Table 18.1 Resolution of (62) by Preferential Crystallization

Run	(±) Added (g)	Seed	Time (minutes)	EE of Solution (%EE)	Amount of Crystals (g)	Rotation	%EE of Solid
1	—	(*R*)-(−)	220	22.7/+	2.0	−	95
2	4.0	(*S*)-(+)	210	19.4/−	4.6	+	92
3	4.6	(*R*)-(−)	190	21.2/+	3.8	−	95
4	3.8	(*S*)-(+)	205	21.0/−	3.9	+	95
5	3.9	(*R*)-(−)	210	21.5/+	3.8	−	95
6	3.8	(*S*)-(+)	220	16.4/−	5.0	+	90
7	5.0	(*R*)-(−)	200	21.3/+	3.4	−	92
8	3.4	(*S*)-(+)	215	21.2/−	3.9	+	94
9	3.9	(*R*)-(−)	190	22.2/+	4.0	−	93
10	4.0	(*S*)-(+)	220	21.4/−	4.0	+	95
11	4.0	(*R*)-(−)	200	20.8/+	4.0	−	95

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efficiently entrained to the single required enantiomer (113).

5 ENZYME-MEDIATED ASYMMETRIC SYNTHESIS

Enzymes have found frequent use in the synthesis of single isomer drugs from racemic or prochiral compounds at the larger manufacturing scales. The use of enzymes to effect chiral transformations in the medicinal chemistry laboratory has been far less frequent; however, the increasing availability of immobilized and stabilized forms of enzymes has made their use easier and the resultant transformations more predictable.

By virtue of their complex macromolecular structure, including a highly defined active site, enzymatic transformations generally proceed with a high degree of chemical selectivity and stereospecificity. Reactions are typically conducted under mild conditions of temperature, pressure, and pH, thus minimizing losses caused by unwanted side reactions or partial racemization. The use of extremophiles or cross-linked enzymes such as CLECs do enable the use of higher temperatures, pressures, and organic solvents.

Enzymes can be utilized to affect a number of transformations; the broad spectrum of reactions, including amide bond formation, hydrolysis, esterification, reduction, oxidation, and carbon–carbon bond formation, has been reviewed elsewhere (114).

5.1 Amide Bond Formation

The use of enzymes to stereospecifically form amide bonds has been described in many texts (115); however, the commercial availability of cross-linked enzyme crystals (CLECs), for example, PeptiCLEC-TR, which is an immobilized form of Thermolysin protease, has been used in the synthesis of D2163 (68), a novel matrix metalloproteinase inhibitor (116). In vitro enzyme screening identified the all-natural SSS-isomer as the active product. The elegant CLEC (117) technology used in this example makes the enzyme stable to typical organic reaction conditions and enables facile removal of the enzyme at the end of the reaction by simple filtration. On this basis, it is

Table 18.2 Properties of (63) Indicating Conglomerate Nature

Compound	MP (°C)	Solubility (g/100 mL) THF	Solubility (g/100 mL) DMF	IR Spectrum
(±)-4.2	123–124	14.0	13.0	Identical
(−)-4.2	139–141	6.7	6.9	Identical