Table 18.3 Stereochemical Variation

(3α, 6)	K_i (nM versus HIV-1)	IC_{95} (μM, cell HIV-1)
R, R Tipranavir	0.008	0.03
R, *S*	0.018	0.14
S, *R*	0.032	0.41
S, *S*	0.22	1.7

and is held rigid by chelation to the carbonyl oxygen of the oxazolidinone. The major stereoisomer then results from alkylation of this chelated enolate anion from the least hindered "upper" face to yield (103) as the major product. There are many strategies for removal and recovery of an oxazolidinone auxiliary (141). In this case, hydrolysis with lithium peroxide provides the acid that is transformed into Atrasentan through a cyclization-ring contraction strategy controlled by the chirality present in (**103**).

Tipranavir (PNU-140690)is a potent third-generation HIV protease inhibitor in clinical development by Boehringer Ingelheim (under license from Pharmacia). The biological activity of such 5,6-dihydro-4-hydroxy-2-pyrone sulfonamides shows considerable stereochemical variation (Table18.3) (**144**). The *R*-configuration is preferred at both chiral centers (3α and 6), and Tripanavir is more than 50 times as potent as its enantiomer in a cell culture assay using $HIV\text{-}1_{IIIB}$–infected H9 cells. An asymmetric synthesis (**145**) begins with the Michael addition of an aryl cuprate (derived from commercially available Grignard reagent 105) to the unsaturated oxazolidinone imide (**104**), yielding the adduct as a single diastereomer (106). The nitrogen protecting group was changed and an acetyl group introduced to give ketone (**107**), which undergoes a stereoselective aldol reaction with an acetylenic ketone (108). The highest diastereoselectivity was obtained for this reaction using $Ti(O^nBu)Cl_3$ as the Lewis acid. Both of the critical asymmetric steps to form new chiral centers are controlled by the (*R*)-phenyl oxazolidinone. The chiral auxiliary is removed when (**109**) is treated with base to form the lactone ring. This is followed by two further steps that generate PNU-140690 (110) as a single enantiomer.

The enantioselective synthesis of dopaminergic benzyltetrahydroisoquinolines and their binding to D_1 and D_2 dopamine receptors was investigated by Cabedo et al. (146). The synthetic route, illustrated by the preparation of the (1s)-isomer involves stereoselective reduction of the isoquinolinium salt (114) with (*R*)-phenylglycinol (introduced in protected form as 112) as the chiral auxiliary. The (1*R*)-enantiomer of (**115**), prepared in an analogous fashion using (*S*)-phenylglycinol, binds to dopamine receptors with considerably less affinity (>100 μM versus D_1 and 61.2 μM versus D_2). In contrast, stereochemical differentiation was not observed at the dopamine uptake site for these compounds.

Two different chiral auxiliary approaches have been applied to the synthesis of NPS 1407 and it's enantiomer (119) (**147**). NPS 1407 is an antagonist of the glutamate NMDA receptor that has in *vivo* activity in neuroprotection and anti-convulsant assays. The *R*-enantiomer was synthesized in four steps from (116)with the chiral center introduced by. a completely stereoselective alkylation of hydrazone (**117**). The chiral auxiliary, *S*-(−)-1-amino-2-(methoxylmethyl)pyrrolidine (SAMP), was introduced by condensation with aldehyde (116) and removed by catalytic hydrogenolysis. In the second method, the *S*-enantiomer was formed in a four-step sequence with the chiral center installed by the Michael addition of chiral amine (121) (formed in one step from the readily available α-methylbenzylamine) to benzyl crotonate (120). NPS 1407 (**123**) was found to be 12 times more potent than it's enantiomer (119)at the NMDA receptor in an in *vitro* assay.

An example of the use of a terpene as a chiral auxiliary is provided by the synthesis of the anti-viral reverse transcriptase inhibitor Lamivudine (148). The nucleoside analog is marketed by Biochem Pharma (now Shire Pharmaceuticals) and Glaxo Wellcome (now GlaxoSmithKline) for the treatment of HIV and hepatitis B virus infection. In the