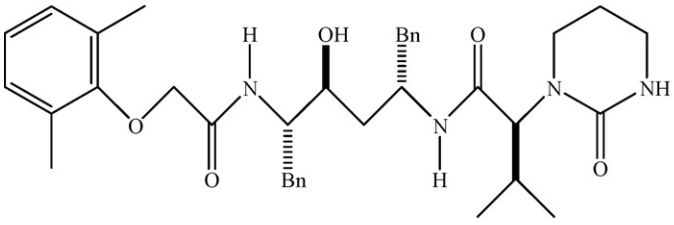
Ritonavir (RTV, **41**) and lopinavir (LPV, **42**) are protease inhibitors that share the same hydroxyethylene dipeptide core **43** (Kempf et al., 1995).



Synthetic approaches to **41** and **42** by making peptide bonds are obviously practical. Sequential coupling of the amines of a pseudo-C_2 symmetric core with activated ester "wings" suggests the option of a common intermediate to both RTV and LPV.



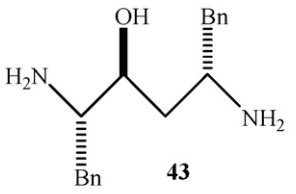
Ritonavir (41)



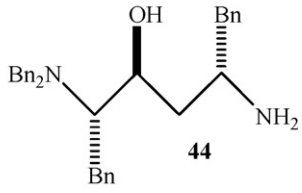
Lopinavir (42)

Different strategies in developing industrial routes to lopinavir and ritonavir deserve attention. Kaletra® is the trademark of a ritonavir/lopinavir fixed-dose combination. Lopinavir – like most other protease inhibitors – is extensively metabolized by cytochrome P450 oxidase isoform 3A4 (CYP_{3A4}) while ritonavir is a CYP_{3A4} inhibitor. Ritonavir is no longer a standard of care for treatment in itself, yet RTV inhibition of CYP_{3A4} "boosts" the circulating drug levels of other PI's. Ritonavir is used, therefore, in less than therapeutic doses to enhance the systemic exposure of lopinavir (Corbett et al., 2002). The history of Ritonavir was published by Kempf et al. (1998).

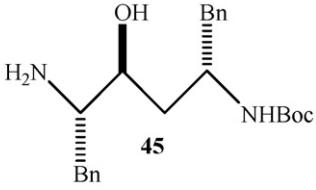
Early syntheses of the core **43** were reported from Merck (Ghosh et al., 1993), and Abbott (Kempf et al., 1994) using different approaches (Fray et al., 1986; Ghosh et al., 1991). A key approach from L-phenylalanine **46** was published by Stuk et al. (1994). Additional information has been published by Haight et al. (1997, 1999). Addition of benzyl Grignard reagent to keto-nitrile **48** is followed by reduction of ketoenamine **49** with a sodium borohydride:methanesulfonic acid complex to give **44**. This intermediate possesses the three chiral centers of **43** and is obtained in good overall diastereoselectivity. This reduction proceeds through the ketoenamine **49**, in which the enamine is the first-reduced functionality.



43

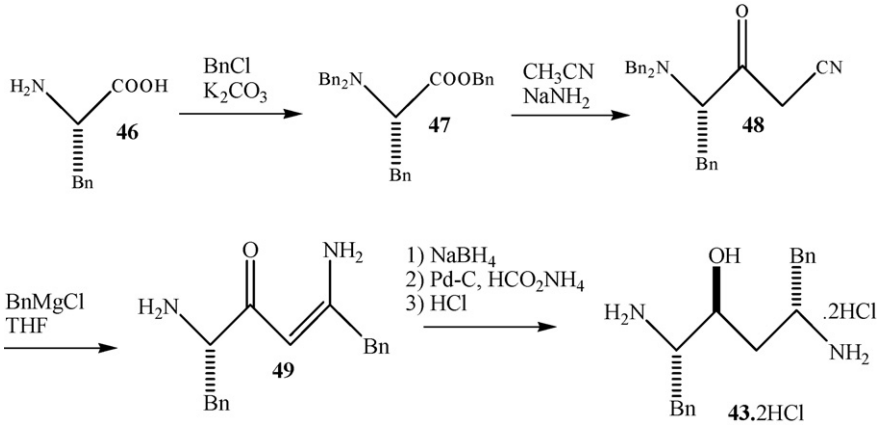


44



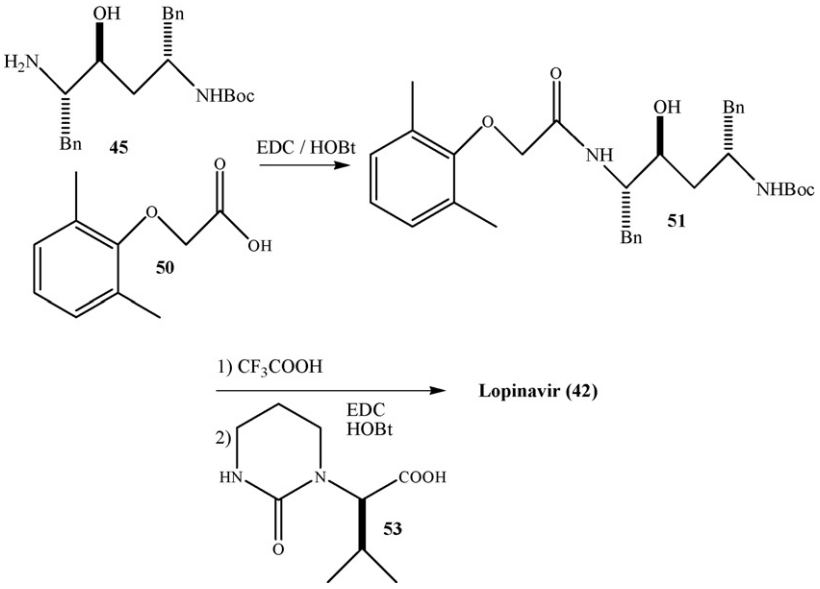
45

Abbott has multiple patents covering RTV, LPV and analogues (Kempf et al., 1996; Sham et al., 1999). Kempf et al. (1996) described different methods for the peptide couplings using expensive reagents, although alternatives have been published (Stoner et al., 1999). Dimethylphenyloxyacetic acid (**50**) was reacted with **45** (HOBt, EDC), yielding **51**. After deprotection with trifluoroacetic acid, deprotected intermediate **53** was condensed with **54**, yielding lopinavir (**42**, Haight et al., 1999).

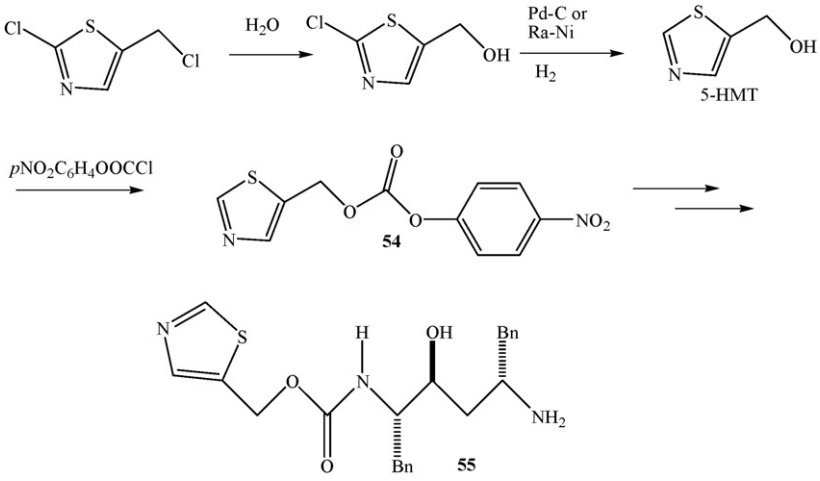


46 **47** **48** **49** **43.2HCl**

Other interesting chemistry towards LPV and RTV has been published (Benedetti et al., 2002; Sham et al., 2001; Benedetti and Norberto, 2000, 2001; Ghosh et al., 1999; Adamo et al., 2006; Menche et al., 2007). Production of the *N*,*N*-dibenzyl core **44** and the Boc-core hemisuccinate salt **45** are keys to the effective syntheses of LPV and RTV. The heterocyclic wings of ritonavir are both thiazoles. The "A-Wing" 5-hydroxymethylthiazole (5-HMT) is made effectively from 2-chloro-5-chloromethylthiazole, available ($22–24/kg on metric ton scale) for the production of insecticides. Displacement of chloride by hydroxide is followed by hydrogenolysis of the thiazolyl chloride to yield 5-HMT (Leanna, 1996; Leanna et al., 1998; Allen, 1999). Hydrogenation over Pd/C or Raney Nickel are both effective for this purpose. 5-HMT can be produced through condensations of thioformamide with 2-halomalonaldehyde (Kraus and Fiege, 1998), condensation of thiourea with epoxy-propanal (Coppola, 2003) or a halo derivative of formylacetic ester (Jin et al., 2004). Esterification of 5-HMT with *p*-nitrophenyl chloroformate gives activated carbonate **54** ready for coupling with the core of RTV, so yielding **55** (Langridge, 1998).



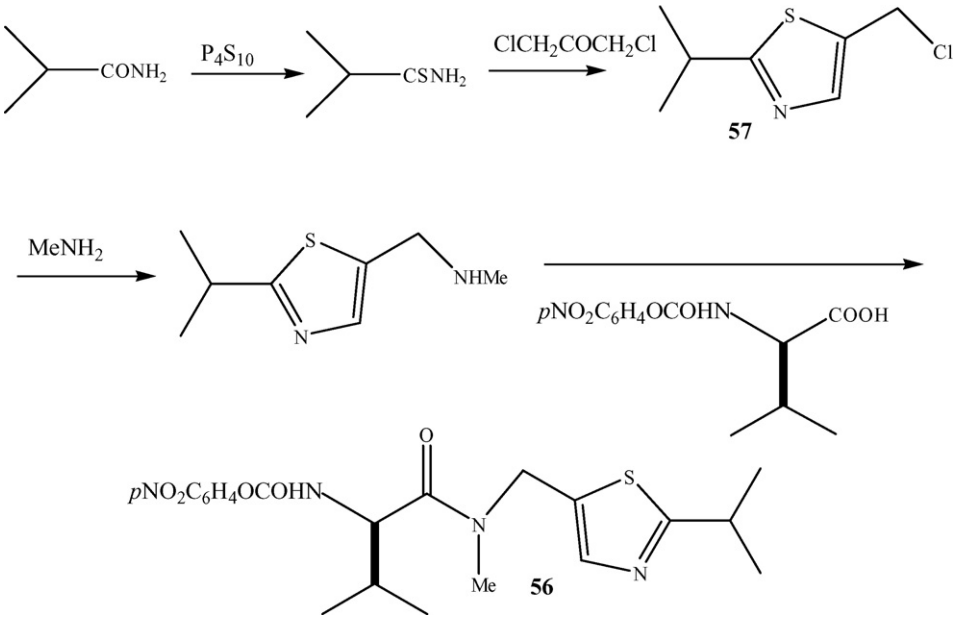
The second thiazole (B-Wing) is produced via reaction of isobutyramide with P_4S_{10} followed by condensation with 1,3-dichloroacetone to give **57**. The desired **56** is produced after displacement with methylamine and coupling with *N*-protected valine as shown. Carbodiimide-mediated coupling of **55** with **56** yields ritonavir **41**.



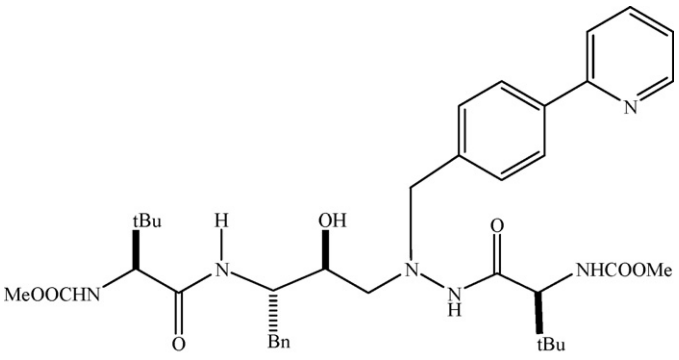
For both RTV and LPV **43** must be made available at a low price. Significant cost contributors to **43** are benzyl Grignard reagent, palladium-on-carbon, the atom-inefficient use of three benzyl groups that are later discarded and the number of processing steps. The cost of **45** as the hemi-succinate salt is approximately $500/kg on metric ton scale produced by Divis in India. The "A-wing" of lopinavir is inexpensive, while the "B-wing" containing valine is available from multiple sources for approximately $100–130/kg. The A-wing of RTV is a particular issue; vendors advertising production capability have provided recent quotes on the metric ton scale ranging from $85 to $325/kg. The cheapest generic prices offered for either of the APIs ritonavir or lopinavir by WHO prequalified providers are approximately $1000/kg.

8. Atazanavir

Atazanavir (BMS-232632, **58**) is an aza-peptide isostere first registered in the USA in 2005 (Robinson et al., 2000; Gong et al., 2000). Voluntary licenses from the innovator company Bristol–Myers Squibb have been granted for generic production of this drug in India.

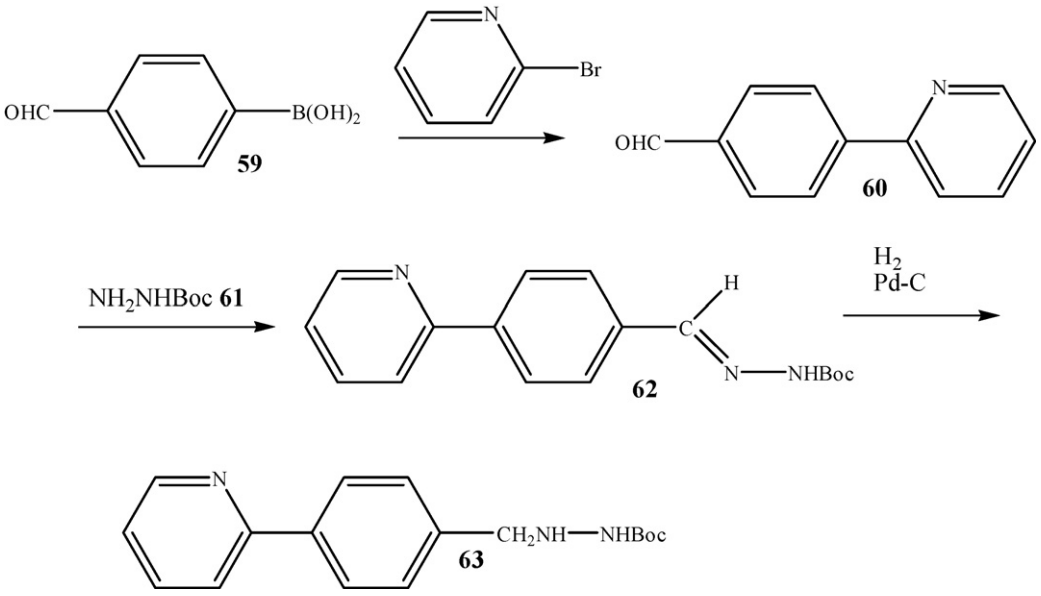


Bristol–Myers Squibb (Xu et al., 2002) has published details of the process used for production. Boronic acid derivative **59** is submitted to the Suzuki–Miyaura coupling with 2-bromopyridine using Pd catalysis. The reaction product **60** is allowed to react with carbazate **61**, producing **62** that is then reduced to **63**.

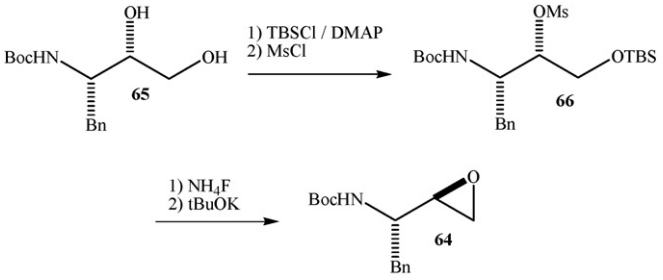


Atazanavir (58)

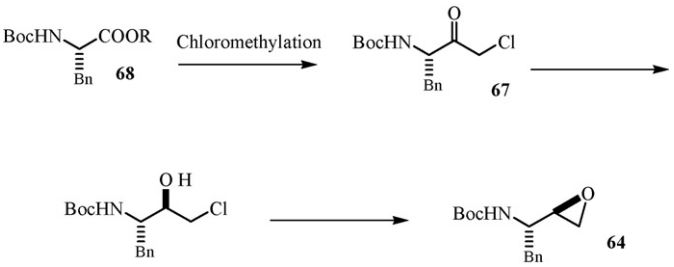
Suzuki–Miyaura coupling proved to be straightforward, in toluene/ethanol with Pd loadings as low as 0.1 mol%. Condensation with $H_2NNHBOC$ (**61**) to yield the hydrazone proceeded well. However, **62** must be directly reduced to **63** without isolation. The amino acid-derived **64** is the "other" key intermediate required. This represents a *threo-N*-protected 3-amino-1,2-epoxybutane. Compound **64** was originally produced from commercially available diol **65**.



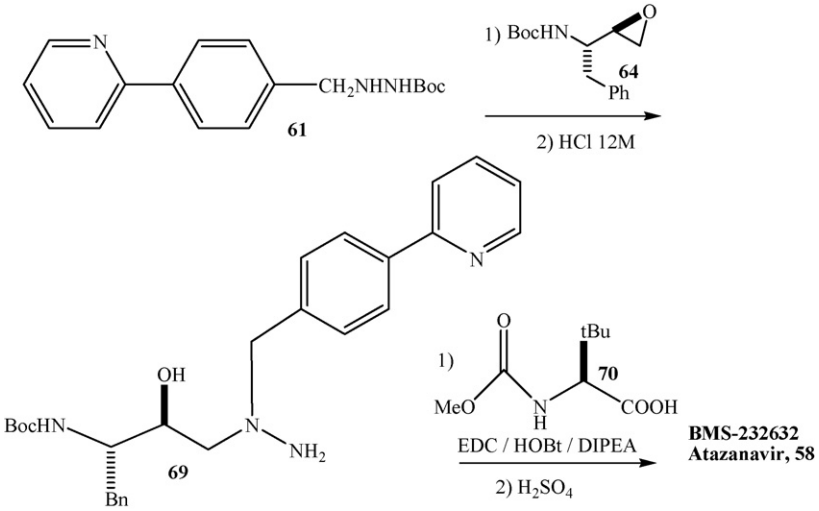
An excellent alternative process is shown below. The chloromethylation of *N*-protected phenylalanine or related esters can be accomplished in a number of different procedures (Reeder and Anderson, 2006). The *threo*-selective reduction of alpha-chloroketone **67** or analogues then allows efficient production of **64** (Izawa and Onishi, 2006).



Condensation of epoxide **64** with hydrazino carbamate **61** and hydrolysis yielded hydrazide **69**. Peptide bond formation by coupling with two equivalents of *N*-Moc-*tert*-leucine **70** and formation of the sulfate salt gave Atazanavir **58**. EDC was successfully substituted for the expensive coupling agent TPTU (Jones, 1994; Gutte, 1995). Bisulfate salt formation is needed to produce a soluble Atazanavir salt as a convenient and reproducible crystalline form. Palladium must be controlled by processing at intermediate stages in order to prevent contamination above acceptable levels in the final API.



A number of processes have been published for the production of **64**. Evans et al. (1985) reported the use of the *N*-Boc-alanine aldehyde **71** to produce a mixture of epoxides, one carbon homologation via sulphur ylide attack. These compounds were separated and characterized (Luly et al., 1987; Ghosh and Fidanze, 1998). Cyanide addition to *N*-Boc-phenylalaninaldelyde **71** (Fässler et al., 1998) produced the *threo*-diastereoisomer **72** in good selectivity. Reduction in the presence of the required hydrazine led to the corresponding hydrazone **73**.

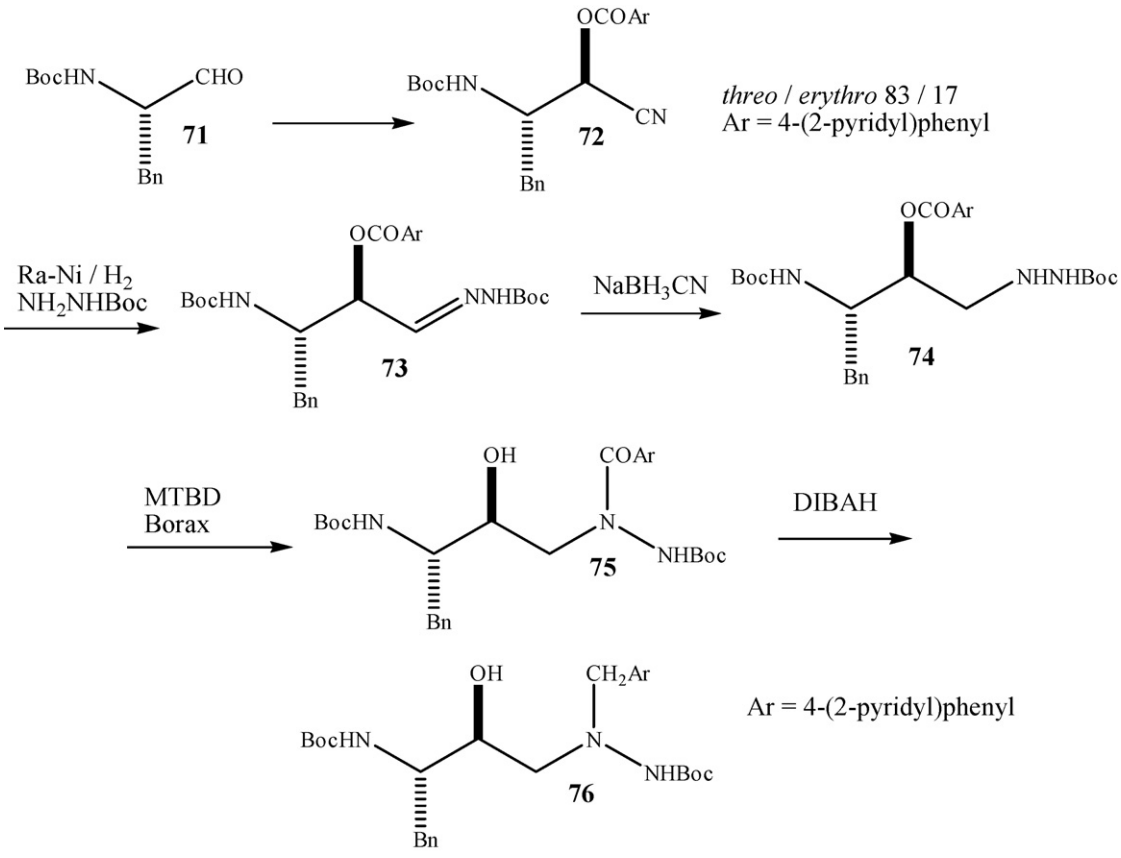


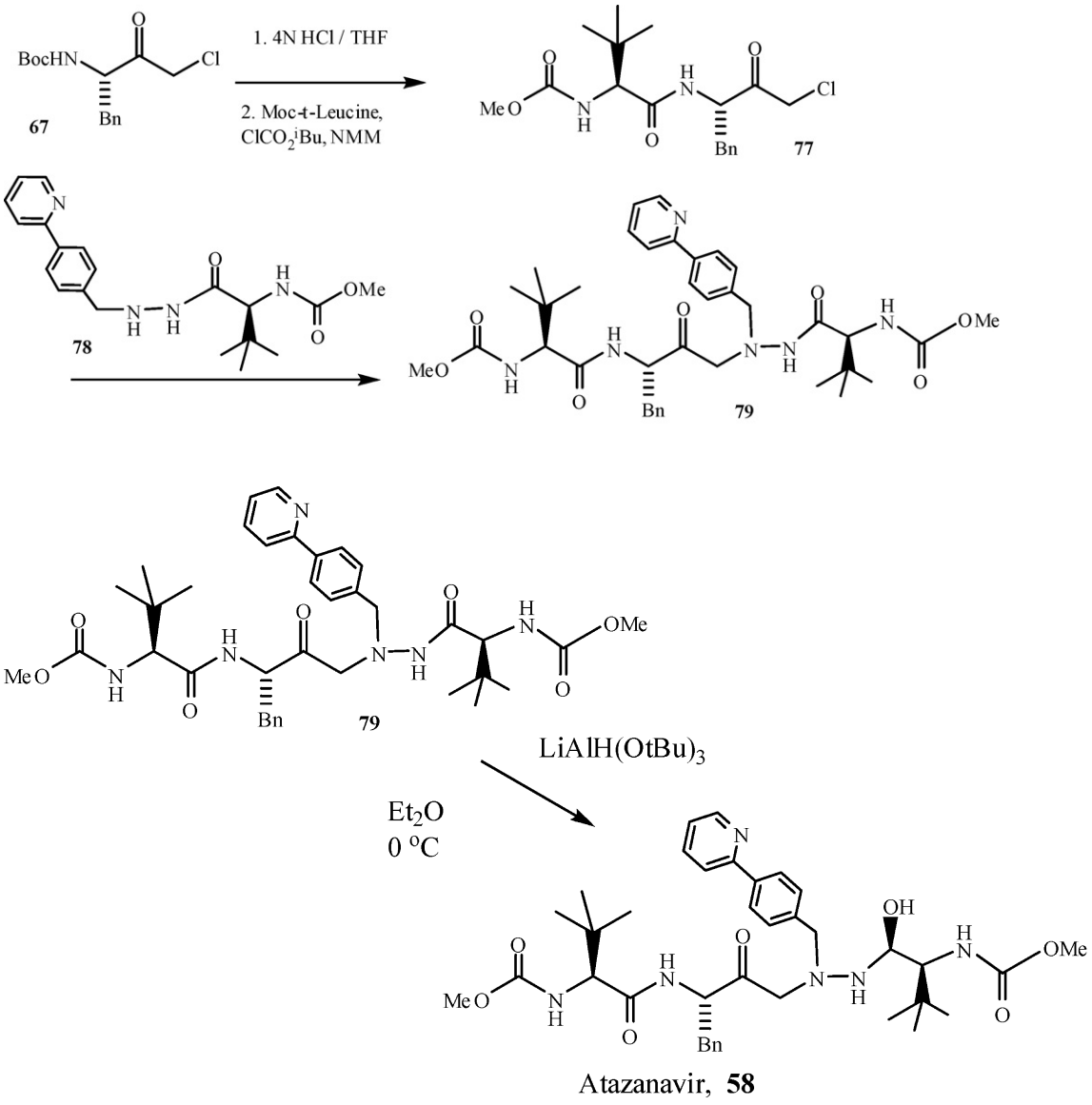
Reduction of hydrazone **73**–**74**, followed by an acyl transfer catalyzed by MTBD under anhydrous conditions led to **75**. Amide reduction afforded **76**, a surrogate of **69**. Bold et al., 1998, described the production of CGP 73547 (BMS-232632). A series of papers concerning similar chemistry have been published (Bold et al., 1998; Fässler et al., 1998; Nogami et al., 2001, 2003; Hamashima et al., 1999, 2001). Epoxide **64** in the diastereoisomeric series is obtained via a procedure established by Kang and Ryu (1995). The diol substrate in this case, can be produced from D-mannitol (Bergmeier and Stanchina, 1999).

In the production of the biaryl moiety, a Suzuki–Miyaura coupling (Kotha et al., 2002) is the successor of the Ullmann procedure. Although $NiCl_2/PCy_3$ or $NiCl_2$/(dbpf) (Saito et al., 1996, 1997) can be used, an enormous number of procedures based on traditional palladium catalysts have been published (Oliveira and Antunes, 2007; Hodgson and Salingue, 2004; Kabalka and Yao, 2003; Cheng et al., 2003; Hutton and Skaff, 2003; Chen and Cammers-Goodwin, 2003; Potuzak and Tan, 2004; Ali et al., 1992). Giordano et al. (2001) described different methods of production of the 2-pyridinphenyl system.

The patents dealing with BMS-232632 and analogous compounds (Giordano et al., 2001; Fässler et al., 1997, 1999, 2001) described in detail the different reaction steps in the synthesis, along with many examples of final products. In the US patent 6,225,345 (Fässler et al., 2001) numerous processes and compounds are described. This patent does not exemplify Atazanavir, although the different processes and unit operations regarding the production of analogous compounds are described in useful detail.

A novel route was recently published by the Shanghai Institute of Materia Medica (Fan et al., 2008) that circumvents the need for Boc-epoxide **64** in the synthesis of atazanavir. Removal of the Boc protecting group from the early intermediate **67** is followed by coupling via the mixed anhydride to put the requisite Moc-*t*-leucine group on nitrogen. The biaryl hydrazine **78** is then reacted with chloromethylketone **77** to produce a final intermediate **79** that is reduced to give atazanavir with moderately good diastereoselectivity (28:1 syn:anti selectivity using $LiAlH(OtBu)_3$ in diethyl ether, 0 °C). It is not entirely clear that this route yields a substantial cost advantage over the route of commercial manufacturing, but Boc-epoxide **64** is a critical cost component for this particular synthesis.





Atazanavir, **58**

The route involving epoxide **64** and the Boc-protected Suzuki–Miyaura derivative **63** is a direct and simple approach to atazanavir. Moc-L-*t*-leucine **70** is available at about $240/kg. At the present time the price of atazanavir is limited by the lack of a large-volume demand in emerging nations, rather than by the inherent cost of intermediates. Presuming that atazanavir "boosted" with ritonavir is essentially equivalent to Aluvia™ (lopinavir:ritonavir), it is likely that ATV will capture much of the future market based on cost due to a lower daily dose (300 mg ATV + 100 mg RTV versus 800 mg LPV + 200 mg RTV daily).

9. Conclusion

From the literature it is very clear that there are several suitable (and simple) processes to produce APIs of the selected critical ARV drugs. In some cases new routes to some feedstocks are needed in order to drive cost reduction for access. There is significant scope to reduce the production costs of several critical APIs. Most importantly, Izawa and Onishi (2006) have recently disclosed some industrial process to manufacture the core of the HIV protease inhibitors.

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